

Hepatitis B revaccination for healthcare workers who are anti-HBs-negative after receiving a primary vaccination series

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ABSTRACT

Introduction: This study aimed to evaluate the response to hepatitis B (HB) revaccination of healthcare workers (HCW) who are negative for antibodies to HB surface antigen (anti-HBs) after a complete vaccination series. **Methods:** HCW whose anti-HBs test was performed > 90 days after a HB vaccination course were given a 4th dose. A post-vaccination test was done within 30 to 90 days. **Results:** One hundred and seventy HCW were enrolled: 126 (74.1%) were anti-HBs-positive after the 4th dose. **Conclusions:** Rechecking anti-HBs after the 4th HB vaccine dose is a practical approach in case of post-vaccination tests performed >90 days after the full vaccination course.

Keywords: Hepatitis B vaccination. Healthcare workers.

A primary 3-dose hepatitis B (HB) vaccination series induces protective serum levels of antibodies to HB surface antigen (anti-HBs ≥ 10 mIU/mL) in 90% of healthy adults and 95% of children and adolescents. A 2nd full-course vaccination induces protection in $\geq 50\%$ of those who did not respond to the 1st vaccination series¹. Vaccine-induced antibodies to HB decline over time: Up to 60% of persons who initially respond to the vaccine will lose detectable antibodies over 5 to 15 years (waning immunity)². Despite the decline of anti-HBs concentration to < 10 mIU/mL, persons who initially responded to the HB vaccine remain protected against chronic HB infection due to immune memory³.

Hepatitis B vaccination is recommended for all healthcare workers (HCW) who have a chance of exposure to blood or body fluids. Post-vaccination testing for anti-HBs is recommended for persons whose subsequent clinical management depends on knowledge of their immune status, such as healthcare personnel¹. When recommended, post-vaccination testing should be performed within 30 to 90 days of the last dose of the vaccine¹.

Healthcare workers frequently do not perform post-vaccination anti-HBs testing. Although HB vaccination has been recommended for HCW since the 1980s, routine post-vaccination testing has not yet been incorporated in the care of HCW in Brazil. Additionally, the adherence of HCW to vaccination and post-vaccination testing is poor. Furthermore, the frequency of HCW who were vaccinated when they were children or adolescents is increasing, and post-vaccination testing is not recommended in routine HB immunization.

In the management of HCW who are anti-HBs-negative after a full-course vaccination, the first step is to check the interval between

the last dose of HB vaccine and the post-vaccination testing. If it exceeds 6 months, a single dose of HB vaccine helps to differentiate between non-response and waning immunity. A booster dose of the vaccine induces an anamnestic response among persons with waning immunity, whereas non-responders will have no detectable serum anti-HBs or a very small rise⁴⁻⁶. Persons who are anti-HBs-negative after the 4th dose of HB vaccine should receive two more doses. Those who present as anti-HBs-negative after a 2nd full vaccination course (total of 6 doses) are considered true non-responders⁴.

The aim of this study was to evaluate the response to hepatitis B revaccination among HCW who are anti-HBs-negative after receiving a primary 3-dose HB vaccination series at any time in the past.

This prospective study was conducted at the *Centro de Referência para Imunobiológicos Especiais of Hospital das Clínicas (CRIE-HC)*, a tertiary teaching hospital attached to the Faculdade de Medicina of Universidade de São Paulo, in the City of São Paulo, southeast of Brazil, from February 2006 to September 2007.

In this hospital, HCW who are anti-HBs-negative (< 10 mIU/mL) in routine assessment by the occupational health service are referred to the CRIE to have their vaccination status evaluated. HCW who are anti-HBs-negative and who reported a prior 3-dose HB vaccination series at any time in the past were asked whether they had had a previous post-vaccination test. We also searched for previous anti-HBs tests in the hospital laboratory database. HCW who were previously documented as anti-HBs-positive (≥ 10 mIU/mL) were considered protected. HCW who had not been tested before or who did not know whether they were tested or not were administered a 4th dose of HB vaccine and were invited to participate in this study.

