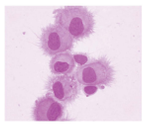
Human Vaccines & Immunotherapeutics



ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

Long-term immune protection against HBV: associated factors and determinants

Marianna Mastrodomenico , Mario Muselli , Luca Provvidenti , Maria Scatigna , Serena Bianchi & Leila Fabiani

To cite this article: Marianna Mastrodomenico , Mario Muselli , Luca Provvidenti , Maria Scatigna , Serena Bianchi & Leila Fabiani (2021): Long-term immune protection against HBV: associated factors and determinants, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2020.1852869

To link to this article: https://doi.org/10.1080/21645515.2020.1852869

© 2021 The Author(s). Published with license by Taylor & Francis Group, LLC.

Published online: 31 Jan 2021.

Submit your article to this journal

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at https://www.tandfonline.com/action/journalInformation?journalCode=khvi20

HUMAN VACCINES & IMMUNOTHERAPEUTICS
https://doi.org/10.1080/21645515.2020.1852869

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

Long-term immune protection against HBV: associated factors and determinants

Marianna Mastrodomenico, Mario Muselli, Luca Provvidenti, Maria Scatigna, Serena Bianchi, and Leila Fabiani

Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

ABSTRACT

In Italy, vaccination against hepatitis B became compulsory for all the newborns and 12-years-old adolescents in 1991. The main purpose of this study was to evaluate the persistence of long-term protection against HBV in medical students of the University of L'Aquila and in postgraduates Medical Doctors (HCWs) working in San Salvatore Hospital. The second aim was to study the variables associated with a protective anti-HBs antibody level, such as age at vaccination, gender, time elapsed from the last dose of vaccination.

Three hundred and forty-two subjects were enrolled from January 2017 to January 2019 and a blood sample was collected to evaluate the levels of serum HBsAg, anti-HBs and anti-HBc. Statistical analysis calculated a multivariable logistic regression model to examine predictors of a protective anti-HBs titer. The larger part (239, 70%) of the students had an anti-HBs titer >10 mIU/mL, those were statistically significant older (26.7 vs 24.5 years, $p < .001$), vaccinated at age 12 years (83.5% vs 59.9% among vaccinate at infancy, $p < .001$) and more frequently attending postgraduate medical school (80.8% vs 57.5% among healthcare profession school, $p < .001$). The multivariable logistic regression model showed that HBV vaccination at age of 12 was significantly and independently associated with protective titers (OR = 10.27, $p = .019$).

The results agreed with literature on HBV vaccination, confirming the efficacy of vaccination after 20 years. In particular, our results suggest that adolescent administration is the main predictor of a protective title, regardless of gender, course and years since vaccinations.

ARTICLE HISTORY
Received 15 July 2020
Revised 2 November 2020
Accepted 13 November 2020

KEYWORDS
HBV; healthcare workers; vaccination; protection; surveillance

Introduction

Hepatitis B Virus (HBV) represents a major cause of acute and chronic liver disease. In Italy, since the 80s are available safe and effective vaccines to prevent HBV infection and its serious complications, including cirrhosis and hepatic cancer. In particular, this country was one of the first, in 1983, to implement a program of vaccination against hepatitis B targeted at the immunization of person at high risk due to behavioral and professional risks of exposure, including healthcare workers (HCWs). In 1991, vaccination against hepatitis B became obligatory for all the newborns and 12-years-old adolescents.[1] This campaign, with a three-dose vaccine schedule, reached millions of children in the following years, with immunization rates approximately of 95%: only when the first cohort of infants immunized in 1991 reached the age of 12 years, universal vaccination was stopped in this age target and continued as mandatory among newborns.[2,3] Moreover, screening for HBsAg became mandatory for pregnant women in the third trimester of pregnancy, in order to identify babies in need of treatment combining hepatitis B immune globulin (HBIG) and hepatitis B vaccine at birth. In this way, according to the Italian Law (Law n. 165 enacted on 27th May 1991), two cohorts of people were vaccinated starting from 1991. The decision to vaccinate two cohorts of people has the aim to accelerate the reduction in incidence intervening on the intrafamilial transmission using new-born vaccination and taking action also on sexual transmission. In particular administering the first vaccine dose to 12 years old people from 1991 to 2000, it has been achieved antibody coverage against HBV in people from 0 to 24 years old.

