Evaluation of algorithms for the diagnostic assessment and the reentry of blood donors who tested reactive for antibodies against hepatitis B core antigen

David Juhl, Jürgen Luhm, Siegfried Görg, Malte Ziemann, and Holger Hennig

BACKGROUND: Screening of blood donations for antibodies against hepatitis B core antigen (anti-HBc) is an accepted method to prevent some transfusion-transmitted hepatitis B virus (HBV) infections. However, anti-HBc testing may result in donor loss due to unspecific results in the currently available anti-HBc tests. Algorithms to distinguish true-positive from false-positive results and for reentry of those donors who tested false anti-HBc positive were evaluated retrospectively.

STUDY DESIGN AND METHODS: Samples that tested reactive for anti-HBc by chemiluminescent microparticle immunoassay (CMIA) were investigated for anti-HBc by microparticle immunoassay, for anti-HBs and hepatitis B surface antigen (HBsAg) by CMIA, and for HBV DNA by individual-donor nucleic acid testing. Results were classified true positive, indeterminate, and false positive for anti-HBc. Donors who tested indeterminate and false positive were admitted for reentry if follow-up testing for anti-HBc became negative and no further evidence for an HBV infection was apparent.

RESULTS: A total of 554 of 148,000 samples, taken from 30,000 individuals within 3 years tested reactive for anti-HBc by CMIA. Of those, 553 could be further classified: 142 (26%) true positive, 76 (14%) indeterminate, and 335 (60%) false positive. A total of 214 of 411 (52%) samples termed indeterminate or false positive were admitted for reentry and able to provide further donations. In one donor, anti-HBc–positive/HBsAg- and HBV DNA–negative HBV DNA was detectable during follow-up.

CONCLUSION: According to our proposed algorithm, 26% of anti-HBc–reactive results tested by CMIA were true positive. Many donors tested indeterminate or false positive can provide future donations if our proposed algorithm for reentry is applied. One donor at risk for transmitting HBV was identified solely by anti-HBc testing.

First-generation hepatitis B surface antigen (HBsAg) assays were implemented in blood donor screening in the early 1970s to avoid transfusion-transmitted hepatitis B virus (HBV) infections and although their sensitivity increased continuously,[1] transfusion-transmitted HBV infections were still reported.[2,3] This fact might occur due to several reasons: first taking donations from individuals in the very early phase of the HBV infection;[4] second, after disappearance of detectable HBsAg in a not definitely resolved, late HBV infection (called low-level carrier or occult HBV infection[5,6]); or third, due to new HBsAg mutants, which cannot be recognized despite using sensitive HBsAg assays,[7] also called occult HBV infection.

Miscellaneous reports[8,9] gave evidence that antibodies against hepatitis B core antigen (anti-HBc) testing of blood donors is a simple precautionary measure in preventing transfusion-transmitted HBV infections because in both settings of occult HBV infection, anti-HBc is detectable. Occult HBV infection is responsible for transfusion-transmitted HBV infection in many of those cases in whom no HBsAg is detectable.[8,10]

Thus, testing of blood components for anti-HBc was recommended by the Food and Drug Administration (FDA)[11] already in 1991 and was enacted by the Paul-Ehrlich Institute (PEI), the German national authority, in 2006.[12]

ABBREVIATIONS: CMIA = chemiluminescent microparticle immunoassay; MEIA = microparticle enzyme immunoassay; PEI = Paul-Ehrlich Institute; S/CO = sample-to-cutoff ratio.

From the Institute of Transfusion Medicine, University Hospital of Schleswig-Holstein, Lübeck, Kiel, Germany.

Address reprint requests to: David Juhl, MD, Institute of Transfusion Medicine, University Hospital of Schleswig-Holstein, Ratzeburger Allee 160, 23538 Lübeck, Germany; e-mail: david.juhl@uk-sh.de.

