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Prevalence of Occult Hepatitis B Virus Infection in Blood Donors with Negative ID-NAT in Switzerland

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Keywords
Occult hepatitis B virus infection · Anti-HBc screening · Blood donors · HBV-ID-NAT

Abstract

Introduction: Screening of hepatitis B surface antigen (HBsAg) and individual-donation nucleic acid amplification testing (ID-NAT) of blood donors have become standard to detect hepatitis B virus (HBV) infection. However, there is still a residual risk of HBV transmission by blood components of donors suffering from occult HBV infection (OBI). Therefore, many countries implemented universal testing of anti-HBV core antigen (anti-HBc) antibodies in order to increase blood safety. In Switzerland, anti-HBc testing is not part of the routine blood donor-screening repertoire. Therefore, we sought to assess prevalence of donors with OBI in a Swiss blood donor collective. ***Methods:*** Blood donations were prospectively investigated for the presence of anti-HBc antibodies during two time periods (I: all donors, March 2017; II: first-time donors only, April 2017 until February 2018). Anti-HBc-positive findings were confirmed by an anti-HBc neutralization test. Discarded plasma samples of anti-HBc-confirmed positive donors were ultracentrifuged and subsequently retested by regular HBV-ID-NAT to search for traces of HBV. ***Results:*** During time period I, 78 (1.6%) individuals out of 4,923 donors were confirmed anti-HBc-positive. Sixty-nine (88%) anti-HBc-positive samples were available and processed by ultracentrifugation followed by repeat HBV-ID-NAT. Four samples (5.8%) were found positive for HBV DNA. Sixty-five (94.2%) samples remained HBV NAT-negative upon ultracentrifugation. During time period II, 56 (0.9%) donor samples out of 6,509 exhibited anti-HBc-confirmed positive. Fifty-five (98%) samples could be reassessed by HBV-ID-NAT upon ultracentrifugation. Three (5.5%) samples contained HBV DNA and 52 (94.5%) samples remained HBV NAT-negative. ***Conclusion:*** Overall, we detected 7 viremic OBI carriers among 11,432 blood donors, which tested negative for HBV by standard HBV-ID-NAT and HBsAg screening. In contrast, OBI carriers showed positive anti-HBc findings which could be confirmed in 83.8% of the cases. Thus, OBI might be missed by the current HBV screening process of Swiss blood donors. We suggest to review current HBV screening algorithm. Extended donor screening by anti-HBc testing may unmask OBI carriers and contribute to blood safety for the recipient of blood products.

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Introduction

In 2019, the World Health Organization estimated that 296 million persons worldwide were chronically infected with hepatitis B virus (HBV). The main HBV transmission routes are from mother-to-child during birth, through contact with body fluids, unprotected sex with an infected partner, parenteral drug use, and exposure to infected blood products. Globally, HBV transmission by blood products is a recognized transfusion risk. Therefore, the World Health Organization recommends to screen blood donations for hepatitis B and to discard positively tested donations from supply chains. Standard routine screening tests target HBV markers which reflect actively replicating virus such as hepatitis B surface antigen (HBsAg). Additionally, screening for HBV DNA by nucleic acid amplification testing (NAT) became standard. Nevertheless, HBV transmission still occurs usually by blood products contaminated with HBV below detection limits of current screening tests. The so-called occult hepatitis B infection (OBI) is characterized by trace amount of HBV DNA in blood and absence of detectable HBsAg [1, 2]. The concentration of HBV DNA in affected individuals' blood is usually <200 IU/mL. Transmission of HBV by blood products donated from OBI carriers has been reported [3–6]. In consequence, several European countries implemented universal anti-HBV core antigen (anti-HBc) screening of blood donors [7–9]. Anti-HBc serves as a surrogate for past HBV infection and may be suitable to identify OBI carriers.

In Switzerland, screening of blood donors comprises HBsAg and individual donation HBV NAT (HBV-ID-NAT) to select HBV-negative blood donors. Since Switzerland is considered a low prevalence country for hepatitis B [10], the residual risk of HBV transmission by blood products was considered negligible, and anti-HBc testing of blood donors was deemed not cost-efficient. However, improvements in HBV NAT techniques, i.e., mini-pool testing replaced by individual donation testing ameliorated sensitivity of 3rd generation HBV NAT revealing donors with trace HBV viremia, which were missed by previous screening protocols. Stolz et al. [11] reported five repeat donors newly discovered HBV-positive upon implementing HBV-ID-NAT. Although most sensitive NAT techniques for mass screening are applied, blood donors with OBI may still escape current screening procedure. This study aims to assess prevalence of OBI carriers among Swiss blood donors, which are missed by current screening process. Improvement of screening strategy will be discussed.

