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HBV seroprevalence after 25 years of universal mass vaccination and management of non-responders to the anti-Hepatitis B vaccine: An Italian study among medical students

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Summary

According to international guidelines, healthcare workers and medical students immunized against HBV are periodically tested for anti-HBs IgG. Subjects who show an anti-HBs titre <10 mUI/mL must receive additional vaccine doses to induce a measurable antibody response. This study aimed to evaluate the long-time immunogenicity of anti-hepatitis B vaccination in a sample of medical students and residents of the University of Bari who attended the Hygiene Department for biological risk assessment (April 2014-June 2017). The strategy for the management of nonresponder subjects was evaluated. A total of 3676 students and residents were invited for testing according to a standardized protocol. Anti-HBs IgG was tested for in 3140 (85.4%) subjects: 1174/3140 (37.7%) subjects were negative. 14.6% (128/808) of subjects who received the vaccine during their 12th year of life and 45.8% (1056/2305) of subjects immunized during the first year of life ($P < 0.0001$) were negative. 1005/1174 (85.6%) seronegative subjects received a booster dose, and 903/1005 (89.9%) were tested for anti-HBs 1 month after the booster dose: 82/903 (9.1%) subjects were still negative. Of these, 56/82 (68.3%) received 2 additional doses of vaccine and 52/56 (92.9%) were tested 1 month after the third dose: 50/52 subjects (96.2%) developed a positive titre. In conclusion, several medical students, immunized at birth or at young age against HBV, did not develop protective titres against the virus. Our management strategy (booster retest; for negative subjects, 2 doses and retest) seems consistent with the purpose of evidencing immunological memory.

KEYWORDS
additional doses of vaccine, booster dose, healthcare workers, long-time immunogenicity

1 | INTRODUCTION

Hepatitis B is one of the world's most common and serious infectious diseases: more than one-third of the world's population has been infected by Hepatitis B virus and, of these, more than 250 million are chronic carriers; WHO estimates that HBV is the cause of 1-2 million deaths. More than 500 000 people become infected every year.[1]

Vaccination is an effective infection prevention tool; mass vaccination programs have been incorporated into national immunization programs in over 150 countries, including Italy. Italy was the first industrialized country that adopted a universal vaccination strategy

Abbreviations: CLIA, Chemiluminescent immunoassay; CMIA, Chemiluminescent microparticle immunoassay; GIAVA, Regional Immunization Database; HBsAg, Australia antigen.

against hepatitis B in 1991.[2-4] The first hepatitis B vaccination strategy was introduced in 1981 for the immunization of hemodialyzed patients and healthcare personnel; in 1983, the active offer of the then anti-HBV vaccine was extended through targeted campaigns to vulnerable population groups. With the Decree of the Health Minister of 22 December 1988, the free vaccination offer was established for all high-risk groups.[4-6]

In 1991, a major change in the vaccination strategy was introduced: anti-HBV vaccination was made compulsory and extended to the entire population through a "two-cohort" universal vaccination strategy that provided:

- The routine vaccination of all newborns;
- The vaccination of adolescents (12-year old);
- HBsAg testing in all pregnant women to prevent perinatal infection;
- Vaccination of adults belonging to groups at high risk.

Vaccination of newborns was performed based on a 3-dose scheme, with immunization at the third, fifth and eleventh month of life at the same time as other mandatory vaccinations (polio, diphtheria, tetanus).[5-9]

Vaccination of 12-year-old adolescents also included 3 doses, the first at 0 and the subsequent 1 and 6 months from the first. Finally, compulsory screening of HBsAg in pregnant women was introduced to identify newborns who need both passive and active immunity induction by concomitant administration of 200 units of immunoglobulin and vaccine within 24 hours from birth.[5-9]

In 2017, with DL 73/2017, Italian legislators made compulsory ten vaccinations (HBV, poliomyelitis, diphtheria, tetanus, pertussis, *Haemophilus influenzae* B, measles, mumps, rubella and varicella) and strictly recommended 4 vaccines (meningococcus B, meningococcus C, pneumococcus and rotavirus). The administration calendar of anti-HBV doses did not change.[10]