Nevertheless, HCWs, Healthcare students (HCSs) and other professional categories, still need to be considered at high risk for HBV exposure[4] with a probability of contracting infection four times greater than the general population.[5] In order to protect these professional categories, the Italian Law Decree 81/2008 regulated the policy of vaccination against HBV in healthcare workers requesting employees to carry out the vaccination, free of charge for those exposed to biological risk.[6]

Currently, the Italian Vaccine Prevention Plan 2017–2019 recommends the routine detection of anti-HBsAg anti-bodies titer in serum together with the vaccination against HBV for all susceptible professional categories, especially for HCWs and HCSs.[7] This type of control is essential to assess a protective immunological memory, in particular, an anti-HBsAg anti-bodies titer higher than 10 mIU/mL is certainly protective.

The immunogenicity elicited by the HBV vaccine has been established in several studies in children, adults and adolescents, both for the monovalent and combined formulation. Several studies have shown that the concomitant administration of other vaccines does not seem to influence the onset of

CONTACT Marianna Mastrodomenico marianna.mastrodomenico@graduate.univaq.it Department of Life, Health and Environmental Sciences, University of L'Aquila, Monte Velino Street N. 25, L'Aquila 67100, Italy.

© 2021 The Author(s). Published with license by Taylor & Francis Group, LLC.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

immunogenicity and long-term follow-up studies investigated the decline of the HBsAg Ab titers following the primary immunization.[8–11] Medical doctors starting the resident program and Medicine Students attending the third year course have received the vaccine dose about 20 years earlier, therefore it is necessary to measure the antibody titer anti-HBV.

After 25 years from the beginning of the universal immunization campaign against HBV in Italy, few published studies in occupational settings confirm the long-term persistence of anti-HBs antibody levels against HBV infection in HCSs and HCWs exposed to biological risk. In order to investigate this point, we conducted an observational study in HCSs and HCWs attending the San Salvatore Hospital and followed within the Occupational Health Surveillance Program at occupational medicine clinic of University of L'Aquila.

Italian Law provides for a booster vaccine dose only when the person is exposed to a professional risk, so our study wants to demonstrate the importance of evaluating antibody titer against HBV during Occupational Health Surveillance in workers exposed to biological risk and, if necessary, of administering a booster dose if the titer is below 10 mIU/mL.

The main aim of this study was to evaluate the persistence of long-term immunogenicity of HBV in students of the School of Medicine at the University of L'Aquila (HCSs) and in postgraduates Medical Doctors (HCWs) who are working in San Salvatore Hospital; to measure and compare the persistence of protective anti-HBs antibody levels in both groups properly immunized during infancy or in adolescence. A second aim was to study the variables associated with a protective anti-HBs antibody level at the first preventive medical examination, such as age at vaccination, gender, time elapsed from the last dose of vaccination.

Materials and methods

According to the Italian Law Decree 81/2008 and the Italian Ministry of Health, students attending schools of the health care professions or postgraduate medical schools of the University of L'Aquila, were examined for professional risks during Occupational Health Surveillance Program at occupational medicine clinic. During the preventive medical examination, a standardized medical record was compiled, including socio-demographic and clinical information. Furthermore, a personal objective exam was conducted for each subject before blood sampling, through which the levels of serum HBsAg, anti-HBs and anti-HBc were evaluated. Data for each subject examined from January 2017 to December 2019 were collected. Subsequently, subjects who met at least one of the following exclusion criteria were excluded: a) HBsAg personal or maternal positivity, chronic diseases or immunosuppression; b) absence of primary documentation of vaccination for HBV; c) recent booster dose of HBV vaccine. According to Italian law, the subjects were requested to provide written informed consent to the processing of data. Moreover, although it is not required in Italy for observational studies, approval of the Local Ethics Committee was also obtained.

