MAJOR ARTICLE

Acute Hepatitis B 14 Years after the Implementation of Universal Vaccination in Italy: Areas of Improvement and Emerging Challenges

Alfonso Mele,[1] Maria Elena Tosti,[1] Andrea Mariano,[2] Renato Pizzuti,[4] Antonio Ferro,[5] Bianca Borrini,[6] Carla Zotti,[7] Pierluigi Lopalco,[8] Filippo Curtale,[3] Emanuela Balocchini,[9] and Enea Spada,[1] for the National Surveillance System for Acute Viral Hepatitis (SEIEVA) Collaborating Group[a]

[1]National Centre of Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità, [2]Clinical Research Department, National Institute for Infectious Diseases Lazzaro Spallanzani, and [3]Public Health Agency of the Lazio Region, Rome, [4]Regional Health Authority, Regione Campania, Naples, [5]Service of Public Health and Screening, Regione Veneto, Venezia, [6]Regional Health Authority, Regione Emilia Romagna, Bologna, [7]Department of Public Health and Microbiology, University of Turin, Turin, [8]Institute of Hygiene, University of Bari, Bari, and [9]Regional Health Authority, Toscana Region, Florence, Italy

(See the editorial commentary by Gervais et al. on pages 876–7)

Background. Italy had intermediate-level endemicity for hepatitis B virus (HBV) infection in the 1970s and 1980s. In 1991, vaccination of infants and adolescents became mandatory. We report the impact of universal vaccination 14 years after its beginning.

Methods. We performed a case–control study within a population-based surveillance for acute viral hepatitis. The incidence of acute hepatitis B (AHB) was estimated for the time since 1991, and the association between AHB and the considered risk factors was analyzed for the period 2001–2005.

Results. The incidence of AHB progressively decreased from 1991 to 2005, mainly for persons in the age groups targeted by the universal vaccination campaign: there was a 24-fold and 50-fold decrease in the 15–24-year and 0–14-year age groups, respectively; for the ⩾25-year age group, the incidence halved. Owing to the persons' ages, ~3% of total AHB cases should have been the target of vaccination campaign. In 2004–2005, foreigners accounted for 14% of total cases and for 57% of persons who should have been targets for vaccination. Missed opportunities for immunization were documented for ~50% of patients with AHB who reported cohabitation with HBV carriers and for 70% of those who reported injection drug use. The strongest associations with AHB were found for blood transfusion (adjusted odds ratio [OR_{adj}], 8.4; 95% confidence interval [CI], 2.7–26), cohabitation with HBV carriers (OR_{adj}, 5.3; 95% CI, 3.6–7.7), injection drug use (OR_{adj}, 3.8; 95% CI, 2.5–5.8), and unsafe sexual practices (OR_{adj}, 2.8; 95% CI, 1.9–4.2).

Conclusion. Universal vaccination has contributed to a decreasing AHB incidence in Italy, especially by reducing the risk of infection among persons aged 15–24 years. Most infections occur in persons aged ⩾25 years in association with injection drug use, unsafe sexual activity, percutaneous treatment, and iatrogenic exposure. Improvement of vaccine coverage in high-risk groups and adherence to infection control measures during surgery and percutaneous treatment are needed. The high risk still associated with blood transfusion needs to be further investigated, with consideration of occult HBV infection in blood donors. The potential spread of HBV infection from the immigrant population deserves adequate health policy prevention programs.

Hepatitis B virus (HBV) infection is a major public health problem worldwide. It is estimated that 2 billion people have been infected with HBV, that 350 million have chronic infection, and that 4 million new acute infections occur each year [1–4]. HBV infection causes >50% of all cases of hepatocellular carcinoma and ~600,000 deaths each year [5].

Traditionally, 3 geographic categories of endemicity have been described, depending on the prevalence of hepatitis B surface antigen (HBsAg): areas with high

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Reprints or correspondence: Dr. Enea Spada, Istituto Superiore di Sanità, National Center of Epidemiology, Surveillance and Health Promotion, Clinical Epidemiology Unit, Via Giano Della Bella, 34-00162 Rome, Italy (enea.spada@iss.it).

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[a] Members of the SEIEVA group are listed at the end of the text.

