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Evaluation of a personalized, dose-sparing revaccination strategy in hepatitis B vaccine non-responders

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ABSTRACT

Objectives: The detection of low levels of antibodies against HBsAg (anti-HBs) below 10 IU/L in non-responders after a primary hepatitis B vaccination, is associated with seroconversion after revaccination. We compared the diagnostic performance of four anti-HBs assays in non-responders in their ability to differentiate between absence or presence of low levels of anti-HBs and propose a revaccination strategy guided by anti-HBs titres.

Methods: Non-responders were revaccinated with Fendrix 20 μg at 0, 1 and 2 months. Anti-HBs titres were determined by Abbott Architect, Diasorin Liaison, Roche Cobas and Siemens ADVIA Centaur. Inter-assay agreement was evaluated with Cohen's Kappa (k) in baseline samples between zero-responders without detectable antibodies and poor-responders with detectable antibodies < 10 IU/L. Seroconversion rates and geometric mean titres were analysed at 0, 1 and 3 months. A titre-based strategy (one revaccination dose and anti-HBs measurement followed by two more revaccination doses if required) was compared with the standard revaccination series of 3 doses.

Results: 57 participants were included in the analysis. k was ≥ 0.65 for all assays except ADVIA ($k \leq 0.41$). After one revaccination dose all assays detected a mean seroconversion rate in zero-responders of 42.9%, compared to 85.1% in poor-responders. The difference between zero- and poor-responders in seroconversion rate per assay was significant ($p < 0.05$). After three revaccination doses the mean seroconversion rate was 88.2% in zero-responders and 98.5% in poor-responders ($p > 0.286$ per assay). A titre-based strategy reduced the amount of revaccinations by 17% compared with the standard.

Conclusions: All assays demonstrated a comparable difference in seroconversion rate between zero- and poor-responders after one revaccination dose. The revaccination strategy could be optimised by differentiation between zero- and poor-responders followed by a titre-guided schedule.

1. Introduction

Vaccination is a safe and effective method of protection against a hepatitis B virus (HBV) infection. However, not all healthy adults develop a protective antibody response after primary vaccination series. This so-called non-response is defined as an antibody titre against HBsAg (anti-HBs) of less than 10 IU/L, measured 1–3 months after the last vaccination. Non-response occurs in 5–30% of healthy vaccine recipients and has been associated with several risk factors [1,2].

To overcome non-response after hepatitis B vaccination, several revaccination strategies have been studied: repeated vaccination, the use of vaccines with a higher antigen dose, a different adjuvant,

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or a more immunogenic antigen [3–7]. Already in the mid-eighties it was known that the height of the anti-HBs titre in non-responders after a primary vaccination series (primary non-responders) is associated with seroconversion rate to a protective anti-HBs titre $\geq$ 10 IU/L after revaccination [8]. In adults with no measurable anti-HBs after primary vaccination, the seroconversion rate after revaccination is remarkably lower than in adults with detectable antibodies below the cut-off of 10 IU/L. Although the effect of the pre-revaccination (baseline) anti-HBs titre was reproduced in several studies, the presence of detectable antibodies has not yet been implemented in a revaccination strategy in non-responders [9–11].

A potential barrier to implement this adaptation is the lack of knowledge on the performance of different commercial anti-HBs assays around the limit of detection (LOD). Studies have compared the quantitative performance of different anti-HBs assays and showed a large variation in titre values below 100 IU/L, with coefficients of variation ranging between 28% and 57% [12,13].

A reduction in number of revaccinations needed to reach seroconversion could lead to additional improvement of revaccination policy. The currently available improved revaccination schemes using higher antigen doses or more potent adjuvants could enable a one-dose revaccination schedule.

In this study we assessed the diagnostic performance of four commercial anti-HBs assays in their ability to differentiate between the presence or absence of hepatitis B antibodies below the titre of 10 IU/L. The clinical applicability of this differentiation was evaluated for a baseline titre-based revaccination strategy with either a one or three doses revaccination schedule, compared to the standard revaccination schedule.

2. Methods

Participant data and serum samples had been collected between 2012 and 2017 and were obtained from a previous multicentre trial, comparing the seroconversion rates of hepatitis B vaccine non-responders after three revaccination doses with three different hepatitis B vaccines [11,14]. Dutch National Trial Register (identifier NL3011). Non-response was defined as anti-HBs of less than 10 IU/L measured 4 weeks to 3 months after the last vaccination. Participants were healthy adult non-responders after one series of three hepatitis B vaccinations at 0, 1, and 6 months with either HBVaxPro-10 or Engerix-B vaccines. Further details on the methods of the multicentre trial have been published previously [11].