The 12-year-old vaccination offer continued for 12 years and was suspended in 2003, because adolescents born in 1991 were immunized in the first year of life. This allowed, in 12 years, to have 24 cohorts of subjects immunologically protected against the risk of infection.[9,11]

As recognized by many authors, the vaccine strategy adopted by Italy has been a success and has been followed by many other countries, which similarly to Italy have introduced universal vaccination for some age classes.[12]

In Italy, in 2003, 12 years after the introduction of compulsory vaccination for infants and adolescents, a vaccine coverage of 95.7% was achieved among subjects, going down to 93.0% in 2016.[13]

The vaccine strategy adopted in Italy was able to reduce the number of cases of acute hepatitis already documented through the data of the SEIEVA surveillance system,[9,14-17] in particular in the age groups targeted by the vaccination campaign.

The hepatitis B vaccine is available in monovalent formulations or in combination with other vaccines. In Italy and in many countries, the anti-HBV vaccine is available in combination:

- Bivalent, with anti-hepatitis A or anti-*H. influenzae* B;
- Tetravalent, with full anti-diphtheria-tetanus-pertussis (DTaP);
- Hexavalent, with DTaP, anti-*H. influenzae B* and inactivated polio.

The immune response and safety of these vaccine combinations are comparable to those of single products.[18-20]

The HBV vaccine's immunogenicity has a huge interindividual variability, and approximately 5%-10% of healthy immunocompetent subjects do not develop an antibody response after a complete vaccination schedule.[21,22]

Anti-HBs IgG is the conventional marker used to study the immunological status against HBV among vaccinated subjects. People who do not show an anti-HBs IgG protective titre (≥10 mU/mL) after the standard 3-dose primary series of anti-HBV vaccine are considered nonresponders. In other words, a nonresponder is a person without HBV infection who has a documented history of an age-appropriate primary course of HBV vaccine, but with a current anti-HBs level <10 mU/mL.[23]

Several factors have been associated with the lack of development of a protective response:

- Male gender;
- Age >40 years at vaccination;
- High BMI;
- Tobacco smoke;
- Drugs use;
- Immunosuppression.[21,24-28]

For nonresponders, particularly those who are at high risk of exposure to HBV, additional vaccine doses are recommended with the purpose of inducing a measurable antibody response.[23,29]

The recommendations for the management of nonresponders include:

- Additional dose(s) at varying times;
- Repeating the standard 3-dose schedule at 0, 1 and 6 months;
- Double the dose;
- Brand of vaccine with higher antigen content;
- Intradermal administration;
- Oral, nasal or combined vaccine.[21,26,27,30]

To cope with the problem of nonresponders, new vaccines have been explored: triple antigen vaccines, adjuvants using granulocyte-macrophage colony-stimulating factors and antigen-pulsed blood dendritic cells.[31-34]

Until today, unfortunately, only few studies have compared the efficacy relative to the above approaches regarding administration of additional doses of vaccine and, consequently, there are no guidelines for the management of nonresponders in daily clinical practice.

In this context, a meta-analysis published in 2015 compared in nonresponders the administration of 20 ug doses of intramuscular vaccine (IM-20), 40 micrograms doses of intramuscular vaccine (IM-40), 5 ug doses of intradermal vaccine (ID-5) and 20 ug

doses of intradermal vaccine (ID-20). The results show that each of the 4 options demonstrated better seroconversion rates after administration of additional doses: after the first additional dose, the seroconversion rate ranged from 54% to 62%, with no significant difference between the options of management; a second dose induced a 50% seroconversion rate for IM-40, 90% for ID-20, with a significant statistical difference between the 2 options ($P = 0.03$). After the third additional dose, seroconversion rates were 53% for IM-40 and 85% for ID-5. Seroconversion rate for IM-40 differed significantly from ID-5 ($P = 0.02$) and IM-20 ($P = 0.01$), respectively.[29]

In addition, it is recommended that the vaccine is administered in the deltoid or anterolateral aspect of the thigh and not in the gluteus: more than 100 reports show low antibody seroconversion rates for injections in the gluteus.[35]

