# Guidance for Industry

# Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc)

## DRAFT GUIDANCE

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For questions on the content of this guidance, contact Robin Biswas, M.D., at 301-827-3011.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**
**May 2008**

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**Contains Nonbinding Recommendations**

*Draft –Not For Implementation*

# Guidance for Industry

# Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc)

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## I. INTRODUCTION

We, FDA, are providing recommendations to you, establishments that collect human blood or blood components, for a requalification method or process for the reentry of deferred donors into the donor pool based on a determination that previous tests that were repeatedly reactive for antibodies to hepatitis B core antigen (anti-HBc) were falsely positive and that there is no evidence of infection with hepatitis B virus (HBV). Currently, donors who are repeatedly reactive on more than one occasion for anti-HBc (samples from more than one collection from the donor are repeatedly reactive for anti-HBc), must be indefinitely deferred, in accordance with Title 21 Code of Federal Regulations, section 610.41(a) (21 CFR 610.41(a)). Although it may seem unlikely that two anti-HBc tests would be false positives, such situations have occurred with some frequency because of the relative non-specificity of these tests. The result is that many otherwise suitable donors are indefinitely deferred because of their anti-HBc test results even though medical follow-up of such donors indicates that they are not infected with HBV.

The availability of an FDA-licensed hepatitis B virus nucleic acid test (HBV NAT), which is particularly sensitive when single samples are tested, provides an additional, powerful method of determining whether a donor who has been deferred because of anti-HBc reactivity is truly infected by HBV. Due to the availability of this licensed HBV NAT and the improved specificity of anti-HBc assays, we are recommending in this guidance a reentry algorithm for donors deferred due to falsely positive repeatedly reactive tests for anti-HBc.

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## II. BACKGROUND

### A. Clinical Significance of Donor Screening for Hepatitis B Virus Infection

HBV is a major human pathogen that causes acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma (Ref. 1). HBV is an enveloped virus with a partially duplex circular deoxyribonucleic acid (DNA) genome of approximately 3,200 bases. Most primary infections in adults are self-limited; the virus is cleared from the blood and liver, and individuals develop a lasting immunity. Fewer than 5% of infected adults develop chronic infections that can be asymptomatic (i.e., a carrier state). About 20% of chronically infected individuals develop cirrhosis. Chronically infected subjects have 100 times higher risk of developing hepatocellular carcinoma than non-carriers. The mortality of acute HBV infection is about 1%. In the United States, deaths from chronic HBV infection are estimated to range from 3,000 to 5,000 individuals per year (Ref. 2).

Currently, HBV is transmitted by blood transfusions more frequently than hepatitis C virus or human immunodeficiency virus (HIV). The residual risk of post-transfusion HBV infection from donations screened for hepatitis B surface antigen (HBsAg) and anti-HBc have been estimated as 1 in 63,000 donations (Ref. 3) to 1 in 180,000 donations (Ref. 4). The major cause of HBV transmission by blood is attributable to donations from asymptomatic donors with acute HBV infections who have not yet developed HBsAg (i.e., donors in the seronegative window period), and from donors with chronic infections in which serological markers are not detected (occult hepatitis B). Seronegative blood donations from infected individuals can transmit hepatitis B. In such cases, lookback studies using polymerase chain reaction have shown that HBV DNA can be detected at low levels in the donor's blood (Ref. 5).

HBsAg becomes detectable in blood 30 to 60 days after infection followed by emergence of anti-HBc. Viremia develops by the time HBsAg is detected, and can reach $10^9$-$10^{10}$ virions/ml in acute infections (Ref. 1). Upon clearance of the HBV infection by the immune response, the HBsAg antigen disappears from the circulation and detectable anti-HBc and antibody to hepatitis B surface antigen (anti-HBs) usually persists indefinitely. There is evidence that anti-HBc can decrease and even disappear over a period of decades in resolved infections (Ref. 6). In chronically infected individuals, tests for HBsAg and anti-HBc usually remain positive for life and lower viral titers can be detected in blood for a long period but tend to decline over time.

