Occult hepatitis B virus infection: implications in transfusion

J.-P. Allain
Division of Transfusion Medicine, Department of Haematology, University of Cambridge, Cambridge, UK

Hepatitis B virus (HBV) presents a higher residual risk of transmission by transfusion than hepatitis C virus (HCV) or human immunodeficiency virus (HIV). While most infectious blood units are removed by screening for hepatitis B surface antigen (HBsAg), there is clear evidence that transmission by HBsAg-negative components occurs, in part, during the serologically negative window period, but more so during the late stages of infection. Donations negative for HBsAg, but positive for HBV DNA, with or without the presence of HBV antibodies, correspond to ‘occult’ HBV infection (OBI). The frequency of OBI depends on the relative sensitivity of both HBsAg and HBV DNA assays. It also depends on the prevalence of HBV infection in the population. OBI may follow recovery from infection, displaying antibody to hepatitis B surface antigen (anti-HBs) and persistent low-level viraemia, escape mutants undetected by the HBsAg assays, or healthy carriage with antibodies to hepatitis B e antigen (anti-HBe) and to hepatitis B core antigen (anti-HBc). Over time, in the latter situation, anti-HBe and, later, anti-HBc may become undetectable. The critical question is whether or not OBI is infectious by transfusion. All forms have been shown to be infectious in immunocompromised individuals, such as organ- or bone marrow-transplant recipients. In immunocompetent recipients, there is no evidence that anti-HBs-containing components (even at low titre) are infectious. Anti-HBc only, with HBV DNA, can be associated with infectivity, as can rare cases of HBV DNA without any serological HBV marker. If HBV nucleic acid amplification technology (NAT) is considered, the OBI viral load would usually be < 500 IU/ml, making testing of plasma pools unsuitable unless the sensitivity of NAT significantly increases by genome enrichment or test improvement.

Key words: hepatitis B, HBV, anti-HBc, occult hepatitis B.
that after HBsAg was no longer detectable, HBV DNA persisted for years in serum (28%) or in the liver (94%) [8,9]. OBI has also been observed in populations without liver disease, such as blood donors, individuals with normal liver function tests and in the general population [10–13]. Occult HBV infection in these asymptomatic individuals is the subject of this review.

HBsAg and HBV DNA testing

Recent data indicate that when HBsAg is present, HBV DNA can be found in the circulation or in the liver [14–16]. Initial data obtained with direct hybridisation, indicating low proportions of HBsAg-positive samples containing HBV DNA, was clearly dependent on the sensitivity of the assay used. It is only with the development of PCR, nested PCR and real-time PCR (QPCR) that a clearer picture has emerged. As shown in Table 1, the percentage of HBsAg-containing samples found to be HBV DNA positive increased with the use of a more sensitive amplification assay [17–19]. Conversely, a decreasing proportion of blood samples containing only HBV DNA was found when HBsAg assays of increasing sensitivity were utilised. This was particularly apparent in panels of samples from seroconverters in the window period [20,21]. Biswas et al. showed that assays detecting < 0.1 ng/ml of HBsAg substantially reduced the window period compared to licensed assays detecting 0.2–0.6 ng/ml. There are no data examining the detectability of HBV DNA and the potential correlation between HBsAg and HBV DNA concentrations at the late stages of HBV carriage. The decreasing proportion of HBsAg-containing samples that are negative for HBV DNA as nucleic acid amplification technology (NAT) sensitivity improves, suggests that most, if not all, HBsAg-positive samples in apparently healthy individuals contain HBV DNA [18,19]. The frequency of HBV DNA detected in HBsAg-negative samples varies considerably according to the prevalence of the infection. In Northern countries, where the prevalence of infection is below 5% and the prevalence of chronic infection is less than 1%, no more than 5% of HBsAg anti-HBc+ blood donor samples contain HBV DNA [17,22]. In contrast, in high-prevalence areas (such as India, Taiwan, Japan and Sardinia), HBV DNA, detected by hybridisation or PCR, is found in 4–24% of the anti-HBc positive population [23–26].

The various forms of OBI

OBI in apparently healthy individuals is essentially found in four types of clinical conditions (Fig. 1):

1. Recovery from infection defined by the presence of anti-HBs.
2. Chronic hepatitis, where the infection is related to escape mutants that are not (or only poorly) recognised by either natural polyclonal or monoclonal antibodies in assays.
3. Chronic hepatitis at the healthy carriage stage marked by the presence of anti-HBc, with or without detectable antibody to hepatitis B e antigen (anti-HBe).
4. Chronic hepatitis or healthy carriage without any marker of HBV infection other than HBV DNA.