The study of the role of genetics in the immune response to vaccination offers exciting prospects in the improvement of knowledge about the biological basis of protection induced by the vaccine, both at start-up of increasingly personalized courses in the field of prevention of infectious diseases.[36-38]

Nonresponding healthcare workers are an important issue in Public Health. Representing a risk both for themselves and for patients, several studies in the literature address this issue by proposing different vaccination strategies. Sangfelt et al[39] in a 2008 study asserted that 3 doses of low-dose intradermal vaccine followed by intramuscular boosters to nonresponders is effective and cost-effective. An Israeli study in 2015 concluded that in healthcare workers vaccinated in infancy, 2 doses of intramuscular vaccine in adulthood will provide maximal protective antibody levels, while one dose will provide sufficient population protection.[40] Paradoxically, a US study of the same year asserts that a rapid and robust response to a booster vaccine suggests a long-lasting amnestic response and so it does not appear to be necessary in fully vaccinated HCWs without protective anti-HBs.[41]

2 | MATERIALS AND METHODS

This study aimed to evaluate the longevity of anti-HBs in a sample of students and residents of the School of Medicine of the University "Aldo Moro" in Bari and the effectiveness of the strategy for the management of nonresponding subjects.

Medical students have training activities within hospital facilities and are constantly exposed to the risk of exposure, and sometimes they can act as sources of contagion to patients in the same way as other healthcare workers. For these reasons, the "National Prevention Immunization Plan 2012-2014" established that every university hospital must promote all initiatives consistent with the purpose of increasing the adherence of medical students to vaccinations recommended for healthcare workers.[42]

In addition, the Ministry of Health, in several documents and rules, indicated that the Schools of Medicine and University Hospitals have to apply for students the same procedures provided by the Italian Law on Occupational Health and Safety for healthcare workers.[43]

To comply with these recommendations, the Hygiene Department of the Bari Policlinico University Hospital organized a biological risk prevention program for students and residents of the School of Medicine of the University of Bari. The activity protocol was approved in the academic year 2013 - 2014 and represented a pilot experience at the national level. The activities were started in April 2014. The immunity/susceptibility status for HBV, Measles, Mumps, Rubella and Varicella was assessed for each enroled subject by blood tests and analysis of vaccination history. The vaccination status of enroled subjects was assessed by the Regional Immunization Database (GIAVA).

Subjects without any doses of HBV vaccine or with <3 doses were offered to start/complete the vaccination schedule. The assessment of biological risk for HBV in subjects who had the regular vaccination series (3 or more doses) provides for a blood test to assess anti-HBs titre, using chemiluminescence techniques (CMIA and CLIA), as described above.[44] For subjects with anti-HBs ≥10 mIU/mL, no measures of prophylaxis are applied, while in case of a titre <10 mIU/mL a booster dose of HBV vaccine is administered; after 30 days, a new blood test is performed for anti-HBs. If the value is ≥10 mIU/mL, the person is not subjected to further vaccine doses; if the titre is still negative, 2 other vaccine doses (after 1 month from the first booster dose and 5 months from the second booster dose) are administered. One month after the third dose, an additional measurement of anti-HBs is performed. Seroconversion is defined as an anti-HBs titre ≥10 after one or thee additional vaccine doses.

The adsorbed recombinant DNA vaccine (HBVAXPRO) was used as booster dose, and it was administered intramuscularly in the deltoid. After 3 additional doses, subjects with anti-HBs ≥10 mIU/mL received 2 doses of HBV vaccine simultaneously and retested after 1 month; subjects still seronegative were definitively classified as "non responders". They are recommended to be evaluated for HBV infection in all cases of exposure and to receive immunoglobulin in case of exposure (Figure 1).

The study sample was composed of students and medical residents of the School of Medicine of the University of Bari who attended the Hygiene Department for biological risk assessment between April 2014 and June 2017. Subjects without an available vaccination history never vaccinated or vaccinated with fewer times than the recommended at baseline were excluded from this study. The database was uploaded as an Excel Spreadsheet, and data were analysed by Stata SE14 software.