All enrolled subjects were asked to draw blood samples for the anti-HBs test (ELISA) 30 to 90 days after the 4th dose of the vaccine, according to a previously proposed algorithm⁴. HCW who developed anti-HBs ≥ 10 mIU/mL following the 4th dose of the vaccine were considered protected. HCW who were anti-HBs-negative after the 4th dose of HB vaccine were given two more doses of the vaccine and had

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their anti-HBs level rechecked 30 to 90 days after the 6th dose. HCW who were anti-HBs-negative following the 6th dose of HB vaccine were considered true non-responders.

The study was approved by the Ethical Committee of the Hospital das Clínicas of the Faculdade de Medicina of Universidade de São Paulo. All subjects signed an informed consent form before enrollment in the study.

A total of 170 HCW who were anti-HBs-negative following a 3-dose primary HB vaccination series were enrolled in the study. There were 60 staff nurses, 21 medical doctors, 28 specialized technicians (physiotherapists and laboratory, X-ray, and pharmacy staff), 21 general services staff (cleaning, laundry, operational services, and kitchen), 12 administrative personnel, 26 medical and nursing students, and 1 retired HCW (the occupation was not informed for 1 subject).

All of them received a 4th dose of the HB vaccine, but only 151 collected blood for post-vaccination anti-HBs retesting (the interval between the 4th dose of HB vaccine and the test ranged from 1 to 22 months, with a mean of 3.2 months): 126 (83.4%) were anti-HBs-positive (≥ 10 mIU/mL) and 25 (16.6%) were anti-HBs-negative. **Table 1** shows the demographic characteristics of the subjects and the interval between the 3rd dose of HB vaccine and the anti-HBs negative test, according to the subjects' anti-HBs status following the 4th dose of HB vaccine.

Healthcare workers who were anti-HBs-positive following the 4th dose of the vaccine were younger at the time of primary HB vaccination series (mean age, 30.9) than those who did not respond to the 4th vaccine dose (mean age, 37), although this difference was not statistically significant (Student's T test, $t=1.865$, $p=0.065$). HCW

who did not collect blood for post-vaccination testing were younger (mean age, 23.1) than those who underwent the test (mean age, 31.9), and this difference was statistically significant (Student's T test, $t=2.599$, $p=0.01$).

There was no statistically significant association of anti-HBs status following the 4th dose of vaccine with sex (Fisher's exact test, $p=0.653$), smoking ($\chi^2=0.751$, $df=2$, $p=0.687$), body mass index (Fisher's exact test, $p=0.114$, for the comparison of underweight plus healthy weight versus overweight plus obesity), presence of chronic conditions ($\chi^2=1.100$, $df=2$, $p=0.577$), and the interval between the 3rd dose of HB vaccine and the post-vaccination testing (Student's T test, $t=-355$, $p=0.723$).

Among the 25 HCW who were anti-HBs-negative after the 4th dose of HB vaccine, 15 (60%) seroconverted after the 6th dose of the vaccine and 4 were true non-responders (the interval between the 6th dose and the test ranged from 1 to 8 months, with a mean of 3.2 months). One of the non-responders seroconverted after the 7th dose. One HCW was HBsAg-positive. **Figure 1** presents an algorithm of the study's events.

Twenty-four (14.1%) of the 170 HCW did not complete the proposed revaccination and post-vaccination testing.

The status of the 170 HCW who were anti-HBs-negative after a primary 3-dose HB vaccination series could have been due to non-response to the vaccine or to waning immunity. Most (74.1%) of them were anti-HBs-positive after the 4th dose of the vaccine. Among the 25 HCW who did not respond to the 4th dose, 60% seroconverted after the 6th dose of HB vaccine; one HCW was HBsAg-positive, and only 4 (2.7%) of the 146 HCW who completed the study did not respond to a 2nd full-course HB vaccination and were considered true non-responders, even though one of them was anti-HBs-positive after the 7th dose of HB vaccine.

