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Diagnostic performance of serological assays for anti-HBs testing: Results from a quality assessment program

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ABSTRACT

Background: Post-vaccination testing after hepatitis B vaccination is indispensable to evaluate long-term immunological protection. Using a threshold level of antibodies against hepatitis B surface antigen (anti-HBs) to define serological protection, implies reproducible and valid measurements of different diagnostic assays.
Objectives: In this study we assess the performance of currently used anti-HBs assays.
Study design: In 2013, 45 laboratories participated in an external quality assessment program using pooled anti-HBs serum samples around the cutoff values 10 IU/l and 100 IU/l. Laboratories used either Axsym (Abbott Laboratories), Architect (Abbott Laboratories), Access (Beckman-Coulter), ADVIA Centaur anti-HBs2 (Siemens Healthcare Diagnostics), Elecsys, Modular or Cobas (Roche Diagnostics) or Vidas Total Quick (Biomerieux) for anti-HBs titre quantification. We analysed covariance using mixed-model repeated measures. To assess sensitivity/specificity and agreement, a true positive or true negative result was defined as an anti-HBs titre respectively above or below the cutoff value by ≥4 of 6 assays.
Results: Different anti-HBs assays were associated with statistically significant ($P < 0.05$) differences in anti-HBs titres in all dilutions. Sensitivity and specificity ranged respectively from 64%-100% and 95%-100%. Agreement between assays around an anti-HBs titre cutoff value of 10 IU/l ranged from 93%-100% and was 44% for a cutoff value of 100 IU/l.
Conclusions: Around a cutoff value of 10 IU/l use of the Access assay may result in false-negative results. Concerning the cutoff value of 100 IU/l, a sample being classified below or above this cutoff relied heavily on the specific assay used, with both the Architect and the Access resulting in false-negative results.

1. Background

The lack of global hepatitis B virus (HBV) vaccination coverage, the absence of sufficient protection in part of the vaccinees and the failure of protection in 10–30% of newborns from highly viremic mothers results in ongoing global transmission of hepatitis B [1,2]. The cornerstone in prevention of hepatitis B infection and the long-term sequelae is immunisation [1]. In 1983, a safe and effective vaccine was introduced, which uses hepatitis B-surface antigen to stimulate the production of protective antibodies. To date approx-

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imately 180 countries have adopted the WHO recommendation of universal childhood vaccination with global vaccination coverage in children of 84% [3,4].

The majority of healthy vaccinees develop a protective antibody response, defined by most countries as an anti-hepatitis B surface antigen (anti-HBs) titre of >10 IU/l, measured 1–3 months after last vaccination [5–7]. Some countries apply an anti-HBs titre >100 IU/l as indication of long-term protection [8,9]. 5–30% of immunocompetent adults fail to develop an anti-HBs titre exceeding 10 IU/l [10]. Well-known risk factors for non-response in healthy persons are obesity, advanced age, male gender, smoking, and genetic predisposition [11–13]. Immunocompromised patients and patients with renal insufficiency are at increased risk of non-response as well [14]. Serological testing for protective immunity is not routinely performed. However, post-vaccination testing is strongly recommended for persons whose subsequent clinical management, including revaccination strategy or post-exposure prophylaxis, depends on knowledge of their immune status. This includes persons with an occupational or non-occupational (e.g. high risk sexual behavior) risk of HBV infection and for immunocompromised persons with an increased risk of severe hepatitis B [15–18]. Additionally, this recommendation applies to persons at increased risk of the previously mentioned vaccination non-response against HBV [10].

Different commercially available diagnostic assays are used to measure the anti-HBs-titre. Since transmission risk-assessment and corresponding policy rely on specific anti-HBs cutoff values, standardisation of anti-HBs assays is of great importance. In most commercial automated assays a WHO International Standard is now used for calibration of the anti-HBs assay [19]. The currently available assays should at least be able to accurately and reproducibly measure anti-HBs cutoff values of 10 or 100 IU/l. However, different studies in the past have raised doubts about this assumption [8,20].

2. Objectives

In this study we aim to assess the performance of currently used and commercially available anti-HBs diagnostic assays using data from 45 laboratories participating in an anti-HBs external quality assurance program.

