WS-4-4　化学療法および造血細胞移植療法実施後にB型肝炎ウイルスの再活性化を生じた、HBs抗原陰性症例の検討
HB virus reactivation in HBs antigen-negative patients after chemotherapy and HSCT

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当科において、化学療法および造血細胞移植療法実施後に、重篤なB型肝炎を生じた症例を複数例経験した。いずれの症例も治療前のHBs抗原は陰性であり、治療経過中に投与された輸血製剤を介した感染や院内感染による伝播は否定的であった。これらの症例の中にはHBs抗体およびHBc抗体の陽性者が存在することが判明しており、免疫状態の変動にともないB型肝炎ウイルス(HBV)の再活性化が生じたことが推察される。肝移植においては、HBc抗体陽性のドナーから移植を受けたレシピエントでは高率にHBVの感染が成立することが以前から知られている。つまりHBc抗体陽性のHBV既往感染例からはHBV遺伝子が完全に排除されておらず、微量の増殖が続いているもののHBs抗体の存在によって沈静化が維持されている状態であり、宿主の免疫状態によっては再燃しうると考えられる。以上をふまえ、当科では治療開始前に可能な症例においてHBs抗原、HBs抗体、HBc抗体を測定し、HBc抗体が高力価陽性(10.0 S/CO以上)の症例には抗ウイルス薬(Lamivudine)を化学療法開始当初から併用する方針を検討しており、文献的考察も含め報告を行う。

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研究報告の概要

○人の咬傷によるB型肝炎感染―唾液中のウイルスの検出及び全ゲノム配列による確認
B型肝炎ウイルス（HBV）はキャリアの唾液中に検出され、疫学調査ではヒト咬傷が感染ルートになり得ることを示唆している。学習障害の人が保護施設の同室者に噛まれた後、急性B型肝炎を発症した例を報告する。噛んだ人はHBVの慢性のキャリアで、唾液中にはウイルスが存在していた。両者のHBVの遺伝子型と塩基配列は一致した。コミュニティでのHBV感染経路の一つとして、唾液の役割についてさらなる調査が求められる。

報告企業の意見	今後の対応
人の咬傷により唾液からB型肝炎ウイルスが感染したことが、遺伝子解析により確認されたとの報告である。	HBV感染の新たな伝播ルート等について、今後も情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

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Case report

Transmission of hepatitis B by human bite—Confirmation by detection of virus in saliva and full genome sequencing

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Abstract

Hepatitis B virus (HBV) can be detected in saliva of carriers and epidemiological studies suggest human bite as a possible route of transmission. We report a case of acute hepatitis B that developed after an individual with learning difficulty was bitten by a fellow resident in a sheltered accommodation. The attacker was found to be a chronic carrier of HBV and virus was present in his saliva. The HBV in both men had identical genotype and sequence. Future studies are warranted to investigate the role of saliva as a vehicle of HBV transmission in the community.

Keywords: HBV infection; Human bite

The presence of hepatitis B virus (HBV) DNA in saliva of carriers of the virus and its correlation with the serum HBV DNA level was nicely described in a recent article in this journal (van der Eijk et al., 2004). The finding has important implication in the infectivity of saliva in patients with HBV infection and offer further insight in it being an alternative route of transmission of the virus. Nevertheless, despite epidemiological data suggesting that human bite can result in HBV infection (Cunningham et al., 1994), this has never been definitely proven by genome sequencing of virus in the carrier and the bitten. We described a case of acute hepatitis B infection as a result of human bite and provided the genotypic evidence of viral transmission with saliva being the vehicle.