A descriptive analysis of the sample was performed by calculating the total number of subjects enroled, the distribution per gender and per age at first immunization cycle (1 year/12th year) and the average age of subjects. For vaccinated subjects who were negative for anti-HBs at the first check, the rate of seroconversion at different follow-up times was calculated. All categorical variables were described as absolute frequencies and proportions. All continuous variables were expressed as means ± standard deviation and range. The chi-square test and exact Fisher test were used to compare the proportions. The Wilcoxon's rank sum test and ANOVA for repeated

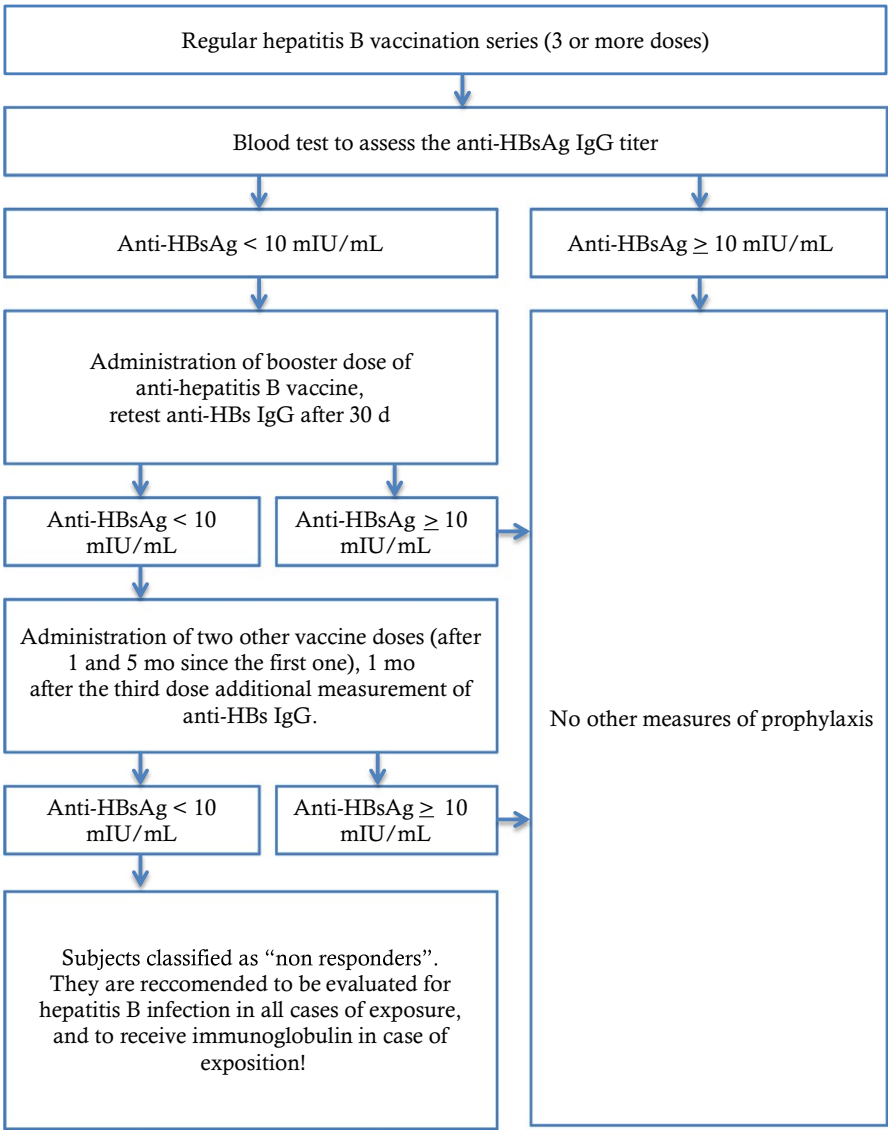

FIGURE 1 Assessment of biological risk of hepatitis B in subjects who have basal vaccination series (3 or more doses) [Colour figure can be viewed at wileyonlinelibrary.com]

measures were used to compare means between the group of subjects immunized during the first year of life and the group of subjects immunized during the 12 years. We considered in the group of subjects immunized during the first year of life also students who received the first dose of vaccine with a delay, from 3 months to 6 years.

