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SaBTO

Advisory Committee on the
Safety of Blood, Tissues and Organs

Occult Hepatitis B Infection in UK Blood Donors Report

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V1.2

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Executive Summary

Following the report of two probable transfusion transmitted cases of Hepatitis B virus (HBV) from donors who had not been identified by routine screening, later identified as having Occult Hepatitis B infection (OBI), SaBTO established a working group in September 2019 to investigate the risk from OBI donors to the blood supply in the UK and what changes could be made to screening strategies to reduce this risk

Key Points

- Two published experimental models were used to estimate the residual risk of an Hepatitis B virus (HBV) infected donation from an OBI donor entering the blood supply in the UK.

- The models, one from a group in the Republic of South Africa (RSA) and one from Australia (AUS) provided different residual risk estimates (7.9 & 41.3/million donations respectively) although both estimates were considerably higher than the residual risk from donors within the window period of an acute HBV infection (0.87/million donations).

- To investigate mitigation of the risk from OBI donors the working group appraised two options for changing the current screening strategy. One was to increase the sensitivity of testing by reducing the mini-pool size used for HBV nucleic acid technology (NAT) testing from the current pool of 24 donations to a smaller pool (4-8 donations) or individual testing of donations. The other was to introduce anti-Hepatitis B core (anti-HBc) testing, initially for all donors then only for new and returning donors. An intermediate pool size was discounted as there would only be a marginal increase in the number of OBI donors detected.

- The modelling assumed that not all OBI donors would be detected by reducing the size of the NAT mini-pool as the viral load for HBV in the blood of some donors would still be below the level of detection even for individual donation testing. Most, if not all, OBI donors would be detected by introducing anti-HBc testing.

- For each option, the increased cost of testing, operational impacts including the additional staff, equipment, space, and for anti-HBc testing, additional costs for confirmatory tests, donor loss and recruitment of replacement donors, were estimated over a 10-year period.

- The modelling only looked at the cost per additional detection rather than conducting a full economic appraisal. The decision to take this approach was based on the additional uncertainties, in terms of infection and long-term clinical outcome of infection in recipients, that would have to be considered. Similarly, the full economic costs of recipient lookbacks were not included in the costs of introducing anti-HBc screening due to a lack of data to estimate the scale of these lookbacks.
- Reducing the mini-pool size for HBV NAT to 4-8 donations or individual donation testing would cost an additional £250,000 or £1 million per infected donation identified respectively, based on the residual risk from the RSA model and an additional £45,000 or £200,000 respectively for the AUS model.

- Introducing anti-HBc testing would cost an additional £63,000 or £12,000 per additional donation detected (RSA and AUS model respectively). However, the majority of the cost and benefit would be in the first phase of testing of all donors.

- Introduction of anti-HBc testing will be more cost effective than reducing the HBV NAT pool size. However, there is considerable uncertainty in the prevalence of OBI in blood donors in the UK and the number of donors with anti-HBc including those who have a resolved HBV infection with high levels of anti-HBs who can continue to donate and the false positive rate of anti-HBc tests.

- It is anticipated that there will be a significant, short-term impact on the donor supply as donors who are anti-HBc positive with low levels of anti-HBs will be deferred from donation.

- Donors who are identified with OBI or at enhanced risk of OBI will be further investigated by testing for HBV DNA by individual donation NAT (ID-NAT) and for other markers of infection.

- Archived samples from previous donations of confirmed anti-HBc positive donors will be used, where appropriate for full recipient lookback. At risk recipients will be investigated for transmission and provided with advice on treatment options where relevant.

Recommendations to SaBTO

The working group has agreed the following recommendations to SaBTO:

- The UK blood services introduce an anti-HBc testing strategy to reduce the number of OBI donations reaching the blood supply. This would be done once on all current donors, subsequently only on new donors or donors who have not donated within the previous two years.

- Given the uncertainties in the data used to provide a cost/benefit analysis, the group recommends that the strategy is reviewed after 12 months of implementation when additional will be available, including the number of donations that are anti-HBc positive, the anti-HBc false positive rate, the proportion of anti-HBc positive donors with anti-HBs levels >100 IU/L, the number of anti-HBc positive donors with HBV DNA detectable by ID NAT, the number and characteristics of donors deferred and data from lookback studies. This information will be used to provide a revised residual risk estimate and a more complete economic appraisal.
- All anti-HBc reactive donations should undergo confirmatory testing; confirmed anti-HBc positive donations must be tested by ID-NAT and anti-HBs levels determined.

