

Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study

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Summary

Background Universal anti-hepatitis-B vaccination of infants and adolescents was implemented in Italy in 1991. We undertook a multicentre study in previously vaccinated individuals to assess the duration of immunity and need for booster, over 10 years after vaccination.

Methods In 1212 children and 446 Italian Air Force recruits vaccinated as infants and adolescents, respectively, we measured the concentrations of antibodies to hepatitis-B surface antigen (anti-HBs) and the presence of antibodies to hepatitis-B core antigen (anti-HBc) at enrolment; postimmunisation values were not available. Individuals positive for anti-HBc were tested for hepatitis B surface antigen (HBsAg) and hepatitis B viral DNA. Individuals with anti-HBs concentrations at 10 IU/L or more were regarded as protected; those with antibody less than 10 IU/L were given a booster dose and retested 2 weeks later. Individuals showing postbooster anti-HBs concentrations of less than 10 IU/L were offered two additional vaccine doses and retested 1 month after the third dose.

Findings Protective anti-HBs concentrations were retained in 779 (64%, 95% CI 61.6–67) children and 398 (89%, 86.4–92.1) recruits. We recorded antibody amounts of less than 10 IU/L in 433 children (36%, 33–38.4) and 48 (11%, 7.9–13.6) recruits. One child and four recruits were positive for anti-HBc, but negative for HBsAg and hepatitis B viral DNA. Antibody concentrations were higher in recruits than in children (geometric mean titre 234.8 IU/L vs 32.1 IU/L, $p=0.0001$). 332 (97%) of 342 children and 46 (96%) of 48 recruits who received a booster showed an anamnestic response, whereas ten (3%) children and two (4%) recruits remained negative for anti-HBs or had antibody concentrations of less than 10 IU/L. Prebooster and postbooster antibody titres were strongly correlated with each other in both groups. All individuals given two additional vaccine doses (eight children and two recruits) showed anti-HBs amounts of more than 10 IU/L at 1 month after vaccination.

Interpretation Strong immunological memory persists more than 10 years after immunisation of infants and adolescents with a primary course of vaccination. Booster doses of vaccine do not seem necessary to ensure long-term protection.

Introduction

Viral hepatitis B is a leading cause of acute and chronic liver disease worldwide, including cirrhosis and hepatocellular carcinoma. WHO estimates that, globally, about 2 billion people have been infected with hepatitis B virus, more than 350 million are chronically infected, and nearly 1 million die every year from acute or chronic sequelae of primary infection of the disease.^{1,2}

Safe and effective vaccines have been available since the early 1980s, offering the opportunity to exert substantial prevention and control of the disease on a global scale.³ For almost a decade, vaccination strategies focused largely on the protection of individuals at increased professional or behavioural risk of exposure to hepatitis B virus.⁴ The failure of such policies to reduce the incidence of the disease in the general population⁵ led to the WHO recommendation that all countries should have universal infant or adolescent hepatitis B vaccination (or both) integrated into their national immunisation programmes by 1997.^{6,7} By the end of 2004, 168 countries implemented these immunisation programmes. Italy was one of the first countries to do

so,^{8,9} and selective immunisation targeted to high-risk groups was implemented in 1983. In 1991, mandatory universal vaccination of infants, hepatitis-B-surface-antigen (HBsAg) screening of pregnant women, and vaccination of 12-year-old adolescents (restricted to the first 12 years of application of the vaccination law) was introduced. As a result of this policy, more than 12 million children had been immunised against hepatitis B (coverage rate of about 95%) by 2003, with an outstanding record of safety and effectiveness.¹⁰ By the end of 2003, the first infant cohort vaccinated in 1991 reached the age (12 years) when adolescents' vaccination takes place. In 2004, vaccination of 12-year-old adolescents was stopped, and that of infants was maintained.