Materials and Methods

Blood donors were prospectively investigated for the presence of anti-HBc-antibodies (Anti-HBc II, ARCHITECT, ABBOTT, Wiesbaden, Germany) in addition to standard HBV screening consisting of HBV-ID-NAT (Cobas MPX-assay, Roche) and HBs-antigen chemiluminescent immunoassay (ARCHITECT, Abbott). During March 2017 (period I), all donations of whole blood, platelets, and plasma were included into the study. From April 2017 to February 2018 (period II), only first-time whole blood donors were included into the study. Anti-HBc-positive samples were confirmed using an anti-HBc inhibition assay performed at the Institute of Virology in Freiburg, Germany [12]. The assay applies a recombinant core antigen of HBV. The assay is approved by the Federal Institute for Vaccines and Biomedics Paul-Ehrlich Institute, Langen, Germany, for confirmatory testing of blood donors. In this study, discarded fresh frozen plasma (dFFP) of anti-HBc-confirmed positive donors were ultracentrifuged and reanalyzed by standard HBV-ID-NAT.

Ultracentrifugation of Anti-HBc-Positive Samples and HBV-ID-NAT

First, 50 mL of dFFP were centrifuged by 1,500 *g* for 5 min to remove cellular debris. Thirty-six milliliter of the supernatant were transferred to a polyallomer tube for ultracentrifugation with 110,000 *g* for 3 h at 4°C in an AH-629 swinging bucket rotor using a Sorvall WX Ultra instrument (Thermo Fisher Scientific). The pellet was then resuspended in 1.5 mL PBS, and 850 µL sample volume was used for the HBV-ID-NAT. Enrichment of HBV by ultracentrifugation was estimated with a low-viremic HBV donor sample. For negative control, 10 donors who tested negative for HBV-ID-NAT/anti-HBc were reanalyzed by HBV-ID-NAT upon ultracentrifugation procedure.

Both, the standard donor screening for HBV and the subsequent sample reassessment upon ultracentrifugation were carried out with the MPX assay on the cobas 6,800 system (Roche). The MPX assay is a qualitative multiplex PCR assay for simultaneous detection of nucleic acid of HBV, HCV, and HIV (HIV-1 group M and group O and HIV-2). The limit of detection for HBV is 1.4 IU/mL (95% confidence limit of 1.2–1.7 IU/mL) according to the manufacturer.

Results

Efficacy of HBV Enrichment by Ultracentrifugation

A low-titer HBV-positive sample (HBV load less than 12 IU/mL, as assessed by the quantitative real-time PCR from Abbott, IL, USA) was analyzed in parallel by the cobas MPX assay. Before and after the clearing step of dFFP sample, cycle of threshold (Ct) values for HBV were 34.62 and 34.56, respectively. Therefore, no virus DNA was lost at clearing. After ultracentrifugation and resuspension of the pellet with PBS, the MPX assay yielded a Ct value of 30.80, reflecting enrichment of input HBV DNA by more than 1 $\log_{10}$ (factor 10). This is in line with previously determined enrichment factor 14 for HBV DNA by our ultracentrifugation procedure. Thus, allowing the detection of HBV DNA concentration of donor plasma sample in the range of approximately 0.1 IU/mL. The 10 negative donor samples remained negative for HBV after the ultracentrifugation and subsequent HBV-ID-NAT, assuring absence of HBV carryover during procedure.