OBI in ‘recovered’ infection

Some individuals who have recovered from HBV infection and produced neutralising anti-HBs may continue to replicate HBV DNA at low levels that are detectable for years in the liver, peripheral blood mononuclear cells or serum [10,13,14,27–33]. In such cases, the virus is either complexed with anti-HBs, or free in the circulation, or both forms might be present [29,31]. In the few cases where HBV DNA has been quantified, the viral load was found to be very low, ranging between 5 and 1000 IU/ml (Table 2). The few published molecular analyses of such cases suggest that the circulating virions are essentially of the wild type [10], but a stop codon at nucleotide 1896 of the precore region was reported in some cases [32,33]. There was no indication of S-gene escape mutants, but other mutations, possibly involved in decreased viral replication, were found [10]. Another explanation might be an incompletely effective cytotoxic T-lymphocyte (CTL) response that would clear most, but not all, of the virus produced [29]. Preliminary data suggest that viral persistence after recovery might be relatively frequent as virus was found

Table 1 Relationship between hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA detection

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>HBV DNA limit of detection (IU/ml)</th>
<th>HBV DNA in HBsAg positive samples</th>
<th>HBV DNA + anti-HBe positivity, irrespective of ALT level</th>
<th>HBV DNA in anti-HBc only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jardi et al. [66]</td>
<td>1000</td>
<td>128/193 (66%)</td>
<td>36/91 (40%)</td>
<td>ND</td>
</tr>
<tr>
<td>Kessler et al. [67]</td>
<td>400</td>
<td>ND</td>
<td>30/37 (81%)</td>
<td>ND</td>
</tr>
<tr>
<td>Loeb et al. [18]</td>
<td>10</td>
<td>164/195 (84%)</td>
<td>83/107 (78%)</td>
<td>10/109 (9%)</td>
</tr>
<tr>
<td>Allain et al. [19]</td>
<td>20</td>
<td>156/159 (98%)</td>
<td>108/112 (96%)</td>
<td>14/107 (13%)</td>
</tr>
</tbody>
</table>

Anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; ND, not determined.
Summary of the multiple potential origins of occult hepatitis B infection

![Diagram of potential origins of occult hepatitis B infection]

Fig. 1 Summary of the multiple potential origins of occult hepatitis B infection (OBI). Recovered infections in children and adults, indicated by the presence of antibody to hepatitis B surface antigen (anti-HBs), are shown above and below the dotted lines (OBI 1 and OBI 7). During the course of chronic hepatitis B virus (HBV) infection, OBI may occur as: 'a' determinant escape mutant (OBI 2); as healthy carriage with antibody to hepatitis B core antigen (anti-HBc) only, or no antibody markers (OBI 3 and 4); as mutants inhibiting viral replication with anti-HBc and undetectable hepatitis B surface antigen (HBsAg) (OBI 5); or as low and incomplete replication of integrated viral DNA in hepatocellular carcinoma (HCC) (OBI 6).

Table 2 Hepatitis B virus (HBV) DNA load in occult HBV infection (OBI), with or without HBV antibody markers

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>HBV DNA in copies, geq or IU/ml, and the antibody markers detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinberger et al. [46]</td>
<td>Anti-HBs and anti-HBc: $&lt;1 \times 10^4$ geq (median $5.0 \times 10^3$)</td>
</tr>
<tr>
<td>Grethe et al. [37]</td>
<td>Anti-HBs and anti-HBc: $1 \times 10^3$–$1 \times 10^4$ geq</td>
</tr>
<tr>
<td>Yotsuyanagi et al. [31]</td>
<td>Anti-HBc only: 1000, 15, 5 IU</td>
</tr>
<tr>
<td>Hennig et al. [13]</td>
<td>Anti-HBc only: 100–10 000 copies</td>
</tr>
<tr>
<td>Jilg et al. [68]</td>
<td>Anti-HBc only: $4 \times 10^4$ copies (median $7.0 \times 10^3$)</td>
</tr>
<tr>
<td>Kessler et al. [67]</td>
<td>Anti-HBc only: $8 \times 10^4$–$4 \times 10^4$ copies</td>
</tr>
<tr>
<td>Weber et al. [69]</td>
<td>Anti-HBc only: 263–646 copies</td>
</tr>
<tr>
<td>Noborg et al. [30]</td>
<td>Anti-HBc only: $&lt;1 \times 10^3$ copies</td>
</tr>
<tr>
<td>Saito et al. [47]</td>
<td>Anti-HBc only: 100–711 copies</td>
</tr>
</tbody>
</table>

*In a mixture of patients of different origins, some with liver disease.
Anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; geq, genome equivalents.
in three of 16 patients followed-up long-term after acute infection [33].