TABLE 1 - Characteristics of the 170 healthcare workers who were anti-HBs negative after a primary 3-dose hepatitis B vaccination series, according to their anti-HBs status following the 4th dose of the vaccine.

| HCW characteristics (total)* | Anti-HBs status after the 4 th dose of HB vaccine | | | | | |
|--|--|------|---------------------------------|------|--------------------|------|
| | positive (n=126) (≥ 10 mIU/mL) | | negative (n=25) (<10 mIU/mL) | | not done (n=19) | |
| | n | % | n | % | n | % |
| Sex | | | | | | |
| female (109) | 77 | 70.6 | 17 | 15.6 | 15 | 13.8 |
| male (61) | 49 | 80.3 | 8 | 13.1 | 4 | 6.6 |
| Age at primary HB vaccination series (years) (136) | | | | | | |
| min-max | 6 | 63 | 18 | 55 | 8 | 42 |
| mean \pm std. dev. | 30.9 \pm 12.9 | | 37.0 \pm 13.3 | | 23.1 \pm 9.6 | |
| Smoking (168) | | | | | | |
| yes (18) | 15 | 83.3 | 2 | 11.1 | 1 | 5.5 |
| no (150) | 109 | 72.7 | 23 | 15.3 | 18 | 12.0 |
| Body mass index (162) | | | | | | |
| <18.5 (underweight) (7) | 4 | | 2 | | 1 | |
| 18.5-24.9 (healthy weight) (88) | 68 | | 8 | | 12 | |
| 25-29.9 (overweight) (49) | 34 | | 10 | | 5 | |
| ≥ 30 (obesity) (18) | 13 | | 4 | | 1 | |
| Chronic condition/immunodepression (169) | | | | | | |
| yes (17) | 12 | 70.6 | 4 | 23.5 | 1 | 5.9 |
| no (152) | 113 | 74.3 | 21 | 13.8 | 18 | 11.8 |
| Interval between 3rd dose of HB vaccine and testing (months) (156) | | | | | | |
| min-max | 8 | 193 | 8 | 144 | 3 | 137 |
| mean \pm Standard deviation | 75.8 \pm 42.3 | | 72.5 \pm 39.3 | | 67.2 \pm 39.0 | |

Anti-HBs: antibodies to hepatitis B surface; HCW: healthcare workers; HB: hepatitis B; *total number of subjects varies due to missing data.

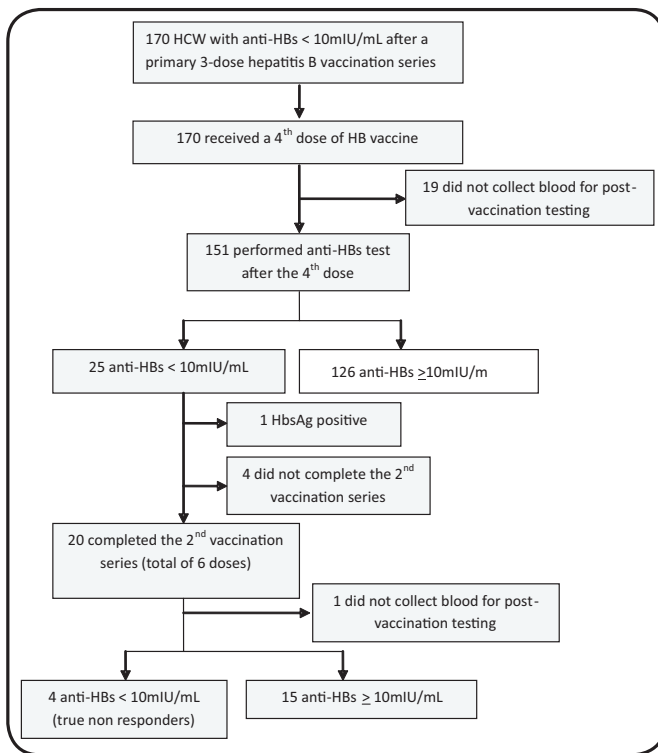


FIGURE1 - Algorithm of study events for 170 healthcare workers with anti-HBs negative after a primary 3-dose hepatitis B vaccination series.

Anti-HBs: antibodies to hepatitis B surface; **HB:** hepatitis B; **HCW:** healthcare workers.

