


# HBV vaccination status among healthcare workers: A cross-sectional study

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## Abstract

**Objective:** The development of a vaccine against hepatitis B virus (HBV) is one of the improvements in strategy prevention during the last decades.

**Aim:** To evaluate HBV-related vaccine status in healthcare workers (HCW) exposed to biological risk.

**Methods:** The serum markers for HBV were collected from HCWs in two tertiary care hospitals in Naples (Italy). Multivariate statistical analysis was then performed to identify associated factors linked to the long-term immunogenicity of the HCWs.

**Results:** All HBV vaccinated individuals were screened for whole marker patterns; all were HBsAg/anti-HBc negative. Of individuals, 20% had an anti-HB antibody titre < 10 IU/L. Multivariate statistical analysis highlighted that women were more protected than men (73.6% vs. 26.4%,  $P < 0.05$ ). Additionally, nurses seem to maintain a higher antibody titre than doctors and other staff, such as auxiliary technicians ( $P < 0.05$ ).

**Conclusions:** Our data support the evidence of a strong immunogenicity against HBV, assessed through the circulating antibody titre, when prophylactic vaccination is conducted in non-infantile age, particularly for women. The outcome of the study supports the central role of occupational physicians within the hospital districts in terms of primary prevention and maximum protection of HCWs.

## Keywords

Vaccination, epidemiology, blood-borne viruses

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## Background

Hepatitis B virus (HBV) is a global health problem. There is evidence that 360 million people are chronically infected and that almost 1 million people die annually from its acute or chronic sequelae, such as fulminant hepatitis, cirrhosis and hepatocellular carcinoma (Ott et al., 2012). The prevalence of HBV-related hepatitis varies across countries: in industrialised countries of Western European and North America, the prevalence of HBV surface antigen (HBsAg) positivity in the general population is < 2% (low

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endemicity); in most Mediterranean countries, in Eastern Europe and Asia, it is in the range of 2–8% (intermediate endemicity). The overall prevalence of Hepatitis B is highest in some developing countries in Far East Asia, sub-Saharan Africa and in the Western Pacific region where about 6% of the adult population is infected (high endemicity) (World Health Organization, 2018).

Healthcare workers (HCWs) are more frequently exposed to the risk of acquiring HBV infection than the general population through mucosal-cutaneous exposure to potentially infectious blood (eyes, oral mucosa or skin) or through percutaneous exposure to contaminated sharp objects (needles, blades, etc.) (Elseviers et al., 2014). According to World Health Organization (WHO) data, there are approximately 36 million HCWs worldwide, 3 million per year suffer a work-related injury occurred by a sharp instrument, resulting in 2 million workers infected by HBV and 1 million by Hepatitis C virus (Lee, 1997). Other studies estimated that HCWs injuries caused by sharp objects are in the range of 1.4–9.5 per 100 workers per year, resulting in 0.42 HBV infections per 100 sharp-object injuries per year (Centers for Disease Control and Prevention, 1997). A range of different measures and interventions, such as the use of safety devices, has helped to reduce the risk of HBV transmission, but the development of HBV vaccines must be considered the major achievement in terms of prevention of HBV infection (De Schryver et al., 2011).

In Italy, universal HBV vaccination of infants was introduced in 1991 and was extended to children aged 12 years during the first 12 years of application, a strategy that ensured coverage of the Italian population aged 0–24 by 2003 (Lamberti et al., 2015; Trevisan et al., 2008). HBV vaccination is also recommended for people at risk of acquiring HBV infection, such as health professionals, according to international Occupational Medicine Guidelines for HCWs (Schillie et al., 2013). The vaccination is recommended at the career start for those not protected to avoid early infection and disease development (Puro et al., 2005).

It is generally observed that antibodies (Abs) titre decline over time following immunisation, resulting in an increased infection rate, especially when the HBsAg titre falls below the protective cut-off level of 10 mIU/mL (Zanetti et al., 2005). The aim of the present study was to evaluate the long-term immunogenicity and effectiveness of HBV vaccination in HCWs in two tertiary care hospitals in the Neapolitan area of southern Italy and to identify independent predictive factors of long-term immunogenicity. In the Neapolitan area, the prevalence of HBV infection was very high until the introduction of HBV vaccination (Sagnelli et al., 2014).