**OBI and escape mutants**

HBV mutants in the S region, which interfere with HBs antigen recognition in diagnostic assays, have been known for many years. Some of these mutations translate into amino acid substitutions in any of the five loops of the ‘a’ region, but particularly in loop 4 at position 145, with an alanine replacing the wild-type glycine [34]. The general mechanism for the occurrence of these variants is the selection of naturally occurring variants by immune pressure. This pressure may originate from the infected host’s own immune response, passive immunisation with anti-HBV immunoglobulins used in neonates or in liver transplant recipients, or selection of infectious mutants by vaccinated individuals exposed to HBV [34–36]. In addition, antiviral drugs directed at the virus polymerase or reverse transcriptase may select escape mutants. Owing to the overlap of the S and replication enzyme protein-reading frames, these mutants may induce other amino acid substitutions in the S protein. In all forms of ‘a’ mutants, the viral load is often low, but may be high [37,38]. The challenge therefore remains for diagnostic companies to utilise reagents able to detect all ‘a’ mutants of HBsAg.

**OBI and anti-HBc**

In the transfusion setting, anti-HBc had been used initially as a surrogate marker for non-A, non-B hepatitis. Since the implementation of anti-HCV screening, this test is no longer relevant but its potential to prevent occult HBV transmission has resurfaced [39]. Several studies have explored the merits of anti-HBc screening by testing deferred donations for HBV DNA. Depending on the epidemiology of HBV in the area concerned, the distribution of other markers of HBV in anti-HBc-positive blood units can be quite different. In low-prevalence areas, such as Northern Europe and North America, the vast majority of anti-HBc-positive samples also carry anti-HBs (Table 3). Samples with high anti-HBs levels are consistently HBV DNA negative but, as described above, some low-level anti-HBs-positive units may contain HBV DNA.

Anti-HBc without anti-HBs is usually called ‘anti-HBc-only’, although samples with a high antibody titre also usually contain anti-HBe. The prevalence of anti-HBc-only in Europe and North America is quite low, overall. As shown in Table 3, the percentage of samples containing HBV DNA, from either blood donors or in the general population, range between 0 and 7.7%. An anti-HBc-only prevalence of 0.07% in the UK and 1.5% in Germany has been reported [13,17]. In countries with a high frequency of HBV infection, such as Greece (15-8%), China (70-0%) and Ghana (83-6%), the prevalence of anti-HBc-only tends to increase to 1.9, 2.7, and 12.7%, respectively [19,40,41]. Comparisons of the anti-HBc prevalence between reports, however, are often made difficult by the relatively low specificity of some anti-HBc screening assays. Algorithms including multiple successive assays are necessary, but not necessarily sufficient, to identify true reactivity [13,17]. To overcome this difficulty, Japanese blood banks have set up an anti-HBc cut-off agglutination titre of ≥ 32 and, below this level, donations are considered non-infectious (presumably false positive or with undetectable anti-HBs) [25].

There are two main interpretations of anti-HBc-only serostatus [42]. The first interpretation is that after many