We selected sera of participants revaccinated with Fendrix 20 μg. Of the 124 participants who were assigned to the Fendrix-group, 112 were revaccinated with Fendrix 20 μg and met the criteria of the per-protocol analysis. Eighty-five gave consent for additional blood tests (Fig. 1). These participants had been revaccinated at 0, 1, and 2 months and serum samples were collected at 0, 1, and 3 months. Participants were excluded if any of the serum samples had insufficient volume for further analysis.

Prior to this study, samples had been analysed, after storage for several years at −20 °C, at the central trial laboratory (Leiden University Medical Center) with the Architect assay (Abbott Laboratories; Chicago, IL, USA) [11]. The additional analyses were performed on the Cobas (Roche Diagnostics, Mannheim, Germany), Liaison XL (DiaSorin, Saluggia, Italy) and ADVIA Centaur (Siemens Healthcare, Erlangen, Germany) assays in 2019. The central laboratory prepared and distributed the samples for analyses to the participating laboratories. All assays were performed according to the manufacturer's instructions. The effect of freeze-thaw cycles on IgG antibody titres is generally considered to be negligible as demonstrated in studies on IgG antibodies produced to several viruses [15–18].

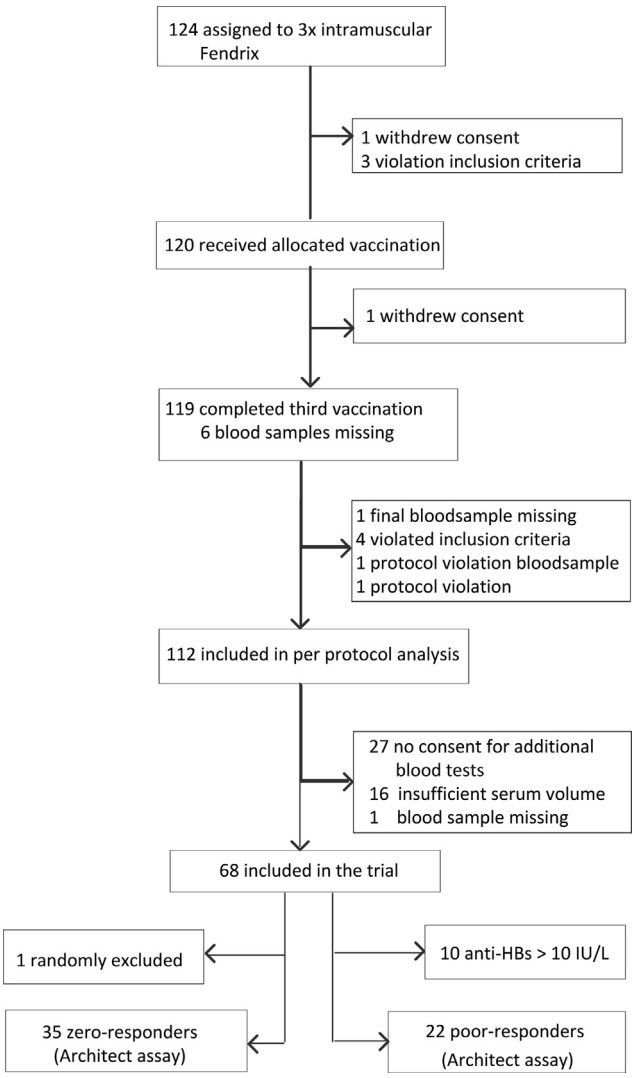

Fig. 1. Trial profile. Inclusion criteria were a revaccination series with Fendrix according to the criteria of the per-protocol analysis, written consent for additional blood tests, and sufficient serum volume for additional tests.

Participant were categorized as either zero- or poor-responder to the primary hepatitis B vaccinations according to the anti-HBs titres at baseline. Zero-response was defined as a baseline titre below the lower LOD. A baseline titre above the LOD but below 10 IU/L was defined poor-response. The LOD of the Architect, Cobas, Liaison, and ADVIA assay were respectively 0.98 IU/L, 2.0 IU/L, 3.0 IU/L and 3.1 IU/L. Titres below the LOD of a specific assay were given a value of half the LOD to be able to calculate the geometric mean titre (GMT). A 'true non-responder' was defined as a participant with a baseline anti-HBs < 10 IU/L on all four assays.