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Although an improvement in transfusion safety is to be expected after performing anti-HBc testing, problems with anti-HBc testing are remaining: the relative poor specificity of the several anti-HBc assays yields in a considerable donor loss,[13] all the more because no accepted confirmation test is defined. The FDA[11] recommended an indefinite donor deferral, if the anti-HBc test is repeatedly reactive on a second occasion. In contrast, the directive of the PEI permits further donations, but only if a donor tested repeatedly reactive for anti-HBc presents both no detectable HBV DNA proved by sensitive individual-donor nucleic acid testing (NAT) with a lower limit of detection of at least 12 IU/mL and an anti-HBs titer above 100 IU/L,[12] irrespective of whether the donor presents a history of vaccination or a history of subsided HBV infection. However, neither the FDA nor the PEI gave recommendations how to differentiate a repeatedly reactive anti-HBc result as true or false positive, and quite recently, the FDA gave recommendations[14] on how to admit a donor who tested false positive on one occasion to future donations.

The performance characteristics of several anti-HBc assays have been evaluated in two reports,[15,16] and in this context, algorithms for the confirmation of a true-positive anti-HBc result were proposed. However, these algorithms seem somewhat cumbersome as their performance requires numerous further HBV tests.[15]

The aims of our study were to evaluate 1) the performance of the Abbott ARCHITECT anti-HBc assay in the blood donor screening, 2) an algorithm for simply distinguishing true from false positive, and 3) an algorithm, different from those proposed by US or German authorities, respectively, which allows future donations despite having tested anti-HBc false positive on more than one occasion and thereby diminishing donor (and donation) loss.

MATERIALS AND METHODS

The Institute of Transfusion Medicine of the University Hospital of Schleswig-Holstein in northern Germany comprises two sites, one located in Lübeck and one in Kiel. In Lübeck, since 1997 all donors were initially tested for HBsAg (Ortho antibody to HBsAg enzyme-linked immunosorbent assay test system 3, Ortho-Clinical Diagnostics, Neckargemünd, Germany) and for anti-HBc by (competitive) microparticle enzyme immunoassay (MEIA, Abbott AxSYM Core, Abbott GmbH & Co. KG, Wiesbaden, Germany) before their first donation (so-called donor candidates). They were admitted to the first donation only if they tested negative for both aforementioned serologic variables. Donors who tested positive for anti-HBc were rejected from donation. In Kiel, the initial serologic investigation was performed routinely at the first donation without anti-HBc testing until April 2006.

Since May 2006, samples taken at both sites from all regular blood donations (whole blood and plateletpheresis) and from donor candidates were screened for anti-HBc and HBsAg by chemiluminescent microparticle immunoassay (CMIA, Abbott ARCHITECT anti-HBc and HBsAg, Abbott GmbH & Co. KG) in Lübeck. Screening for HBV DNA was performed by NAT (COBAS AmpliPrep/COBAS TaqMan HBV test, Roche Diagnostics GmbH, Mannheim, Germany; 95% detection limit, 12 IU HBV DNA/mL pool plasma) on minipools containing up to 96 samples. Plasma specimens of donor candidates were not screened by minipool NAT routinely.

Samples that tested reactive in the (noncompetitive) CMIA were tested again twice with the same method. If they tested repeatedly reactive, donations were abolished and samples were subjected to supplemental testing by anti-HBc MEIA (Abbott AxSYM Core), by testing and quantification for antibodies against HBsAg (Abbott ARCHITECT anti-HBs) and by individual-donor NAT (COBAS AmpliPrep/COBAS TaqMan HBV Test, Roche Diagnostics).

All tests were strictly performed in compliance with the manufacturers' recommendations, and plasma supernatant for NAT was removed within 18 hours after venipuncture. The overall classification (true positive, indeterminate, false positive) of the various supplemental test results are given in Fig. 1.

All donors who tested reactive by CMIA were requested for a follow-up visit within the subsequent 2 weeks to obtain an additional blood sample for reconfirmation of the initial test result and to obtain data about previous vaccination or a history of resolved HBV infection, if a sample had been tested reactive for anti-HBs too. All follow-up samples were tested again for anti-HBc by CMIA and MEIA and for anti-HBs, for HBsAg, and for HBV DNA by individual-donor NAT (Fig. 2).

Donors presenting a false-positive result and donors characterized as indeterminate were approved to further donations (reentry) if both anti-HBc tests, CMIA and MEIA, became nonreactive in the follow-up testing. If those donors presented a test result termed false positive or indeterminate again, a further follow-up sample was acquired within 6 months, and, if results were unchanged anew, within 2 years for reconsideration whether a reentry was possible (Fig. 2).