The management of HCW who were not tested immediately after a complete primary HB vaccination series is controversial¹. In this case, some authors argue that HCW do not need to be tested unless they have been exposed⁷. However, knowledge of post-vaccination anti-HBs status is important to appropriate post-exposure management. In case of occupational exposure to blood and body fluids, unknown anti-HBs status is a cause of anxiety for both the HCW themselves and the health professionals responsible for their care. It may lead to hasty decisions regarding prophylactic measures and unnecessary use of HB immune globulin (HBIG). This is of particular concern in countries with limited resources.

The HCW enrolled in this study were tested for anti-HBs during routine assessment by the occupational health service during admittance exams or periodic check-ups. These HCW did not report an occupational exposure to biological material previous to the anti-HBs negative testing. None of them received HBIG, and most of them responded to the 4th dose of HB vaccine, making it unnecessary to complete the 2nd vaccination series, thus saving time and influencing adherence.

Routine booster doses of HB vaccine and further periodic anti-HBs testing are not recommended for healthy HCW, once response to a full vaccination course has been confirmed by post-vaccination testing^{1-2,8}. However, sometimes the post-vaccination test is performed more than six months after the last HB vaccine dose. The results of this study strengthen the proposed strategy of rechecking anti-HBs status after the 4th dose of the vaccine in such cases. HCW who fail to respond to the 4th dose of HB vaccine should be investigated for HB infection, in case pre-vaccination testing was not performed, and given a 2nd full-course vaccination, followed by retesting of anti-HBs status within 30 to 90 days of the last dose.

Age >40 years; obesity; smoking; presence of chronic conditions, such as human immunodeficiency virus (HIV) infection, advanced liver disease, chronic renal failure, and immunosuppression; and certain human leukocyte antigen (HLA) haplotypes have been associated with decreased response to HB vaccine¹. In this study, no association was observed between negative anti-HBs after the 4th dose and age, sex, smoking, body mass index, and chronic conditions, probably due to the small sample size.

The transmission of the HB virus in healthcare settings still is a problem⁹. A recent study in São José do Rio Preto, State of São Paulo, showed significantly higher prevalence of HB among HCW (0.8%) than among blood-donor candidates (0.2%)¹⁰.

However, the adherence of HCW to HB vaccination and post-vaccination testing is poor. In the United States, 75% of HCW working in hospitals and with frequent or potential exposure to blood or other potentially infectious material were estimated to have been vaccinated against HB¹¹. In a survey in Belo Horizonte, State of Minas Gerais, 73.8% of dentists reported having received a complete 3-dose HB vaccination series, and only 14.8% reported having performed the post-vaccination test¹². In Sertãozinho, State of São Paulo, 82.2% of dentists reported 3 or more doses of the vaccine, but only 12.8% of those who had received at least one vaccine dose reported post-vaccination testing¹³. Among primary healthcare personnel in Florianópolis, State of Santa Catarina, 64.1% of 1,249 HCW reported a complete HB vaccination, and 33% of them had undergone post-vaccination testing¹⁴. In this study, 14.1% of HCW dropped out, despite having been offered free vaccination and testing at the workplace and having been called up in case of delay. Non-adherence was greater among younger HCW.

The results of this study suggest that HCW with a full HB vaccination course whose post-vaccination test was not performed within the recommended 30- to 90-day interval after the last dose of the HB vaccine may be given a 4th dose followed by a post-vaccination test. This approach was confirmed as practical and effective. Simplifying the vaccination process may help to enhance HCW adherence.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABSTRACT IN PORTUGUESE

Revacinação contra hepatite B para profissionais de saúde com anti-HBs negativo após receber esquema primário de vacinação completo

Introdução: Esse estudo avaliou a resposta à revacinação contra hepatite B (HB) entre profissionais de saúde (PS) com anti-HBs negativo após esquema de vacinação completo. **Métodos:** PS cujo anti-HBs foi realizado > 90 dias após a última dose do esquema vacinal receberam 4ª dose da vacina. O anti-HBs foi repetido 30-90 dias após. **Resultados:** Entre 170 PS, 126 (74,1%) tiveram anti-HBs positivo após a 4ª dose. **Conclusões:** Repetir o teste sorológico após a 4ª dose é estratégia prática caso o anti-HBs tenha sido realizado > 90 dias após a última dose da vacina.

Palavras-chaves: Vacinação contra hepatite B. Profissionais de saúde.

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