(≥8%), intermediate (2%–7%), and low (<2%) endemicity [1–4]. Vertical transmission and horizontal transmission during early childhood play a major role in perpetuating the endemicity of HBV infection [1–4]. Other important modes of transmission in countries with high or intermediate endemicity are promiscuous sexual activity and unsafe injection [1–4]. It is estimated that at least 30% of new HBV infections in developing countries are due to reuse of syringes in the health care setting [6]. Promiscuous sexual activity and injection drug use (IDU) are the most important risk factors for infection in countries with low-level endemicity [1–4]. High-endemicity populations may be present in low-endemicity countries, and the impact of immigration is probably overlooked in many countries that face the phenomenon of large-scale migration [2, 7, 8].

The risk of HBV transmission by blood transfusion has been steadily reduced through the use of volunteer donors and increasingly sensitive HBsAg tests [9]. Moreover, in several countries, screening by antibody to hepatitis B core antigen (anti-HBc) and/or HBV nucleic acid amplification test (NAT) have also been introduced, further decreasing the residual risk of transmission [10]. Nevertheless, in most countries, the residual risk of HBV transmission by blood transfusion is higher than the risk for other bloodborne viruses, and it is still particularly high in some developing countries [10–12].

In 1981, a plasma-derived vaccine was licensed, and in 1986, a DNA recombinant vaccine became available. All of these vaccines have proven to be safe and highly effective, and programs of mass immunization during early infancy and adolescence have dramatically decreased the incidence and carriage rate of HBV [2, 4, 13]. In Italy, the mandatory universal vaccination of infants and 12-year-old adolescents was launched in 1991. With use of data from the National Surveillance System for Acute Viral Hepatitis (SEIEVA), we report the epidemiologic profile of acute hepatitis B (AHB) after the implementation of a specific universal vaccination campaign.

METHODS

Participants and setting. SEIEVA is coordinated by the Italian National Institute of Health and was established in 1985 [14]; since then, the number of participating local health units over the country has progressively increased. In 1991, the system covered 28.9% of the Italian population, and it covered 61.8% in 2005. During 2001–2005, the mean percentage of the Italian population covered by the surveillance system was 60%.

Cases of acute viral hepatitis, regardless of whether they are diagnosed in a hospital, are notified to the surveillance system through the local health unit. Case definition is based on clinical and serologic criteria. An AHB case is clinically defined as acute illness compatible with hepatitis and a significant increase in the serum level of alanine transferase (the usually adopted threshold is >10 times the upper limit of the normal range). Serologic criteria to distinguish the different types of acute viral hepatitis are as follows: acute hepatitis A (AHA) is defined as positivity for IgM antibodies to hepatitis A virus (HAV), regardless of other viral markers; AHB is defined as positivity for IgM anti-HBc and negativity for IgM anti–HAV, regardless of HBsAg status; acute hepatitis C is defined as negativity for IgM anti-HAV and IgM anti–HBc and positivity for antibodies to hepatitis C virus (HCV). Acute cases of hepatitis in HBsAg-positive, anti-hepatitis delta virus (HDV)–positive, and IgM anti–HAV–negative persons are classified as cases of acute delta hepatitis.

The study period was 2001–2005, but trends in the incidence and frequency of reported risk factors are reported for the period starting in 1991. The study was approved by the Ethics Committee of the Italian National Institute of Health.

Data collection. Each notified case of viral hepatitis was interviewed by either a public health inspector or a physician of the local health unit, with use of a standard 2-page questionnaire. Information on sociodemographic characteristics, exposure to parenteral risk factors during the prior 6 months, and exposure to fecal or oral risk factors within 6 weeks before disease onset were collected. The results of assays for hepatitis markers are recorded on the questionnaire after the interview. Completed questionnaires are forwarded to the Italian National Institute of Health.

Estimation of the incidence. The incidence rates were calculated using the population of local health units participating in the surveillance system at various points in time as the denominator. No changes were made in the notification system during the study period.

Case-control study. To estimate the association between potential risk factors and AHB, cases of AHA that had been notified during the same period were used as controls. The reported frequencies of considered risk factors during the period 2001–2005 were compared in cases and controls.

Statistical analysis. The crude ORs and 95% CIs for the factors under consideration were calculated by univariate analysis. To identify variables that were independently associated with AHB, we calculated the adjusted OR (OR_{adj}) by multiple logistic regression analysis [15]. Age, sex, area of residence, and level of education were also adjusted for in the analysis. All statistical analyses were performed using Stata software, version 8.1 [16].