HBV NAT assays for detection of HBV DNA have been developed. So far, one test has been licensed for screening blood donations using a minipool sample format. This assay is also indicated for testing samples from individual donations, thus increasing test sensitivity. In a BPAC meeting on October 21, 2004 (Ref. 15), we proposed a revised reentry algorithm in which subsequent testing of the donor for HBsAg and anti-HBc is

retained, but sensitive HBV DNA testing using a licensed NAT would replace anti-HBs testing. While the Committee did not take a formal vote on FDA's proposed algorithm, the Committee did not raise any objections to FDA's proposal. We are not proposing additional testing for anti-HBs as part of donor reentry because extensive hepatitis B vaccination programs have been in place for a number of years, resulting in many individuals having anti-HBs from vaccination. As a result, anti-HBs now has questionable value as a marker of hepatitis B infection.

Since October 21, 2004, we have licensed a qualitative test for the direct detection of HBV DNA in human plasma from donations of Whole Blood and blood components for transfusion, and Source Plasma. The availability of a sensitive, FDA-licensed HBV NAT assay, particularly when single samples are tested, provides an additional, powerful method of determining whether a donor who has been deferred because of anti-HBc reactivity is truly infected by HBV. Due to the availability of a licensed HBV NAT and the improved specificity of anti-HBc assays, we are proposing a reentry algorithm for anti-HBc in this guidance.

### B. Rationale for the Requalification Method for Reentry

Under 21 CFR 610.40(a), you must test each donation of human blood or blood component intended for use in preparing a product, including donations intended as a component of, or used to prepare, a medical device, for evidence of infection due to HBV. Testing for evidence of infection includes testing for the presence of HBsAg and anti-HBc. In addition, some blood establishments also test blood donations for HBV DNA by NAT.

Under 21 CFR 610.41(a), blood establishments must defer donors who test reactive[1] by a screening test for evidence of infection due to a communicable disease agent(s) listed in 21 CFR 610.40(a). However, donors who test repeatedly reactive for anti-HBc on only one occasion need not be deferred (21 CFR 610.41(a)(1)), although the donation collected would be unsuitable (Ref. 11). Donors who test reactive on more than one occasion do not fall within this provision and must be deferred under 21 CFR 610.41(a).

Under 21 CFR 610.41(b), we provided for reentry of a deferred donor who is subsequently "found to be suitable as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA."

Until now, we have not recommended a requalification method for reentry of donors deferred due to repeatedly reactive test results for anti-HBc because there was no

[1] In 21 CFR 610.41(a), FDA requires that blood establishments defer donors who test reactive by a screening test for evidence of infection due to a communicable disease agent listed in section 610.40(a). In section 610.41(a)(1), however, a donor who tests reactive for anti-HBc on only one occasion is not required to be deferred. In this guidance, we refer to reactive test results for HBsAg and anti-HBc as "repeatedly reactive" to accurately describe the testing algorithm for anti-HBc.

supplemental (additional, more specific) test available. Although donor screening for anti-HBc has contributed to blood safety, a large proportion of donors with anti-HBc reactivity who fulfill all other donor suitability criteria have been indefinitely deferred on the basis of potentially false positive anti-HBc test results (Refs. 7, 16). It is estimated that as many as 21,500 potentially eligible donors were deferred annually in the late 1980s and 1990s because of false positive anti-HBc results, and that over 200,000 donors could be eligible for reentry (Ref. 7).

## III. RECOMMENDATIONS

For purposes of reentering into the donor pool a donor who has been indefinitely deferred because of having tested repeatedly reactive for anti-HBc on more than one occasion, we recommend that, after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you obtain a pre-donation blood sample (i.e., a blood sample which is obtained prior to any next donation) from the donor for follow-up testing, using licensed tests for HBsAg, anti-HBc and HBV DNA by NAT. Provided that the blood sample test results are negative for HBsAg, anti-HBc and HBV NAT, the donor may, at a later date, return to donate blood. When the donor returns to donate, subsequent to the negative tests for HBsAg, anti-HBc, and HBV NAT on the pre-donation sample, we recommend that you reenter the donor as eligible to donate Whole Blood and blood components, provided that all other suitability criteria are met.

For donor retesting, we recommend that a minimum 8-week (56 days) period elapse following the last repeatedly reactive anti-HBc test, because this time period provides sufficient confidence that at least one of the three HBV markers (HBsAg, anti-HBc, and HBV DNA) will be detectable if the donor had been truly infected with HBV at the time of that last anti-HBc reactive donation (Ref. 1). In addition, 56 days is the minimum time period permitted between donations of Whole Blood (21 CFR 640.3(b)).