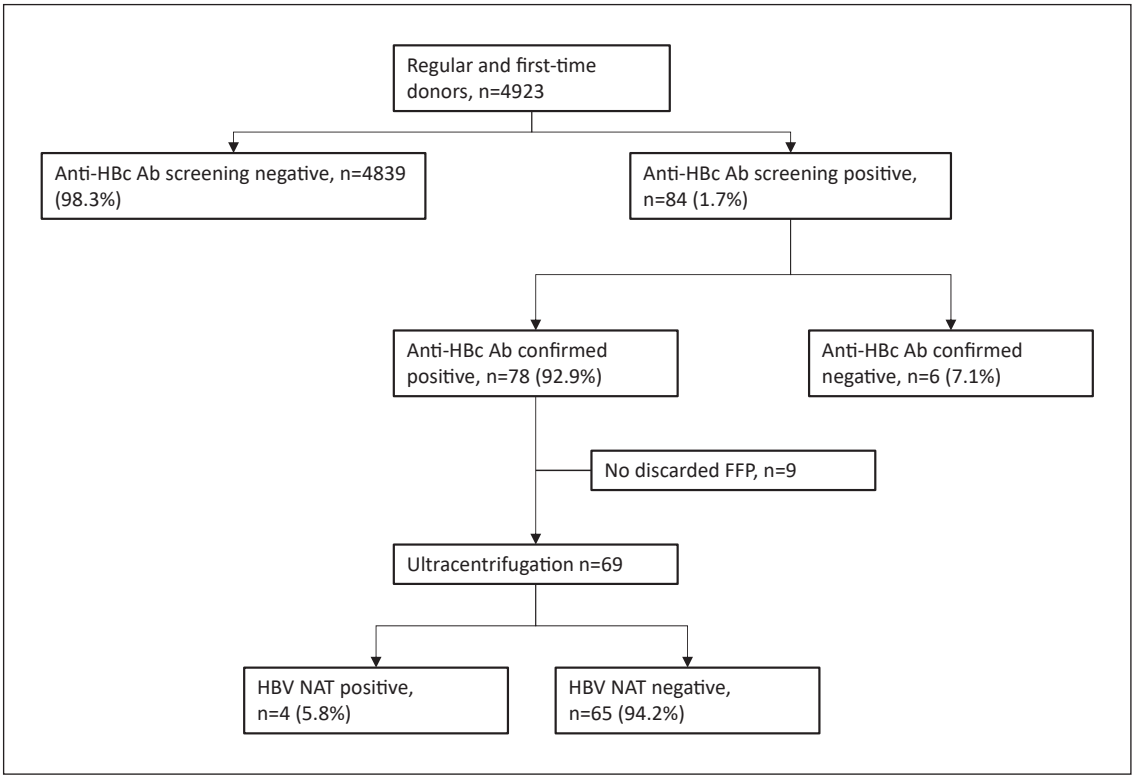

Fig. 1. Assessment of regular and first-time donors of period I (March 2017), *n* = 4,923 donors.

Table 1. Overview of 7 HBV NAT-positive samples by cobas MPX assay (Roche)

Time period	Donor sample ID	HBV-ID-NAT Ct value
I	17	39.17
I	42	40.54
I	51	38.17
I	54	37.24
II	100	39.48
II	148	39.47
II	151	39.2

Table 2. Description of anti-HBc-positive donors (*n* = 134) and viremic OBI donors

	Women	Men
Frequency, *n* (%)	37 (27.6)	97 (72.4)
Median age (range)	51 (25–75)	49 (19–76)
Median anti-HBc S/CO (range)	7.7 (1.01–11.69)	7.61 (1.02–11.62)
First-time donors, *n* (%)	21 (56.8)	43 (44.3)
Repeat donors, *n* (%)	16 (43.2)	54 (55.7)

Identification of Donors with OBI

During time period I, 4,923 donors were screened for anti-HBc in addition to standard HBV screening protocol (HBV-ID-NAT and HBsAg). Eighty-four (1.7%) donor samples were found positive for anti-HBc-only, of which 78 (92.9%) samples could be confirmed by anti-HBc neutralization assay (Fig. 1). Sixty-nine anti-HBc positive samples were reassessed by HBV-ID-NAT upon ultracentrifugation. 4/69 samples (5.8%) turned out positive by HBV-ID-NAT. The Ct values of individual samples are given in Table 1. The remaining 65/69 (94.2%) samples revealed negative HBV-ID-NAT upon ultracentrifugation. Therefore, 5.8% of anti-HBc-only positive donors carry low-titer HBV DNA and fulfill the definition of OBI.

During time period II, 6,509 first-time donors were screened for anti-HBc in addition to standard HBV screening protocol. Seventy-six (1.2%) donor samples revealed positive for anti-HBc only (Fig. 2). In 56/76 (73.7%) samples, anti-HBc findings were confirmed by neutralization. From 55 donations, dFFP was available for ultracentrifugation and reassessment by HBV-ID-NAT. Three (5.5%) reassessed samples were found positive for HBV DNA and 52 (94.5%) of anti-HBc-only samples remained HBV NAT-negative upon ultracentrifugation. The corresponding Ct values of NAT-positive samples are shown in Table 1.