A 43-year-old man with learning difficulty and known history of generalized epilepsy was admitted in May 2004 with another episode of generalized seizure. His convulsion was successfully controlled by adjustment of his anti-convulsant regimen. Coincidentally, he was noted to have isolated elevated alkaline phosphatase (ALP) of 158 IU/L. Though this was likely to be related to his anti-convulsant, hepatitis B surface antigen (HBsAg) was tested for the first time and the result was positive. The patient was readmitted in June with drug-induced hand tremor. Repeat blood test showed that he had grossly deranged liver chemistry (total bilirubin 44 μmol/L, ALP 246 IU/L and alanine transaminase (ALT) 1655 IU/L). His INR was 1.24 (reference range 0.9–1.1). His IgM anti-hepatitis B core antibody was positive. Subsequent retrospective testing of a blood specimen from February 2004 was negative for HBsAg. The patient was diagnosed to have acute hepatitis B and made an uneventful recovery from the disease. He achieved successful HBsAg seroconversion spontaneously within 6 months.

Meanwhile, the route of HBV transmission was investigated. He was sexually inactive and there was no recent operation or transfusion of blood products. On further questioning, patient's relative claimed that patient was bitten on his right hand in February 2004 by another mentally handicapped resident (resident A) in the sheltered accommodation where he was staying. The bite was so severe that it resulted in cellulitis that needed a course of intravenous antibiotic treatment.

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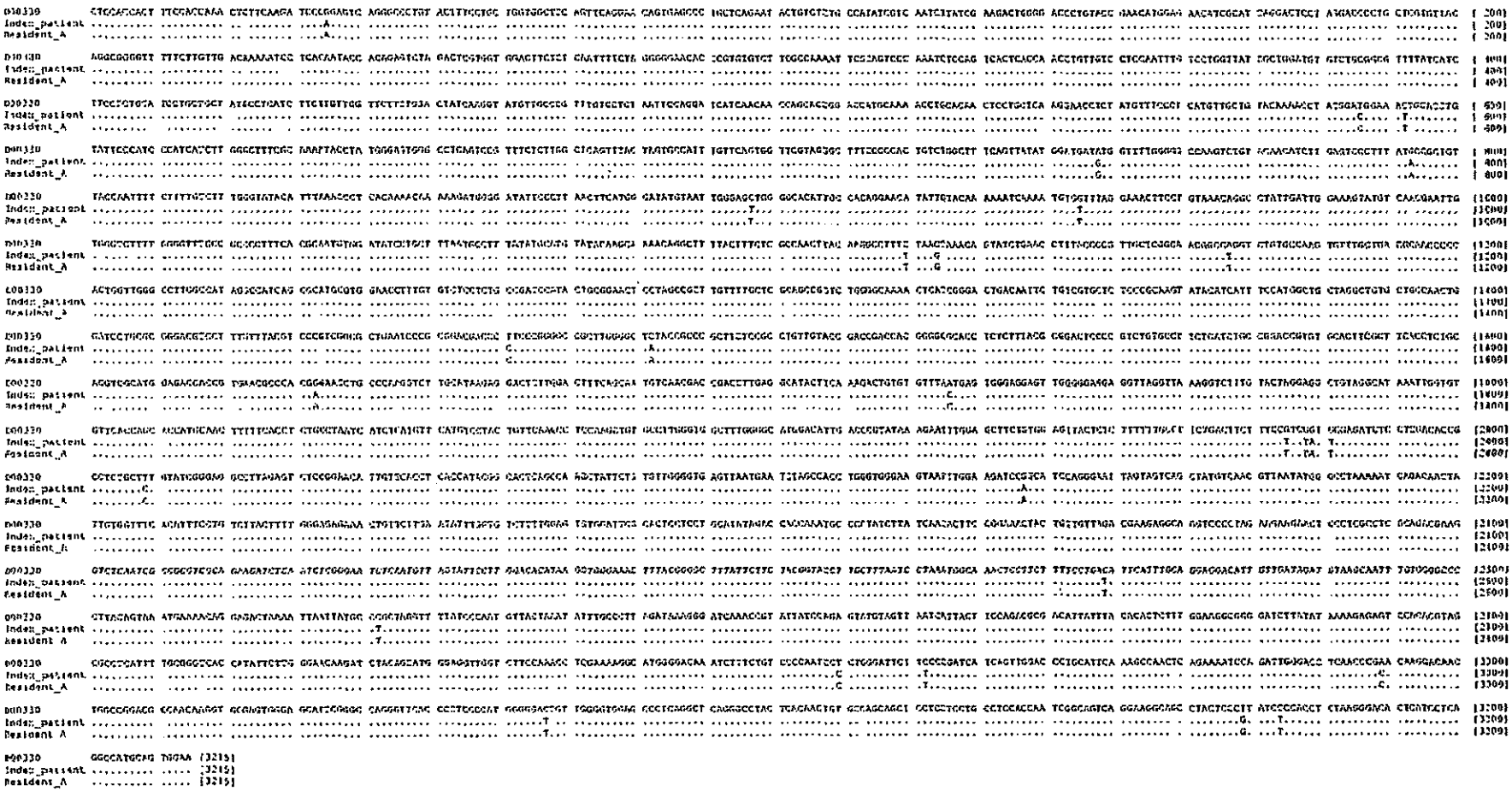