2.1. Outcome measures

Based on previous results [11], our hypothesis was that a single revaccination dose would suffice to induce seroconversion in poor-responders, whereas zero-responders would need three revaccination doses in order to induce the optimal seroconversion rate. This hypothesis was tested for all commercial anti-HBs assays, after

having calculated the agreement between the respective assays in categorizing participants as zero- and poor-responders.

Our hypothesis was tested by measuring the revaccination seroconversion rate of zero- and poor-responders after one and three revaccinations for each assay. Secondary endpoints were the number of revaccination doses and anti-HBs measurements needed, comparing the base-line anti-HBs titre-based strategy and the standard revaccination strategy. The standard revaccination strategy consisted of three revaccination doses with one anti-HBs measurement after the third revaccination. A titre-based strategy was a single revaccination dose for all poor-responders, an anti-HBs measurement, and two more vaccinations if necessary to acquire seroconversion. The zero-responders followed the standard revaccination strategy.

2.2. Ethical approval

The Dutch Central Committee on Research Involving Human Subjects (CCMO, NL36395.058.12) and the Medical Ethics Committee of Leiden University Medical Centre, Netherlands (LUMC) approved the previous multicentre trial of which participant data and serum samples originated. Participants were included after written consent for additional tests on the stored serum samples.

2.3. Statistical analysis

The sample size was calculated based on an expected 35% difference in seroconversion rate between the zero- (42.5%) and poor-responder (77.5%) group after one revaccination dose. This was based on the results acquired with the Architect analyser and previous literature [10,11]. Zhang et al reported that compared to those with an anti-HBs titer <2 mIU/ml (zero-responders) after primary vaccination, those with an antibody titer greater than 2 mIU/ml after primary vaccination had a higher seroconversion rate after the 1st dose of revaccination (38.36% vs. 78.10%, P < 0.001). Raven et al reported a 28% difference between zero- and poor-responders after three vaccinations. Based on these results we expected a difference of seroconversion of approximately 35 % between zero- and poor-responders after one revaccination dose. We also regarded an estimated effect size of 35% to be clinically relevant to justify a possible modification of the revaccination policy. The zero- and poor-responders, based on Architect baseline titers, were equally distributed among participants. To reach a power of 80% at a type 1 error rate of 5%, 32 participants were needed in each group. To compensate for a potential loss of samples, because of material or analytical problems, a margin of 10% was taken. The resulting target group size was 70 participants, equally distributed in 35 zero- and 35 poor-responders. Of the 68 participants eligible for inclusion for this study, 36 were categorised zero-responder and 32 poor-responder according to the Architect results. As only 35 zero-responders were required, one was randomly excluded of this study. A total of 67 participants were included for this study.

Because some baseline samples showed an anti-HBs titre $\geq$ 10 IU/L in one or more assays, all further analyses were performed on the samples with a baseline anti-HBs < 10 IU/L on all assays, the 'true non-responders'. Cohen's Kappa was used to analyse the agreement of the assays in zero- and poor-responder. For each assay the seroconversion rate was calculated based on its differentiation between zero- and poor-responder. A $\chi 2$ -test or a Fisher's Exact Test was used to assess the difference in response of the zero- and poor-responder groups of each assay. The comparison of the standard and titre-based revaccination schemes, was based on the difference in number of revaccinations and anti-HBs measurements. All statistical analyses were performed using SPSS software 24.0 (IBM, Armonk, NY, U.S.A.). The vaccination strategies were compared using Excel 16.0 (Microsoft, Redmond, U.S.A.).

3. Results

At baseline 10 of the 67 participants already had an anti-HBs of 10 IU/L according to one or more assays, other than the Architect assay that was initially used to determine the response. The categorisations between zero- or poor-responder by all assays is shown in Table 1. Of the 57 true non–responders, full agreement was met between all four tests in 36 persons, one test differed from the other three tests in 17 persons, and in four persons there was agreement between two tests only (supplementary table 2). Inter-assay agreement (k) ranged between 0.32 and 0.77 (Table 2). The agreement analysis of all 67 samples, showed an inter-assay agreement (k) ranging between 0.45 and 0.82 (supplementary table 1).