Serological tests. Serological analyses were performed with commercial chemiluminescence assays (VITROS anti-HBs assay on the Vitros ECI Immunodiagnostic system, Ortho-Clinical Diagnostics, UK). In particular, the antibody to the hepatitis B surface antigen (anti-HBs) levels was expressed as mIU/mL. The level of anti-HBs above 10 mIU/mL was considered protective against HBV infection.

Statistical analysis. Statistical analysis was performed with Stata software version 14.1 (February 2016). The significance level chosen for all analyses was.05, 2-tailed. Absolute and relative frequencies were calculated for qualitative variables, whereas normally distributed quantitative variables were summarized as mean (standard deviation). Data normality was verified by the Shapiro–Wilk test for normality. Categorical variables were analyzed using the chi-square test (Mantel–Haenszel), means were compared by using the Wilcoxon rank sum test. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated by a multivariable logistic regression model constructed to examine predictors of anti-HBs titer above 10 mIU/mL assumed as protective. All variables found to have a statistically significant association ($P < .05$) with anti-HBs titer > 10 mIU/mL were entered in multivariate logistic regression model in order to check for independence. In the multivariate analysis, age was included as a continuous variable.

Results

From January 2017 to December 2019, 342 HCWs and HCSs met the inclusion criteria, properly followed all the procedures foreseen in the study protocol and gave a written informed consent. The majority of the subjects were females (216, 63.2%) and had a mean age of 26.1 (4.2 SD). Many subjects (53.2%) enrolled were post-graduate medical doctors.

All considered subjects were vaccinated for HBV and HBsAg/anti-HBc negative. One hundred and ninety-seven (57.6%) students received a course of 3 pediatric doses (10 μg) of recombinant hepatitis B vaccine at their 3rd, 5th and 11th months of postnatal life and 145 (42.4%) received a course of 3 adult doses (20 μg) of the same vaccine when they were 12 years old, according to the current law in Italy. The larger part (70%) of the students had an anti-HBs titer >10 mIU/mL (Table 1).

Students with protective anti-HBs titer were statistically significantly older (26.7 vs 24.5 years, $p < .001$), vaccinated at age 12 years (83.5% vs 59.9% among vaccinate at infancy, $p < .001$) and more frequently attending postgraduate medical school (80.8% vs 57.5% among healthcare profession school, $p < .001$). No statistically significant differences were observed in antibody titer between males and females ($p = .217$) and years after HBV vaccination (20.4 vs 20.9, $p = .119$). The long-term efficacy of HBV vaccination is confirmed when one considers that none of vaccinated subjects in the current study was found to be HBsAg/anti-HBc positive.

The multivariable logistic regression model (Table 2) shows that after controlling for confounding, HBV vaccination at age of 12 was significantly associated with a protective Hepatitis B surface antibody titers (OR = 10.27 95% CI = 1.47–71.81) as well as University Course (Postgraduate medical school vs Healthcare Profession School OR = 2.76 95% CI = 1.31–5.83).

Discussion

HBV infections have been recognized as an important risk for health-care professionals: they are considered to be a population

Table 1. Variables associated with persistence of protective Hepatitis B surface antibody titers.

	Anti-HBs≥10mIU/mL			Anti-HBs <10mIU/mL		
	Vaccinated at infancy	Vaccinated at age 12 years	*P* value	Vaccinated at infancy	Vaccinated at age 12 years	*P* value
N (%)	118 (59.9)	121 (83.5)	<0.001[a]	79 (40.1)	24 (16.5)	<0.001[a]
Sex						
Male, n (%)	41 (12)	42 (12.3)	0.995[a]	33 (9.6)	10 (2.9)	0.993[a]
Female, n (%)	77 (22.5)	79 (23.1)		46 (13.5)	14 (4.1)	
Age in year (mean±SD)	23.3 ± 2.3	30.1 ± 2.8	<0.001[b]	22.8 ± 2.0	29.9 ± 2.0	<0.001[b]
Years since HBV vaccination (mean±SD)	22.4 ± 2.2	18.4 ± 2.9	<0.001[b]	21.8 ± 1.6	18 ± 2.1	<0.001[b]
University course						
Healthcare profession school, n (%)	85 (24.9)	7 (2.1)	<0.001[a]	67 (19.6)	1 (0.7)	<0.001[a]
Postgraduate students, n (%)	33 (9.6)	114 (33.3)		12 (3.5)	23 (6.7)	
GMC of anti-HBs (mIU/mL)	53.7	191.1	0.0025[b]	2.5	2.1	0.8653[b]

[a]Pearson chi-squared test for categorical variables.
[b]Mann–Whitney U Test.