A substantial reduction of newly acquired infections of hepatitis B, carrier rate, and hepatitis-B-related mortality has been reported in countries where universal vaccination has been implemented.^{11–17} Long-term protection of 10 years or more seems to occur in children vaccinated during infancy in hyperendemic areas.^{18–22} However, data are scarce for the duration of immunity in

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vaccinated infants and teenagers in countries at low endemicity,^{23,24} and needs to be further corroborated. Therefore it is urgent to assess whether vaccinated infants maintain protection until the time when risk of infection (either by lifestyle or professional exposure) may be expected, or whether they need booster vaccination to sustain immunity into adolescence and adulthood.

We undertook an extensive study to assess the anamnestic response to a booster injection of vaccine in children vaccinated as infants and in Italian Air Force recruits vaccinated as adolescents who showed antibodies to hepatitis B surface antigen (anti-HBs) below the protective concentration (10 IU/L) more than 10 years after the primary course of vaccination.

Methods

Patients and procedures

Enrolment took place from March 1, to Dec 15, 2003. The study population consisted of children born to HBsAg-negative mothers and of recruits vaccinated more than 10 years before, according to the mandatory universal vaccination as infants or as adolescents, respectively. No control group was specified in the study protocol, because virtually the entire Italian population younger than 25 years has been vaccinated. Children were enrolled in nine health-care districts in Italy (three in the north centre, three in the south, and three on the major islands). Participants were selected from lists of people vaccinated as infants by use of a systematic random sampling procedure to ensure 150 children for every health-care district. Of the 1350 selected individuals, 1259 (93%) agreed to participate in the study. 47 were excluded because they were born to HBsAg-positive mothers and were treated with hyperimmune gammaglobulin and vaccine at birth, or because their vaccination schedule had not been completed properly. Thus we enrolled 1212 children in the study.

Air Force recruits were residents from all Italian regions who were consecutively referred to the recruitment centre of Viterbo, central Italy. All recruits vaccinated as adolescents in 1991–94 were selected. 468 (82%) of the 571 initially invited individuals agreed to participate in the study. 22 individuals were excluded because their vaccination schedule had not been completed properly, and 446 were enrolled.

For both groups, sociodemographic information was obtained with a precoded questionnaire. Health-care district registries for children and individual vaccination certificates for recruits were reviewed to assess the completeness of the vaccination schedule.

Vaccination schedules consisted of three paediatric doses (10 µg) of recombinant hepatitis B vaccine (Engerix B, SmithKline Beecham Biologicals, Rixensart, Belgium) given at 3, 5, and 11 months of age to individuals vaccinated as infants. According to Italian guidelines at that time, vaccinated adolescents were

given three adult doses (20 µg) of the same vaccine at 0, 1, and 6 months of age.

Testing of anti-HBs after immunisation to confirm a response to the vaccination was not available for any study participant. At enrolment, all vaccinated individuals were in good health and none had a history or presented signs or symptoms of clinically overt hepatitis. Ethics approval was obtained from the ethics committee of the Italian National Health Institute. All recruits gave written informed consent to the participation in the study. For children, parents provided written informed consent and verbal assent was obtained from every participant.

A blood sample was obtained from every individual at enrolment to measure the concentration of anti-HBs and the presence of antibodies to hepatitis B core antigen (anti-HBc) as a serological marker of hepatitis B infection. According to the study algorithm, individuals with anti-HBs concentrations of 10 IU/L or more were regarded as immune, whereas those with amounts lower than 10 IU/L were offered a booster dose of vaccine (Engerix B, GlaxoSmithKline Biologicals, Rixensart, Belgium; paediatric dose for children and adult dose for recruits). A second blood sample was obtained 2 weeks after the booster dose to quantify anti-HBs amounts. An anamnestic response was arbitrarily defined as a rise in anti-HBs to at least 10 IU/L. Individuals showing antibody concentrations less than 10 IU/L were then offered an additional complete course of vaccination. Additionally, all individuals found to be positive for anti-HBc were further tested for the presence of HBsAg and hepatitis B viral DNA.