To assess the determinants of seroconversion after the vaccine basal cycle, simple logistic regression was used, considering the seroconversion as outcome and gender, age of the subject at the time of the baseline vaccination cycle and time from vaccine and serological test as determinants; the values of OR (Odds Ratio) were calculated with 95% confidence intervals and were backed by *z*-score test.

For the previous outcome, a multivariate logistic regression model was built, using as determinants the determinants associated in the simple logistic regression. The adjusted Odds Ratio (aOR) values were calculated with the IC 95% and were backed by *z* score test.

To assess the determinants of seroconversion after a booster dose, simple logistic regression was used, considering the seroconversion after booster doses as outcome and gender, time between vaccine and serological evaluation, age of the subject at the time of the booster dose and age of the subject at the time of the baseline vaccination cycle and time between the first dose of vaccine in the baseline cycle and antibody titre evaluation as determinants; the values of OR (Adjusted Odds Ratio) were calculated with 95% confidence intervals and were backed by *z*-score test.

For the previous outcome, a multivariate logistic regression model was built, using as determinants the determinants associated in the simple logistic regression. The adjusted Odds Ratio (aOR) values were calculated with the IC 95% and were backed by *z*-score test.

To evaluate the goodness of fit of both multivariate logistic regression models, chi-square, Pearson and Hosmer-Lemeshow tests were used.

For all the tests, a $P < 0.05$ was considered statistically significant.

3 | RESULTS

From April 2014 to June 2017, 3676 students and medical residents were invited to be tested. Of these, 1285 (35.0%) were male and

2391 (65.0%) female. The mean age was 24.0 ± 5.0 years (range: 18.0-66.0); in particular, the average age in male subjects was 24.1 ± 4.9 (range: 18.0-59.0), in female subjects 24.0 ± 5.0 (range: 18.0-66.0), without any significant difference ($z = 1.0$; $P = 0.309$).

The vaccination certificate was available for 3403 (92.6%) enroled subjects. Of these, 3140 (92.3%) had had the regular anti-HBV vaccination schedule (3 or more doses).

Of the subjects with a complete baseline vaccination cycle, 3113 (99.1%) were tested for anti-HBs: 1939 (62.3%) had an anti-HBs titre ≥10 mIU/mL. The proportion of immune subjects did not show a difference between males (n = 641/1048; 61.2%) and females (n = 1298/2065; 62.9%; $X^2 = 0.8$; $P = 0.357$), while the percentage was higher among subjects who received the basal cycle at 12 years of life (n = 690/808; 85.4%) than among subjects who received the basal cycle during the first year of life (n = 1249/2305; 54.2%; $X^2 = 248.1$; $P < 0.001$).

The overall geometric mean anti-HBs titre was 22.3 (CI 95% = 20.5-24.2), not different between males (21.2; CI 95% = 18.4-24.4) and females (22.8; CI 95% = 20.6-25.3; $z = 1.1$; $P = 0.286$) while the value was higher among subjects who started the basal cycle at age of 12 years (90.7; CI 95% = 79.1-104.0) than among subjects who started the basal cycle during the first year of life (13.6; CI 95% = 12.4-14.9; $z = 20.5$; $P < 0.0001$),

Of 1174 seronegative subjects, 1005 (85.6%) received a booster dose. Of these, 903/1005 (89.9%) were tested for anti-HBs: 821/903 (90.9%) subjects were positive and 82/903 (9.1%) negative. The seroconversion rate after a booster dose did not show differences between males (n = 280/315; 88.9%) and females (n = 541/588; 92.0%; $X^2 = 2.4$; $P = 0.120$), and between subjects who received the basal cycle at 12 years of life (n = 84/90; 93.3%) and subjects who received the basal cycle during the first year of life (n = 737/813; 90.7%; $X^2 = 0.7$; $P = 0.401$).

The anti-HBs geometric mean titre after a booster was 228.7 (CI 95% = 199.5-262.1), lower among males (179.5; CI 95% = 141.6-227.5) than females (260.3; CI 95% = 220.3-307.4; $z = 2.6$; $P = 0.009$) and higher among subjects who started the basal cycle at 12 years (445.6; CI 95% = 293.9-675.6) than subjects who started the basal cycle during the first year of life (212.3; CI 95% = 183.9-245.2; $z = 3.6$; $P < 0.0001$).