3. Study design

To achieve standardisation among laboratories in the industrialised world and to support the quality of measurement procedures, laboratories participate in external quality assurance (EQA) programs. Data for this study were obtained from the EQA program 'anti-HBs screen' organised by the Dutch Foundation for Quality Assessment in Medical Laboratories (SKML) during three different test rounds in 2013.

3.1. Test samples

One SKML laboratory prepared the different test samples for all laboratories and collected all test results of participating laboratories. Pooled anti-HBs serum originated from a mixture of various positive anti-HBs sera, most probably consisting of mixed serum from both vaccinees as well as patients infected with HBV. The negative samples were made by using pooled anti-HBs negative serum.

The serum pool was diluted to various dilutions that were distributed in various combinations in three different test rounds. These serial dilutions were split in identical test samples of which one was sent to each participating laboratory. Not every laboratory participated in each test round. We analysed the quantitative results of selected dilutions 1:512, 1:128, 1:64, 1:8 and 1:4 besides the negative sample for anti-HBs, which represented anti-HBs results around the cutoff values 10 IU/l and 100 IU/l. The number of different anti-HBs assays per sample dilution are provided in Supplementary Table 1. This resulted in a total of 494 anti-HBs measurements. Sample results were collected in a coded manner and outcomes were reported in a standardised manner (IU/l). An anti-HBs result that was not quantified around the lower limit of detection, was arbitrarily assigned a value half of the lower limit of detection (e.g. anti-HBs < 10 IU/l was recoded to an anti-HBs titre of 5 IU/l). According to Dutch legislation this study did not need an ethics approval.

3.2. Anti-HBs assay systems

45 laboratories (37 Dutch and 8 participants from outside the Netherlands) participated in the EQA program. Excluded were those laboratories that did not specify the manufacturer or test method used (two laboratories) or used an assay not in use in any other laboratory (Enzygnost, Dutch laboratory). We included 42 laboratories and the participating laboratories used either Axsym (Abbott Laboratories), Architect (Abbott Laboratories), Access (Beckman-Coulter), ADVIA Centaur anti-HBs2 (Siemens Healthcare Diagnostics), or Vidas Total Quick (Biomerieux) assay system for anti-HBs titre quantification (Table 1). One of the following three assays from Roche Diagnostics was used without separate registration; Elecsys, Modular or Cobas. However as all assays from Roche diagnostics used a same kit applicable to these assays (Anti-HBs), results were taken together in further analysis. 38 laboratories made use of one and 4 laboratories of two assays to determine anti-HBs titres.

3.3. Statistical analysis

Primary outcome measure was the anti-HBs titre. The mean anti-HBs titre and the coefficient of variation (CV) were calculated for each sample separately. The CV was excluded for the negative sample as this is based on a mean titre close to zero and therefore less meaningful.

Analysis of covariance using mixed-model repeated measures with test round and test method (assay) as fixed effects was carried out to assess quantitative differences between test methods. Using the mixed-model (random intercept with two levels; measurements within specific test methods), we were able to take together results from the same dilutions from different rounds, thereby increasing our number of results.

For the assessment of agreement and sensitivity/specificity a true positive or true negative result was defined as an anti-HBs titre respectively above or below the cutoff value by $\geq$4 of 6 assays. Performance of anti-HBs results are presented in each dilution as a percentage agreement of assays compared to the true positive or negative value.

Statistical analysis was performed using SPSS version 22 (IBM Corp; Armonk, NY, USA).

4. Results

Results of the serial dilutions from the pooled sera for different assay systems are shown in Figs. 1 and 2. Mean anti-HBs results are shown for each sample by different assay systems. The Access assay reported anti-HBs titres below <10 IU/l for dilution 1:64 sample, while all five other assays had results above the cutoff (Fig. 1).

Sensitivity and specificity ranged respectively from 64%–100% and 95%–100% (Table 2).

Table 1
Source and type of antigen used as a reagent (human/recombinant) in anti-HBs assays.