In donors with prior negative anti-HBc tests, who were considered true positive or indeterminate in the first follow-up sample also, an archive sample of the previous, anti-HBc–negative donation was investigated by individual-donor NAT to rule out an HBV transmission by an early HBV infection. By database query, all donations and donor candidates tested repeatedly reactive for anti-HBc by CMIA within a 3-year period ranging from July 2006 through June 2009 were identified and evaluated retrospectively.

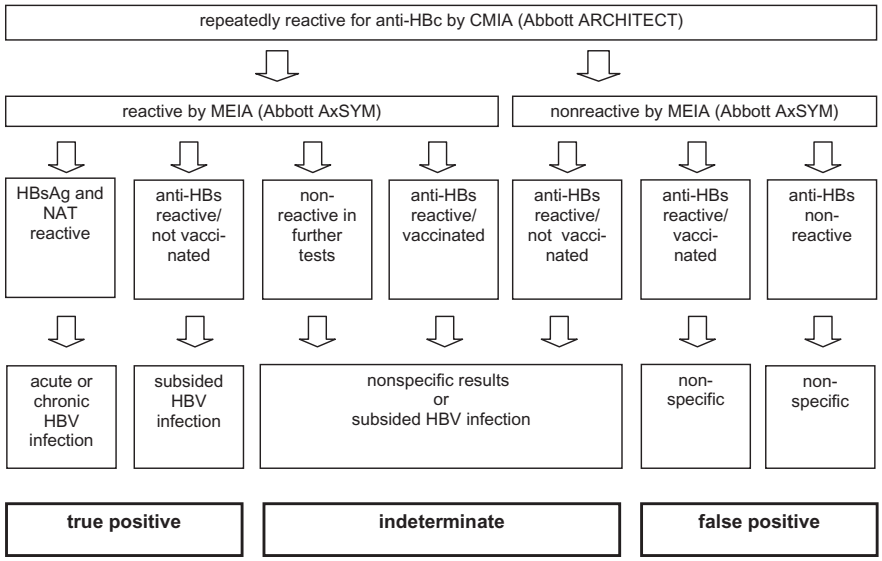

Fig. 1. Classification of the various anti-HBc confirmation test results.