RESULTS

The incidence of AHB decreased from 5.1 cases per 100,000 person in 1991 to 1.3 cases per 100,000 persons in 2005 (table 1). The decrease was especially evident in the 15–24-year-old age group (a 24-fold decrease from 1991 to 2005) and the 0–14-year-old age group (a 50-fold decrease from 1991 to 2005), even if, for the latter group, the 1991 incidence was already

low, because trend toward a decreasing incidence had started before 1991. Among persons aged ⩾25 years, the incidence halved from 1991 to 2005.

Table 2 shows the trends in the frequency of risk factors reported by persons with AHB during 1991–2005. Unsafe sexual practices (defined as no or occasional condom use), dental therapy, treatments or procedures with percutaneous exposure (defined as tattoos, piercings, acupuncture, barber-shop shaving, or use of a manicurist/chiropodist), and promiscuous sexual activity (defined as >2 sex partners in the previous year) were the most frequently reported risk factors throughout the study period. The yearly percentage of persons with AHB who reported surgical intervention, cohabitation with a chronic HBsAg carrier, and blood transfusion was steady during the study, whereas the percentage of persons with AHB who reported IDU decreased over time.

In 1992, compulsory HBV vaccination of all newborns and 12-year-old adolescents became operative in Italy. Two hundred eighty-nine (3.2%) of 9160 cases of AHB reported to SEIEVA since that time were represented by persons who, on account of their age, should have been targeted by the vaccination program. Thirty (10.4%) of 289 persons with AHB had undergone vaccination (5 had received 1 dose, and 13 had received 3 doses; for 12 persons, the information was missing); of the remaining persons, 194 (2.1% of the total number of people with AHB) had not been vaccinated, and for 65 persons, the information was not reported. Nonvaccinated persons with AHB in Sicily and Campania (southern Italy) represented 7.6% and 4.4% of the total cases notified in these regions, respectively (data not shown). Since 2004, data on nationality have been collected for all cases of viral hepatitis notified to SEIEVA; during 2004–2005, 45 (57%) of 79 persons with AHB, who should have been targeted by the vaccination program, were foreigners; most came from Romania (20 persons) or other eastern European countries.

During 2001–2005, a total of 2740 cases of AHB were reported to SEIEVA. Table 3 presents the patients' sociodemographic characteristics. Twelve of the persons with AHB (median age, 66 years; range, 33–90 years) died, 3 of whom were anti-HCV positive. Information on anti-HDV test results was available for 5 of the 12 persons with fatal AHB; 2 persons had anti-HDV positive results, and one of these persons (an IDU) was also coinfected with HCV.

Eighty-eight (47%) of 186 persons with AHB who shared a home with HBsAg-positive subjects were aware of the carrier condition of the cohabitant; nevertheless, 88% of these patients had not been vaccinated. Likewise, 88.7% of patients who reported IDU had not received HBV vaccine, although 72.5% of these patients had already attended a center for the treatment of addiction.

The 2740 AHB cases were compared with 4893 AHA cases notified to SEIEVA during the same period (table 3). Table 4 shows the crude and adjusted ORs for considered risk factors. An independent association with AHB was found for all but 1 of the risk factors, but the strongest associations were detected for blood transfusion (OR_{adj}, 8.4; 95% CI, 2.7–26), cohabitation with an HBsAg carrier (OR_{adj}, 5.3; 95% CI, 3.6–7.7), and IDU (OR_{adj}, 3.8; 95% CI, 2.5–5.8). After adjustment, promiscuous sexual activity was not found to be associated with AHB, whereas a significant association persisted for unsafe sexual practices (OR_{adj}, 2.8; 95% CI, 1.9–4.2).

In 2004–2005, a total of 129 (14%) of 948 notified AHB cases occurred in people who had come from eastern Europe, Asia, or Africa. Eight percent of these people reported promiscuous sexual activity, and 17% resided in households with a chronic carrier (data not shown).

DISCUSSION

The decrease in incidence of AHB started before the implementation of the vaccination program. In fact, the incidence was 10.4 cases per 100,000 persons in 1987 and 5.4 cases per 100,000 persons in 1990 [17]. This pattern is consistent with figures from seroepidemiological studies performed in Italy during the 1980s and 1990s [18–20] and must be attributed to the socioeconomic changes that occurred in Italy during recent decades. The vaccination program implemented in 1991 further contributed to this decrease mostly in the 15–24-year-old age group, who had a higher risk of infection associated with the beginning of sexual activity. Because the vaccination program

Table 1. Incidence of acute hepatitis B cases notified in Italy, by age group, National Surveillance System for Acute Viral Hepatitis (SEIEVA), 1991–2005.