Anti-HBs assay[a]	Antigen	No. of laboratories[b]/no. of assays
Access (Beckman-Coulter)	Human (ad/ay)	3/3
ADVIA Centaur (Siemens Healthcare Diagnostics)	Human (ad/ay)	3/3
Elecsys —Cobas –Modular (Roche Diagnostics)	Human (ad/ay)	10/10
Architect (Abbott Laboratories)	Recombinant; E. coli (ad/ay)	20/22
AxSYM (Abbott Laboratories)	Recombinant; L. mouse cell (ad/ay)	6/6
Vidas (Biomerieux)	Inactivated plasma (ad) and recombinant (ay)	2/2

[a] All assays were calibrated against the 1 st International Reference Preparation WHO 1977.
[b] The same laboratory could use more than one assay, resulting in 44 laboratories representing only 42 unique laboratories.

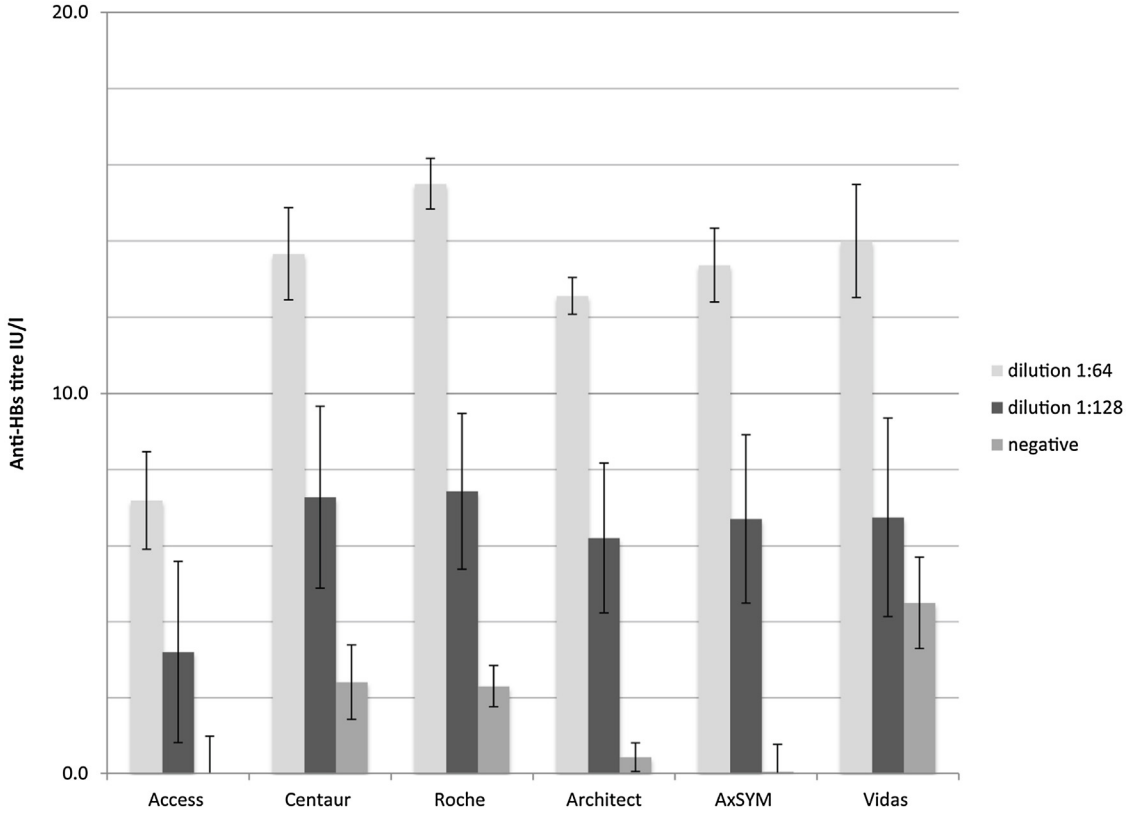

Fig. 1. Mean anti-HBs results (95% CI) of different dilutions repeatedly analysed with different test methods.

Table 2
sensitivity and specificity calculated for different assays compared to an anti-HBs titre cutoff of 10 IU/l and 100 IU/l.