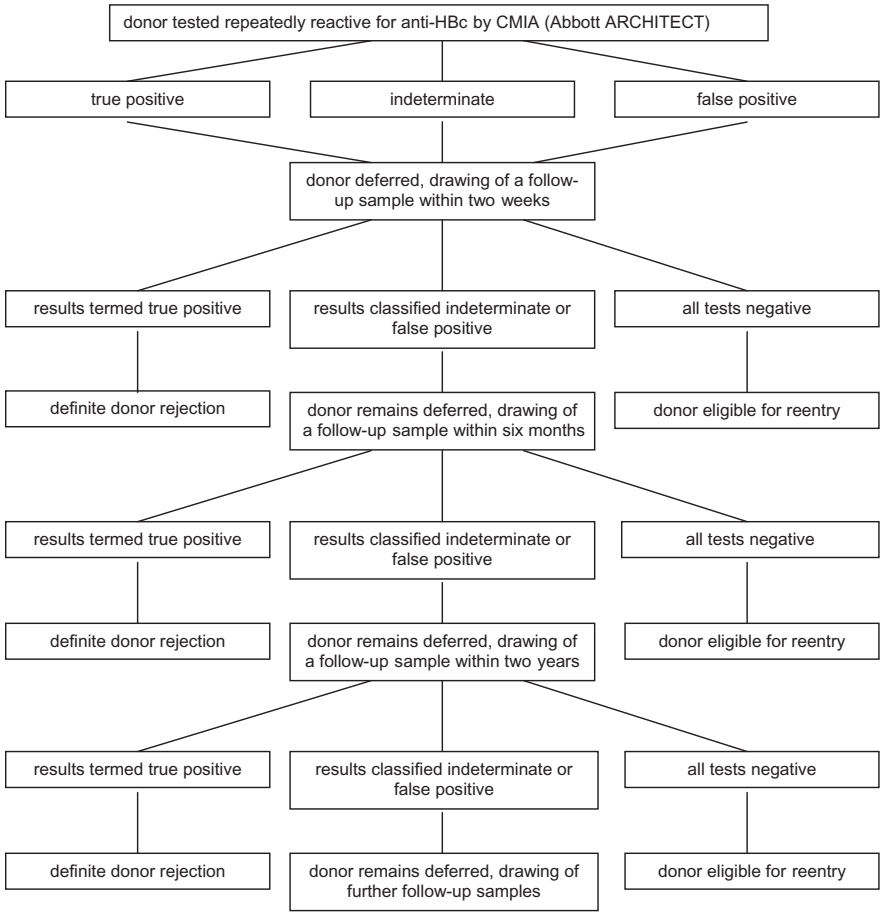

Fig. 2. Presentation of the reentry algorithm.

Prevalence of anti-HBc was calculated by the ratio of anti-HBc–reactive first-time donors and donor candidates to all first-time donors and donor candidates. The incidence was calculated by the ratio of anti-HBc–reactive repeat donors to all repeat donors.

For statistical analysis, we used computer software (SPSS, Version 15.0, SPSS GmbH, Munich, Germany). Significances of differences were analyzed using the t test. A p value of less than 0.05 was considered as significant.

RESULTS

Results of HBV serology

Overall 148,000 samples, taken from 30,000 individuals (approximately 13,000 first-time donors or donor candidates and 17,000 repeat donors) either before the first donation or during whole blood donation or plateletpheresis, respectively, were investigated within the 3-year period from July 2006 through June 2009. Of the 148,000 samples, 554 (0.37%, Figs. 3 and 4) tested repeatedly reactive for anti-HBc by CMIA. The samples were taken from 522 (245 female and 277 male) donors with a median age of 38 years.

Of the 554 samples, 553 were tested by MEIA, by individual-donor NAT, and by anti-HBs CMIA. In one sample (HBsAg negative, anti-HBs positive, and individual-donor NAT negative), no MEIA testing was performed due to lack of material and the sample was excluded from further analysis.

A total of 174 first-time donors and donor candidates and 347 repeat donors tested repeatedly reactive for anti-HBc by CMIA, suggesting a prevalence of 1.3% and an incidence within 3 years of 2.0%. A total of 142 (26%) samples of the 553 reactive ones were considered as true positive, 76 (14%) were termed indeterminate, and 335 (60%) were false positive (for details, see Fig. 4). Recalculating the epidemiologic data in consideration of only those samples termed true positive yielded a prevalence of 0.62% (80 first-time donors and donor candidates true positive) and a 3-year incidence of 0.36% (62 repeat donors true positive).

The mean sample-to-cutoff ratio (S/CO) values measured by CMIA (Fig. 5A) were higher in the groups termed true positive (8.09; standard deviation [SD], 4.05) compared to those considered indeterminate (4.05; SD, 3.79) and false positive (1.67; SD, 0.93) just as the S/CO values measured by MEIA (true positive 0.112, SD 0.085; indeterminate 0.773, SD 0.57; and false positive 1.614, SD 0.274; for details, see Fig. 5B). All differences were significant ($p < 0.001$).

Overall 379 donors provided the 411 samples termed false positive or indeterminate (Fig. 3). In 214 of these 411