HBsAg, anti-HBc, and anti-HBs were detected by commercially available kits (IMx MEIA, Abbott Laboratories, Abbott Park, IL, USA). Anti-HBs titres were measured and expressed in IU/L by comparison with a calibrators curve standardised against the WHO reference standard. Hepatitis B viral DNA was detected by the COBAS Ampliscreen assay (Roche, Branchburg, NJ, USA) with a threshold sensitivity concentration of 20 IU/mL (100 copies per mL).

Statistical analysis

Since the rate of vaccine non-responders after a primary course of vaccination is expected to be about 5%, the sample size of our study allowed us an estimated accuracy of 2% for recruits and less than 2% for children. Hence, our sample estimate roughly had a 95% confidence level of being within 2% of the true value. Anti-HBs titres were compared by use of the non-parametric Mann-Whitney U test. In the case of undetectable concentrations, an arbitrary value of 0.5 IU/L was assigned to allow for calculation of the geometric mean titre. We tested differences in frequency with the χ^2 test, and regarded $p < 0.05$ as significant. 95% CIs for geometric mean titres and frequencies were also calculated, if appropriate. Statistical calculations

	Children (n=1212)	Recruits (n=446)
Sex		
Male	612 (50%)	446 (100%)
Female	600 (50%)	0
Age at enrolment (years; mean [SD])	10.9 (0.30)	21.8 (1.21)
Residential location		
North-Centre	372 (31%)	113 (25%)
South	424 (35%)	249 (56%)
Islands	416 (34%)	84 (19%)
Year of vaccination*		
1992 or 1991-92	847 (70%)	155 (35%)
1993 or 1993-94	365 (30%)	291 (65%)
Length of follow-up (years; mean [SD])	10.6 (0.33)	10.3 (0.96)

Data are number (%) unless stated otherwise. *For children, vaccination took place in 1992 and 1993; for recruits, vaccination took place in 1991-92 and 1993-94.

Table 1: Study population demographics

were undertaken with Stata Statistical Software, version 8.

Role of the funding source

The sponsor of the study (Italian Ministry of Health) had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the main characteristics of the two study groups. 64% of the children examined had protective concentrations of anti-HBs (≥ 10 IU/L) over 10 years after the primary course of vaccination, including one child who was positive for anti-HBc but negative for HBsAg and hepatitis B viral DNA (table 2). 27% of children had antibody titres of less than 10 IU/L, and 9% had undetectable amounts. Of the 446 recruits, 89% had protective concentrations of antibodies (including four individuals who tested positive for anti-HBc but negative for HBsAg and hepatitis B viral DNA), 7% had anti-HBs concentrations less than 10 IU/L, and 4% had undetectable antibodies. Antibody concentrations were significantly higher in recruits than in children (geometric mean titre 234.8 IU/L vs 32.1 IU/L, $p=0.0001$).

Socioeconomic factors such as residential location, family size, fathers' level of education, year of initial vaccination, and sex (in the children group) did not affect the probability of protective antibody concentrations in either group (data not shown).

We gave a booster dose of vaccine to the 342 (79%) children and all 48 recruits who had anti-HBs concentrations that were lower than 10 IU/L or were undetectable at enrolment. The proportion of children who refused the booster vaccination did not differ significantly between those with undetectable

	Children (n=1212)	Recruits (n=446)
Undetectable concentrations	106 (9%, 7.2-10.3)	17 (4%, 2-5.6)
1 to <10	327 (27%, 24.5-29.5)	31 (7%, 4.6-9.3)
Subtotal <10	433 (36%, 33-38.4)	48 (11%, 7.9-13.6)
10 to 100	424 (35%, 32.3-37.7)	85 (19%, 15.4-22.7)
>100 to 1000	321 (26%, 24-29)	216 (48%, 43.8-53.1)
>1000	34 (3%, 1.9-3.7)	97 (22%, 17.9-25.6)
Subtotal ≥ 10	779 (64%, 61.6-67)	398 (89%, 86.4-92.1)
Geometric mean titre (95% CI)	32.1 (28.6-36.0)	234.8 (190.3-289.6)

Data are number (%), 95% CI unless stated otherwise.