Table 2. Multivariable logistic regression model including variables associated with Hepatitis B surface antibody titers ≥ 10 mIU/mL.

	P value	OR	C.I.
University course, n (%)			
• Healthcare profession school			
• Postgraduate medical school	0.008	2.76	1.31–5.83
Vaccination period			
• Vaccinated at infancy			
• Vaccinated at age 12 years	0.019	10.27	1.47–71.81
Sex			
• Male			
• Female	0.356	0.79	0.48–1.30
Age[a]	0.082	0.56	0.29–1.08
Years since HBV vaccination	0.096	1.17	0.97–1.42

[a]as class of age on 4-points ordinal scale.

at high-risk to develop HBV infection due to the high transmissibility of the virus and the risk related to occupational injuries.[12,13] The World Health Organization (WHO) estimates that more than 300,000 HCWs are exposed every year to accidental percutaneous contact with contaminated fomites, and that about 66,000 of them become infected.[12–14] Thus, anti-HBV vaccination is recommended for all HCWs independently of job duty.[4,15] Furthermore, the healthcare profession and postgraduate medical students have a high occupational risk for HBV infection, also in countries with a low incidence of the disease.[16–18] Particularly, in Italy several studies have demonstrated that healthcare workers and students could have a risk that is low but not negligible. Despite such evidence, for health professionals as well as for students there is no obligation of vaccination, which is recommended only.[7,19] Fortunately a large majority of young Italian students have been vaccinated according to the national immunization program that, since 1991, has included HBV vaccination as compulsory for infants and adolescents aged 12 years. Adolescent's vaccination was restricted to the first 12 years of the implementation of the vaccination law and, thus, in 2004, vaccination of 12-year-olds was stopped, but retained for infants. Although in the Italian Ministry of Health recommendations there are currently no indications to test the antibody titer after administration of the complete HBV vaccination cycle in the general population, the results of our study highlight that up to 35% of people tested 20 years after the primary vaccination had a titer <10 mIU/mL, showing a potential lack of protection, at an age in which the exposure to HBV from nonprofessional sources may happen (sexual activity, drug abuse, etc.).

In particular, our study shows suboptimal levels of protection among HCWs vaccinated during infancy or adolescence. The prevalence of a protective anti-HB titer in pre-employment screening was statistically associated with the age of vaccination, attending to post-graduated medical school and age. No association was found with sex and time elapsed from last vaccination. Subjects vaccinated at an age of one year were significantly less protected than HCWs vaccinated at 12 years, even after controlling for the possible confounding effect of time elapsed from the vaccination, sex and university course. Our results suggest that adolescent administration is the main predictor of a protective title, regardless of gender, course and years since vaccinations. The most significant variable is the vaccination period. However, by including age in the multivariate analysis, the University course emerged as a significant determinant of immunization status. This association probably is due to an interaction effect between age and course: a subgroup of older postgraduate medical doctors received the first vaccination dose in the adolescent period according to the Italian Law (no. 165 enacted on 27th May 1991).

To explain the fact that post-graduate medical doctors, who received 20 μg dosage, have a higher antibody titer than medical students, it is worth to remember that higher seroconversion and response rates were elicited by the higher dose.[20]

Moreover it is widely known that in older children and adults, higher primary vaccine dosages also elicit greater antibody response and persistence.[21]

Many studies suggest that enhance vaccine antigen dosages can yield better seroconversion rates for adults[22,23] and better immunogenicity may be obtained in elderly adults by administering 20 μg or more of the vaccine.[24]