The anti-HBs GMTs in baseline samples of all assays ranged between 0.5 and 1.6 IU/L and 2.2–5.0 IU/L in zero-responders and poor-responders respectively. After one revaccination dose the mean seroconversion rate and GMTs of all assays in zero-responders were 42.9% and 11.8 IU/L respectively, compared to 85.1% and 86.8 IU/L in poor-responders. The seroconversion rate and GMT's ranged in zero-responders after one revaccination dose between 37.1% – 47.1% and 6.1 IU/L – 15.6 IU/L respectively depending on the assay. Poor-responders showed a seroconversion rate and GMT's that ranged between 81.0% and 100% and 61.4 IU/L-102.0 IU/L respectively (Fig. 2, Fig. 3, supplementary table 3, 4). Differences in seroconversion rate were significant after one revaccination dose between zero- and poor-responders for each assay ($p \leq 0.05$). After three revaccination doses the mean seroconversion rate was 88.2% (range 85.7–89.7%) in zero-responders and 98.5% (range 95.5% – 100%) in poor-responders. There was no significant difference in seroconversion rate after three revaccination doses between zero- and poor-responders for any of the assays ($p > 0.286$). See Fig. 2 and supplementary table 4.

The titre-based revaccination strategy was compared with a standard revaccination series based on the true non-responders. For 57 participants, the standard series would result in 171 vaccinations and 57 anti-HBs measurements. The titre-based strategy started with one revaccination dose for all poor-responders and three revaccination doses for the zero-responders. After one revaccination dose between 81.0% (Liaison) and 100% (ADVIA) of the poor-responders acquired protective antibodies. The poor-responders without protective antibodies, would then be given 2 more vaccinations and one additional anti-HBs measurement. This strategy resulted in a substantial reduction of the number of revaccinations in all assays except the ADVIA, ranging between 32 (19%, Liaison) and 36 (21%, Architect) compared to the standard revaccination strategy. The limited increase in the number of anti-HBs measurements for these assays ranged between 2 (3.5%) to 4 (7.0%). Using ADVIA, the titre-based revaccination strategy showed only a minor reduction of 12 vaccinations (7%) compared to the standard series, with no effect on the number of anti-HBs measurements.

4. Discussion

To overcome hepatitis B vaccine non-response multiple revaccination strategies have been studied [3–7]. To our knowledge, this study is the first study to assess the diagnostic performance of anti-HBs assays in the detection of antibodies in blood samples of primary non-responders and its application in a titre-based revaccination strategy. All assays, except the ADVIA, showed a substantial inter-assay agreement in categorising non-responders as

Table 1
Baseline characteristics according to Architect's distribution between zero- and poor-responders.

	Zero-responders (n = 35)	Poor-responders (n = 22)
Mean age, years (SD)	46.3 (12.0)	47.5 (12.1)
Sex, male (%)	22 (63%)	12 (55%)
Active smoking* (%)	9 (26%)	5 (23%)
Mean BMI,kg m^{-2}* (SD)	26.4 (4.2)	25.4 (4.1)
Diabetes* (%)	0 (0%)	3 (14%)
Median interval 3rd vaccine dose / primary titre measurement, weeks (IQR)	6 (4–6)	5 (5–6)
Categorization of anti-HBs result:		
Architect	35	22
Cobas	36	21
Liaison	39	18
ADVIA	51	6

*Missing information in 1 zero-responder on, active smoking, BMI and diabetes.

either zero- or poor responders and all assays showed a significant, clinically relevant difference in seroconversion rate after one revaccination dose between both categories. The titre-based revaccination strategy resulted in a substantial reduction of revaccination doses compared to the regular revaccination strategy. To enable this policy, laboratories should routinely quantify and report the anti-HBs result of a non-responder.

The ADVIA showed a higher threshold to categorise a sample as a poor-responder, resulting in a fair agreement with the other assays. The ADVIA uses a sensitive technique, based on antibody-capture microparticles and chemiluminescent detection. This can be advantageous in other assays. It may explain the high sensitivity of this assay in the lower ranges. The demonstrated differences don't seem to reflect the differences in LOD as reported by manufacturer's instructions, as the reported LOD's of the Liaison (3.0 IU/L) and ADVIA (3.1 IU/L) are similar.

After one revaccination dose, all assays demonstrated a similar significantly higher seroconversion rate in the poor-responder group compared to the zero-responders. Although the ADVIA categorised more participants as a zero-responder, this did not result in a different seroconversion rate in this category after one revaccination dose. After three revaccination doses there was no significant difference in seroconversion rate, regardless of the assay or baseline categorisation. Despite differences in agreement between assays the classification into zero-and poor-responders results in strikingly similar seroconversion rates within these two categories. The use of the LOD seems to be a reliable cutoff for all assays to differentiate in clinical practice between a zero- and poor-responder.