Fig. 1. Full genomic DNA sequence of the hepatitis B virus extracted from the sera of index patient and resident A. Accession number of reference sequence: D00330 (Okamoto et al., 1988).

Although it was believed that human bites could inoculate HBV, the best evidence was based on history and serological results (MacQuarrie et al., 1974; Stornello, 1991). Epidemiological data are suggestive that human bites could have contributed to the higher risk of hepatitis B transmission in institutions (Cunningham et al., 1994). We sought to confirm this route of transmission by further investigations including genotypic investigations. Resident A was found to be HBsAg and HBeAg positive with mildly elevated ALT at 99 IU/L. His serum HBV DNA level was 71×10^6 copies/mL (Taqman real-time PCR assay). Hepatitis B virus was also detected in his saliva (HBV DNA level: 3.2×10^6 copies/mL). We then sequenced the HBV DNA genome of the virus in the sera of Resident A and the index patient (HBV DNA level: 5.5×10^6 copies/mL). The two sequences were both genotype B and were identical with each other (Fig. 1). Dental and oral examination of resident A revealed only mild periodontal disease and no overt bleeding source.

A recent study demonstrated that the HBV could be detected in the saliva of between 42% and 80% of chronic hepatitis B (CHB) patients (van der Eijk et al., 2004). Paired quantitative measurements of HBV DNA showed correlation between the levels of HBV DNA in saliva and serum in these patients. Our finding clearly demonstrated the infectivity of saliva in a CHB patient. The importance of screening of HBV status and HBV vaccination of residents in institutions cannot be overemphasized. Further studies are also warranted to investigate the importance of saliva as a vehicle of transmission of HBV in the community.

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別紙様式第 2-1

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研究報告の概要

米国では，HIV-1 および HCV に対して 1999 年から血漿ミニプールに対する核酸増幅検査 (NAT) が実施され，2002 年には FDA による承認が得られた。また西ナイルウイルス (WNV) についても実施されている。一方 HBV については，1971 年に B 型肝炎表面抗原 (HBsAg) スクリーニングが実施されて以降，検査の感度は飛躍的に向上し，現在では主要な HBsAg サブタイプに対する感度は 0.5ng/ml にまで高まっている。また，HBV のコア抗原 (抗 HBVc) に対するスクリーニングも実施されている。

2003 年に報告された急性 B 型肝炎は 7381 例のうち，最終的に発症が輸血の 6 ヵ月以内であったことが確認されたのは 10 例であり，感染が確認された供血者は 1 名のみであった。米国赤十字社の公表によると，2000 年から 2001 年の 1 年間における B 型肝炎感染の可能性は，205,000 例中 1 例である。この数字は HIV-1 の感染リスクよりも高いが，実際には輸血による B 型肝炎の感染はほとんど報告されていない。

この数年間で HBV に対する NAT アッセイが開発された。本稿では，FDA が実施した Roche COBAS AmpliScreen HBV assay の試験およびヨーロッパでの Gen-Probe/Ghiron Ultrio assay の多施設試験の結果について報告する。HBV NAT 導入の検討に当たっては，現行の HBsAg 検出法と比較して感度および費用対効果の面で優れているかどうかを検討する必要がある。この 2 試験を検討した結果，NAT が現行の HBsAg 検出法および HBc アッセイと比較してそれほど優れた検査法でなく，費用対効果もわずかであることが判明した (Roche の試験で 1/250,000 の感染率)。これらの結果から，FDA は，「NAT の実施は現時点ではミニプールおよび個別ドナーに対して任意で実施されるべきである。現行のスクリーニングに本方法を追加することの利点は非常に限られている」との見解を示した。