We should also consider that the infant immune system has been characterized as immature, with a restricted immunoglobulin repertoire having low-affinity antibody responses as well as an impaired T cell function with poor B and T cell interaction.[25] The Th2/regulatory T cell-type response and reduced B cell somatic hypermutation that predominates in early infancy results in immune tolerance and a diminished humoral response, which shifts to a Th1-type response and a progressive maturation of immunoglobulin class switching and responses through the first year of life.[26]

Although HBV vaccination has been carried out for several years, the debate on the duration of protection is still open. Furthermore, the fact that the post-immunization (four weeks after the first series of vaccinations) is not always available and the questions on the real need and effectiveness of booster doses still remain unanswered. Experts have been dealing with these issues since the creation of the universal HBV vaccine policy for infants, children and adolescents. In 1996, notably five years after the institution of mandatory vaccination of infants and 12-year-old children, research was conducted to verify the persistence of anti-HB concentrations >10 mIU/mL in the population who underwent the vaccine. It was found that 92.9% of children and 94.1% of teenagers were protected against HBV (anti-HB titer >10 mIU/mL). In adolescents, the antibody levels were much higher than in children.[27]

As demonstrated by several studies, administration of HBV as part of a combination vaccine or as a monovalent vaccine induces long-lasting immune memory against HBV with long-term antibody persistence. Several studies have reported that 85–90% of those vaccinated as adolescents have anti-HBs levels >10 mIU/mL when measured 10 years after vaccination. This percentage was 40–60% for those vaccinated as infants, as measured 15–20 years after vaccination.[28,29] These data are consistent with results obtained by the authors of the presented study, since more than 60% of their students had anti-HBV titers above 10 mIU/mL, also more than 20 years after vaccination. Moreover, it should be pointed out that none of them received a booster dose after the primary vaccination program, and in the primary documentation of vaccination for HBV no date was indicated for its administration. In the experience of the authors, they observed that this habit is also common among the general population. Despite declining serum levels of antibody, international evidence shows that vaccine-induced immunity continues to prevent clinical disease or detectable viremic HBV infection.[30] So, it would seem that administering the vaccine at 12 years of age induces a better immune system response. Such a better response could suggest the usefulness of administering, in addition to compulsory vaccination at birth, a dose booster in professionally exposed persons. In this context, the evaluation of serum levels during Occupational Health Surveillance Program is of crucial importance in order to detect and possibly subject a dose booster to those who have received vaccination in childhood and are now unprotected (33.9% in this study). However, the fact that vaccination at 12 works better must not be taken into account: it is not a data of operational health significance because according to the Italian Law it is compulsory to vaccinate all newborns.

In fact, even the CDC recommends pre-exposure assessment of current or past anti-HBs results upon matriculation, followed by one or more additional doses of HBV vaccine for subjects with anti-HBs <10 mIU/mL, if necessary, helps to ensure HBV protection after contacts with blood or body fluids.[4]

This research has some limitations: it was a retrospective, observational study, and we had no data available on the formulation, and sociodemographic characteristics. Despite these limitations, this study enriches the literature on HBV vaccination and offers additional knowledge and reflections on the persistence of anti-HBV immunity approximately two decades after vaccination from early childhood. Moreover, this investigation highlights that although anti-HBV vaccination is associated with long persistence of protective titers, several students and post-graduates of the Medical School could benefit from a booster dose.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

ORCID

Marianna Mastrodomenico http://orcid.org/0000-0002-2502-3431
Mario Muselli http://orcid.org/0000-0001-5816-2393
Luca Provvidenti http://orcid.org/0000-0003-1985-6741
Maria Scatigna http://orcid.org/0000-0003-1995-072X
Serena Bianchi http://orcid.org/0000-0003-3731-5463
Leila Fabiani http://orcid.org/0000-0002-0597-1450