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Country</th>
<th>Population</th>
<th>Number screened</th>
<th>Anti–HBc</th>
<th>HBsAg</th>
<th>Anti–HBs</th>
<th>Anti–HBc-only (%)</th>
<th>HBV DNA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hennig et al. [13]</td>
<td>Germany</td>
<td>First-time donors</td>
<td>14 251</td>
<td>200</td>
<td>180</td>
<td>20 (0.14)</td>
<td>3 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Jilg et al. [68]</td>
<td>Germany</td>
<td>General</td>
<td>5305</td>
<td>544</td>
<td>432</td>
<td>81 (1.5)</td>
<td>5/65 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Tseliou et al. [70]</td>
<td>Greece</td>
<td>Blood donors</td>
<td>10 629</td>
<td>2050</td>
<td>1543</td>
<td>507 (4.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Zervou et al. [40]</td>
<td>Greece</td>
<td>Blood donors</td>
<td>6966</td>
<td>282</td>
<td>177</td>
<td>105 (1.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bart et al. [71]</td>
<td>Switzerland</td>
<td>Random women</td>
<td>9006</td>
<td>571</td>
<td>467</td>
<td>104 (1.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Allain et al. [19]</td>
<td>UK</td>
<td>Blood donors</td>
<td>103 869</td>
<td>586</td>
<td>515</td>
<td>68 (0.07)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Kleinman et al. [22]</td>
<td>USA</td>
<td>Blood donors</td>
<td>1231</td>
<td>844</td>
<td>387</td>
<td>4/107 (3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almeida-Neto et al. [45]</td>
<td>Brazil</td>
<td>Blood donors</td>
<td>112</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ren et al. [72]</td>
<td>China</td>
<td>Blood donors</td>
<td>297</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sato et al. [73]</td>
<td>Japan</td>
<td>Blood donors</td>
<td>540 161</td>
<td>14 963</td>
<td>1103 (0.2)</td>
<td>12 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernvil et al. [74]</td>
<td>Saudi Arabia</td>
<td>First-time donors</td>
<td>6035</td>
<td>125 (2.1)</td>
<td>4 (3.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allain et al. [19]</td>
<td>Ghana</td>
<td>Blood donors</td>
<td>242</td>
<td>184</td>
<td>46</td>
<td>110 (45.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen.
years of HBV chronic carriage with non-productive infection, the level of HBsAg in the circulation becomes too low to be detected. This possibility is supported by the increasing number of HBsAg-containing blood units detected with HBsAg assays of increasing sensitivity [19]. In a variable proportion of these samples, anti-HBe is detected, but with the titre of anti-HBe being lower than anti-HBc, there comes a point when the former is no longer detectable, leaving the latter as the only serological marker of infection.

The second interpretation takes into consideration the relatively brief persistence of anti-HBs in individuals who have recovered from HBV. Over time, anti-HBs in immune individuals becomes no longer detectable and only anti-HBc remains. Several studies have demonstrated this phenomenon by stimulating anti-HBc-only blood donors with HBV vaccine and monitoring the timing and the magnitude of the anti-HBs immune response [43–45].

Molecular data from the promoter, precore and S genes might provide information to differentiate between OBI in anti-HBc-only samples from recovered infection (wild type) and healthy carriage (precore stop codon). The little data available indicate a wide variety of S mutants in one study from Germany [46] and a mixture of wild-type and precore stop codons in others from Japan [10,38].

**OBI without serological markers**

In all three types of circumstances described above (recovered infection, escape mutants and anti-HBc-only), blood screening for anti-HBc would eliminate the risk of HBV transmission by transfusion. The frequency of HBV DNA detected in the absence of any serological marker of HBV is relevant to the design of a blood-safety strategy.

Several groups have described the presence of HBV DNA alone in cases of cryptogenic hepatitis or HCC [6,47–49]. In one patient, the HBV DNA load was determined and found to be < 1000 copies/ml. More recently, several reports have found, in HCV infection, low levels of HBV DNA in the absence of serological HBV markers [50]. Similar features were described in vaccinated children who no longer had detectable anti-HBs [8]. In a look-back study for post-transfusion hepatitis B, one case was found [51]. No studies have systematically screened HBV-seronegative individuals for HBV DNA in low or high endemic areas. This very limited data suggests that HBV DNA might be the only marker of chronic infection. The true frequency of this condition remains unknown, as its determination would require the screening of HBV DNA in large numbers of individual samples, particularly in areas of low prevalence.

A study of 30 patients with unclassified chronic hepatitis showed 21 with DNA detectable only by nested PCR (indicating a low viral load) and no HBV serological markers [52]. Sequencing of the X-precore region showed the high frequency of an eight-nucleotide deletion in the X gene and the constant presence of the classical precore 1896 stop codon. This finding suggests that these individuals are at a late stage of chronic infection, having lost detectable anti-HBe and anti-HBc. However, the mechanisms leading to these situations remain unclear. The level of viraemia might reflect a very low level of replication, or replication of incomplete fragments of the HBV genome, as described in some cases of HCC [49]. Over time, all serological markers of HBV might become undetectable, leaving DNA as the only marker. This last category of OBI needs to be actively explored to determine its place in the large spectrum of clinical and biological conditions elicited by HBV infection.