Figures 2 and 3 describe the proportions of subjects with protective anti-HBs titre and mean geometric mean titre values per group (immunized at 1 year/immunized at 12 year) after the basal cycle and after a booster dose. We observed a statistically significant difference in seroprevalence between groups at baseline ($X^2 = 248.1$; $P < 0.0001$), after booster dose ($X^2 = 17.1$; $P < 0.0001$) and between times ($X^2 = 1.1*10^3$; $P < 0.0001$).

Analysis of ANOVA for repeat measurements showed a statistically significant difference in the GMT value per group ($F = 365.4$, $P < 0.0001$), time ($F = 582.5$, $P < 0.0001$) and interaction between group and time ($F = 167.3$; $P < 0.0001$).

56/82 (68.3%) seronegative subjects received 2 additional doses of vaccine, and 52/56 (92.9%) were retested for anti-HBs : 50/52 subjects (96.2%) had an anti-HBs ≥10 mIU/mL. Of the 2 negative subjects, patient 1 was male, vaccinated for the first time at age of 1 year and received a booster dose at age of 23 years; patient 2 was female, vaccinated for the first time at age of 1 year and received a booster dose at age of 25 years. Patient 1 was subjected to a double dose of vaccine at the same time, but anti-HBs remained negative; no further doses were given to patient 2.

The simple logistic regression showed that the outcome of seroconversion after 3 doses of vaccine is associated with age at the time of first vaccination (OR = 4.9; 95% CI = 4.0-6.1; $z = 14.8$; $P < 0.0001$) and the time between the first dose of vaccine in the baseline cycle and the antibody titre evaluation (OR = 0.96; 95% CI = 0.94-0.98; $z = 4.0$; $P < 0.0001$); there is no association with gender (OR = 0.9; 95% CI = 0.8-1.1; $z = 0.9$; $P = 0.357$). The multivariable logistic regression model confirms the association showed in the simple regression (Table 1).

The simple logistic regression shows that the outcome of seroconversion after a booster dose of vaccine is associated with the time between the first dose of vaccine in the baseline cycle and the antibody titre evaluation (OR = 0.85; 95% CI = 0.78-0.94; $z = 3.2$;

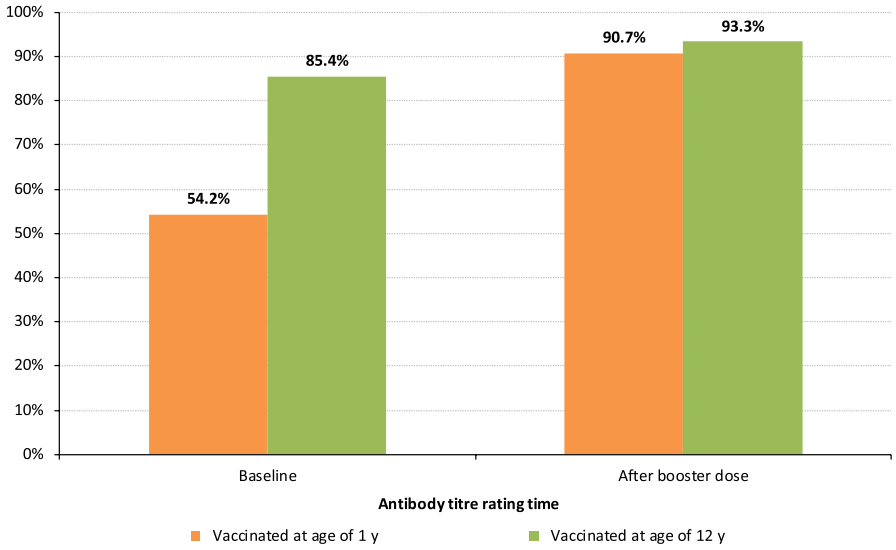

FIGURE 2 Proportions of subjects with protective anti-HBs titres per group (vaccinated at 1 y/immunized at 12 y) after the basal cycle and after a booster dose [Colour figure can be viewed at wileyonlinelibrary.com]

