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## The role of hepatitis B vaccine challenge dose in patients with underlying health conditions

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### ABSTRACT

We have evaluated the immunological response to Hepatitis B virus (HBV) booster vaccine dose in 129 adults with underlying diseases in comparison with 694 subjects at occupational risk of infection, who have previously completed the primary series and resulted with anti-HBs <10 mIU/mL. After booster dose, 60.5% of the patients with underlying diseases and 14.8% of the subjects at occupational risk resulted seronegative. By comparing two groups, rate of subjects with anamnestic response was higher in at occupational risk group respect to that at risk for medical conditions (OR: 5.99 [95%IC, 3.81–9.41],  $p < .001$ ). This difference was associated to gender (males/females: OR: 0.619 [95%IC, 0.421–0.910],  $p = .015$ ) and age (better response for younger people,  $p = .011$ ).

### ARTICLE HISTORY

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### KEYWORDS

HBV; health care workers; immunocompromised; vaccination; Italy

Sir,

we read with great interest the article of Grazzini et al.<sup>1</sup> In this study, authors assessed the effectiveness of Hepatitis B virus (HBV) booster vaccine dose in eliciting the immunological response in seronegative (anti-HBs level <10 mIU/mL) healthcare workers (HCWs) and students of Careggi Teaching Hospital (Florence, Italy), vaccinated during childhood or adolescence. As with other Italian experiences,<sup>2,3</sup> they observed that 87.8% (698/795) of the study population responded to the challenge dose. Moreover, among those persistently seronegative, 76.2% (32/42) who received the fifth dose and 60.0% (3/5) who completed the second vaccination course seroconverted.<sup>1</sup> In their final considerations, the authors highlighted the importance of receiving all the three additional vaccine doses, in order to obtain protection.

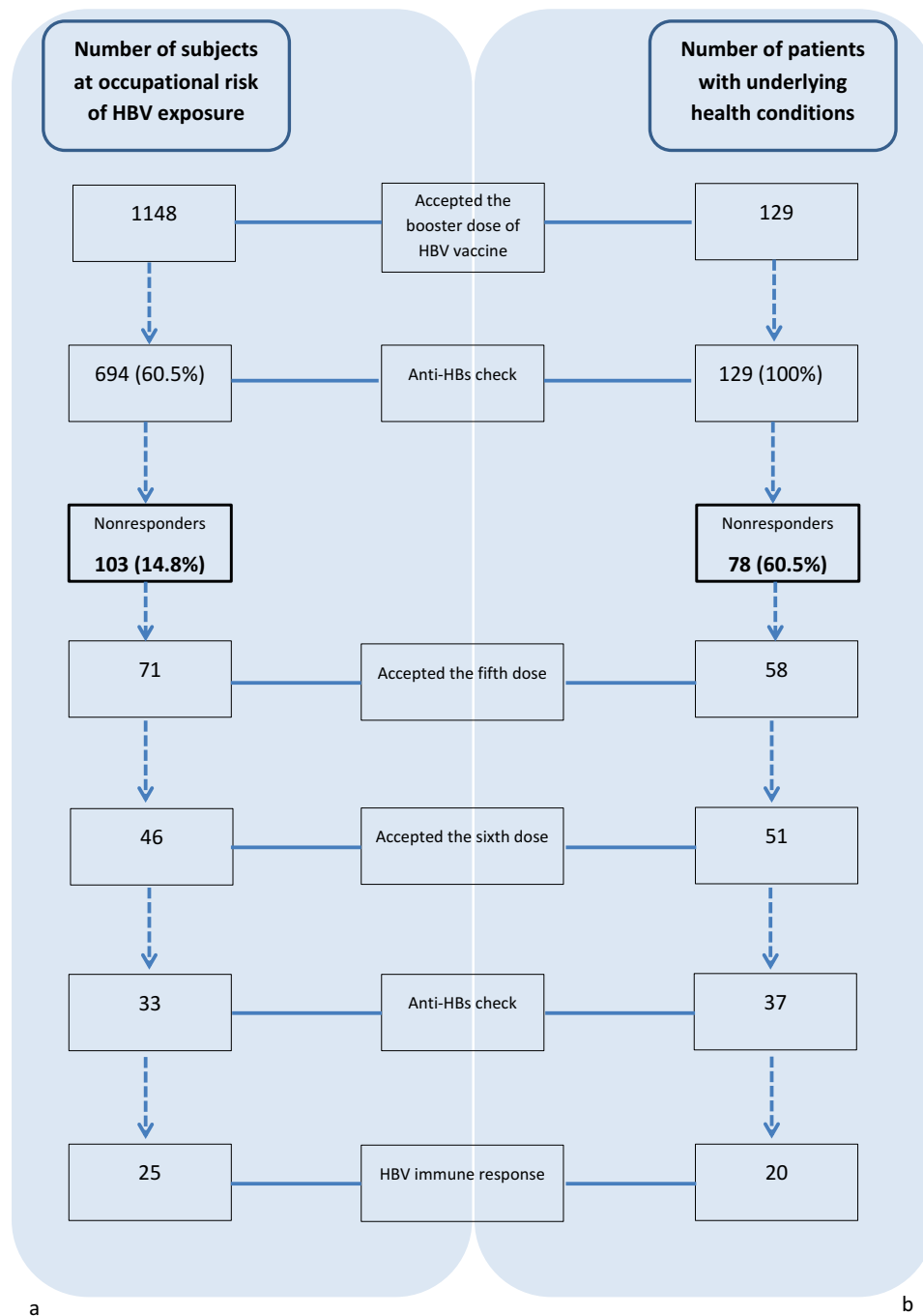
These results are in line with a similar analysis that we have retrospectively conducted in 1148 subjects at occupational risk of HBV infection (51.6% females; mean age  $28.7 \pm 4.81$  years), followed up at San Martino's Hospital outpatient vaccination clinic (Liguria Region, Italy). One thousand sixty-three (92.6%) students or clinicians of health disciplines and 85 (7.4%) scavengers, who have previously completed the primary series and resulted with anti-HBs concentrations <10 mIU/mL, received a single challenge HBV vaccine dose. Of them, only 694 subjects (60.4%) accepted serological testing at least 1 month after immunization (Figure 1a). The majority of patients were females (58.8%) and had a mean age of  $28.7 \pm 12.15$  years. The proportion of subjects with available serological testing resulting seroprotected (anti-HBs  $\geq 10$  mIU/mL) was 85.2% (591/694). Four hundred sixty (66.3%) were vaccinated in the first year of life, 148 (21.3%) in adulthood and 86 (12.4%) were vaccinated in adolescence; as the results observed by Grazzini et al., we didn't find any statistically significant difference

