RESEARCH LETTER

Interchangeability of 3 recombinant anti-HBV vaccines in primary schedule, irrespective of dose and HBsAg subtype: the first prospective, open-label, randomized study in healthy adult population

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Introduction Vaccination against hepatitis B is the most effective method to prevent hepatitis B virus (HBV) infection and its consequences (ie, liver cirrhosis, hepatocellular carcinoma, liver failure). The active substance in the vaccine is the hepatitis B surface antigen (HBsAg), which is currently obtained by DNA recombination from yeast cells. Second-generation recombinant vaccines are based on S-polypeptide, which contains the 'a' determinant, common to all HBsAg subtypes, and variable fragments (d/y, w/r) determining the subtypes. The 'a' determinant is recognized by B lymphocytes, and the conservative character of this region allows cross-protection after vaccination regardless of the HBsAg subtype used in the vaccine.[1] Therefore, the effect of antigen variants on the immune response is generally assumed to be negligible. However, Heijtink et al[2] discussed the differences in the amino acid sequence between adw, adr, and ayw subtypes and their effect on vaccination efficacy and capability of antibody binding to surface antigens of HBV subtypes other than the one used in the vaccine.[2] Despite those observations, Avazova et al[3] confirmed the efficiency of HBV vaccination in vertical transmission, irrespective of the HBsAg subtype used.[3]

To elicit the immune response against HBV, administration of a few doses of vaccine in the basic schedule is needed (2- to 4-dose schedules are possible). The World Health Organization and the guidelines and product information of some countries allow for an interchange of the monovalent formulation, especially in cases where the brand of vaccine used for previous doses is not known.[4-6] Despite this possibility, little is known about the effectiveness of such management. Vaccine formulations are not considered equivalent, unlike the original and generic medicines. Differences in the manufacturing process, including the antigen subtype, adjuvant type, excipients, and technologic details, affect the amount of antigen needed to induce an adequate antibody response.[7] Only a handful of studies have assessed the efficacy of schedules using anti-hepatitis-B vaccines of different manufacturers. Regimens using 2 products of different manufacturers[8-10] or 2 formulations (monovalent/polyvalent) of 1 manufacturer[11] were assessed in such trials.

Our objective was to assess the efficacy of interchangeability of 3 types of recombinant anti-hepatitis-B vaccines (differing by dose and HBsAg subtype).

Patients and methods This randomized, prospective study was conducted from September 2012 to March 2014. Healthy volunteers were randomly assigned to 2 groups vaccinated by the 0–1–6 month schedule. The dosing regimen in the study group was as follows: first dose, 20 μg of HBsAg; antigen variant, adr (HepavaxGene TF, lot no: 0431043 [IBSS BIOMED S.A., entity: Crucell Italy S.r.1., Baranzate, Italy]); second dose, 10 μg; antigen variant, adw2 (HBVaxPRO, lot no: H002335 [Merck Sharp & Dohme, B.V.; entity: Sanofi Pasteur MSD SNC, Lyon, France]); third dose, 20 μg HBsAg; antigen variant, adw2 (Engerix-B, lot number AHBVC134CA

TABLE 1 Anti-HBs antibody response after vaccination doses

Vaccination dose	Number of respondents, %			Antibody concentration[a], mIU/ml		
	study group, n = 26	control group, n = 25	*P* value	study group, n = 26	control group, n = 25	*P* value
first dose	2 (7.7)	2 (8.0)	0.6	23 (10.00–36.00)	31 (10.00–52.00)	0.7
second dose	13 (50.0)	19 (76.0)	0.1	87 (14.25–139.25)	181 (57.00–285.25)	0.1
third dose	25 (96.2)[b]	25 (100.0)	0.98	1400 (301.00–2333.75)	1850 (476.50–7480.00)	0.4

Data are presented as number (percentage) of patients or median (interquartile range).

a only cases where antibody titers were positive
b 1 subject in the study group was finally classified as a nonresponder. This patient subsequently started the standard primary schedule of only Engerix-B vaccination; after the second dose there was still no response (anti-HBs, 0.0 mIU/ml); the third dose was not administered because the patient was lost to follow-up

[GlaxoSmithKline Biologicals S.A., Rixensart, Belgium]). The dosing regimen in the control group was as follows: all 3 doses, 20 μg HBsAg; antigen variant, adw2 (Engerix-B, lot number AHBVC-134CA [GlaxoSmithKline Biologicals S.A., Rixensart, Belgium]). The characteristics of the vaccines are presented in Supplementary material online, *Table S1*. All vaccines were administered intramuscularly in the deltoid muscle.

Subjects enrolled in the study were aged from 35 to 60 years and had no history of hepatitis B vaccination. The exclusion criteria were as follows: a history of HBV infection or positive anti-HBc or anti-HBs, human immunodeficiency virus infection, abnormalities in humoral response (abnormal immunoglobulin levels) or complete blood count, or other factors potentially influencing the immune response (eg, diabetes, history of neoplastic or autoimmune disease, immunosuppressive therapy). The above tests were performed 4 weeks before the first vaccination dose. Patients were randomly assigned to either of the groups, stratified by age, sex, and body mass index (BMI). Randomization application created for the study was used.