For purposes of reentry, we recommend that you use a licensed HBV NAT labeled as having a sensitivity of $\leq$10 copies /mL (at 95 % detection rate). This sensitivity reflects the current technological capabilities regarding sensitivity of HBV NAT assays. Depending upon the assay and the platform used, this sensitivity may only be achieved when testing individual donor samples.

Donor reentry following deferral for repeatedly reactive tests for anti-HBc on more than one occasion:

A. You may reenter into the donor pool a donor who has been indefinitely deferred solely because of repeatedly reactive tests for anti-HBc on more than one occasion if (see flow chart in the Appendix):

    1. After a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you collect a follow up sample from the donor, and this sample tests

negative on licensed tests for HBsAg, anti-HBc, and HBV DNA by NAT (sensitivity at 95% detection rate of ≤ 10 copies/mL)

and

2. When the donor presents to donate, subsequent to the negative tests for HBsAg, anti-HBc, and HBV NAT, you determine that the donor meets all eligibility criteria for donors of Whole Blood and blood components

**B.** You should continue to indefinitely defer a donor who was deferred for anti-HBc reactivity on more than one occasion and whose sample or donation tests repeatedly reactive on the: 1) HBsAg test (whether or not the neutralization test is positive), 2) anti-HBc test, or 3) HBV NAT. Positive results on tests for HBsAg, anti-HBc or HBV NAT may be useful in donor counseling.

**C.** If you wish to perform follow-up testing on a donor who is deferred because of anti-HBc test results, you may do so before the end of the 8-week waiting period for donor notification purposes or for medical reasons. Negative test results on follow-up for HBsAg, anti-HBc, and HBV NAT (sensitivity at 95% detection rate of ≤ 10 copies/mL), may be useful in donor counseling. However, only negative results for all three tests, obtained at least 8 weeks after the last repeatedly reactive anti-HBc result, would qualify the donor for reentry. If you obtain a reactive HBV NAT, or repeatedly reactive HBsAg or anti-HBc, or positive HBsAg result on any of these tests during this 8-week waiting period, the donor would not be eligible for reentry, and we recommend that you defer the donor indefinitely.

## IV. IMPLEMENTATION

This guidance is being distributed for comment purposes only.

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## APPENDIX

## REENTRY FOR DONORS DEFERRED BECAUSE OF REPEATEDLY REACTIVE TEST RESULTS FOR ANTI-HBc

Donors previously deferred solely because of repeatedly reactive anti-HBc test on more than one occasion

↓

After a minimum of 8 weeks[1] following the last repeatedly reactive anti-HBc test results on more than one occasion, test a follow-up sample using licensed HBsAg and anti-HBc tests, and HBV NAT[2]

↓

| HBsAg RR[3] or Anti-HBc RR or HBV NAT Reactive | All tests non-reactive |
|---|---|
| ↓ | ↓ |
| Defer donor indefinitely | Reenter donor (Donor eligible to donate) |

[1] If the donor sample is tested before 8 weeks following the last repeatedly reactive anti-HBc test results on more than one occasion, a) if the sample tests HBsAg RR or anti-HBc RR or HBV NAT reactive, the donor is indefinitely deferred, and b) if the sample tests negative on all three of these tests, the donor should be retested after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test result on more than one occasion using licensed HBsAg and anti-HBc tests, and HBV NAT.

[2] The sensitivity of the HBV NAT used should be $\leq$ 10 copies/mL, at 95% detection rate.

[3] Regardless of the neutralization test result.

別紙様式第２－１



# 医薬品　研究報告 調査報告書

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**研究報告の概要**

潜在性 B 型肝炎ウイルス感染者 (OBI) の血液は抗 HBs 抗体が陽性であれば感染性がないと考えられているが、スロヴェニアにおいて、冠動脈バイパス術で濃厚赤血球と新鮮凍結血漿 (HBs 抗原陰性で抗 HBc 抗体陽性、抗 HBs 抗体低力価陽性、HBV DNA 陽性) が輸血された 59 歳の患者が、その 4 ヵ月後に急性 B 型肝炎を発症した。
また、もう一例、先の例の感染源と同じ供血血液から得られた濃厚赤血球 (RCC) の輸血を受けた 71 歳の患者が、受血の 7 ヵ月後に HBV 感染を認めた (HBV に感染した 2 例はドナーと同じ配列を有するジェノタイプ D 型が感染していた)。
原因となった供血血液は、抗 HBc 抗体及び抗 HBs 抗体 (12IU/L) が陽性であったが、HBV DNA も陽性であり、この供血者のこれまで及びそれ以後のサンプルには低量のウイルスと抗 HBs 抗体が含まれていたが、過去 2 回分の供血血液では HBV 感染は起きていなかった。
今回の 2 例の受血者は手術の外傷に加え、加齢により免疫が低下していたことがウイルスに対する感受性を増大させたとも考えられる。
OBI は感染性を持つが HBV DNA スクリーニングで検出可能であるので、抗 HBc 抗体も HBV NAT も実施されていない国の保健当局は慎重に考慮すべきである。