among groups stratified by age at the time of the first vaccination course (Chi-square = 2.87;  $p = .24$ ). Being female was associated with a higher rate of seroprotection with anti-HBs  $\geq 10$  mIU/mL (OR: 1.65 [95%IC, 1.06–2.55],  $p = .026$ ).

Seventy-one (68.9%) and 46 (44.7%) of those persistently seronegative after the booster vaccine dose (N = 103) accepted the fifth dose and sixth dose, respectively. Only 71.7% (33/46) of subjects who completed the second vaccination course had post-immunization serology; 75.6% (25/33) of them responded to revaccination (Figure 1a).

In Italy, the National Immunization Plan 2017–2019 recommends HBV vaccination to newborns and to categories of subjects with an increased risk of infection for occupational exposure or for specific behaviors. Vaccination is also recommended to adults with high-risk medical conditions (for example chronic liver disease, hemophilia, hemodialysis, psoriasis/eczematous lesions, HIV infection).<sup>4</sup>

We have evaluated the immunological response rate to HBV booster vaccine dose in adults with underlying diseases in comparison with the response rate observed in the at occupational risk group previously described. A total of 129 patients who have received the primary three-doses vaccination course in the past and resulted with anti-HBs level <10 mIU/mL were included in this study. Seventy-five (58.1%) of them were HIV infected patients, 28 (21.7%) candidates to/received a solid organ transplantation (SOT), 18 (14.0%) with HCV infection, 1 of them undergoing chemotherapy, 8 (6.2%) with other underlying health conditions, 4 of them treated with immunosuppressants (Table 1). Mean age was  $45.0 \pm 14.98$  years, 72.9% of the subjects were males. Seventy-eight (60.5%) had an anti-HBs concentration < 10 mIU/mL after the booster vaccine dose and 15 of the 51 (29.4%) patients who mounted an



**Figure 1.** Flow-chart of patient population, by study groups.

anamnestic response were low-responders (anti-HBs titer 10–100 mIU/mL) (Figures 1b and 2). Although a second vaccination course was offered to all seronegative subjects, only 51 of them (65.4%) received all three additional doses and 37 had an available blood test after the last dose. Twenty patients (20/37, 54.0%) responded to the second vaccination course (Figure 1b).