## Methods

The authors designed a cross-sectional study conducted from January to December 2016, enrolling all HCWs

working in two tertiary care hospitals in Naples, Italy. The hospitals provide outpatient and inpatient services for all medical and surgical specialties. HCWs (whose activities involved contact with patients' blood or other bodily fluids while providing care) such as physicians, surgeons, nurses, midwives, physiotherapists, lab technicians, radiographers and blood-bank workers were enrolled for the study. All data were obtained from the hospitals' Health Surveillance Program, required by law in Italy. This program includes a blood sample from all exposed workers to evaluate their health status, including HBV immunisation. This is established by the Legislative Decree n.81, April 2008.

After obtaining informed written consent, all recruited HCWs completed a pre-coded questionnaire stating their age, gender, HBV status, previous exposure to HBV and educational level. Eligible individuals were those who received a three-dose series of either plasma-derived or recombinant HBV vaccine and could provide documentation of the dates of vaccination. In the absence of such documentation, individuals were requested to obtain a note from their general practitioner indicating the vaccination dates.

A blood sample was taken from each worker included in the hospitals' Health Surveillance Program under strict aseptic conditions using a plain vacutainer. Blood was allowed to clot and serum was separated and stored at  $-20^{\circ}\text{C}$  until testing. HBV serum markers (HBsAg, anti-HBs and anti-HBc) were determined using commercial immuno-enzymatic assays (Abbott Laboratories, North Chicago, IL, USA). Anti-HBs titres were extrapolated from a calibration curve generated using the WHO reference standard and were expressed in IU/L. In particular, actual values were obtained for anti-HBs titres in the range of 10–400 IU/mL; for this interval, the geometric mean was calculated using standard procedures. The laboratory readout indicated only either "under 10 IU/mL" or "over 400 IU/mL," respectively.

According to Italian legal guidelines for observational studies, ethical approval for conducting this survey was unnecessary and, accordingly, cross-sectional studies do not require approval by the local institutional review boards. Personal information on the individuals included in the study was protected according to Italian law (Italian Medicines Agency, 2008).

Statistical analysis using StatGraph v3.0 was performed. Continuous variables were given as mean  $\pm$  standard deviation (SD), and categorical variables as the absolute value and relative frequency. Differences in mean were evaluated using an unpaired Student's *t*-test; the chi-squared test was applied to categorical variables. A *P* value  $< 0.05$  was considered statistically significant.

## Results

By the inclusion criteria outlined by the authors, 956 individuals were recruited. The entire cohort was vaccinated for HBV and screened for the complete pattern of markers,

**Table 1.** Examined cohort characteristics.

Workers	n = 956
Age (years) (median (range))	47 (21–71)
Age (years) (mean $\pm$ SD)	46.7 $\pm$ 11.1
Sex (n (%))	
M	516 (54)
F	440 (46)
Nationality (n (%))	
Italian	939
Others	17
Working classes (n (%))	
MD	288 (30)
Nurse	510 (53.5)
Other	158 (16.5)
Age at vaccination (n (%))	
At birth	22 (2)
Adulthood	934 (98)
Abs titre, HCWs (n (%))	
HBsAb < 10 UI/mL	189 (20)
HBsAb $\geq$ 10 UI/mL	767 (80)
Time since vaccination (years) (mean $\pm$ SD)	21 $\pm$ 4.9

all resulting negative for HBsAg/anti-HBc. There was no relevant difference between HCW distribution in the two studied sites. The selected cohort is composed almost exclusively of Italian workers born in Campania region, with a slight prevalence of female workers (516 men [54%], 440 women [46%]) and at 21 years (SD  $\pm$  4.9) since date of vaccination. All included HCWs were HBV immunised according to the national vaccination plan and did not report accidents linked to contact with biological fluids, in agreement with the predefined inclusion criteria.

The mean age of the cohort was 46.7 years (SD  $\pm$  11.1). The largest group of HCWs were nurses (510, 53.5%), whereas medical doctors were 288 (30%) and other HCWs were 158 (16.5%).