	No. of cases per 100,000 persons, by age group				
Year	0–14 years	15–24 years	⩾25 years	Total	Population surveyed
1991	1	12	4	5.1	16,401,503
1992	1	10	3	4	22,622,762
1993	1	10	4	4	22,622,762
1994	1	6	4	3	22,804,610
1995	1	6	3	3	23,060,981
1996	1	5	3	3	25,900,850
1997	0.5	5	4	3	31,882,134
1998	0.4	4	3	3	31,882,134
1999	0.3	3	3	2	32,331,986
2000	0.1	2	2	2	33,429,357
2001	0.5	1.5	2.5	2	33,429,357
2002	0.2	1.3	2	1.5	33,429,357
2003	0.1	0.9	2.3	2	33,429,357
2004	0.1	0.7	2.3	1.6	33,701,132
2005	0.02	0.5	1.8	1.3	35,194,296

Table 2. Frequency of risk factors reported for persons with acute hepatitis B cases notified in Italy, National Surveillance System for Acute Viral Hepatitis (SEIEVA), 1991–2005.

Risk factor[a]	Year														
	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Blood transfusion	3	3	3	2	2	2	2	3	3	2	3	2	3	3	3
Injection drug use	25	27	27	19	20	19	17	15	18	14	11	9	9	6	5
Household shared with a chronic HBsAg carrier	13	13	14	12	11	15	12	11	12	9	10	11	11	9	13
>2 Sex partners[b]	21	21	24	25	26	24	24	23	18	24	21	23	32	26	34
Condom use (occasional/never vs. always)[b]	36	34	51	57	51	48	38	42	35	31	31	34	50	51	56
Surgical intervention	11	11	12	14	12	10	13	14	14	14	16	13	14	15	13
Treatments or procedures with percutaneous exposure[c]	25	27	31	30	36	30	32	31	30	31	32	33	30	33	30
Dental therapy	25	27	28	28	28	31	28	30	26	31	32	30	36	33	35
Total no. of cases	669	654	826	683	640	639	842	837	654	648	631	540	550	563	457

NOTE. Data are percentage of cases, unless otherwise indicated. HBsAg, hepatitis B surface antigen.

[a] Exposure within 6 months of disease onset. Patients may report >1 risk factor.

[b] Age, >14 years.

[c] Piercing, tattooing, acupuncture, manicurist/chiropodist attendance, and barber-shop shaving.

actually started in 1992, the impact of vaccination of 12-year-old boys on the decrease in the incidence of AHB became evident only in 1994, and as the percentage of vaccinees in the 12-year-old cohort increased, the incidence progressively fell. Instead, the decrease in the incidence was less evident for persons aged 0–14 years, in part because of the lower risk of infection and because the incidence had already been low since 1991; the same was true for persons aged ⩾25 years, who were not a target of the vaccination program.

As a result of the vaccination campaign, >12 million children have been immunized against hepatitis B [21], with 93.6% coverage among teenagers [22]. In 2004, the vaccination program for 12-year-old adolescents ended, whereas the program for infants was maintained. Notwithstanding, since 1992, a total of 289 cases of AHB have occurred among subjects who should have been targeted by the vaccination program; 194 of these patients had not been vaccinated, and cases could have been prevented. The number of patients with AHB in some southern regions who had not been vaccinated previously but who, owing to their age, should have been vaccinated in the past was not negligible. However, it is necessary to emphasize that, in 2004–2005, a total of 57% of AHB cases among subjects targeted for vaccination occurred in foreigners. Because the vaccination calendar in developing countries is different from that adopted in Italy, at present, immigrants who were born abroad or were 12 years old while abroad are unlikely to have been vaccinated against hepatitis B; furthermore, immigrants often do not comply with the compulsory vaccination program [23]. Thirty of 289 persons with AHB who should have been targeted by the vaccination program had received at least 1 dose of vaccine. Because vaccine escape mutants do not seem to play an important role in vaccine failure [24], these cases should be traced to the percentage of healthy vaccinees (5%–10%) who do not mount an adequate antibody response [25].