By comparing two groups, the rate of subjects showing an anamnestic response after the booster dose was higher in HCWs and scavengers group respect to that at risk for medical conditions (OR: 5.99 [95%IC, 3.81–9.41],  $p < .001$ ) (Figure 2).

Moreover, this difference between groups in the anamnestic response to HBV booster dose was also associated

to gender (males vs females: OR: 0.619 [95%IC, 0.421–0.910],  $p = .015$ ) and age (better response for younger people,  $p = .011$ ). Differences between two groups in the rate of response was not influenced by the time elapsed between the date of last vaccine dose of the primary course and the date of booster dose ( $p = .57$ ) (data available for 448 subjects at occupational risk and 92 patients with underlying diseases, respectively).

By considering the antibody titer after the second vaccination course, no difference was revealed in the rate of response between two groups ( $p = .83$ ).

Our results emphasize the importance of serological testing in patients at high-risk in order to identify those non

**Table 1.** Study population according to medical condition.

	N (%)
Solid organ transplantation:	28 (21.7)
• Liver transplantation	24 (18.6)
• Kidney transplantation	2 (1.5)
• Lung transplantation	2 (1.5)
Chronic diseases:	8 (6.2)
• Neurological diseases (i.e. multiple sclerosis)	1 (0.8)
• Hematological diseases (i.e. hypogammaglobulinemia)	2 (1.5)
• Inflammatory bowel disease	1 (0.8)
• Rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis)	3 (2.3)
• Asplenia	1 (0.8)
HIV infection	75 (58.1)
HCV infection	18 (14.0)
Total	129 (100.0)

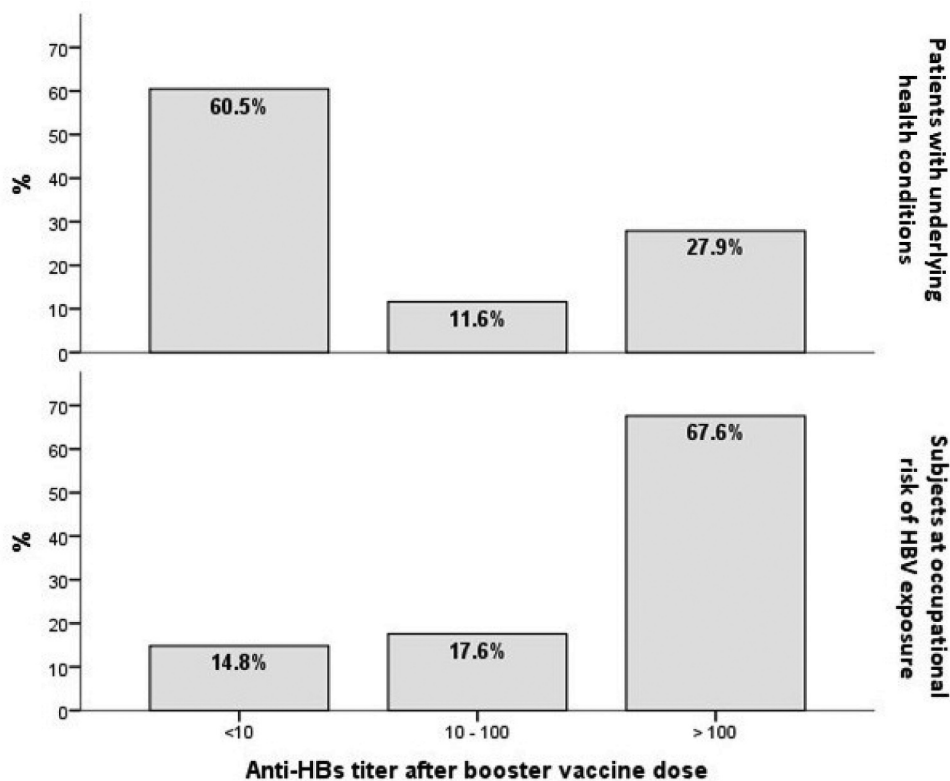
responders to the primary vaccination and to protect them through revaccination; this advice becomes even stronger in patients with underlying health conditions, who in our study have shown to be less likely to immunologically respond to the booster dose.