**使用上の注意記載状況・その他参考事項等**

**重要な基本的注意**

(1) 本剤の原材料となる (献血者の) 血液については、HBs 抗原、抗 HCV 抗体、・・・・陰性で、かつ ALT (GPT) 値でスクリーニングを実施している。さらに、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査 (NAT) を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。

| 報告企業の意見 | 今後の対応 |
|---|---|
| HBs 抗原陰性で抗 HBs 抗体低力価陽性、HBV DNA 陽性の血液による B 型肝炎感染の報告である。<br>血漿分画製剤の原料血漿はミニプール血漿における NAT 検査で HBV DNA 陰性を確認しており、最終製品においても HBV DNA 陰性を確認している。 | 今後ともに潜在性 B 型肝炎ウイルス感染に関する安全性情報に留意していく。 |



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Case Report

# Anti-HBs positive occult hepatitis B virus carrier blood infectious in two transfusion recipients☆

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***Background/Aims*: Occult hepatitis B infection (OBI) in blood donations is not considered infectious when anti-HBs is present.**

***Methods*: Four months after transfusion of eight blood components during coronary arterial bypass surgery, a 59-year-old patient developed acute hepatitis B. A second 71-year-old patient transfused with a red cell concentrate (RCC) from one of these donations had early HBV infection 7 months post-transfusion. Samples were tested for HBV serological markers and HBV DNA was quantified and sequenced.**

***Results*: One implicated donation contained anti-HBc, anti-HBs (12 IU/L) and 180 IU/ml of HBV DNA. Previous and subsequent samples contained 3–10 times lower viral load and slightly variable anti-HBs. Two previous donations did not cause HBV infection. Recipients of the FFP and RCC from the index donation were both HBV infected and carried genotype D strains with sequences identical to the donor strain.**

***Conclusions*: Despite anti-HBs, an OBI carrier transmitted HBV to two immunocompetent transfusion recipients.**
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***Keywords*: HBV; Occult HBV; Infectivity; Blood transfusion**

## 1. Introduction

In Slovenia, approximately 100,000 donations per year are collected. However, in 2005–2007, six cases of HBV transmission by transfusion were reported. Incidence was probably underestimated due to a high frequency of subclinical infection. Since HBsAg serological screening with a sensitive assay is systematically performed, transfusion transmission of HBV can originate from either recent infections in the pre-HBsAg seroconversion window period or occult HBV infection (OBI). OBI is defined as an atypical carrier state characterized by the presence of HBV DNA in plasma without detectable hepatitis B surface antigen (HBsAg) with or without antibodies to hepatitis B core antigen (anti-HBc) and hepatitis B surface antigen (anti-HBs) [1].

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☆ The work reported has in part been presented in abstract form at the European congress of the International Society of Blood Transfusion in Madrid, Spain, June 2007. Dr. Nico Lelie is an employee of Chiron/Novartis but was not involved in the writing of the drafts of the manuscript except for specific comments. Prof J.P. Allain has been an occasional speaker at meetings organised by Chiron/Novartis but does not otherwise have a conflict of interest. The other co-authors do not have any declared conflict of interest.

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*Abbreviations:* OBI, occult HBV infection; HBV, hepatitis B virus; RCC, red cell concentrate; FFP, fresh frozen plasma; anti-HBc, antibody to hepatitis B virus core antigen; anti-HBs, antibody to hepatitis B virus surface antigen; QPCR, real-time PCR; BCP/PC, basic core promoter/pre-core.

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It is generally accepted that HBV DNA in blood may carry the risk of transmission, particularly in the pre-HBsAg window phase [2]. However, the transmission risk of OBIs is not well defined, although some cases of OBIs with anti-HBc only infectious by transfusion were described [2,3].

HBV transmission by blood components from a single anti-HBs positive OBI donation to two recipients is presented.