Table 2: Anti-HBs concentrations (IU/L) in children and recruits vaccinated more than 10 years previously

concentrations and those with concentrations less than 10 IU/L (18 [17%] of 106 vs 73 [22%] of 327, $p=0.241$).

2 weeks after the booster was given, ten children (3%, 95% CI 1.1-4.7) still had antibody concentrations of less than 10 IU/L (including six with undetectable amounts), whereas the remaining 332 (97%, 95.3-98.9) showed an anamnestic increase in concentration (table 3). Anti-HBs titres after booster were higher in children whose prebooster antibody was positive (but less than 10 IU/L) than in those with undetectable prebooster antibody (table 3, $p=0.0001$).

46 of 48 recruits (96%, 90.2-100) showed a postbooster increase of anti-HBs to more than 10 IU/L (table 4). The remaining two recruits (4%, 0-9.8) who were initially antibody-negative seroconverted to anti-HBs but had concentrations less than 10 IU/L. Similar to our findings in children, antibody amounts were higher in those with prebooster anti-HBs positivity of less than 10 IU/L than in those with undetectable prebooster antibody (table 4, $p=0.0001$).

Prebooster anti-HBs concentration (IU/L)	Postbooster anti-HBs concentration (IU/L)				Geometric mean titre (95% CI)
	<10	10 to 100	>100 to 1000	>1000	
Undetectable (n=88)	10* (11%)	24 (27%)	41 (47%)	13 (15%)	135.1 (82-222.6)
<10 (n=254)	..	13 (5%)	96 (38%)	145 (57%)	1698.8 (1366-2112.2)
Total (n=342)	10 (3%)	37 (11%)	137 (40%)	158 (46%)	885.6 (698.9-1122)

Data are number (%) unless stated otherwise. *Six children remained negative for anti-HBs.

Table 3: Anti-HBs concentrations at 2 weeks after booster vaccination in children with non-protective antibody concentrations at enrolment

Prebooster anti-HBs concentration (IU/L)	Postbooster anti-HBs concentration (IU/L)				Geometric mean titre (95% CI)
	<10	10 to 100	>100 to 1000	>1000	
Undetectable (n=17)	2* (12%)	6 (35%)	4 (24%)	5 (29%)	188.0 (54.8-644.8)
<10 (n=31)	7 (23%)	24 (77%)	5764.3 (3211-10347.8)
Total (n=48)	2 (4%)	6 (13%)	11 (23%)	29 (60%)	1715.1 (826.7-3558.1)

Data are number (%) unless stated otherwise. *No recruits remained negative for anti-HBs.

Table 4: Anti-HBs concentrations at 2 weeks after booster vaccination in recruits with non-protective antibody concentrations at enrolment

	Anti-HBs titre (IU/L)			
	2 weeks after first booster dose	At injection of second dose (1 month)	At injection of third dose (6 months)	1 month after third dose (7 months)
Child 1	Undetectable	Undetectable	Not tested	92.6
Child 2	Undetectable	Undetectable	10	61.6
Child 3	Undetectable	2.7	41.2	143
Child 4	Undetectable	14.1	63.3	24
Child 5	Undetectable	3.8	17.1	24
Child 6	4	8.7	51.1	509
Child 7	6.8	58.8	194.1	240
Child 8	6.9	Not tested	7	36.6
Recruit 1	4.8	41.9	45.2	50.2
Recruit 2	9.3	2.8	37	66.2

Table 5: Anti-HBs response after a second full course of vaccination according to anti-HBs concentrations elicited after first booster injection