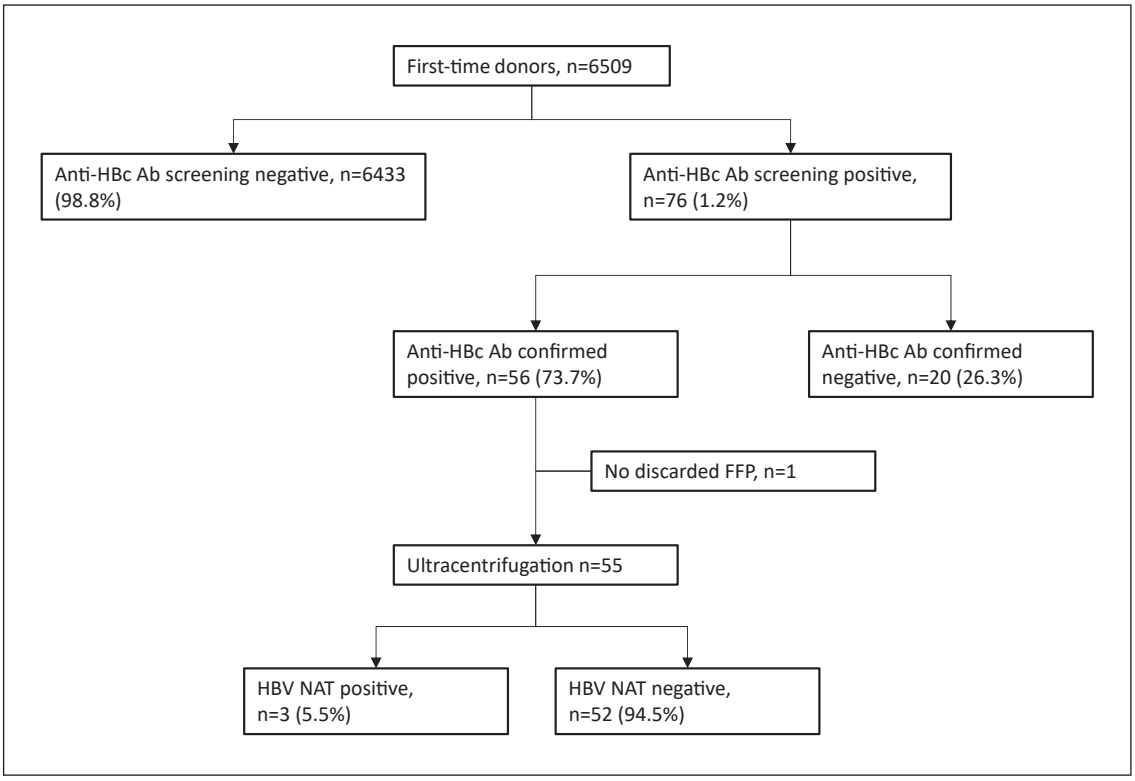

Fig. 2. Assessment of first-time donors of period II (April 2017 to February 2018), *n* = 6,509 donors.

Characterization of Donors with Confirmed Positive Anti-HBc Result

The majority of donors with confirmed positive anti-HBc findings were males (Table 2). This is in disproportion to the sex composition of the Swiss donor pool (male donors: 57%). First-time donors and repeat donors with positive anti-HBc were found in almost equal proportion. Median anti-HBc ratios (S/CO) are virtually identical in men and women.