Almost the whole examined population received the anti-HBV vaccination as young adults. The mean time since vaccination was 21 years (SD  $\pm$  4.9). A sufficiently high HBsAb titre level was maintained in about 80% of the studied cohort with only 189 (20%) individuals resulting in an anti-HBs antibody titre < 10 IU/L. The overall characteristics of the enrolled cohort are described in Table 1.

Subsequently, the authors stratified the data in order to analyse the differences between protected and unprotected workers, i.e. between HCWs presenting high/low titres (10 IU/mL considered as the cut-off). The statistical analysis showed that female nurses had higher Abs titres compared to men (565 vs. 202, 73.6% vs. 26.4%,  $P = 0.05$ ) (Table 2).

Furthermore, the multivariable analysis highlighted the HCWs' gender and tasks within the hospital facilities in relation to Abs titre, showing the female nurses as the most protected HCW profile, because of their maintaining a higher Abs titre compared to the medical doctors and the other personnel such as technicians or assistants ( $P = 0.05$ ) (Table 3).

## Discussion

Hepatitis B and C represent a significant problem in healthcare professionals; the prevention of hepatitis among workers through the involvement of Occupational Health Doctors is recommended by all international institutions. The development of a specific vaccine has represented a benchmark in terms of workplace HBV prevention.

The objective of this study was to evaluate long-term immunogenicity and efficacy of HBV vaccination in two hospitals in the Neapolitan area, Campania region, southern Italy, where the prevalence of HBV infection was very elevated until the introduction of HBV vaccination. An additional objective was to identify the independent predictors of long-term immunogenicity.

This cross-sectional study analysed the situation 25 years after the introduction of the vaccination in the Campania region. The data analysis, detailed in Table 1, shows a vaccination coverage rate of around 80%, in accordance with the national data. The characteristics of vaccinated HCWs are described in Table 2 and multivariate analysis in Table 3.

The average age of enrolled individuals was 46.7 years (SD  $\pm$  11); SEVEIA (Integrated Epidemiological System of Acute Viral Hepatitis) data show that this age seems to be more related to hepatitis B infection (aged 35–54 years), especially considering the potential risk exposure due to intrinsic healthcare activities (Istituto Superiore di Sanità, 2017). As already mentioned, the Abs titre stayed over the cut-off (10 UI/mL) for about 80% of the sample, representing a good protective rate. Of HCWs, 20% proved to be unprotected and did not show substantial differences in terms of averages/medians age compared to the protected sample.

As previously described, most of the examined individuals received HBV vaccination in adulthood; however, the statistical analysis of the vaccination year did not show a significant difference. Consequently, this lack of significance linked to a 'not normal' cohort distribution between 'vaccinated at birth' and 'adult vaccinated' workers needs further investigation that should be conducted by increasing the sample size.

The univariate statistical analysis defined the cohort characteristics according to the anti-HBs titres in order to stratify workers based on circulating Abs titre at the time of the examination. Significant findings were demonstrated about gender. Female HCWs are more protected than their male colleagues ( $P < 0.05$ ; Table 2). This finding results in

**Table 2.** Healthcare workers (HCWs) stratified by HBsAb titre: variables compared.

	HCWs (n (%))	Age (years) (median (range))	Age (years) (mean $\pm$ SD)	Sex ( $P = 0.009$ ) (n (%))	Age at vaccination (birth/adulthood) (n (%))	Time since vaccination (years) (mean $\pm$ SD)	Working categories ( $P < 0.05$ ) (n (%))
HBsAb < 10 mIU/mL	189 (20)	47 (21–68)	46.7 $\pm$ 11.3	F: 86 (45.5) M: 103 (54.5)	7 (3.7)/182 (96.3)	19.3 $\pm$ 4.76	MD: 49 (26) Nurse: 95 (50) Other: 45 (24)
HBsAb > 10 mIU/mL	767 (80)	47 (23–71)	46.8 $\pm$ 11	F: 565 (73.6) M: 202 (26.4)	15 (2)/752 (98)	21.3 $\pm$ 7.33	MD: 239 (31.2) Nurse: 415 (54.1) Other: 113 (14.7)

**Table 3.** Multivariate analysis showing the highest antibody titre for women and nurses ( $P < 0.05$ ).

Variables	Odds ratio	95% CI	$P$
Gender: male vs. female	1.57	1.13–2.18	0.01
Age at vaccination: at birth vs. as adult	1	0.99–1.2	0.88
Work category: nurse vs. other	0.49	0.31–0.79	0.00

agreement with recent evidence in the scientific literature (Muvunyi et al., 2018).