現行の HBsAg 検査の感度や近い将来さらに感度の上昇した HBsAg 検査が利用可能になることを鑑みればミニプール NAT の導入の利点は少ないと考えられる。

使用上の注意記載状況・その他参考事項等

報告企業の意見	今後の対応
本論文は，HBsAg 検出検査が非常に有効でありその感度は今後さらに改良されていくであろうということが示唆されている。弊社の血漿分画製剤の血漿プールレベルでは，HBV ウイルス検出に関しては NAT と抗原検出検査を組み合わせて実施しており，感染リスクは極めて低いと考えられる。	現時点で弊社が新たな安全対策上の措置を講じる必要はないと考える。引き続き関連情報の収集に努める。

EDITORIAL

Pooled hepatitis B virus DNA testing by nucleic acid amplification: implementation or not

The blood banking community went through a major technological advancement in 1999 with the implementation of minipool nucleic acid amplification testing (MP NAT) for human immunodeficiency virus-1 (HIV-1) and hepatitis C virus (HCV). Tests were FDA-licensed in 2002, and NAT for these agents is now required in the United States and many other countries throughout the world. In the United States alone, it is estimated that HIV-1 and HCV NAT prevent the transmission of 5 HIV-1 and 56 HCV infections annually.[1] This significant accomplishment has reduced the residual risk of transfusion-transmitted HCV to 1 in 1.390 million units, and HIV-1 to 1 in 1.525 million units, factoring in donations from both repeat and first-time donors and determining risk in first-time donors by multiplying repeat donor risk by 2.4.[2] Debate continues regarding the need to reduce pool size or even to perform NAT on every donation for HIV-1 and HCV; this debate is fueled by the fact that MP NAT–negative units from donors having low viral loads will transmit to a recipient.[3-6] The availability of NAT technology also permitted the very rapid implementation of routine testing for West Nile virus.[7-9] WNV NAT is considerably more complex than for HIV-1 or HCV because the need exists to adjust the testing algorithm from pooled to an individual donation (ID) format during epidemic time periods.

Now our focus is once again on hepatitis B virus (HBV). The debate about whether to implement more sensitive testing for this agent is not new; since the implementation of hepatitis B surface antigen (HBsAg) screening in 1971, there has been continued improvement in test sensitivity. The first methods used included gel precipitation, counterelectrophoresis, and reverse passive hemagglutination, followed in 1974 by radioimmunoassay, and finally in 1979 to 1980, by a series of enzyme immunoassays (EIAs). As assays were optimized and relicensed, all EIAs used for donor screening until 2003 have had sensitivities for the major HBsAg subtypes of approximately 0.5 ng per mL. This represents a significant reduction from the previous immunologic-based assays having greater than 10 ng per mL sensitivity (some of these assays still exist outside of the United States).[10] With the exception of the United States, and since 1997, the use of HBsAg chemiluminescent assays is common (such as the Abbott PRISM automated analyzer); however, in the United States, this assay is still awaiting FDA licensure. The sensitivity of the US version of the PRISM HBsAg assay is estimated at 0.08 ng per mL, corresponding to 720 to 1644 HBV DNA copies per mL or a 9-day window-period reduction;[10,11] once licensed, this assay will likely see widespread implementation. So, in looking back at the prior 34 years of HBsAg screening, the ability to detect this antigen has improved by greater than 2 $\log_{10}$. The success of HBsAg screening is a remarkable example of continuous improvement.