Test assay	Sensitivity% ([a])		Specificity% ([b])	
	10 IU/l	100IU/l	10 IU/l	100 IU/l
Architect	99 (1/94)	69 (18/58)	100 (0/133)	100 (0/169)
Vidas	100 (0/10)	100 (0/6)	100 (0/14)	100 (0/18)
ADVIA Centaur	100 (0/15)	100 (0/9)	95 (1/21)	100 (0/27)
Roche	100 (0/48)	100 (0/28)	100 (0/68)	100 (0/88)
AxSYM	100 (0/23)	93 (1/14)	100 (0/33)	100 (0/42)
Access	64 (5/14)	67 (3/9)	100 (0/21)	100 (0/26)

[a] 100–(No. false-negative/total no. of true positive samples (at least 4 of 6 assays anti-HBs ≥10 IU/l or ≥ 100IU/l)) × 100.
[b] 100–(No. false-positive/total no. of true negative samples (at least 4 of 6 assays anti-HBs <10 IU/l or <100 IU/l)) × 100.

Table 3
Number of assays providing results in categories of anti-HBs titres based on cutoff value of 100 (IU/l) with dilution 1:8 (N = 39).

Test assay	1–9 (IU/l)	≥10–99 (IU/l)	≥100 (IU/l)	Agreement[a]
Architect	–	18	0	0%
Vidas	–	0	2	100%
ADVIA Centaur	–	0	3	100%
Roche	–	0	9	100%
AxSYM	–	1	3	75%
Access	–	3	0	0%

[a] percentage agreement compared to the true positive value in sample 1:8 with an anti-HBs titre cutoff ≥100(IU/l).

Percentage agreement of each assay compared to the true negative value (negative sample, dilution 1:512 and 1:128) and the true positive value (dilution 1:64) with an anti-HBs titre cutoff ≥10 IU/l resulted in respectively 100%, 100%, 99% and 93%. In dilution 1:8 the percentage agreement compared to the true positive value with an anti-HBs titre cutoff ≥100(IU/l) dropped to 44% (Supplementary Table 2). Agreement within an assay was remarkably consistent for this sample, except for AxSYM (Table 3). Agreement compared to the true positive value for all assays was met for the 1:4 sample.

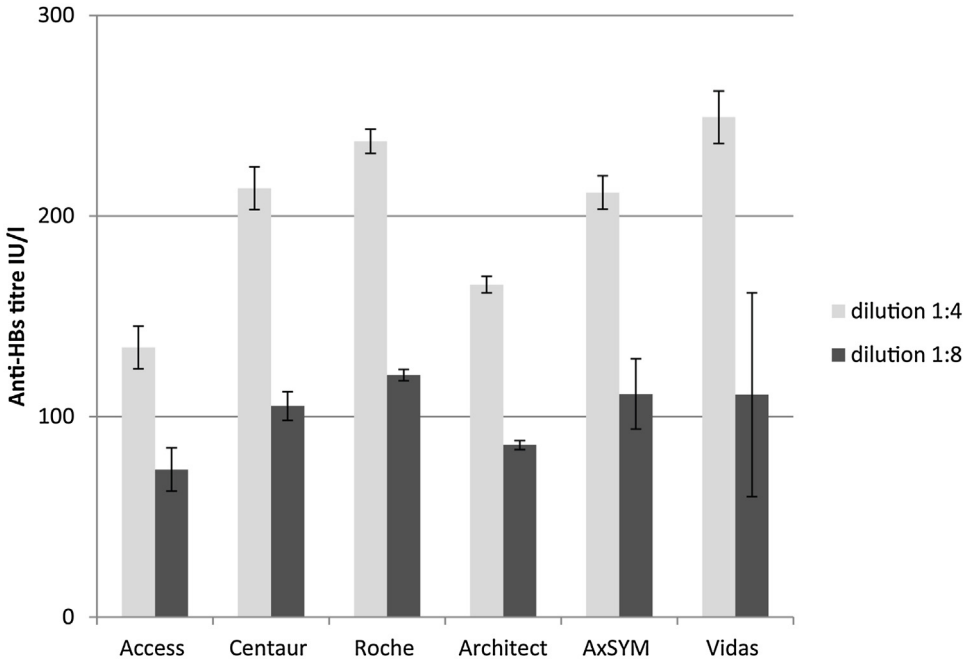

Fig. 2. Mean anti-HBs results (95% CI) of diluted sample 1:4 and 1:8 repeatedly analysed with different test methods.