Discussion

In Switzerland, HBV-ID-NAT in addition to HBsAg testing for HBV has been mandatory for screening of voluntary blood donors since 2012. This screening protocol has been claimed cost-efficient for selection of HBV-negative blood donors [13]. During the past 10 years, HBV-ID-NAT screening identified 149 infectious donor samples among 1,830,657 donations in Switzerland [13]. Because of low incidence of HBV in Switzerland, anti-HBc screening was not included into the screening algorithm. Even more, by retrospective analysis of Swiss blood donors' HBV markers, Stolz et al. [13] recommended reentry of blood donors past HBV infection into the donor pool if the donor proved negative for HBV DNA by HBV-ID-NAT. This is in contrast to France, which has a comparable HBV prevalence but requires negative tests for anti-HBc, HBV NAT, and HBsAg to qualify for voluntary blood donation [9]. The annual epidemiological report of 2019 from the European Centre for Disease Prevention and Control showed incidence of acute HBV cases of <0.5–0.9/100,000 population in France, Germany, and Austria [14]. For Switzerland, the incidence of acute HBV was <0.4/100,000 population [15]. Niederhauser et al. [10] reported variable prevalence data of anti-HBc between 1.2 and 1.7% assessing more than 22,000 Swiss blood donors. However, recent data showed increasing numbers of chronically HBV-infected individuals in Switzerland, linked to immigration activity [16]. Between European countries, broadly different rates of anti-HBc-positive blood donors were observed ranging from 0.3% in England up to 8.3% in Italy [17–21]. A retrospective analysis in Germany revealed anti-HBc prevalence of 0.2% in 31 million blood donations justifying the implementation of routine anti-HBc screening [22]. Given the well-known transmission of HBV by blood products donated by blood donors suffering from OBI, the re-evaluation of the Swiss screening algorithm seems timely. Therefore, we launched a prospective donor study by complementing the standard screening procedure (HBsAg and HBV-ID-NAT) with universal anti-HBc

testing and reassessing confirmed anti-HBc-positive donor samples by HBV-ID-NAT upon HBV enrichment by ultracentrifugation.

Overall, the rate of anti-HBc-only-positive blood donors was 1.4% (160/11,432 donors), and the confirmation of anti-HBc by neutralization assay was successful in unselected blood donors (92.9%) and in first-time blood donors (73.7%), respectively. Confirmation among all anti-HBc-positive donors was achieved in 83.8%. Since confirmation assays were performed with identical reagents and protocol on both donor groups, the different confirmation rates of anti-HBc may be explained by unequal preselection for HBV of the two donor groups. In 7/134 cases (5.2%) with confirmed anti-HBc-only-positive findings, we detected HBV DNA upon ultracentrifugation. These blood donors satisfy the definition of OBI and pose a potential risk for transmission of HBV through the donated blood products. Therefore, they need to be deferred from blood donation. However, the viral load in these donors was below the detection limit of modern HBV-ID-NAT screening and was detectable only upon ultracentrifugation. Therefore, the blood products would have been released based on routine donor screening including HBV-ID-NAT. The viral dose (viral load × plasma volume transfused) in blood product is critical for the transmission of HBV to the recipient of blood product [4]. The seven viremic donors identified in this study revealed Ct values by the cobas MPX PCR assay after ultracentrifugation between 37 and 40 (Table 1). Based on dilution studies, the Ct value of 37 corresponds to 3 IU HBV DNA/mL and the Ct value of 40 corresponds to 0.3 IU HBV DNA/mL, respectively (data not published). Thus, for donor No. 42 (Table 1), a viral dose of 6 IU and 60 IU is estimated in red cell concentrate containing 20 mL and in platelet concentrate containing 200 mL of plasma, respectively. Based on mathematical models, Candotti et al. [23] provided evidence for HBV transmission by blood products donated by OBI carriers containing 3 IU and 30 IU of HBV DNA in 20 mL and 200 mL plasma components [24]. Thus, the FFP donation of 200 mL of donor No. 42 might be infectious. For donor No. 54, it is even more impressive. Blood components containing 20 mL plasma would end up with a viral dose of 60 IU HBV DNA and components containing 200 mL plasma would transmit approx. 600 IU HBV DNA, respectively. Using ultracentrifugation before cobas MPX PCR, a theoretical LOD of 0.1 IU/mL was achieved, which is slightly below the infectious threshold of 0.15 IU HBV DNA/mL claimed by Candotti et al. [23]. However, complex enrichment procedure such as ultracentrifugation is not suitable for donor screening. Thus, a surrogate marker of past HBV infection such as anti-HBc may serve better.