This aspect is also particularly relevant considering the severity of chronic HBV in immunocompromised hosts. HIV-infected people, for example, are prone to develop HBV coinfection due to the shared transmission routes and among them HBV infection is more likely to progress to chronic hepatitis and cirrhosis,<sup>5-8</sup> but the immune response to the vaccination in this population is less effective compared with HIV negative adults.<sup>9-15</sup> In HIV-infected persons the immunogenicity ranges from 18% to 72% and, in terms of magnitude and antibody persistence, is lower than in the general population.<sup>5,16,17</sup> Higher CD4 counts and lower HIV viral loads have been

associated with improved immunological response to vaccination.<sup>9,18-20</sup> Seventy-four patients (74/75, 98.7 %) of our study population had CD4-T cell count higher than 200 cells/mm<sup>3</sup> and 68 (68/75, 90.7%) had HIV-RNA below 50 copies/mL, in the 6 months preceding the booster dose.

The serological evaluation after the third dose is so important among these patients as their poor response to the primary vaccine series.<sup>10</sup> In case of anti-HBs non-protective levels after an initial vaccination course, a single challenge dose seems to be able to implement the proportion of subjects with protective antibody concentrations,<sup>10,21,22</sup> but in another study just a small increase was reported.<sup>10,23</sup> However, revaccination is effective in increasing the response to the vaccine<sup>10,22</sup> and have been observed as 36–85%.<sup>9,19,24,25</sup> Some experts recommend deferring the second vaccination course up to antiviral therapy has been started and an adequate CD4 count has been reached.<sup>9</sup> Some studies have demonstrated the efficacy of high-dose rechallenging vaccination,<sup>9,26</sup> while other studies have not confirmed these findings.<sup>9,27</sup> Of note, non-responders to the primary vaccination course who responded to revaccination lost HBV protective antibody level more rapidly respect to those who responded to the first three doses; therefore, these patients could take more advantage by serological follow-up.<sup>9,24,28</sup>

For patients with other underlying diseases, similar to the HIV-infected patients, the seroconversion rates to HBV vaccination are affected by impaired immunity. Immunization of patients with liver cirrhosis with the standard dose has been shown to be ineffective<sup>29-31</sup> with a response rate that ranged from 16% to 79%.<sup>29-31</sup> In order to improve the immunogenicity double-dose vaccine or accelerated dose schedules have been used.<sup>29,32-35</sup>

**Figure 2.** Anti-HBs titer after booster vaccine dose, by study group.

Because of the poor responsiveness to vaccination, as for HIV-infected patients, serological testing after the primary course is advised in immunocompromised patients to check if revaccination is necessary.<sup>29,36,37</sup> Has been demonstrated that a second vaccination course could increase the response rates in cirrhotic patients who are unresponsive to the primary vaccination.<sup>29</sup>

HBV vaccination efficacy could also be compromised by immunosuppression. Patients not treated with immunosuppressant had a higher probability to obtain a better immune response to the vaccination than those on immunomodulatory (RR 1.33; 95% CI 1.08–1.63) or anti-TNF therapy (RR 1.57; 95%-CI 1.19–2.08).<sup>38</sup> Timeliness of the serological testing is crucial especially in those candidates to long-term immunosuppressive, before the start of the treatment.





Twenty-eight patients of our study population were solid organ transplanted or candidates to transplantation, of whom 24 for liver dysfunction (85.7%). HBV immunization before organ transplantation is recommended for all nonimmune patients as reduce the risk of infection from hepatitis B virus core antibody-positive donors<sup>39</sup> and because of the high risk of severe HBV infection after transplantation.<sup>40</sup> However, the seroconversion rates in these patients are suboptimal.<sup>40</sup> In addition, antibody levels in those who have responded to the primary course drop rapidly and up to 35% of patients become seronegative after liver transplant.<sup>40,41</sup> Vaccination before transplantation is to be preferred because of the better efficacy profile. The majority of our study cohort (20/28, 71.4%) received the HBV booster dose after transplantation.

In conclusion, our study confirms the importance of assessing the need for revaccination in order to quickly protect nonresponders. Consistent with the evidence by Grazzini et al.<sup>1</sup> we observed a poor compliance to revaccination among both at risk for medical conditions and at risk for occupational exposure study groups (only 65.4% and 44.7% of them accepted all three additional doses proposed, respectively). It becomes even more crucial in fragile and immunocompromised patients, in which a greater lack of antibody response after the challenge dose has been observed. These data underline the importance of offering adequate counseling and addressing the misperception of risk and uncertainties about the vaccine effectiveness.

## Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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