References

1. Compulsory vaccination against hepatitis B virus. 1991 Jun 1. [accessed 2020 Jun 24]. http://old.iss.it/binary/tras/cont/19910527_LEGGE%2027%20maggio%201991%20vaccinazione.1181036033.pdf
2. Piazza M, Da Villa G, Picciotto L, Abrescia N, Guadagnino V, Memoli AM. Mass vaccination against hepatitis B in infants in Italy. Lancet. 1988;332:1132. doi:10.1016/S0140-6736(88)90540-5.
3. Mele A, Stroffolini T, Zanetti AR. Hepatitis B in Italy: where we are ten years after the introduction of mass vaccination. J Med Virol. 2002;67:440–43. doi:10.1002/jmv.10092.
4. Schillie S, Murphy TV, Sawyer M, Ly K, Hughes E, Jiles R, de Perio MA, Relly M, Byrd K, Ward JW. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. MMWR Recomm Rep. 2013;62:1–19.
5. Lamberti M, De Rosa A, Garzillo EM, Corvino AR, Sannolo N, De Pascalis S, Di Fiore E, Westermann C, Arnese A, Di Giuseppe G, et al. Vaccination against hepatitis b virus: are Italian medical students sufficiently protected after the public vaccination programme? J Occup Med Toxicol. 2015;10:41. doi:10.1186/s12995-015-0083-4.
6. Italian Law decree n. 81 of 9h April 2008. [accessed 2020 24 June]. http://www.lavoro.gov.it/documenti-e-norme/studi-estatistiche/Documents/Testo%20Unico%20sulla%20Salute%20e%20Sicurezza%20sul%20Lavoro/Testo-Unico-81-08-Edizione-Giugno%202016.pdf
7. Italian Ministry of Health. National vaccination prevention plan 2014–2018. 2014 Nov 13. [accessed 2020 Jun 24]. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2285_allegato.pdf
8. Durando P, Crovari P, Ansaldi F, Sticchi L, Turello V, Marensi L, Giacchino R, Timitilli A, Carloni R, et al. Universal childhood immunisation against Streptococcus pneumoniae: the five-year experience of Liguria Region, Italy. Vaccine. 2009;27:3459–62. doi:10.1016/j.vaccine.2009.01.052.
9. Zanetti AR. Hepatitis B immune memory in children primed with hexavalent vaccines and given monovalent booster vaccines: an open-label, randomised, controlled, multicentre study. Lancet Infect Dis. 2010;10:755–56. doi:10.1016/S1473-3099(10)70195-X.
10. Gabutti A, Romanò L, Blanc P, Meacci F, Amendola A, Mele A, Mazzotta F, Zanetti AR. Long-term immunogenicity of hepatitis B vaccination in a cohort of Italian healthy adolescents. Vaccine. 2007;25:3129–32. doi:10.1016/j.vaccine.2007.01.045.
11. Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC, Cuccia M, Mangione R, Marrone F, Negrone FS, et al. Long-term immunogenicity of hepatitis B vaccination and