Ten children and two recruits who had postbooster anti-HBs concentrations of less than 10 IU/L were offered to complete a second course of vaccination with two additional vaccine doses given at 1 and 6 months after the first booster injection. Eight of these ten children (including five of the six who remained anti-HBs-negative at the postbooster check) and both recruits accepted. All vaccinated individuals presented antibody concentrations of more than 10 IU/L at 1 month after the third immunisation (table 5). In particular, the five children who did not respond to the first booster injection (Child 1 to Child 5) showed a poor rise in antibody titres (median 61.6 IU/L, IQR 24–96.2 IU/L) after the second course of vaccination was completed. After the third vaccination dose, two children (Child 6 and Child 7) had antibody amounts of more than 100 IU/L, whereas the remaining child (Child 8) and both recruits had increased antibody concentrations to values less than 100 IU/L.

Discussion

This study, designed to determine the duration of immunity and the need for booster vaccinations, showed that more than 60% of children and nearly 90% of recruits maintained anti-HBs amounts that were regarded as protective (≥ 10 IU/L) more than 10 years after vaccination. We recorded undetectable concentrations in about 9% of children and 4% of recruits and detectable amounts lower than 10 IU/L in 27% and 7%, respectively. However, all recruits and all but six children responded to a booster dose of vaccine. Prebooster and postbooster antibody titres were strongly correlated with each other. Overall, the booster dose elicited a rapid and vigorous anamnestic response. Increase of anti-HBs titres was greater in children and adolescents with preboosting anti-HBs positivity, even if at low amounts (< 10 IU/L), than in those with preboosting undetectable antibody.

1 month after receiving a second full course of vaccination, seven of ten vaccinated individuals (including five children who were non-responsive to one

booster dose of vaccine, and three children and two recruits who developed antibody amounts less than 10 IU/L) had poor anti-HBs responses with antibody concentrations increased to less than 100 IU/L. We can infer that these vaccinated individuals were hyporesponsive to the immunisation and that their antibodies may rapidly wane over time. However, even in these instances, loss of antibody does not necessarily imply loss of protection, since the long incubation period of hepatitis B virus could allow time for the immunological memory to protect them against acute disease or the development of chronic carriage.

During the past 20 years, the frequency of hepatitis B infection has declined greatly in Italy, as a result of social, behavioural, and demographic changes; the general improvement in standard of living and hygiene; and the introduction of public-health measures including refinement in blood screening, use of universal precautions in medical settings, and implementation of universal vaccination policies.^{25,26}

Because of the high quality of the vaccination delivery services and public awareness of the disease, Italy's hepatitis B vaccination programme has been successful with a good coverage rate, although there is a somewhat lower acceptance in the south than in the northern regions. According to the national surveillance system for acute viral hepatitis (SEIEVA, Rome, Italy), the incidence of acute hepatitis B has fallen greatly after the implementation of vaccination. This decline was even more striking in individuals aged between 15 and 24 years, in whom the morbidity rate per 100 000 inhabitants fell from 17 in 1990 to less than one in 2003. Additionally, a generation of children and teenagers (24-year age cohorts) is emerging with almost no markers of hepatitis B viral infection. An added benefit of the anti-hepatitis-B vaccination is that hepatitis δ has also declined substantially.²⁷

No clinically overt hepatitis has been reported so far in successfully vaccinated individuals. Occasional breakthrough infections, due to S-gene mutants of hepatitis B virus, have been seen in children born to HBsAg-positive mothers who were given hyperimmune gammaglobulin and vaccine but, at present, such mutants do not pose a public-health threat.²⁸

Italy's priorities for the future include the maintenance of mandatory vaccination of infants, catch-up immunisation of unvaccinated adolescents, and examination of the potential need for vaccine booster doses. A consensus on this last point is urgently needed in Italy, since the vaccination of 12-year-old adolescents was abandoned at the end of 2003 when the first cohort of infants vaccinated in 1991 reached the age for adolescent vaccination.