In the United States, we also have a second safeguard to prevent HBV transmission, which is to screen for antibodies to the core antigen of HBV. Screening for anti-HBc began in 1986 to 1987 as a surrogate for non-A, non-B hepatitis but was licensed in 1991 to prevent the transmission of HBV when HBsAg declines to below detectable levels, and anti-HBs has not yet appeared. It is now well accepted, however, that this "anti-HBc window period" no longer exists owing to the increased sensitivity of HBsAg assays. The use of anti-HBc has been one of the most frustrating experiences for US blood bankers and donors because the specificity of the available assays is far from optimal, no confirmatory assay has ever been licensed, and there has never been a donor reentry protocol for the hundreds of thousands of healthy individuals who have been deferred because of the nonspecificity of these assays. So, the question is, why do we still use this test? This will be discussed later in this editorial.

With these comments as background, where do we stand today with HBV and the safety of the blood supply? In reviewing the literature and from discussions with the CDC (M. Alter, personal communication), there have been few well documented US cases of transfusion-transmitted HBV in the recent past. Through the National Notifiable Diseases Surveillance System (CDC, unpublished), an enhanced surveillance for acute HBV occurred. Of 7381 cases of acute hepatitis B reported in 2003, 49 of these cases were initially reported as associated with a transfusion, and of those, 10 were confirmed by the CDC as acute cases of hepatitis B corresponding to the time of transfusion (i.e., transfusion within the prior 6 months). Of those 10, only 1 case could be associated with a single infected donor. It is hard to equate this observed risk with the current estimates of residual risk. Schreiber and colleagues[12] published a figure of 1 in 63,000, which is commonly cited as the per unit risk of HBV transfusion transmission. The

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donor base for this estimate was the five REDS centers that reported HBsAg "converters" from 1991 to 1993 in donations from repeat donors; owing to the transient nature of HBsAg, a correction factor was applied to the 4.12 HBsAg incidence rate to bring the incidence rate for HBV to 9.80 per 100,000 person-years of observation. This number was multiplied by the window period from presumed infection to the appearance of HBsAg (59 days) to give the residual risk of 1 in 63,000. A more recent figure of 1 in 205,000 for the residual risk was published for donations to the American Red Cross.[2] The calculation used the same 59-day window period (because the same HBsAg assays had been used) but included an observed HBsAg incidence rate of 1.27 (adjusted to 3.02) per 100,000 for the period of 2000 to 2001. Consequently, owing to the decline in the incidence of HBsAg in the donor population from 1991 to 1993 compared to 2000 to 2001, the residual risk was calculated as 1 in 205,000 in donations from repeat donors or 1 in 144,000 for all donations. This residual risk is considerably higher than that estimated for HIV-1 or HCV, but with little to no transfusion-transmitted HBV reported, one wonders why this theoretical risk does not result in more documented infection or disease. Likely explanations include the very conservative assumption that the entire 59-day window period is infectious, which then would overestimate risk, coupled with the fact that HBV infection in adults infrequently results in recognized acute or chronic disease (the virus is cleared in 95% of infected adults) so that even if infection occurs, it is not reported.