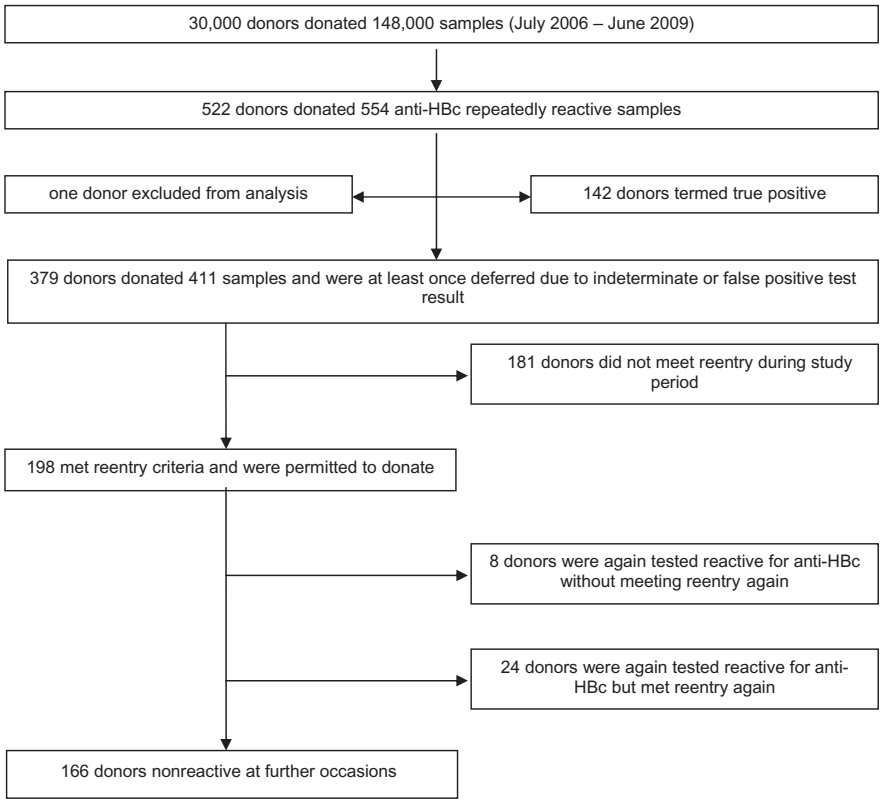

Fig. 3. Overview of those donors who became eligible for reentry and their donations. Thirty-two donors provided two samples tested anti-HBc reactive during study period. Twenty-four of them achieved reentry a second time.

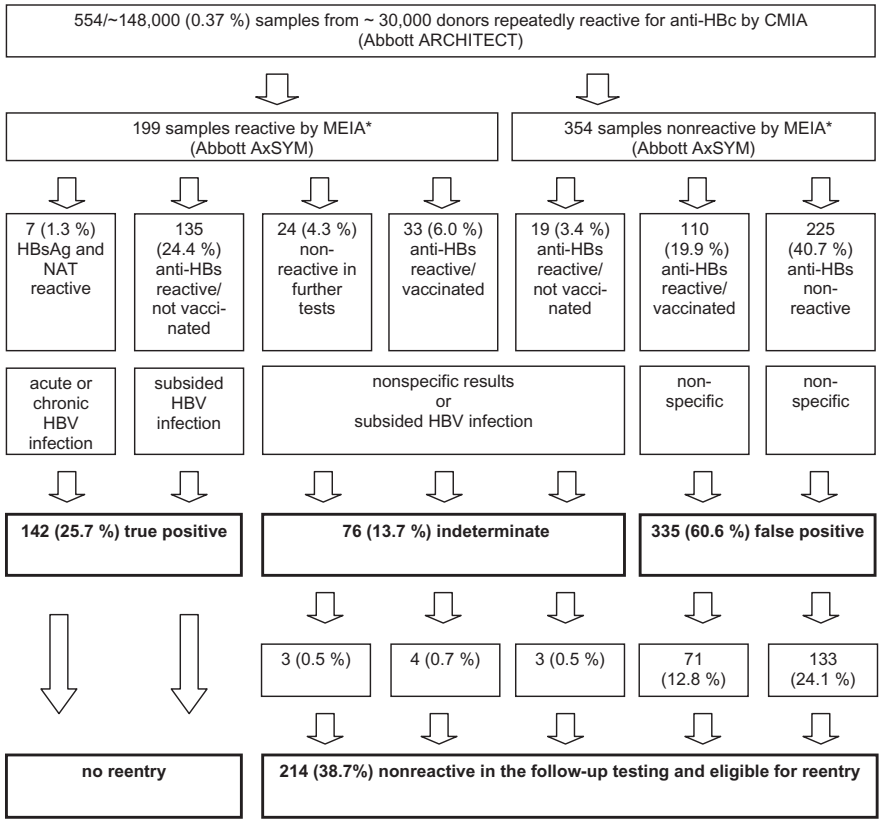

Fig. 4. Results of anti-HBc confirmatory testing. *One sample not tested by MEIA.

samples, the criteria for reentry were met until the end of the study period by a subsequent nonreactive anti-HBc testing without any further evidence for HBV infection (Figs. 3 and 4). Of those 214 samples, 67 became eligible for reentry within the following month, all in all 87 within 2 months, 109 within 6 months, and altogether 189 within 24 months. In the residual 25 cases, reentry was possible after more than 24 months. The mean S/CO ratio of the donors who became eligible for reentry subsequently was 1.58. A total of 24 of 214 again tested reactive for anti-HBc after achieving the reentry once but achieved reentry a second time (Fig. 3). In 124 of 214 samples (57.9%), reentry was achieved by the first follow-up, in 78 (36.4%) by the second follow-up, in eight (3.7%) by the third follow-up, and in four (1.9%) by the fourth follow-up.