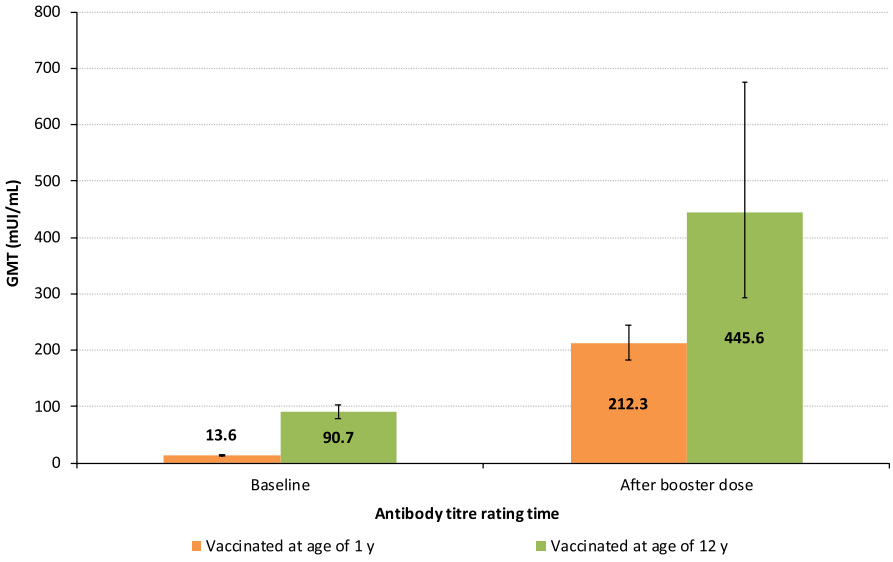

FIGURE 3 GMT value per group (vaccinated at 1 y/immunized at 12 y) after the basal cycle and after a booster dose. [Colour figure can be viewed at wileyonlinelibrary.com]

P = 0.002), while it is not associated with the age at the time of the booster dose (OR = 0.95; 95% CI = 0.86-1.02; *z* = 1.4; *P* = 0.152), age at the time of first vaccination (OR = 1.4; 95% CI = 0.6-3.4; *z* = 0.8; *P* = 0.403) and gender (OR = 0.7; 95% CI = 0.4-1.1; *z* = 1.6; *P* = 0.122). The multivariable logistic regression model shows no association between the outcome and the determinants (*P* > 0.05; Table 2).

4 | DISCUSSION

In our study, we noted that 38% of students and residents enroled showed an anti-HBs titre <10 mUI/mL after 3 doses of vaccine and needed one or more booster doses. With specific reference to the clinical–diagnostic path of the prevention of HBV infection, from the analysis of follow-up data of vaccinated subjects, there was no difference in the distribution of seropositivity per gender, while the seroprevalence rate per age at basal cycle was significantly different (vaccinated during the first year of life vs vaccinated at 12th year of life; *P* < 0.0001). This difference remained consistent if we considered as confounding factor the time between vaccine administration and the test; therefore, it would appear that there was a different immune imprinting in the vaccination of the 2 groups.

The percentage of seroconversion after booster was very high and equal to almost all subjects who received a booster dose (91%); with regard to the small percentage of nonresponders to the first booster dose, the seroconversion rate after completion of the vaccination cycle was of 94%.

Several studies are consistent with our observation: in 2015, a national community-based cross-sectional study was carried out in Egypt. A sample of 3600 children aged from 9 months to 16 years fully vaccinated with the HBV vaccine during infancy were recruited. The laboratory results revealed that 1535 (42.8%) children had no seroprotective anti-HBs titres. A booster dose was administered to 1070 children, and after a month, a new blood test was performed. A total of 967 children (90.4%) achieved a positive response. Of the 103 children with a nonprotective antibody titre, 94 were given another 2 doses of vaccine: 87 subjects (92.3%) achieved a positive titre, while 7 (7.7%) remained negative.[45,46] The results and the composition of the sample are similar to those of our study; the main difference is that we have evaluated the difference in seroprevalence among subjects who received the vaccine at different ages (1 and 12 years).