Blood transfusion, cohabitation with chronic HBsAg carriers, IDU, invasive surgical procedures, treatments or procedures with percutaneous exposure, and unsafe sexual practices are the major risk factors associated with AHB. The high risk associated with blood transfusion deserves detailed comments. A residual risk of HBV infection associated with blood transfusion still exists even in countries where HBsAg screening of donors is routinely performed [10]. Furthermore, using NAT, investigators have highlighted the role that occult hepatitis B in donors contributes to the residual risk of HBV transmission [26]. The residual risk of infection associated with the window period in Italy was estimated to be 15.8 units per million units

Table 3. Demographic characteristics of patients with acute hepatitis B and acute hepatitis A cases notified in Italy, National Surveillance System for Acute Viral Hepatitis (SEIEVA), 2001–2005.

Characteristic	No. (%) of patients	
	Hepatitis B (n = 2740)	Hepatitis A (n = 4893)
Sex		
Male	2041 (75.6)	3250 (67.4)
Female	660 (24.4)	1575 (32.6)
Age, years		
⩽14	24 (0.9)	905 (19.4)
15–24	253 (9.4)	1088 (23.4)
⩾25	2418 (89.7)	2664 (57.2)
No. of years of schooling		
⩽5	238 (12.9)	491 (14.8)
6–8	749 (40.7)	1335 (40.3)
⩾9	852 (46.3)	1486 (44.9)
Geographic area		
Northern and central	2382 (86.9)	2802 (57.3)
Southern and islands	358 (13.1)	2091 (42.7)

Table 4. Frequency of risk factors reported by patients with acute hepatitis B cases and acute hepatitis A cases (control group) notified to SEIEVA in 2001–2005.

Risk factor[a]	Percentage of patients		Crude OR (95% CI)	Adjusted OR (95% CI)
	Hepatitis B (n = 2740)	Hepatitis A (n = 4893)		
Blood transfusion	2.7	0.3	8.7 (4.8–15.4)	8.4 (2.7–26.0)
Injection drug use	8.2	2.6	3.4 (2.6–4.3)	3.8 (2.5–5.8)
Surgical intervention	14.3	4.5	3.5 (2.9–4.2)	2.1 (1.6–2.8)
Dental therapy	33.0	19.8	2.0 (1.7–2.2)	1.5 (1.2–1.7)
Treatments or procedures with percutaneous exposure[c]	31.6	18.6	2.0 (1.8–2.2)	1.9 (1.5–2.2)
>2 Sex partners[b]	25.1	13.7	2.1 (1.8–2.5)	0.8 (0.6–1.2)
Condom use (occasional/never vs. always)[b]	41.9	16.1	3.8 (3.1–4.5)	2.8 (1.9–4.2)
Household shared with a chronic HBsAg carrier	10.5	2.5	4.6 (3.5–5.8)	5.3 (3.6–7.7)

NOTE. Crude ORs were estimated by univariate analysis, and adjusted ORs were estimated by multiple logistic regression analysis. HBsAg, hepatitis B surface antigen.

[a] Each risk factor is adjusted for the confounding effect of all other listed risk factors and of sex, age, number of years of education, and area of residence.

[b] Age, >14 years.

[c] Piercing, tattooing, acupuncture, manicurist/chiropodist attendance, and barber-shop shaving.

of blood [27]. Recently, in a study performed in certain regions of Italy, implementation of NAT screening of blood donations was adopted [28, 29]. The most recent data from this study [28] revealed that 80 of 1,298,187 blood units were HBsAg negative but HBV DNA positive during the period 2001–2005 (overall HBV NAT yield, $6.16/10^5$ blood units). Ninety-nine percent of these donors who had serologic and anamnestic information available had occult hepatitis B; the remaining were in the window period during acute infection. Previous epidemiological data from other developed countries are in agreement with these results [30–32]. Data on the infectivity of donors with occult hepatitis B are limited and vary widely [26]. However, infectivity data could be underestimated, mainly as a result of posttransfusion asymptomatic HBV infection. All of these findings may explain the number of AHB cases that were associated with transfusion in the SEIEVA population notwithstanding screening; they also justify, in part, the high relative risk still associated with blood transfusions. On the other hand, the risk associated with blood transfusion could be overestimated: a case of AHB that occurs after a blood transfusion is not necessarily a case of transfusion-transmitted hepatitis, because blood transfusions are usually administered in health care settings, where many other iatrogenic sources of HBV infection are present [33]. Moreover, transfusion-associated cases of AHB represent only a small proportion of all cases of AHB (table 2).