Among 142 samples with true-positive anti-HBc testing, seven samples, all of them taken from donor candidates, tested positive for HBsAg. All of them were HBV NAT positive, in none of these samples anti-HBs was detectable (Fig. 4).

Results of individual-donor NAT

Only in donors who tested positive for both anti-HBc in each assay *and* for HBsAg was HBV DNA detectable (Fig. 4). However, one first-time donor (mean S/CO ratio of anti-HBc [CMIA, noncompetitive assay; cutoff, ≥1.0], 7.05; S/CO ratio of anti-HBc [MEIA, competitive assay, cutoff ≤ 1.0], 0.685; anti-HBs, 62.68 IU/L; HBsAg and individual-donor NAT negative) presented a weak, but clear positive result in the individual-donor NAT in a follow-up sample taken 12 months later. The result was repeatedly below the linear range of the assay, indicating a very low viral load, which cannot be exactly quantified. The mean S/CO ratio (CMIA) measured from the follow-up sample for anti-HBc was 6.39 and 0.1 (MEIA), respectively, anti-HBs was 48.63 IU/L, and HBsAg was not detectable again.

Nine donors previously known seronegative for anti-HBc tested positive for anti-HBc and were termed "indeterminate." In eight of them, an archive sample of the last anti-HBc–negative donation was available for individual-donor NAT. No HBV DNA was detectable in any of these archive samples.

DISCUSSION

The overall prevalence of anti-HBc–reactive individuals in our donor population of approximately 1.3% is comparable to those found in other blood donor–related serosurveys in Germany, Switzerland, and Canada[15-19] but less than the estimated anti-HBc prevalence reported for the

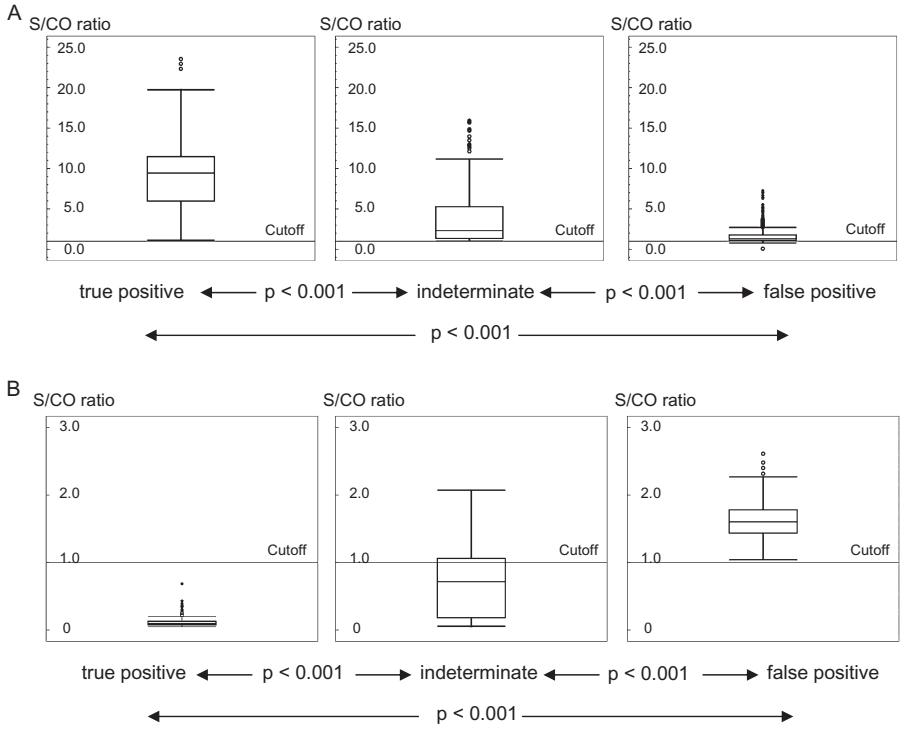

Fig. 5. (A) S/CO values, measured by CMIA (Abbott ARCHITECT), of the different groups. All samples were measured in triplicate. Results are given as median and 25% to 75% quartiles of the S/CO ratio. (B) S/CO values, measured by MEIA (Abbott AxSYM), of the different groups. Results are given as median and 25% to 75% quartiles of the S/CO ratio.