**Clinical significance of OBI**

The clinical significance of OBI remains largely unknown. OBI was initially detected in patients with HCC or unclassified chronic liver disease [1,47]. There is therefore a clear association between OBI and liver disease in the absence of other causes, such as HCV infection or excessive alcohol intake. However, it is probable that most OBI carriers are asymptomatic and would only be detected by the systematic screening of large populations. All individuals with OBI, in the presence of anti-HBs, have normal alanine aminotransferase (ALT) levels [27]. In blood donors with anti-HBc only, most reports do not mention ALT levels and, because donors were asymptomatic, few liver-disease investigations were conducted and no liver biopsies performed. In a study of 20 blood donors with OBI and either anti-HBs or anti-HBc only, there was no indication of biological or anatomical liver disease [33]. In another study of 19 donors, 18 had normal ALT levels and, after discontinuation of alcohol excessive intake, the ALT level returned to normal in the one patient with elevated levels [31]. However, one should remember studies conducted prior to the availability of sensitive HBV DNA assays that showed the benefit of ALT and anti-HBc screening to prevent post-transfusion non-A, non-B hepatitis. Although most of the infectious cases were related to HCV, some might have been anti-HCV negative with both elevated ALT and anti-HBc. It would be very interesting to analyse old and more recent archive samples, exhibiting this association of test results, using current HBV DNA assays. In a series of over 1000 patients referred for a chronically elevated ALT level, 19 carried detectable HBV DNA only and one of the 19 was a blood donor [48].

**Infectivity of OBI**

As in other viral infections, HBV infectivity depends on two main factors: the infectious dose; and the immunocompetence of the host. Considering the volume of infectious material involved in the transfusion of whole blood or a
blood component, it is generally accepted that should any HBV DNA be present, infection may occur. The available studies are of three origins: retrospective studies of clinical cases of post-transfusion HBV infection; look-back studies involving recipients of blood from anti-HBc-positive donors; and systematic studies of donor–recipient pairs. No prospective studies have been conducted because of the very high cost involved to achieve statistical significance in Western countries where the prevalence of HBV is very low. This problem was well illustrated in a donor–recipient prospective study conducted in England, involving over 20 000 blood units that did not show any HBV transmission [53].

Blood components containing anti-HBc with anti-HBs, do not appear to transmit HBV [9]. Mosley’s study clearly showed the inverse correlation between anti-HBs level and infectivity; only 10% of blood units with low anti-HBs were infectious. Although some samples were tested for HBV DNA, there was no attempt to correlate infectivity with the presence of detectable DNA. Our own look-back study [17] examined the potential infectivity of 97 components containing anti-HBc and low anti-HBs (< 0·1 IU/ml) transfused to 131 recipients; no evidence of transmission was found.

The infectivity of anti-HBs-containing blood components in immunodeficient or immunosuppressed recipients has not been systematically explored. Some data are available from organ donors, in particular livers for transplantation [54,55]. In one study that included 14 organs from anti-HBs-positive donors, three livers and one kidney transmitted HBV. No details regarding the titre of anti-HBs, or the presence of detectable HBV DNA, was reported.

In contrast, more information is available regarding the infectivity of anti-HBc-only blood products or organs. The infectivity of blood donations containing anti-HBc as the only marker of HBV infection has been known for several decades [56–59]. This data was based solely on serological assays, but indicated that no more than 4% of recipients of anti-HBc-only blood developed HBV infection post-transfusion. More recently, the subject was revisited with the availability of sensitive assays for HBV DNA detection [39,60]. Epidemiological data confirmed that investigations of post-transfusion hepatitis B more often implicated donors carrying anti-HBc (11 cases) than donors in the window period (three cases) [61]. Mosley reported 17% infectivity of anti-HBc-only blood products [9]; the immune status of the recipients was not indicated. Another study reported probably 3%, and possibly 10%, HBV transmission in such circumstances [17]. In that study, HBV DNA was not detected in the implicated donors, a finding compatible with the case for a very low viral load being sufficient for infection. As shown in Table 2, viral loads below 3 × 10^7 copies/ml (or 300 IU/ml) are frequently found.

In developing countries where the prevalence of HBV is high, the frequency of post-transfusion HBV infection is also high. In a study from India, 10% of unselected recipients who received 3–19 units of blood for cardiac surgery developed HBV infection, and 11/24 HBsAg-negative units from implicated donors contained HBV DNA [62]. The discrepancy between the high frequency of HBV DNA and a relatively lower frequency of post-transfusion infection suggests that not all HBV DNA-containing units are infectious. However, no systematic study of the correlation between viral load and infectivity has been conducted. In chimpanzees, 100 virus particles appear to be the minimum infectious dose [63].