From January to June 2000, at the Faculty of Medicine of the University of Colombo (US), 258 medical students were tested for anti-HBs. 9.5% were nonresponders and neither sex nor BMI was associated with antibody levels. After a booster dose, 86.3% seroconverted.[47] Our seroconversion rates were higher than this study, and we also evaluated serum prevalence by age at immunization, although we did not evaluate BMI as a determinant of response to booster doses.

TABLE 1 Analysis of determinants of seroconversion after 3 doses of vaccine in a multivariate logistic regression model

Determinants	aOR	95% CI	*z*	*P*
Age at time of first vaccination	9.9	7.4-13.2	15.5	0.000
Time between the first dose of vaccine and antibody titre evaluation	1.13	1.10-1.16	7.9	0.000
Gender	0.9	0.8-1.1	0.7	0.496

Pearson chi-square = 84.1; *P* = 0.270.

TABLE 2 Analysis of determinants of seroconversion after a booster dose of vaccine in a multivariate logistic regression model

Determinants	aOR	95% CI	z	P
Age at time of first vaccination	0.72	0.14-3.85	0.4	0.704
Time between the first dose of vaccine and antibody titre evaluation	0.89	0.75-1.07	1.3	0.210
Age at time of the booster dose	0.95	0.89-1.02	1.4	0.155
Gender	0.86	0.36-2.04	0.3	0.739

Hosmer-Lemeshow chi-square = 4.1; $P = 0.844$.

According to our results, seroconversion is associated with age at immunization and the time between the first vaccination and the serological evaluation. This result is consistent with several studies in the literature; in a 2017 Italian cross-sectional observational study, the anti-HBs titre was evaluated in 2114 medical students of the University of Palermo. This study concluded that HBV vaccination at age of 12 years was significantly associated with having protective anti-HBs. In particular, a protective anti-HBs titre was about fourfold more frequent among subjects vaccinated during adolescence than those vaccinated at infancy.[48] In a similar study, 2 groups of students attending the University of Padova Medical School were enroled between 2004 and 2011 and HBV antibodies and antigens were measured. The first group enroled students vaccinated at 3 months of age and the second group students immunized after the first year of life. Students vaccinated at 3 months of age had a higher rate of nonprotective antibodies (47.2%) compared to those vaccinated after the first year of life (17.0%, $P < 0.0001$) with a significantly lower antibody level ($P < 0.0001$). Both groups showed a good immunological memory as evidenced by the achievement of protective antibody level after the booster dose in 97.8% of subjects.[49]

The strong point of our study is the relevant sample size and the analysis of subjects vaccinated at 1 year of age and those vaccinated at 12 years, comparing the 2 schedules; furthermore, the issue of vaccinations in healthcare workers is extremely topical and fundamental in future decisions on vaccination strategies. The major limitation is related to the impossibility of analysing the subjects vaccinated for HBV in relation to the type of vaccine used (hexavalent, pentavalent, bivalent, monovalent); furthermore, another limitation is the impossibility of evaluating the response of seronegative subjects receiving a booster dose of adjuvanted vaccine and whether there are differences in efficacy with the adsorbed recombinant vaccine.

Our study highlights the importance of assessing the immune status in healthcare professionals, a high-risk category which comes into contact with the virus and, consequently, infecting themselves and patients. Given the adverse effects of antibody titre negativity over 10-15 years, and the fall in vaccine coverage in Italy, the introduction of a routine booster dose in some high-risk categories, such as healthcare providers, on the dTaP vaccine model, becomes a strategic consideration in Public Health.

Our recommendation is to include the screening model described in the routine assessment of biological risk of medical students and healthcare professionals. One of the most prominent research questions in future studies is to understand what the most effective formulation of booster vaccine doses is to achieve seroconversion in seronegative subjects yet immunized, and also evaluate the adverse effects.

The impact of the vaccine on the burden of disease is strictly related to the economic benefits in terms of savings on state funds,[50] and therefore, in this light, any investment on the routine introduction of a booster dose in certain categories would be repaid over the years in savings on pathology management costs.

It will be appropriate for the future to repeat the evaluation of the management of the nonresponder subjects, on the one hand by expanding the sample in the study, and on the other prolonging the time of follow-up after execution of the basic cycle, in order to define the trend in immunogenicity over the years.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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