An effect of the baseline anti-HBs titre on revaccination response was first noted by Hadler and colleagues in 1986 [8]. However, that study demonstrated an almost 40% difference in seroconversion rate between zero- and poor-responders after three revaccination doses which was not reproduced in our study. The vaccine with an AS04 adjuvant (Fendrix 20 μg) used in our study compared to a plasma derived vaccine, could possibly explain the difference in percentage of responders. Our zero- and poor-responder response results with Fendrix are in line with the results of Zhang and colleagues who used two recombinant vaccines with 20 μg of HBsAg and a cut-off value of 2.0 IU/L on an Abbott assay [10]. Diagnostic performance in this low analytical range has been studied for six anti-HBs assays, of which three were also used in this study [13]. The coefficient of variation in the lowest analytical range was between 30% and 57% for samples with a mean anti-HBs of 6.4 IU/l and 2.1 IU/l respectively.

Comparing the standard three revaccinations scheme with a titre-based revaccination scheme, showed a substantial reduction of vaccinations with a limited increase in extra anti-HBs measurements. The titre-based revaccination strategy using the LOD as a cut-off can be safely introduced, as additional vaccinations can still be given if necessary to acquire immunity. After a primary vaccination series, the percentage of non-responders with a poor response ranged in previous studies between 42% and 54% [10,11]. This is a substantial percentage of the non-responders for which the titre-based revaccination strategy can be applied. In practice, the reduction of vaccinations by the titre-based revaccination scheme brings a financial benefit. This holds true in countries where hepatitis B serology is affordable and readily available. In many low- and middle-income countries, hepatitis B testing can be limited and costly compared to a hepatitis B vaccine, negating the added value of a titre-based revaccination strategy [19,20]. Finally, the reduction of revaccination doses shortens the time interval to determine seroprotection and could improve patient compliance, as multi-dose hepatitis vaccine adherence and completion in adults has been demonstrated to be suboptimal [21–23].

This study has some limitations. First, the categorisation into zero- or poor-responder based on the Architect's results included some samples that were classified as a responder by other assays used in this study. As we did not include these samples in the analysis, this did not affect our results. The other way round, if the initial inclusion of samples was not based on the Architect's results but on one of the other assays used, a sample that was classified as a responder could have been classified differently by one of the other assays. As the result of the Architect's anti-HBs titre quantification is in general slightly lower compared to other assays, making this misclassification unlikely. To reduce a possible misclassification into non-responder and responder, the ADVIA assay recommends retesting in duplicate in case of test results between 7.5 and 12.4 IU/L. If two out of three test results agree, this is considered the final test result. By following this procedure, the amount of responders that become non-responders or vice versa by retesting, can be reduced.

Second, the titre-based revaccination strategy introduced in this study is based on a single revaccination dose with a highly immunogenic vaccine. This vaccine is registered for use in patients with end-stage renal disease, but it has been used in healthy adults without serious adverse events. However this revaccination strategy is likely to be applicable to other types of vaccines, as a difference in proportion of responders between zero- and poor-responders after one revaccination dose has also been demonstrated with other vaccines in previous trials [9–11]. Third, few studies documented long-term protection after revaccination resulting in a titre of 10 IU/L or more compared with the well-

Table 2
Inter-assay agreement (Cohen's Kappa) based on the categorisation of the true non-responder participants (n = 57) as either zero- or poor-responders.

Test system	Architect	Cobas	Liaison	ADVIA
Architect		0.66 (0.56–0.77)	0.77 (0.68–0.86)	0.32 (0.21–0.42)
Cobas	0.66 (0.56–0.77)		0.65 (0.54–0.76)	0.34 (0.23–0.45)
Liaison	0.77 (0.68–0.86)	0.65 (0.54–0.76)		0.41 (0.28–0.53)
ADVIA	0.32 (0.21–0.42)	0.34 (0.23–0.45)	0.41 (0.28–0.53)	

k (95% CI).