Table 4
Descriptive statistics of all anti-HBs results per dilution and results of mixed-model repeated measures with test round and test method as fixed effects (N = 494).

Sample (N)		Anti- HBs Mean (SD) (IU/l)	Anti- HBs Range (IU/l)	Coefficient of variation (%)	Fixed effect *P*- value	
					test method	test round
Negative	123	1.1 (1.5)	0.0–5.0	–	<0.05	0.60
1:512	83	2.1 (1.2)	0.0–5.0	57%	<0.05	0.69
1:128	84	6.4 (1.9)	0.0–10.8	30%	<0.05	0.81
1:64	80	13.2 (2.3)	6.0–18.1	17%	<0.05	0.19
1:8	39	98.4 (17.5)	71.0–126	17%	n.a.*	n.a.
1:4	85	192 (37.7)	127–263	20%	<0.05	0.58

SD: standard deviation. Range: Range of anti-HBs measurements are minimum and maximum values.
* n.a.: not applicable, measurements available of one test round and therefore not suitable for a mixed model.

Table 4 shows the mean anti-HBs titres from all serological assays for each of the six different dilutions. The coefficient of variation (CV) ranged from 57% to 17%. The CV was in general lower in less diluted samples (i.e. 1:4, 1:8 and 1:64) with consequently higher anti-HBs titres.

In our mixed model only 'test method' was statistically significant ($P < 0.05$) on the outcome of anti-HBs titre. Adding a third level 'laboratory' next to specific test method and measurements in our mixed model did not have an impact on random effects and was therefore left out of the model.

5. Discussion

To achieve standardisation among laboratories and to support the quality of measurement procedures laboratories participate in external quality assurance (EQA) programs. Results of EQA 'anti-HBs screen' used in this study confirm quantitative differences between assays as previously have been described [8,20–25]. The mean coefficient of variation (CV) was 28% (range 17%–57%) and lower than the CV of another study comparing nine anti-HBs assays with a mean CV of 47.1% (range 15%–201%) [8]. An explanation for the difference in CV could be the more diverse anti-HBs samples originating from individuals instead of pooled serum samples. In our study pooled samples probably consisted of a mixture of antibodies originating from vaccinees and infected HBV patients. Huzly et al. concluded that anti-HBs levels determined by one assay cannot be compared with those by other systems. Results from our mixed model confirmed that a different test method was statistically significant as a variable to explain differences in anti-HBs titres.

Quantitative differences between test assays will be inevitable to some extent. More important are differences in performance in relation to clinically relevant cutoff values, being that of 10 IU/l as a correlate of protection and that of 100 IU/l as a differentiator for risk of chronic, contagious, hepatitis B virus (HBV) [26]. Dilutions around the cutoff value of 10 IU/l (i.e. 1:64 and 1:128) showed solely in the 1:64 dilution a percentage agreement lower than 95%. The Access assay reported anti-HBs titres below 10 IU/l in the 1:64 dilution, compared to five other assays that had results above the cutoff value. These Access results may be regarded as false-negative taking the other assay results into account. A study in 2002 reported samples from Engerix-B vaccinees with anti-HBs levels up to 150 IU/l in AxSYM and Architect assays to appear sometimes negative in Access [20]. In a direct comparison between Access and AxSYM assays of 1207 samples, 51 (4.2%) samples were discrepant and of 369 true positive samples, 8 samples (2%) remained false-negative by Access assay after retesting [24]. A false-negative outcome may result in unease concerning an erro-

neous lack of immunity against HBV, additional testing to rule out a HBV infection and unnecessary revaccination. Luckily a possible false-negative result is less harmful than a false-positive outcome, as the superfluously administration of vaccination or administration of immunoglobulins is less potentially harmful than falsely refraining of additional protective measurements against HBV. A false-positive anti-HBs result is worrisome as this may result in clinically apparent HBV infection or chronic HBV infection. Fortunately clinically important breakthrough HBV infections after vaccination are rare and mainly described in case reports and point to primary vaccine failure (anti-HBs < 10 IU/l), escape-mutant HBV strains and waning immunity as explanations of infection [27–29].