## 2. Case report

A patient who had been transfused 4 months previously with five units of fresh frozen plasma (FFP) and three units of RCC was suspected of acute hepatitis B. Stored samples from each implicated donation were tested for HBV markers. Seven samples were HBV marker negative. One sample was anti-HBc reactive and contained HBV DNA. The implicated donor was identified and stored samples from eight previous donations and one donation subsequent to the index donation as well as three follow-up samples were tested for HBV markers.

The first recipient of an FFP unit from the index donation was a 59-year-old male who was screened negative for HBV markers 3 days prior to cardiac arterial bypass. He was transfused on 23rd June, 2005. Four months later, clinical and laboratory evidence of acute Hepatitis B was obtained. ALT level was 1821 IU/L, HBsAg and anti-HBc IgM became reactive. No sample was available for HBV DNA testing. In a sample collected 4 months later, HBsAg was undetectable, IgM anti-HBc remained present and HBV DNA was at low level (Table 1).

The second recipient of the index donation was a 71-year-old female who received two units of RCC following orthopedic surgery. No pre-surgical HBV screening was performed and no post-surgical evidence of HBV infection was noted. A blood sample obtained 7 months after transfusion was anti-HBc negative but HBsAg positive and contained a high level of HBV DNA (Table 1). Nine months post-transfusion, ALT level was 566 IU/L. At 14 months post-transfusion the patient had recovered.

### 2.1. Methods

Routine blood donation screening for HBsAg was performed using Abbott PRISM (Abbott laboratories, Delkenheim, Germany). HBsAg repeat testing, anti-HBc and anti-HBs assays were performed with Abbott AxSYM. Cobas Amplicor HBV Monitor (Roche, Basel, Switzerland) and in-house real-time PCR (QPCR) as previously described were used to detect and quantify HBV DNA [4]. Basic core promoter/pre-core region (BCP/PC), Pre-S/S regions and full HBV genome were amplified, sequenced and phylogenetically analyzed as described [5].

## 3. Results and discussion

The index donation met the criteria defining 'occult' hepatitis B virus carriage since the plasma contained no detectable HBsAg but HBV DNA, anti-HBc and low titer of anti-HBs. This pattern was consistent 7 and 16 months after the index donation. Seven prior donations carried anti-HBc and anti-HBs although HBV DNA ranged between 7 and 63 IU/ml when tested

**Table 1**
**Hepatitis B virus markers in the OBI donor and two HBV infected recipients**

| | Time from Index donation (m) | HBsAg | Anti-HBc | Anti-HBc IgM | Anti-HBs (IU/L) | HBV DNA (IU/ml) | | HBV genotype |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Amplicor | QPCR | |
| Donor | −45 | − | + | ND | 29 | Neg | 63 | |
| | −37 | − | + | ND | 15 | Neg | Neg | |
| | −31 | − | + | ND | 16 | Neg | 35 | |
| | −23 | − | + | ND | 16 | Neg | 45 | |
| | −19 | − | + | ND | 19 | Neg | 7 | |
| | −13 | − | + | ND | 15 | Neg | ND | |
| | −6 | − | + | ND | 15 | Neg | ND | |
| | Index | − | + | ND | 12 | <60 | 180 | D |
| | +3 | − | + | ND | 53 | Neg | ND | |
| | +7 | − | + | ND | 31 | Neg | 16 | |
| | +12 | − | ND | ND | ND | ND | Neg | |
| | +16 | − | + | ND | 25 | Neg | 40 | |
| Recipient 1 | −3 days | − | − | ND | − | ND | ND | |
| | +4 | + | + | + | − | ND | ND | |
| | +8 | − | + | + | − | 12 | 185 | D |
| Recipient 2 | +7 | + | − | − | − | $1.1 \times 10^6$ | $1.7 \times 10^8$ | D |
| | +14 | − | + | + | − | Neg | ND | |

−, non-reactive; ND, not done; Neg, negative.

with a sensitive in-house assay but was consistently undetectable by a commercial assay except in the Index sample. This pattern indicates recovery from >5 years past HBV infection (Table 1). Despite being tested with the high sensitivity assay, two of the nine donor samples tested remained HBV DNA negative, suggesting fluctuations of viremia. Prior to the index donation, anti-HBs levels were essentially stable (15–29 IU/L) but increased from 12 to 53 IU/L 3 months later suggesting minimal immune response. There was no clinical evidence that 14 previous donations and one subsequent donation were infectious to recipients. Pre- and post-transfusion samples from recipients of −71 and −13 month-donations showed no serological evidence of HBV infection. The −71 recipient was negative for HBsAg, anti-HBc and anti-HBs pre-transfusion, and 4 months post-transfusion, HBsAg was negative but anti-HBc was not tested. The −13 month recipient did not carry HBsAg, anti-HBc or anti-HBs 42 months after transfusion.