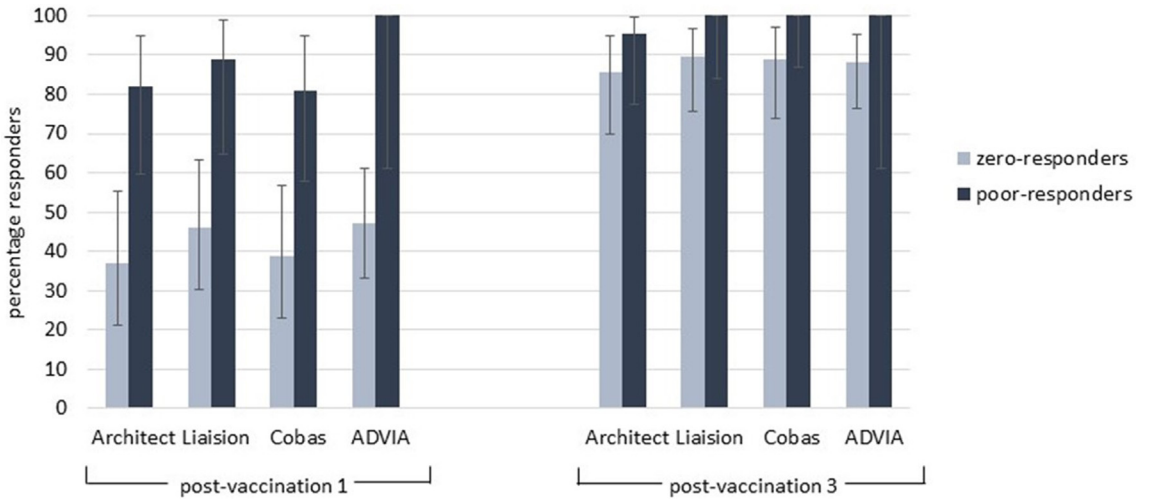

Fig. 2. Per assay zero- and poor-responder revaccination seroconversion rates (%) after one and three revaccinations in previous true non-responders (n = 57).

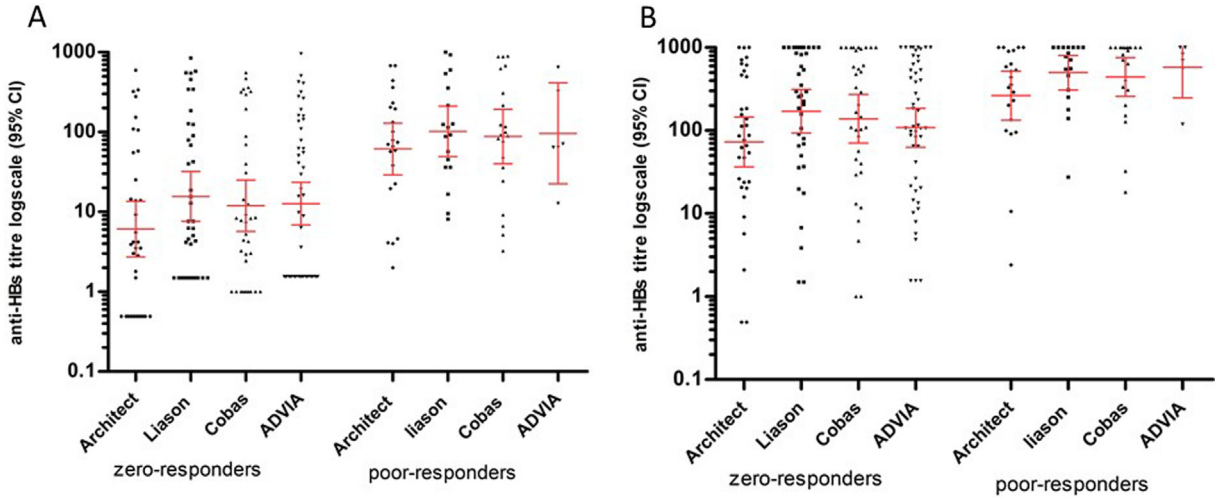

Fig. 3. Geometric mean titres of serum anti-HBs titres in IU/L in zero-responders and poor-responders after one (A) and three (B) revaccinations. Dots represent individual anti-HBs titres and bars represent the geometric mean titres and 95% CIs per assay.

established evidence originating from long-term follow-up studies of primary vaccination series [24–26].

In conclusion, this study demonstrates that differentiation between zero- and poor-responders based on the baseline anti-HBs titre of primary non-responders is possible using multiple commercial anti-HBs assays. The titre-based revaccination strategy results in a substantial reduction of revaccination doses needed to induce a protective anti-HBs titre, compared to the regular revaccination strategy. As this strategy is accompanied by only a marginal increase in additional serology tests it could be used for a more efficient revaccination strategy in hepatitis B non-responders.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GlaxoSmithKline and Merck Sharp & Dohme provided the vaccines used in the trial from which we obtained the participant data and serum samples for this study. Neither manufacturer was involved in the study design, data collection, data analysis, interpretation of the results, or writing of the report.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.04.042.

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