Extrapolating data from this study to entire Switzerland, in 2017, approximately 3,600 donors (1.6% of 230,190 donors) would have been expected anti-HBc-positive which might have donated approx. 4,600 blood products, of which around 240 (5.2%) products may have contained traces of HBV. Thus, these blood products pose a potential risk for transmission of HBV to the recipient. Although at best, HBV is present only in traces, still HBV transmission may occur [6, 25]. Niederhauser et al. [26] described a case of transfusion-transmitted HBV infection caused by the donation of a newly infected donor who carried HBV DNA of 17 IU/mL at time of donation. The HBV viral load of OBI carriers varies between <10 IU/mL and 50 IU/mL and may be complicated by intermittent viremia [27]. Based on lookback investigations of HBV transmission by blood products from OBI carriers, the minimal HBV infectious dose was estimated at 3 IU HBV DNA/mL [23]. Hence, effective donor screening would require HBV NAT sensitivity of less than 0.15 IU/mL, which is technically challenging [23]. Therefore, commercially available donor screening platforms fail to deliver sufficient diagnostic accuracy and may miss OBI-infected donations [2]. On the other hand, pathogen reduction technology is very efficient for low titer virus-contaminated blood donations. Amotosalen treatment with UVA light irradiation results in reduction of HBV titers of >5.5 log10 [28]. However, since pathogen reduction technology is applicable only for plasma and platelets, the majority of transfused blood products such as red cell concentrates are not suitable to be processed by pathogen reduction technology. Therefore, sophisticated donor screening strategy is crucial for transfusion safety.

Our data document insufficient capacity of HBV-ID-NAT technology to identify OBI-infected blood donors. Virus enrichment procedures such as ultracentrifugation or vastly increased extraction volume of donor's sample are not feasible for mass screening. Therefore, a surrogate marker for OBI such as anti-HBc testing might be suitable to close the safety gap of current screening protocol. Candotti et al. [23] reported nine incidents of HBV transmission by OBI blood donations, which escaped HBV NAT screening. Retrospectively, the donations were anti-HBc-only–positive, and transmission of HBV would have been prevented based on anti-HBc donor testing [23]. An Australian patient-triggered lookback study on hepatitis B revealed possible HBV transmission by OBI donations in 0.2–3.3% of cases [3]. Moreover, an unexpectedly high proportion of OBI-infected blood donors were discovered in the Australian donor population by anti-HBc testing during a 2-year study period [29]. Taken together, anti-HBc screening might be critical even in countries with a low prevalence of HBV and having implemented state of the art HBV-ID-NAT screening of blood donors.

False-positive anti-HBc test results may result in inappropriate donor loss and donor uncertainty. Nevertheless, anti-HBc confirmation assays by antibody neutral-

ization as applied in this study may improve specificity of anti-HBc screening [30]. However, this may complicate anti-HBc screening approaches. From our data, the rate of falsely positive determined anti-HBc tests may result in about 300 Swiss donors inappropriately lost per year. Considering the entire pool of more than 250,000 regular donors, such a small number of inappropriately lost blood donors is not of major concern. Preventing HBV transmissions by discarding anti-HBc-positive donations may outweigh the risk of inappropriate donor loss. Moreover, Styles et al. [31] challenge the capacity of HBV-ID-NAT to identify OBI-infected donors. They propose to discard anti-HBc-positive donations despite negative HBV-ID-NAT. This is in line with our findings.

Apart from Switzerland, other HBV low endemic countries such as Germany, France, the Netherlands, and Canada already had adopted anti-HBc screening of blood donors [7–9, 32]. Currently, the HBV screening of blood donors in Germany consists of mandatory HBsAg and anti-HBc testing, followed by HBV NAT in reactive samples [7]. A study by the Paul-Ehrlich-Institute covering about 95% of all blood and plasma donations in Germany found 0.64 HBV-infected donations per million donations by HBV NAT and 0.55 anti-HBc-only cases per million blood donations [7]. Therefore, Fiedler et al. [7] concluded that anti-HBc combined with HBV-ID-NAT might be the most efficient strategy to identify HBV infectious blood donations. In the Netherlands, the implementation of anti-HBc screening of 382,173 blood donors yielded 13 donors with recent HBV infection, which would have been missed by HBsAg and HBV NAT screening [8]. Overall, including anti-HBc testing into the already established HBsAg and HBV-ID-NAT screening protocol identifies carriers of HBV viremia which would otherwise be missed, prevents the release of HBV contaminated blood products, and may therefore increase blood safety.

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Statement of Ethics

Ethics approval was not required. The authors confirm that the study and data accumulation conform to all federal or state laws and that the study was in adherence to the tenets of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Andrea Zbinden: formal analysis, investigation, conceptualization, supervision, writing – original draft, and writing – review and editing; Judith Ries: methodology and acquisition of laboratory data; Patrick M. Redli and Cyril Shah: methodology and performance of experiments; Andreas Glauser and David Goslings: conceptualization; Daniela Huzly: performance of immunoassay diagnostics; Jürg Böni, Jochen Gottschalk, and Beat M. Frey: conceptualization, supervision, and writing. All authors read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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