Results showed that nurses had higher Abs titre compared to doctors and other hospital staff members, such as technicians and assistants ( $P = 0.05$ ). This may be due to more direct and frequent contact with patients and their body fluids compared to the other health professionals, such as the medical class that works in a clinical area or healthcare technicians less exposed to biological fluids. Furthermore, in the case of such probable ‘inapparent’ occupational exposure, an important fact seems to be that 67.7% of the nursing staff, who maintain a high Abs titre, are occupied in several departments at risk, with a possible increase in HBV transmission, assuming hidden exposures when injuries and/or possible contacts with contaminated biological fluid are not demonstrable (i.e. surgical activities and microsurgery, interventional, endoscopy, etc.) (Makvandi, 2016).

Nurses in this study with titres about the cut-off level appear to be protected against HBV infection. However, it is possible that vaccinated HCWs presenting Abs titre under the cut-off are also protected. Indeed, some recent studies showed that despite the absence of HBsAb expression in the peripheral circulation, cytochemical activation assay through ELISPOT has defined the permanence of immunogenic memory and the strong probability of reactivation and antibodies production following HBs antigen exposure (Saffar et al., 2014).

Several scientific studies have reported that about 85–90% of those vaccinated during adolescence showed a high anti-HBs Abs titre level 10 years after vaccination. The

percentage is reduced for those who were vaccinated in childhood, about 40–60% (Chiara et al., 2013), probably due to a lower interaction between B and T lymphocytes in childhood; and in some cases, anti-HBs in maternal serum could alter the immune response in newborns (Zhu et al., 2011).

Thus, our data support the evidence of immunogenicity against HBV, assessed through the circulating Abs titre, when HCWs were vaccinated as young adults and according to the cycle indicated by the current vaccination plans. In our study, the variation in the Abs titer did not seem to be associated with the age when the vaccination took place. However, this observation was not supported by the univariate analysis.

The variables considered in our multivariate analysis are described in Table 3. This analysis has enabled us to define the profile of the workers more protected from the risk of HBV, considering that the protection conferred was a higher antibody titer. Women (odds ratio [OR] = 1.57,  $P = 0.01$ ), with regard to gender, and nurses, with regard to the working classes, prove to be more protected (OR = 0.49); this statistical analysis allowed us to consider the cohort’s ‘gender’ and ‘working task’ as independent variables.

## Conclusions

The evaluation of HBV markers in HCWs is useful to identify and reduce the number of unprotected workers who have not been vaccinated or show a low antibody titre. The result of the study corroborates the central role of the Occupational Health Service in hospital facilities related to

primary prevention and maximum protection of workers in the healthcare environment, particularly those highly exposed to the risk of exposure to body fluids and at increased risk of sharps injuries.