Households of chronic carriers and IDUs are still at high risk of infection. In this study, alarming missed opportunities for immunization were documented in these risk groups. In one-half of the cases occurring in household members of HBsAg carriers, infected persons with AHB were aware of carrier condition of their cohabitant(s), yet most of them were not vaccinated. Likewise, in almost all cases occurring in IDUs, the individuals had not been vaccinated, although 72.5% of them had already attended a center for the treatment of addiction. It is noteworthy that, for both these groups, HBV vaccination is strongly recommended and is offered free of charge. Vaccine coverage of these at-risk groups should be strongly enhanced. For IDUs, the possible inability to complete the vaccination regimen should not preclude its initiation at the first admission to a center for the treatment of addiction, because protective antibody levels develop in 35%–55% of adults after a single vaccine dose and in 75% of adults after 2 doses [34]. However, an accelerated vaccine schedule should be the most desirable choice for IDUs [35, 36].

An independent association with AHB was found for unsafe sexual practices, but not for promiscuous sexual activity. These findings have great epidemiological significance, because they once again underline the importance of using a condom during occasional sexual intercourse.

It is worth noting that, in HBV screening conducted in Italy in 2001, among 10,881 pregnant women, 597 were from foreign countries (mostly developing areas), and the prevalence of HBsAg was 5.9% in this group, whereas the prevalence among pregnant Italian women was 1.4% [37]. In addition, 14% of notified AHB cases during 2004–2005 occurred in people from eastern Europe, Asia and Africa. Thus, the immigration of people from developing countries (often countries where HBV infection is highly endemic), in addition to being an important cultural, social, and economic phenomenon, has become a relevant public health problem in recent years, because it could affect the future diffusion of HBV infection in the general population, as well as the epidemiologic profile of other infectious diseases [7, 8, 38]. This problem should be dealt with by offering

appropriate health services, including vaccination, to the communities of immigrants living in our country.

At present, very few AHB cases are reported in children and young adults; most infections occur in nonimmunized persons aged ⩾25 years. The case-fatality rate during the study period was similar to that during a previous survey in 1995–2000 [39]. One-fourth of persons with fatal AHB were HCV positive; HDV coinfection was detected in 2 of 5 cases in which anti-HDV was tested, and 1 of these 2 HDV-positive patients was also HCV positive. These findings confirm that acute superinfection in patients with chronic hepatitis may increase the risk of severe hepatitis and underline the often overlooked role of HDV coinfection [40, 41]. It follows that HDV tests should be performed in all severe AHB cases.

Patients with AHA were used as control subjects to estimate the strength of the association between AHB and various exposures. HAV has different modes of transmission than does HBV, although they can occasionally share the same risk factors (e.g., IDU, blood transfusion, and male homosexual activity). However, percutaneous transmission of HAV has to be considered a very rare event in the general population: only a very low percentage of the patients with hepatitis A used as control subjects in this study reported the risk factors of blood transfusion (0.3%) or IDU (2.6%). However, overinclusion of exposed persons in the control group would have, at most, led us to underestimate the related OR. Moreover, it should be considered that, in case-control studies, the comparability between case patients and control subjects is a crucial factor. In fact, all individuals with acute hepatitis in this study had notified cases, came from the same geographic area, were identified through the same surveillance system, and were interviewed by the same blinded interviewer; thus, they were exposed to the same selective factors, if any. Therefore, the use of AHA cases represents a valid, feasible choice in this study, allowing savings in both time and expenses.

In conclusion, the implementation of a mass-vaccination campaign, complemented with socioeconomic changes in Italian population, has contributed to the progressive decrease in the incidence of AHB in our country. At present, most cases of AHB occur in nonimmunized people aged ⩾25 years who acquire infection through IDU, household contact with an HBV carrier, unsafe sexual activity, treatments or procedures with percutaneous exposure, and iatrogenic exposures. Additional efforts are needed to improve vaccine coverage in groups at higher risk (including IDUs, households with HBsAg carriers, and people at risk of sexually transmitted diseases) and to enhance the infection control measures during invasive procedures performed inside and outside of health care settings. Occult hepatitis B seems to be an overlooked source of HBV infection associated with transfusion, and additional studies are needed to investigate the prevalence and infectivity of occult hepatitis B in transfusions. The potential spread of HBV infection from the immigrant population—particularly children—must be carefully considered and deserves an adequate health policy program of prevention.