general population in Germany (7%).[20,21] This is partly caused by the selection of anti-HBc–negative blood donors in Lübeck since 1997. Additionally, rejection of donors at risk for infectious diseases before donation should have contributed to the reduced anti-HBc prevalence in our donor population.

Because no standard is accepted for the confirmation of a positive anti-HBc test, different further investigations for confirmation were performed in other serosurveys:[15,18] Both performed additional anti-HBc tests and an anti-HBs test; furthermore, in one report,[15] additional anti-HBe testing was conducted. Thus, the percentage of *true* anti-HBc–positive samples in both serosurveys was estimated to be between 50% and 60% of all anti-HBc–reactive tested samples, more than in our study. The algorithm of supplemental testing in our survey was easier; we omitted the anti-HBe test and performed only one additional anti-HBc test system, resulting in a proportion of 25.7% true anti-HBc–positive samples, less than described for the CMIA in a more clinical setting.[22] By follow-up testing, it was possible to clarify 10 of 76 samples termed indeterminate (Fig. 4). Additional anti-HBe testing could be useful to further clarify even more of our indeterminate results, but considering the relatively small proportion of indeterminate samples, the rate of samples termed "true positive" is likely to increase marginal if additional anti-HBe testing would be performed. And owing to the increasing prevalence of HBeAg-deficient HBV variants in Europe, the validity of anti-HBe tests in the confirmation of subsided HBV infection could be insufficient as many individuals potentially do not form any anti-HBe.[9,23-25]

Therefore, we consider the lesser rate of 25.7% true-positive samples as a correct assessment, although we did not perform any anti-HBe testing. This could mean that the Abbott ARCHITECT yields a higher rate of false-positive results compared to the PRISMHBc, PRISMHBcore,[15] and the Enzygnost anti-HBc.[18] Otherwise, a higher rate of false-positive results may be the result of a better sensitivity: we cannot exclude that some of the samples that tested reactive for anti-HBc by the CMIA only, especially those that tested reactive for anti-HBs also without a history of vaccination, were taken from individuals with a subsided HBV infection in whom the MEIA failed to detect anti-HBc. Finally, results may be different in different populations.

To diminish the donation loss due to false-positive anti-HBc results, consideration of the S/CO values measured by CMIA in the different groups (true positive, indeterminate, false positive) in our study might be helpful: the samples termed "false positive" presented a significantly lesser mean S/CO ratio compared to those considered "true positive" and even some of the samples termed indeterminate presented such a close to cutoff S/CO ratio

(Fig. 5A). This assumption has been recently reported for other anti-HBc tests.[15,16] Our study is the first that suggests that this assumption is similar to the CMIA in a transfusion medicine setting. Although the CMIA used in our study is a qualitative assay, and therefore caution is advised in interpreting any S/CO ratio, donors presenting a S/CO ratio below 4.0 by the CMIA test should carefully be applied to follow-up investigations, if no other serologic marker or individual-donor NAT give evidence for active or subsided HBV infection. Approximately 50% of those donors, as shown by our data, become eligible for reentry and may provide numerous donations in the future.

We are aware that it might be somewhat problematic to confirm reactive results in the CMIA by another related assay; however, the aim of our study was to evaluate a pragmatic algorithm for further classification of the CMIA results. Such an algorithm should be as simple as possible, and our classification (true positive, indeterminate, false positive) of test results describes an actual status and gives instructions how to proceed with a donor who tested reactive for anti-HBc once in the absence of an appropriate confirmation assay. A definite estimation whether an initial test result is true or false positive is aimed as often as possible by performing the follow-up. In this context, the decline of anti-HBc reactivity indicates an unspecific result rather than a decrease of the titer of a real antibody against HBc. If the latter scenario even occurs in single cases, it requires many years to decades.