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### References

- Centers for Disease Control and Prevention (CDC). (1997) Immunization of health-care workers: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recommendations and Reports* 46(RR-18): 1–42.
- Chiara F, Bartolucci GB, Mongillo M, Ferretto L, Nicolli A and Trevisan A. (2013) Hepatitis B vaccination at three months of age: a successful strategy? *Vaccine* 31(13): 1696–1700.
- De Schryver A, Claesen B, Meheus A, van Sprundel M and François G. (2011) European survey of hepatitis B vaccination policies for health-care workers. *European Journal of Public Health* 21(3): 338–343.
- Elseviers MM, Arias-Guillén M, Gorke A and Arens HJ. (2014) Sharps injuries amongst healthcare workers: review of incidence, transmissions and costs. *Journal of Renal Care* 40: 150–156.
- Istituto Superiore di Sanità (ISS), Sistema Epidemiologico Integrato dell'Epatite Virale Acuta. (2017) Incidenza dei casi per classe di età dal 2009 al 2017 delle epatiti Virali Acute. Available at: <http://www.epicentro.iss.it/epatite/bollettino/Bollettino-n.2-2017.pdf> (accessed 10 September 2018).
- Italian Medicines Agency. (2008) Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci. *Gazzetta Ufficiale* 2008, 76. 31/03/ 2008. (Italian). Available at: [http://www.agenziafarmaco.gov.it/allegati/det\\_20marzo2008.pdf](http://www.agenziafarmaco.gov.it/allegati/det_20marzo2008.pdf) (accessed 10 September 2018).
- Lamberti M, De Rosa A, Garzillo EM, Corvino AR, Sannolo N, De Pascalis S, Di Fiore E, Westermann C, Arnese A, Gabriella DG, Nienhaus A, Sobrinho APR and Coppola N. (2015) Vaccination against hepatitis B virus: are Italian medical students sufficiently protected after the public vaccination programme? *Journal of Occupational Medicine and Toxicology* 10: 41.
- Lee WM. (1997) Hepatitis B virus infection. *New England Journal of Medicine* 337: 1733–1745.
- Makvandi M. (2016) Update on occult hepatitis B virus infection. *World Journal of Gastroenterology* 22(39): 8720–8734.
- Muvunyi CM, Harelimana JD, Sebatunzi OR, Atmaprakash AC, Seruyange E, Masaisa F, Manzi O, Nyundo M and Hategekimana T. (2018) Hepatitis B vaccination coverage among healthcare workers at a tertiary hospital in Rwanda. *BMC Research Notes* 11(1): 886.
- Ott JJ, Stevens GA, Groeger J and Wiersma ST. (2012) Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 30: 2212–2219.
- Puro V, De Carli G, Cicalini S, Soldani F, Balslev U, Begovac J, Boaventura L, Campins Martí M, Hernández Navarrete MJ, Kammerlander R, Larsen C, Lot F, Lunding S, Marcus U, Payne L, Pereira AA, Thomas T and Ippolito G. (2005) European recommendations for the management of healthcare workers occupationally exposed to hepatitis B virus and hepatitis C virus. *Eurosurveillance* 10: 260–264.
- Saffar H, Saffar MJ, Ajami A, Khalilian AR, Shams-Esfandabad K and Mirabi AM. (2014) Long-term T-cell-mediated immunologic memory to hepatitis B vaccine in young adults following neonatal vaccination. *Hepatitis Monthly* 14(9): e22223.
- Sagnelli E, Sagnelli C, Pisaturo M, Macera M and Coppola N. (2014) Epidemiology of acute and chronic hepatitis B and delta over the last 5 decades in Italy. *World Journal of Gastroenterology* 20(24): 7635–7643.
- Schillie S, Murphy TV, Sawyer M, Ly K, Hughes E, Jiles R, de Perio MA, Reilly M, Byrd K and Ward JW. (2013) CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. *MMWR Recommendations and Reports* 62: 1–19.
- Trevisan A, Bruno A, Mongillo M, Morandin M, Pantaleoni A, Borella-Venturini M and Giraldo M. (2008) Prevalence of markers for hepatitis B virus and vaccination compliance among medical school students in Italy. *Infection Control and Hospital Epidemiology* 29(12): 1189–1191.
- World Health Organization (WHO) Hepatitis B Fact sheet revised. Available at: <https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b> (accessed 20 October 2018).
- Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC, Cuccia M, Mangione R, Marrone F, Negrone FS, Parlato A, Zamparo E, Zotti C, Stroffolini T, Mele A and Study Group (2005) Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *Lancet* 366: 1379–1384.
- Zhu CL, Liu P, Chen T, Ni Z, Lu LL, Huang F, Lu J, Sun Z and Qu C. (2011) Presence of immune memory and immunity to hepatitis B virus in adults after neonatal hepatitis B vaccination. *Vaccine* 29(44): 7835–7841.