HBV transmission by anti-HBc-only blood or organs has been described. In two studies, 18/23 (78%) and 15/16 (94%) recipients of anti-HBc-only organ donors developed HBV infection [64,65]. In the latter, HBV DNA was not detected in the donors’ serum. In contrast, another study found that 0/11 transmitted [54]. Although not extensive, these data suggest that even when HBV DNA is undetected (presumably because it is present at a very low concentration), anti-HBc-only carriers are highly infectious in immunodeficient individuals. This situation could probably be projected from organs to blood components.

Conclusion

The development of extremely sensitive methods to detect HBV DNA by amplification revealed a considerable discrepancy between the detection of HBsAg and HBV DNA. This technological development substantiated the older clinical observation that HBsAg-negative blood (in addition to that in the window period) could sometimes transmit HBV. The main feature of OBI is that it constitutes a disparate group of HBV-related conditions whose link is a low-level of HBV DNA in the circulation.

Virologically, a considerable amount of research is required to characterise and classify the molecular forms of OBI and their relative frequency. Tools and algorithms for differential diagnoses need to be developed using serological and molecular methods. The clinical significance of each of these forms remains to be determined, as does their prognosis. Most critically, from a blood safety point of view, the infectivity of OBI by transfusion should be explored in relation to virological type and to the susceptibility of the potential recipients regarding immunocompetence. All the above elements that are still missing are important to evaluate the risks for the donor and for the recipient of infected blood in order to appropriately inform and counsel blood donors identified as OBI carriers.

Two main approaches have been proposed, and are currently implemented in some areas to limit the transfusion risk of OBI: anti-HBc screening; and HBV NAT. Anti-HBc screening has the potential of excluding the vast majority of OBIs, leaving only the probably rare cases with HBV DNA alone. This approach has two main drawbacks: it does not detect the preseroconversion window-period infections;
and would not be practical in most of the world where the prevalence of anti-HBc is > 10%, as too many donors will be ineligible (unless anti-HBs is also tested for and quantified in the anti-HBc-positive donors).

NAT has been implemented for HCV screening in many countries – in some for human immunodeficiency virus (HIV) and in a few for HBV. In nearly all cases, testing is performed on plasma pools of various sizes. Despite the pooling, the efficiency of this approach is relatively high because of the rapid rate of replication to a high viral load (especially with HCV) once viral multiplication commences. Recent data confirms that the replication rate of HBV is slow and reaches relatively low levels of viral load, while OBI is essentially characterized by very low levels of viral load (< 1000 IU/ml). Currently available assays (having a sensitivity of 20–50 IU/ml) would only detect OBIs with > 320–800 IU/ml HBV DNA when diluted in the smallest pool size of 16. Preliminary data, reported in this review, suggest that many cases of OBI in blood donors are below that threshold. The argument has been made, by some proponents of pooled NAT, that ultracentrifugation might improve sensitivity. However, no direct comparison between ultracentrifuged plasma pools and individual testing has been performed. Unless new data, as called for above, become available, individual sample testing might need serious consideration.

Automated multiplex NATs, simultaneously detecting all three main blood-borne viruses at a cost not too much greater than the testing of one or two genomes, are becoming available. Automation is a prerequisite for single-donation NAT and multiplexing might limit the additional cost attached to single-unit NAT.

On the basis of available data, anti-HBc screening might carry a higher cost-effectiveness than NAT in areas of low HBV prevalence, while NAT is the only choice in countries where the prevalence is high; paradoxically, most of these countries could ill afford to implement it.

References

1 Brechot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Brechot P: Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely ‘occult’? Hepatology 2001; 34:194–203
14 Zhang YY, Hansson BG, Kuo LS, Widell A, Nordenfelt E: Hepatitis B virus DNA in serum and liver is commonly found in Chinese patients with chronic liver disease despite the presence of antibodies to HBsAg. Hepatology 1993; 17:538–544


70 Tseliou P, Spiliotakara A, Dimitracopoulos G, Christofidou M: Detection of hepatitis B virus DNA in blood units with anti-Hbc as the only positive serological marker. Haematologica (Budap) 2000; 30:159–165

71 Bart PA, Jacquier P, Zuber PL, Lavanchy D, Frei PC: Seroprevalence of HBV (anti-Hbc, HBsAg and anti-HBs) and HDV infections among 9006 women at delivery. Liver 1996; 16:110–116

72 Ren F, Li H, Zhao H: Studies on hepatitis B virus infection in blood donors with positive anti-Hbc and negative HBsAg. Zhongguo Yu Fang Yi Xue Za Zhi 1998; 32:7–9


学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：
图书馆首页　文献云下载　图书馆入口　外文数据库大全　疑难文献辅助工具