Many years ago, an indefinite donor deferral was proposed by the FDA,[11] if the donor tests repeatedly reactive for anti-HBc on a second occasion. Thirty-seven percent of those donors could become eligible for reentry if tested by a more specific anti-HBc test.[26] In this regard, our data indicate that this percentage can be further increased, if anti-HBc testing is performed subsequently more than only once, because nearly half of our donors eligible for reentry satisfied the criteria after taking at least the second follow-up sample. And it is to be expected that many donors will achieve reentry a long time after the end of our study. Beyond that, the statement "anti-HBc positive"—even if false positive—might be unsettling for many donors and therefore it is desirable to acquire a negative result at any later occasion as common as possible.

No anti-HBc–positive, HBsAg-negative, *and* clearly HBV DNA–positive donor was detected in our study, unlike another study, in which three of 17 anti-HBc–positive and HBV DNA–positive donors tested negative for HBsAg in a period from 1997 until 2001.[9] This possibly indicates an improvement in the sensitivity of the currently used HBsAg assays, compared to those used in the past,[27] more so as in none of the archive samples from our newly seroconverted donors HBV DNA was detectable by individual-donor NAT.

Whether a lookback investigation of the recipients of the products obtained from our seroconverted donors would have been useful for definite confirmation that none was infectious is debatable. Such an investigation would have limitations due to the retrospective nature of our study: first, requirement of a follow-up sample from the recipients for HBV serologic testing years after transfusion is disproportionally unsettling for the recipient, and second, no data about the HBV serology of the recipients before transfusion were existent. Testing the last anti-HBc–negative archive sample by a high sensitive individual HBV NAT might be therefore a practical routine approach to exclude a HBV transmission after anti-HBc seroconversion and testing of the recipient should be limited to those occasions with strong suspicion of HBV transmission, for example, detection of HBV DNA in the archive sample as reported.[28]

However, one first-time donor in our study presented a reproducible weak positive result of individual-donor NAT in a follow-up sample taken 1 year after the anti-HBc–positive donation. This borderline result suggests an intermittent, fluctuating, low-level viremia ranging near the 95% detection limit, which can only occasionally be detected even by individual-donor NAT and which has not been detectable at the date of donation. The anti-HBs titer at the time of donation was below 100 IU/L and therefore below the titer that is considered as being protective for transfusion-transmitted HBV infection by the PEI.[12] Thus, we identified by anti-HBc testing one donation among 148,000, which was potentially at risk for transmitting HBV, less than the estimated rate of approximately 1:50,000 reported by other authors.[8,29,30] This at-risk donation was detectable neither by HBsAg testing nor by minipool NAT and not even by individual-donor NAT.

This raises the issue whether additional HBV NAT in blood donor screening is useful or whether it might replace HBsAg and/or anti-HBc testing. Acute HBV infections can be detected by NAT as well as by HBsAg testing and in individual cases of early, acute preseroconversion and HBsAg-negative HBV infections, NAT, even by minipool, might prevent a transfusion-transmitted HBV infection.[30] Hence, performing a sensitive HBV NAT instead of HBsAg testing might be possible. However, our data indicate that anti-HBc testing cannot be replaced by minipool NAT, which is in line with other reported data,[30] because many of the HBsAg-negative but HBV DNA–positive cases are chronic carriers, in whom only very low levels of HBV DNA—undetectable by minipool NAT—are existent.[9,31] Although our study population might not be adequate to clarify this issue and investigations with larger populations are necessary, the poor cost-effectiveness of such a precautionary measure like minipool or even individual-donor NAT should be considered.[32,33]

In conclusion, anti-HBc testing using the Abbott ARCHITECT CMIA yields an overall prevalence of anti-HBc–reactive results comparable to those reported by other serosurveys. However, taking into account solely

those donors termed true positive, the prevalence and incidence of anti-HBc in our donor population are low. The reentry mechanism proposed in our report might be an alternative to those suggested by US or German authorities: by applying our reentry mechanism, especially in those donors presenting low S/CO ratios, donor loss due to false-positive anti-HBc testing can be considerably reduced, in contrast to the aforementioned established reentry mechanisms. Besides HBsAg testing, anti-HBc testing seems to be a more simple, convenient, and effective method to prevent HBV infections by transfusion compared to NAT, either by minipool NAT or by individual-donor NAT.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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