Differences of the anti-HBs assays have led to the advice of Huzly et al. to raise the current cutoff values in order to prevent false-positive outcomes [8]. Several national advisory groups on immunisation, a.o. Germany and The United Kingdom, adopted this recommendation, maintaining the cutoff value for complete protection at 100 IU/l [15,16]. Hardly any false-positive results were seen in our data. However, the use of pooled serum samples instead of individual samples may have led to less diverse anti-HBs results. In other countries this elevated cutoff is only applied in a specific group of healthcare workers (HCWs) with an occupational risk of hepatitis B, that are also at risk of transmitting HBV to patients during the performance of exposure prone procedures. The anti-HBs titre cutoff is raised for these HCWs to ≥100 IU/l to minimise risks of erroneously suggesting immunity with absence of HBV infection. Above this cutoff the risk of a HCW with concurrence of anti-HBs antibodies and a HBV carrier state is minimal [26–30]. Concerning this second cutoff value the performance of the different assays could be compared using the 1:8 sample which had a mean anti-HBs titre of 98.4 (IU/l). In this sample the agreement was 44% between different assays. A sample being classified below or above this cutoff relied heavily on the specific assay used, with both the Architect and the Access resulting in false-negative results.

Various authors have offered possible explanations for differences in anti-HBs titres between assays, for example differences in vaccine antigens used to elicit antibodies against HBsAg, diversity of individual immune response, interference with other substances or a matrix effect [20–24]. In our study, samples were derived from pooled serum, which may not be fully comparable to single human sera. On the other hand, because the composition, the matrix and possible interfering substances in the samples are the same, the assays may be compared. It is however possible that different types of assays react differently on the same matrixes or substances. Use of a different International Standard for hepatitis B immunglobulin may have a minor influence on anti-HBs results [19]. As all assays were calibrated against the 1st International Reference Preparation this cannot explain any differences in anti-HBs results.

A final explanation for differences between assays could be the differences in HBsAg antigen, serotype and source, used as a test reagent [21]. One study concluded that discrepancies between assays were depending on the combination of antigen in vaccine and antigen in the assay used [20]. However, two more recent studies do not support this hypothesis, since assays using the same antigen still showed large discrepancies and minimal differences existed with assays using different antigens [8,19]. Indeed, results by Access were below a cutoff titre of 10 IU/l and 100 IU/l in respectively dilution 1:64 and 1:8, whereas results by ADVIA Centaur and Roche were above the cutoff, all using the same HBsAg antigen (ad ay) from human origin (Table 1). However, one cannot rule out that a different antigen production, purity and concentration could possibly explain differences in anti-HBs results.

Detailed information was lacking on the origin of the pooled serum samples, probably consisting of a mixture of antibodies originating from vaccinees and infected HBV patients. Consequently this limits the external validity of our results to a specific situation of measuring antibodies against HBsAg after vaccination or HBV infection. In future research it is preferable to test assays from a known serum pool or from individual blood donations collected after vaccination with a recombinant vaccine or collected after HBV infection. Anti-HBcore status of samples (positive or negative) did however not influence the CV of anti-HBs titres in a previous study [8].

In earlier studies, detailed information was lacking on the number of assays that were compared within a laboratory. If only one laboratory per type of assay was used, it leaves the possibility that differences did not result from differences between assays but from differences between laboratories. Adding laboratories as another level in our mixed model did not change our results, which indicates that the influence of a specific laboratory on anti-HBs results is negligible. However because of the small number of four laboratories testing samples with more than one assay, we may not have been able to detect a possible difference.

This study confirms an influence of different anti-HBs assay systems on quantification of anti-HBs titres around clinically important cutoff values. Concerning the cutoff value 10 IU/l use of the Access assay may result in false-negative results. Around a cutoff value of 100 IU/l, a sample being classified below or above this cutoff relied heavily on the specific assay used, with both the Architect and the Access resulting in false-negative results.

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Competing interests

None declared.

Ethical approval

Not required.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2016.12.002.

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