In contrast, there is strong evidence that both recipients of the index donation were HBV infected since acute hepatitis B occurred in recipient 1, 4 months after transfusion. In recipient 2, the 7-month post-transfusion sample containing HBsAg and high HBV DNA load without anti-HBc strongly suggested recent acute HBV infection and was followed by serological evidence of recovery (Table 1). A high ALT level 9 months post-transfusion that normalized after 14 months further supported this conclusion. The 4-month and probably 7-month long incubation time observed in recipients 1 and 2, respectively, could be explained by a relatively low infectious dose further decreased by partial anti-HBs neutralization (calculated on the basis of 180 IU/ml of HBV DNA and 200 ml of FFP for recipient 1 at 200,000 copies and 20,000 copies in 20 ml of RCC plasma for recipient 2). Published data indicated that lower infectious dose prolonged HBV incubation time and milder symptoms [6]. Transfusion transmission was further demonstrated by the Pre-S/S sequence identity between the index donation, recipient 1 and recipient 2 strains from follow-up samples. The whole genome sequences of recipient 2 and index donation were identical. Strains were of genotype D. Of note, the deduced amino acid sequence of the S protein was wild-type when compared to the genotype D consensus sequence except for A117T and S133Y, neither of these substitutions being recognized as escape mutants. An escape mutant mechanism explaining the infectivity of the index donation but not of the other donations from the donor was thus excluded. Similar cases of breakthrough HBV infection with wild-type strains have been described [7]. Although suppression of the HBV replication and gene expression is a reported cause of occult HBV [8], no mutation in the parts of the genome implicated in replication was found. Imperfect containment of viral replication by the donor immune system is the most likely cause of low levels of HBV DNA.

The stability of HBV DNA load and anti-HBs in multiple samples preceding the index donation and tested simultaneously contained 6–10 times less viral DNA than the index donation (Table 1). It is therefore speculated that the main factor singling out the index donation was a temporarily higher viral load sufficient to overcome the relatively weak neutralizing capacity of a low anti-HBs level (Table 1). This interpretation is supported by the subsequent increase in anti-HBs level suggesting a weak immune response.

Published data reporting the infectivity of OBIs by transfusion are rare. One case of transmission by a donation carrying anti-HBc without anti-HBs was reported in Japan [2]. Another study reported five donors (4 genotype D, one genotype A2) with OBI also carrying only anti-HBc transmitting to recipients. Of 51 traced recipients, 28 (54.9%) either developed fulminant, fatal, hepatitis B (3 cases) or carried anti-HBc post-transfusion although no pre-transfusion testing was performed [3]. In the Japanese study, 16 donations contained both anti-HBc and anti-HBs and no evidence of HBV transmission was found [2] confirming previous results [9]. The two cases reported here appear to be the first related to an OBI donor with anti-HBs. Data collected in Poland indicated that approximately 50% of OBIs in asymptomatic, apparently healthy, blood donors carry anti-HBs [10] and that levels of DNA and anti-HBs are variable as reported here.

Considering that the recipients at age 59 and 71, respectively, might have presented a mild, age-related, immunodeficiency added to the trauma of major surgery might have played a role in increasing susceptibility to viral infection [11]. The fact that approximately 50% of recipients of blood components in Western Europe present some degree of immunodeficiency related to age, chemotherapy or therapeutic immunosuppression suggests an increased susceptibility to HBV infection [12]. Limited but convincing evidence that OBIs can be infectious and can be detected by HBV DNA screening should be carefully considered by the health authorities of countries where neither anti-HBc nor HBV NAT are implemented.

Despite their apparent uniqueness, our two cases of HBV transmission need to be factored in discussions regarding HBV blood safety policy. They clearly illustrate that the neutralizing capacity of low-level anti-HBs is limited and reinforce the validity of considering anti-HBs below 100 IU/L to be poorly protective from infectivity when HBV DNA is present. However, even in the presence of higher levels of anti-HBs, in a severely immunodeficient recipient, HBV DNA-containing blood might be infectious and the clinical expression severe.

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