SEIVA COLLABORATING GROUP

F. Marzolini (Istituto Superiore di Sanità, Roma); L. Sudano (USL Valle d'Aosta, Aosta); J. Simeoni and M. Fischer (ASL Prov. Aut. Bolzano, Bolzano); V. Carraro and C. Grandi (ASL Prov. Aut. Trento, Trento); G. Lanci (Università di Torino); M. Meda and G. Vizzani (ASL Torino); A. Gallone and L. Muratori (ASL Collegno, Torino); M. T. Galati and L. Signorile (ASL Chiasso, Torino); G. Valenza, A. M. Scala, and P. Castagno (ASL Chieri, Torino); M. P. Alibrandi and E. Bresaz (ASL Ivrea, Torino); A. Incarbona and E. De Luca (ASL Pinerolo, Torino); V. Silano and A. De Simone (ASL Vercelli); G. Ara (ASL Biella); A. Cipelletti (ASL Novara); S. Iodice (ASL Verbania, Vercelli); A. Costantino and M. Boscardo (ASL Cuneo); A. Bertorello (ASL Mondovì, Cuneo); R. Barberis (ASL Savigliano, Cuneo); F. Giovanetti (ASL Alba, Cuneo); M. A. Marchisio (ASL Asti); B. Rizzi (ASL Tortona, Alessandria); B. Prosperi and F. Fossati (ASL Acqui Terme, Alessandria); M. D'Angelo (ASL Casale Monferrato, Alessandria); S. Crippa and G. Altomonte (ASL 3 Monza, Milano); F. Zorzut (ASL Trieste); L. Donatoni (ASL Gorizia); T. Gallo and G. Brianti (ASL Udine); E. Zamparo (ASL Pordenone) A. Ferro A, G. Niero, and F. Bressani (Assessorato Sanità, Venezia); R. Mel (ASL Belluno); M. Soppelsa (ASL Feltre, Belluno); M. Sforzi (ASL Bassano del Grappa, Vicenza); F. Russo (ASL Thiene, Vicenza); E. De Stefani (ASL Arzignano, Vicenza); A. Todescato (ASL Vicenza); P. Paludetti (ASL Pieve di Soligno, Treviso); D. Rizzato (ASL Montebelluna, Treviso); M. Forte (ASL Treviso); L. Nicolardi (ASL San Donà di Piave, Venezia); G. Marchese (ASL Zelarino, Venezia); G. Marchioni (ASL Dolo, Venezia); M. Boscolonata (ASL Chioggia, Venezia); G. D'Ettore (ASL Camposampiero, Padova); L. Gottardello (ASL Padova); R. Bisi (ASL Conselve, Padova); L. Gallo (ASL Rovigo); L. Caffara (ASL Adria, Rovigo); G. Zivelonghi (ASL Verona); S. Soffritti (ASL Legnago-Verona); M. Foroni (ASL Villafranca, Verona); R. Rangoni, B. Borrini, A. Cappelletti, A. Furini, and C. Ancarani (Assessorato Sanità, Bologna); A. Capra (AUSL Piacenza); B. M. Borrini, F. Zilioli, F. Copelli, A. Alessandrini, and A. Morelli (AUSL Parma); P. Camerlengo, M. Greci, L. Monici, A. Bertazzoni, M. Bigliardi, and S. Santacroce (AUSL Reggo Emilia); L. Gardenghi, G. Casaletti, R. Cagarelli, F. Errani, A. Lambertini, A. Bulgarelli, D. Vaccina, E. Casolari, and A. Pezzi (AUSL Modena), R. Todeschini, C. Andalo, G. Domeniconi, A. Calzolari, E. Dalle Donne, M. L. Dimaggio, and M. Fabbri (AUSL Bologna); N. Savoia (AUSL Imola); F. Taddia, M. Cova, and A. Califano (ASL Ferrara); G. Savelli, G. P. Casadio, and B. Calderoni (AUSL Ravenna); E. Fiumana (AUSL Forlì); M. Franceschini (AUSL Ce-