Evidence shows that in healthy vaccinated individuals, immunological memory for HBsAg may outlast the presence of antibody, providing effective protection even in those showing waning (< 10 IU/L) or absent

concentrations of anti-HBs after vaccination.²⁹ Hence, booster doses of vaccine may not be necessary to sustain long-term immunity in healthy vaccinated individuals.³⁰

Although this study was not specifically designed to compare the duration of immunity between the two study groups, our findings have indicated that both anti-HBs amounts and percentage of individuals with protective antibody titres were higher in recruits than in children. Previous findings have shown that male sex was associated with extended persistence of anti-HBs.²⁰ However, we could not detect any difference between male and female individuals vaccinated as infants. Hence, the difference between the two vaccinated groups could be attributed to a different response to the primary course of vaccination due to different age and vaccine doses (three paediatric doses vs three adult doses), or to a different degree of exposure to natural boosters, conceivably higher in adolescence than in childhood. Four (nearly 1%) recruits had markers of hepatitis B infection (anti-HBc). Since serological data were not obtained either before or after vaccination, it is impossible to conclude whether these individuals were already infected at the time of vaccination or whether they were infected with hepatitis B virus subsequently.

For the one child found to be positive for anti-HBc, we can infer (assuming that he was born to an HBsAg-negative mother and that his family had no HBsAg carriers) that he acquired hepatitis B virus horizontally after vaccination. Since most children who become infected develop a chronic carrier state, we can speculate that vaccination might have partly protected this child whose exposure to the hepatitis B virus resulted in subclinical infection.

In conclusion, Italy's programme of hepatitis B vaccination has resulted in substantial progress towards the prevention and control of hepatitis B infection. 12 years after the implementation of universal vaccination of both infants and adolescents, the Italian population under 25 years of age is protected against infection with the hepatitis B virus. The immunisation programme targeting 12-year-old adolescents was withdrawn at the beginning of 2004 since all children at this age are already covered.

The importance of vaccination against hepatitis B in infancy is universally accepted. However, the duration of protection in children born to HBsAg-negative mothers and vaccinated during the first year of life in countries at low or moderate endemicity is not yet clearly established. In other words, will vaccinated babies maintain immunity into adulthood or are additional boosters necessary? Our data provide evidence that a strong immunological memory persists for more than 10 years after immunisation of healthy infants and adolescents with a primary course of hepatitis B vaccination. The selection criteria adopted in this study (random sampling procedure for children) and the wide geographical distribution of both groups

ensure the validity and representativity of the observed findings.

The rate of anti-HBs persistence recorded in Italian children and recruits compare favourably with results reported elsewhere.^{14,15,18-22} However, unlike previous studies, our study was undertaken in a lower endemicity country, in which the presence of natural boosters is conceivably scarce, which suggests that the protective effect against hepatitis B infection could be due to the sole administration of vaccine.

In light of our findings, the use of routine booster doses of hepatitis B vaccine does not seem necessary to maintain long-term protection in immunocompetent individuals vaccinated as infants and teenagers. Clearly, this observation is specific to the 10-year checkpoint. Additional follow-up is warranted to establish whether a primary course of vaccination in infancy or adolescence may confer life-long protection or whether boosters may be needed at a later point in life.

Study Group

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Contributors

A R Zanetti, R D'Amelio, T Stroffolini, and A Mele contributed to the study design, collection, analysis and interpretation of the data, drafting the manuscript, and critical revision of the article. A Mariano and L Romanò participated in the laboratory analysis, collection and interpretation of data, design of the study, and critical revision of the article. M Chironna, R C Coppola, M Cuccia, R Mangione, F Marrone, F S Negrone, A Parlato, E Zamparo, and C Zotti contributed to the follow-up of vaccinated individuals, collection and interpretation of data, and critical revision of the article. The final version was written by A R Zanetti and was seen and approved by all the authors.

Conflict of interest statement

The members of the writing committee declare that they have no conflict of interest.

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