Over the past several years, HBV NAT assays have been developed that shorten the remaining window period to varying degrees.[10,11] This month's **TRANSFUSION** reports on the results of the US FDA clinical trial of the Roche COBAS AmpliScreen HBV assay[13] and a European multicenter study of the Gen-Probe/Chiron Ultrio assay (simultaneous detection of HIV-1 and HCV RNA and HBV DNA).[14] The assay formats, pooling and testing procedures, and equipment for both manufacturers are the same as those used today for HIV-1 and HCV. As we consider whether or not to implement HBV NAT, several key questions require resolution. Do the assays have the same performance characteristics that we have come to expect from NAT assays, which frequently out perform serologic assays? How does this performance compare to the best HBsAg detection assays? Should we consider the assay in a MP or ID format? Are the residual risk and clinical consequences of HBV significant enough for us to invest another huge amount of financial and personnel resources into an HBV NAT assay at all? Many of the critical items necessary to answer these questions are outlined in the two HBV NAT studies[13,14] and are best framed by the opening remarks in the discussion by Kleinman and colleagues. "Whether HBV MP NAT should be part of routine donor screening is impacted by multiple factors including the risk of HBV transfusion transmission, the yield of window-period cases detected by MP NAT, other performance characteristics of the assay system, the clinical consequences of transfusion-transmitted HBV infection, and the cost-effectiveness of MP NAT." The debate of whether or not to license and ultimately to mandate the Roche HBV test in the United States occurred at two advisory committee meetings held before the test being licensed (on April 21, 2005). The first was the Blood Products Advisory Committee and the second was the Advisory Committee on Blood Safety and Availability. Discussion points at both meetings, made by the AABB, focused on the fact that HBV is a clinically important viral infection that may be transfusion transmitted, that the yield observed in the Roche clinical trial of 1 in 250,000 to 1 in 300,000 is the same as the HCV NAT yield and substantially higher than the HIV-1 NAT yield, and that the observed HBV NAT yield has been consistent with estimates.[11] However, due to low concentrations of HBV DNA present early in acute infection when both MP NAT and HBsAg would be non reactive, ID NAT would have a much higher yield, increased window-period closure, and consequently greater benefit. Also, HBsAg tests with high sensitivity (<0.1 ng/mL) would be predicted to have a comparable yield to MP NAT. Finally, owing to the relatively low yield of MP NAT in comparison to the safety afforded by HBsAg and anti-HBc assays, coupled with low rates of chronic HBV infection and clinical disease, HBV MP NAT offers only marginal cost-effectiveness.[15] In terms of quality-adjusted life-years (QALYs) and window-period closure, HIV-1 has a calculated QALY per infection avoided that is 44 times higher than HBV, with an HIV-1 window-period reduction by MP NAT of just over half in comparison to that projected by ID NAT. For HCV, the QALY per infection avoided is four times higher than for HBV, but 95 percent of the window period has already been reduced by HCV MP NAT.

The study by Kleinman and coworkers[13] reports the extended use of the Roche HBV test beyond that formally presented to FDA for licensure; with these and additional data (D.M. Strong, personal communication), HBV MP NAT yield remained consistent at approximately 1 in 340,000 (five yield donors per 1.7 million units screened). With an incidence rate of 5.1 per 100,000 and a 49-day window period (59 days minus 10), the MP NAT expected yield was 1 in 370,588. Although the observed and predicted yields were similar, these determinations may overestimate the long-term yield owing to the fact that lower HBV incidence rates have been reported and are continuing to decline.[2,16] Finally, using the observed yield, this study projected that MP NAT would likely interdict 39 HBV window-period units and prevent 56 cases of transfusion-transmitted HBV infection annually.

The yield in the study by Kleinman and colleagues[13] was achieved with a MP sample preparation method referred to as multiprep with a sensitivity of 20 copies (or

5 IU) per mL (at 95% confidence) and 480 copies per mL in a pool of 24; the ID and pool resolution sensitivity was 60 copies per mL (also at 95% confidence). Viral loads for the four yield samples (and a fifth not reported in the article) were 200 copies per mL in an individual who had high-titer anti-HBs and never produced HBsAg, 2,000 to 37,000 copies per mL for three samples from donors who developed HBsAg 7 to 17 days after the index donation and finally 61,000 copies per mL; this index donation sample was also reactive by the Ortho HBsAg System 3 assay. It is unknown how many of these samples would have detectable HBsAg if they were tested with more sensitive HBsAg assays, including the US version of PRISM. HBV NAT specificity was 99.9964 percent for pools of 24 (including 21 false-positive donors); however, it is worth noting that when a substudy was performed as part of the licensing clinical trial with ID NAT, that specificity decreased to 98.4 percent.[17] One other assay variable that was stated by Kleinman and coworkers to be "acceptable" for the Roche HBV NAT assay was the invalid rate of 3.29 percent. Interestingly of the invalid assays, 40 percent were invalid because of low-level HBV DNA contamination of the negative plasma used to manufacture the negative control. For most laboratories, an invalid rate of 3.29 percent is excessively high in contrast to the performance of other assays, both serologic and NAT-based having invalid rates of 1.0 to 1.5 percent.