sena, Forlì); A. Pecci (AUSL Rimini); M. Mela (ASL Imperia); M. P. Briata and R. Carloni (ASL Savona); W. Turello (ASL 3 Genova); G. Zoppi (ASL 4 Chiavari, Genova); A. Bertone (ASL La Spezia); F. Mazzotta and G. Graziani (Assessorato Sanità, Firenze); L. Barani and G. Ghiselli (USL Massa-Carrara); A. Di Vito (USL Capannoni, Lucca); F. Mazzoli and W. Wanderlingh (USL Pistoia); A. C. Epifani (USL Prato); N. Galletti and F. Sbrana (USL Pontedera, Pisa); M. Battaglini, G. Marinari, A. Lombardi, and L. Genghi (USL di Piombino, Livorno); J. Lezzi (USL di Poggibonsi, Siena); F. Verdelli, R. Bindi, E. De Sanctis, A. Beltrano, and R. Conti (USL Arezzo); G. Boncompagni, P. Piacentini, M. Di Cunto, T. Papalini, and L. Incandela (USL Grosseto); S. Baretti, R. Cecconi, C. Staderini, and G. Ciampi (USL Firenze); P. Filidei (USL Empoli, Firenze); C. Raffaelli (USL di Viareggio, Lucca); E. Carducci (Assessorato Sanità, Ancona); A. R. Pelliccioni (ASL Pesaro); G. Peccerillo (ASL Urbino); M. Agostani (ASL Fano, Ancona); R. Rossini (ASL Senigallia, Ancona); G. Grilli (ASL Jesi, Ancona); N. Burattini (ASL Fabriano, Ancona); P. Marcolini (ASL Ancona); R. Passatempo (ASL Civitanova Marche, Macerata); F. Migliozzi (ASL Macerata); G. Moretti (ASL di Camerino, Macerata); M. Nucci (ASL di Fermo, Ascoli Piceno); S. Impulliti (ASL San Benedetto del Tronto, Ascoli Piceno); C. Angelini (ASL Ascoli Piceno); G. Taccaliti (USL Teramo); G. Guaitini and A. Tosti (Assessorato Sanità, Perugia); A. Pasquale, M. Rossi, and A. Buscosi (ASL Città di Castello, Perugia); O. C. Penza and C. Ciani (ASL Perugia); F. Santocchia (ASL Foligno, Perugia); M. L. Proietti (ASL Terni); A. Romizi (ASL Orvieto); A. Corbo, D. Corpolongo, P. Porcelli, A. Ruta, and G. Ciarlo (ASL Latina); P. Dionette and R. Guadagnali (ASL Rieti); A. Ercole, G. Esterini, A. Piccoli, R. Boggi, P. Russo, P. Napoli, M. G. Catacchio, C. Cerocchi, D. Linari, P. Grillo, M. T. Tedeschi, C. Gnesivo, M. Loffredo, V. Labriola, A. Pendenza, E. Tanzariello, E. Santarelli, P. Bueti, M. Ferrucci, S. Ursino, S. L. Torchia, L. Santucci, F. Alicata, S. Viafora, R. Cecere, F. Pepe, P. Patti, M. Pesoli, C. Aiello, M. Ruiu, F. Beato, and M. Mathis (ASL Roma); P. Vilecco, D. De Santis, S. Aquilani, A. Passini, and O. Micali (ASL Viterbo); V. Pagano (Osservatorio Epidemiologico Regionale, Napoli); N. Minichiello and M. A. Ferrara (ASL Avellino); A. Citarella and E. Fossi (ASL Benevento); C. Bove, M. Trabucco, and A. D'Argenzio (ASL Caserta); A. Simonetti, A. Parlato, R. Alfieri, F. Peluso, R. Palombino, and F. Giugliano (ASL Napoli), A. L. Caiazzo, M. G. Panico,V. Della Greca, and A. M. Trani (ASL Salerno); S. Barbuti and M. Quarto (Università di Bari); R. Matera, R. Colamaria, A. Madaro, G. Scalzo, and F. Avella (ASL Bari); E. Bellino (ASL Brindisi); M. Masullo, I. Pagano, and V. Di Martino (ASL Foggia); A. Fedele, G. Turco, and S. Minerba (ASL Lecce); F. S. Negrone, M. Maldini, M. De Lisa, E. Polani, and R. La Vecchia (ASL Potenza); F. Mauri and T. Russo (ASL Montalbano Ionico, Matera); F. Aloia and S. Giuffrida (ASL Castrovillari, Cosenza); G. Peritore and R. Mangione (USL Licata, Agrigento); M. Cuccia and S. Rinnone (USL Catania); S. Cau (ASL Sassari); A. Saba (ASL Olbia, Sassari); D. Fracasso and O. Frongia (ASL Macomer, Nuoro); and M. V. Marras and G. Mereu (ASL Cagliari).

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