Immunogenicity was assessed by measuring the anti-HBs titer after the first dose (directly before administration of the second dose), after the second dose (directly before the third dose), and at 1 month after the third dose of the vaccine. Anti-HBs titers were measured using a commercial enzyme immunoassay, Monolisa anti-HBs Plus (Bio-Rad, Marnes-la-Coqette, France). The protective level of anti-HBs was defined as 10 mIU/ml or higher.[7] The method did not allow for titer measurement below the level of 10 mIU/ml, and the value of 0 was arbitrarily attributed in such situations.

The normality of data was assessed using the D'agostino–Pearson test. Statistical significance was calculated using the χ^2 test when comparing categorical data and the Mann–Whitney test when comparing quantitative data between the study and control groups. The Friedman test was used to calculate the changes in the antibody concentration between doses. To assess the efficacy of vaccination, only data of patients who finished the study according to the protocol were used. The flow of participants is described in Supplementary material online, *Figure S1*.

Results A total of 51 subjects finished the full vaccination course and had the immune response evaluated after the third dose. Both groups were comparable in terms of sex distribution, mean age, and BMI values (Supplementary material online, *Table S2)*. All subjects were Caucasians. There were no significant comorbidities or medications used.

In both groups, a significant increase in the anti-HBs concentration was observed (study group: 1st vs 2nd dose, $P = 0.0006$; 2nd vs 3rd dose, $P = 0.0001$; control group: 1st vs 2nd dose, $P = 0.0001$, 2nd vs 3rd dose $P = 0.0001$). The overall response rate was high in both groups. There was no significant difference between the groups (TABLE 1), although a significantly better antibody response was observed after the second dose in the control group (after the 1st dose, $P = 0.96$; after the 2nd dose, $P = 0.016$; and after the 3rd dose, $P = 0.3$).

Discussion It is commonly believed that all hepatitis B vaccine preparations are equivalent, and sometimes they are used interchangeably during 1 course of vaccination. The possibility of using 2 different preparations in 1 vaccination schedule has been confirmed in a few studies. Bush et al[8] proved the efficacy of Engerix B (Smith-Kline-Beecham) as the third dose of the primary schedule after 2 doses of Recombivax (MSD) in adults. Tregnaghi et al[9] confirmed the efficacy of the schedule composed of Engerix B (GSK) as the first dose followed by 2 doses of Euvax (Lucky Goldstar) in children. Piazza et al[10] also confirmed interchangeability of Engerix-B (SK&F) and Recombivax (MSD). Preparations containing the same antigen subtype (adw2) were used in these studies. In the studies by Bush et al[8] and Piazza et al,[10] the doses of antigen were different (Engerix B, 20 μg; Recombivax, 10 μg). Lim et al[11] noted a comparable antibody response in children after the use of a polyvalent vaccine containing a HBV component to a separate vaccine as the third dose of the primary regimen of hepatitis B vaccination; however, all the vaccines were produced by the same manufacturer. Our study is the first to confirm the efficacy of the primary vaccination schedule despite the use of vaccines produced by different manufacturers, and, moreover, independently of different HBsAg subtypes and doses.

A strong immune response following the second and third doses was observed in both groups, although in the control group, a higher number of subjects achieved a protective concentration of anti-HBs after the second dose, and the concentration was also higher in this group. This difference, although relatively weak, was statistically significant. The determination of factors negatively affecting the dynamics of the postvaccination response in the study group requires further research. Some factors, such as a change of vaccine antigen (from adr to adw2), a lower dose of HBsAg in the second dose of the vaccines, and adjuvants used in the vaccines, should be considered. Irrespective of the fact that the differences in a definite response between the groups were not significant, the difference in the dynamics of antibody response development seems to be important. In immunocompromised subjects, the change of vaccine preparations in the primary schedule may be an additional factor impairing the immune response. However, further research is needed on this particular population.

We limited the age range to 35 to 60 years (commonly described as middle age) because the population of adults in the immune postvaccination response is heterogeneous. By excluding young adults and older individuals, we were able to observe differences in the dynamics of the immune response between the study and control groups without additional interfering factors. A gradual decrease of the immune response following vaccinations is observed in the age group above 40 years.[12] The upper age range allowed us to exclude the effect of immunodeficiency related to advanced age.

The present study has several limitations including a small sample size. However, although the study group was relatively small, antibody titers in both groups were about 100-fold higher compared with the minimal protective level, so potential differences between the groups were not clinically significant. The age range was narrow, and the study group included only healthy volunteers (without additional factors potentially affecting the immune response). However, in immunocompromised populations, such as elderly patients or patients with chronic disorders known to affect the immune response, it is reasonable to exert caution when changing the HBV formula during vaccination and carefully monitor a response to vaccination. Another limitation of our study is that the results may be attributed only to certain preparations and their particular sequence within the schedule and cannot be generalized to all mixed regimens.

Although HBV vaccinations have been widely used for 30 years, there are still some controversies. Our study is the first to confirm the efficacy of the interchangeable use of 3 different preparations in the primary vaccination schedule, regardless of the dose and antigen subtype. In conclusion, primary vaccination against HBV with a schedule consisting of preparations of 3 different manufacturers is effective; however, the antibody response should be more carefully monitored owing to the distinct dynamics of antibody production.

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Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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