The study by Kleinman and associates[13] tried to address the question of whether HBsAg screening could be replaced by HBV NAT (MP or ID NAT). HBV DNA was detected by MP NAT in 84 percent of the HBsAg-positive, anti-HBc-reactive donations versus 94 percent detection by ID NAT. Of those not detected by MP NAT, the viral loads ranged from less than 100 to 5900 copies per mL. If HBsAg screening were eliminated, would anti-HBc screening coupled with HBV NAT be adequate to protect recipient safety? Complicating the question of whether HBsAg testing may be eliminated is the issue of false-positive HBsAg neutralization results. This study reported four donations that were confirmed positive for HBsAg, anti-HBc nonreactive and negative for HBV DNA. Follow-up of all four donors documented that the test-of-record neutralization results were false-positive. False-positive neutralization results due to intraassay contamination are more common than is documented. This primarily occurs while performing the assay from carryover of high-titer samples into adjacent wells containing negative donation samples.

Although very few anti-HBc–reactive donations that were HBsAg-nonreactive were detected as HBV DNA–positive by MP NAT (0.03%), with ID NAT, detection increased to 0.41 percent, which was higher than a previously reported study of 0.24 percent[18] but lower than in a study performed by the American Red Cross of 0.63 percent[19] and 1.1 percent as reported by the Japanese Red Cross.[10] In all studies, the vast majority of samples identified by ID NAT had viral loads too low for quantitation (i.e., less than 100 copies/mL); of the two that had quantifiable virus reported by Kleinman[13] and colleagues, 1200 copies per mL was the maximum concentration reported. The finding of low-level HBV DNA positivity reinforces the fact that even if ID NAT for HBV were to be implemented, anti-HBc testing would still be required. The estimate of 1 percent or less of HBV DNA–positive, anti-HBc–reactive donors is likely an underestimate of the true number of HBV DNA–positive samples that occur in anti-HBc–reactive individuals because the sensitivities of the tests used in all studies ranged from 36 to 100 copies per mL, and more sensitive HBV DNA tests are available (on a research basis).

The FDA licensure of the Roche COBAS AmpliScreen assay was accompanied by answers to the questions raised regarding mandating the use of the HBV MP NAT in the United States and whether the test could replace either HBV serologic test (HBsAg and/or anti-HBc).[20] In response to the first question, the FDA stated, "The use of this test is currently considered optional both in MP and ID formats. FDA regards the use of this test for donor screening as voluntary because the estimated individual and public health benefits of adding this test to available screening tests are thought to be very limited." They continued that, "Public health officials will reconsider possible recommendations for routine donor screening for HBV by nucleic acid tests based on experience with and results of voluntary use of the test, further technology development, and any other factors that might affect the health benefits expected from such testing." Regarding replacing either HBV serologic test, the FDA stated, "Data on the use of either MP or ID formats are insufficient at the present time to allow the replacement of either the HBsAg test or the anti-HBc test."

Koppelman and colleagues[14] evaluated the performance of the Procleix Ultrio Assay (Gen-Probe/Chiron) at four European sites. Variables studied were analytic sensitivity by serially diluted international reference materials, genotype A through G detection at 0.1 to 1000 copies per mL, and seroconversion sensitivity with 15 commercial plasma panels. Detection of HBV DNA in undiluted seroconversion samples or with samples diluted 1:8, 1:16, and 1:24 was compared to HBsAg detection by the Abbott PRISM analyzer (European reagents/software). In addition, 23,296 blood donations were tested by Ultrio in pools of 8 (2,912 pools).

Ultrio detected the HBV WHO reference material (97/746) at a 95 percent detection rate of 11 IU per mL with a range of 7.3 to 22 IU per mL (vs. the AmpliScreen multiprep method at 5 IU/mL).[13] Conversion from IU per mL to copies per mL previously WHO collaborative studies was 7.4 copies per IU but in this evaluation was 20.7 copies per IU. Regardless, Ultrio demonstrated lesser sensitivity than the AmpliScreen multiprep method (81-228 copies/mL for