policy for booster: an Italian multicentre study. Lancet. 2005;366:1379–84. doi:10.1016/S0140-6736(05)67568-X.
12. Zaffina S, Marcellini V, Santoro AP, Scarsella M, Camisa V, Vinci MR, Musolino AM, Nicolosi L, Rosado MM, Carsetti R, et al. Repeated vaccinations do not improve specific immune defenses against Hepatitis B in non-responder healthcare workers. Vaccine. 2014;32:6902–10. doi:10.1016/j.vaccine.2014.10.066.
13. Batra V, Goswami A, Dadhich S, Kothari D, Bhargava N. Hepatitis B immunization in healthcare workers. Ann Gastroenterol. 2015;28:276–80.
14. Tajiri K, Shimizu Y. Unsolved problems and future perspectives of hepatitis B virus vaccination. World J Gastroenterol. 2015;21:7074–83. doi:10.3748/wjg.v21.i23.7074.
15. Centers for Disease Control and Prevention (CDC). Viral Hepatitis Statistics and Surveillance. 2020 May 8. [accessed 2020 Jun 24]. http://www.cdc.gov/hepatitis/statistics/index.htm
16. Riva MA, Madotto F, Conti S, Fornari C, Patronella G, Sormani M, Dorso MI, De Vito G, Latocca R, Cesana G. Hepatitis B vaccination coverage and booster dose: results from a survey on healthcare students. G Ital Med Lav Ergon. 2012;34:283–85.
17. Spradling PR, Williams RE, Xing J, Soyemi K, Towers J. Serologic testing for protection against hepatitis B virus infection among students at a health sciences university in the United States. Infect Control Hosp Epidemiol. 2012;33:732–36. doi:10.1086/666335.
18. Bruno A, Borella-Venturini M, Giraldo M, Mongillo M, Zanetti E, Beggio M, Davanzo E, Trevisan A. Prevalence of virus hepatitis B markers among medical students. G Ital Med Lav Ergon. 2007;29:752–54.
19. Repubblica Italiana, Ministero della Salute. Protocollo per l'esecuzione della vaccinazione contro l'epatite virale B (D.M. 20 novembre 2000). 2020 Nov 30. [accessed 2020 Jun 24]. http://www.salute.gov.it/imgs/C_17_normativa_1517_allegato.pdf
20. Venters C, Graham W, Cassidy W. Recombivax-HB: perspectives past, present and future. Expert Rev Vaccines. 2004;3(2):119–29. doi:10.1586/14760584.3.2.119.
21. Kang G, Chen H, Ma F, Yang Y, Wang Z, Guo S, Song J. Comparison of the effect of increased hepatitis B vaccine dosage on immunogenicity in healthy children and adults. Hum Vaccin Immunother. 2016;12(9):2312–16. doi:10.1080/21645515.2016.1172757.
22. Li J, Yao J, Shan H, Chen Y, Jiang ZG, Ren JJ, Xu KJ, Ruan B, Yang SG, Wang B, et al. Comparison of the effect of two different doses of recombinant hepatitis B vaccine on immunogenicity in healthy adults. Hum Vaccin Immunother. 2015;11:1108–13. PMID:25607773.
23. Lin CS, Xie SB, Liu J, Zhao ZX, Chong YT, Gao ZL. Effect of revaccination using different schemes among adults with low or undetectable anti-HBs titers after hepatitis B virus vaccination. Clin Vaccine Immunol. 2010;17:1548–516. PMID:20719983. doi:10.1128/CVI.00064-10.
24. Gilbert CL, Klopfer SO, Martin JC, Schodel FP, Bhuyan PK. Safety and immunogenicity of a modified process hepatitis B vaccine in healthy adults >/=50 years. Hum Vaccin. 2011;7:1336–42. doi:10.4161/hv.7.12.18333.
25. Saso A, Kampmann B. Vaccine responses in newborns. Semin Immunopathol. 2017;39(6):627–42. doi:10.1007/s00281-017-0654-9.
26. Hong M, Bertoletti A. Tolerance and immunity to pathogens in early life: insights from HBV infection. Semin Immunopathol. 2017;39(6):643–52. doi:10.1007/s00281-017-0641-1.
27. Faustini A, Franco E, Sangalli M, Spadea T, Calabrese RM, Cauletti M, Perucci CA. Persistence of anti-HBs 5 years after the introduction of routine infant and adolescent vaccination in Italy. Vaccine. 2001;19:2812–18. doi:10.1016/S0264-410X(01)00005-6.
28. Chiara F, Bartolucci GB, Mongillo M, Ferretto L, Nicolli A, Trevisan A. Hepatitis B vaccination at three months of age: a successful strategy? Vaccine. 2013;31:1696–700. doi:10.1016/j.vaccine.2013.01.046.
29. Stroffolini T, Guadagnino V, Caroleo B, De Sarro G, Focà A, Liberto MC, Giancotti A, Barreca GS, Marascio N, Lombardo FA, et al. Long-term immunogenicity of hepatitis B vaccination in children and adolescents in a southern Italian town. Infection. 2012;40:299–302. doi:10.1007/s15010-011-0233-2.
30. Verso MG, Lo Cascio N, Noto Laddeca E, Amodio E, Currieri M, Giammanco G, Ferraro D, De Grazia S, Picciotto D. Predictors of Hepatitis B Surface Antigen Titers two decades after vaccination in a cohort of students and post-graduates of the Medical School at the University of Palermo, Italy. Ann Agric Environ Med. 2017;24:303-306. doi:10.26444/aaem/74716.