- Donations which are anti-HBc positive with an anti-HBs titre greater than 100 IU/L can be accepted and the donor may continue to donate although this is at the discretion of individual blood services. If these donors are allowed to donate, they must remain HBV DNA negative by ID-NAT at each subsequent donation, their anti-HBs titre must be retested at least every two years and remain greater than 100 IU/L.

- Lookback investigations should be conducted on previous donations of current donors who are anti-HBc positive, ID-NAT positive and/or have an anti-HBs titre less than 100 IU/L going back a minimum period of 3 years. All archived samples should be tested for HBV DNA by ID-NAT. Blood services have well established lookback protocols and will operationally determine the extent and how best to conduct these investigations. Priority for lookback should be given to donors found at any time in their donation history to be HBV DNA positive by ID-NAT.

- Lookback investigations on lapsed donors are not recommended at this time; this will be reviewed during the initial testing phase as data on existing donors is gathered to allow a more informed risk assessment.

- Lookback policy and recommendations should be reviewed after 12 months. Additional data which can then be considered will include: the distribution of anti-HBc positive donors between risk stratification groups; frequency and stability of ID-NAT positivity in anti-HBc positive donors, the scale of lookback required; the results of 12 months lookback in terms of recipient morbidity identified and the results of further research.

- As an anti-HBc testing strategy is likely to impact disproportionately upon donors and, potentially, recipients from ethnic minority groups, SaBTO should conduct a health impact assessment to minimise unanticipated consequences during the 12-month test period.

Background

Probable HBV transmissions from OBI donors in England

In 2018, an acute hepatitis B virus (HBV) infection in a patient leading to death was traced back to a transfusion of a unit of red cells. The unit originated from a donation by a first-time donor, who met all the eligibility criteria for blood donation. The donation tested negative for HBV according to the current screening algorithm using a HBsAg test and a nucleic acid technology (NAT) test for HBV DNA. NAT testing was performed in pools of 24, with an estimated cut-off sensitivity of 33.6 IU/mL (sensitivity of ID-NAT 1.4 IU/mL).

On further investigation, the implicated unit tested HBsAg negative, anti-HBc positive, HBV NAT negative even by individual donation. HBV DNA was detected in a follow-up sample after concentration but at a level below the detection threshold of the HBV NAT used for routine pooled donation screening. The HBV strain infecting the blood recipient was typed as genotype D2. Although it was not possible to type the HBV strain infecting the donor, genotype D2 is prevalent in the region where the donor originated providing circumstantial evidence to support the transfusion-associated transmission.

A second case of probable HBV transmission was reported to NHS Blood and Transplant (NHSBT) later in 2018 linked to a red cell transfusion in 2015; no other sources of infection were identified. Investigation of donors showed one to be anti-HBc positive but was HBV NAT negative even after sample concentration. The recipient's virus was typed as genotype D2, clustering closely with viruses present in this donor's home country (but being clearly different from virus identified from the first case).

Prior to these cases, a transmission of acute hepatitis B from a window period donor was documented in 2011 and another probable transmission from a donor with resolving acute infection in 2012.

Hepatitis B infection and markers of infection

UK blood services test all blood donors for HBV infection.

- **Hepatitis B surface antigen – HBsAg**: Testing for HBsAg is mandatory in the Blood Safety and Quality Regulations and the Tissue Quality and Safety Regulations. HBsAg is the surface protein of the virus and is present is the blood when the individual is infected with HBV. It is a marker of current infection with HBV (may be acute or chronic).
- However, there is an interval when a recently infected individual may produce virus and be able to infect others through blood transfusion but have HBsAg levels below the detection threshold for the assay. This is known as the window period and for the HBsAg test is approximately 67 days.
- **HBV DNA**: HBV DNA appears in the blood before HBsAg. HBV DNA can be detected by NAT testing which is a highly sensitive test and can reduce the window period for HBV to 30 days with the current screening strategy.
- In the UK, HBV NAT is performed on mini-pools of 24 donations. This is a compromise between cost and the detection sensitivity.
- **Antibody to hepatitis B core antigen – Anti-HBc**: Anyone infected with HBV will make anti-HBc and the antibody is persistent after infection has resolved although

declines over time. Anti-HBc is therefore a marker of either active or past infection with HBV.

- Tests for anti-HBc have a measurable false positive rate and additional testing with an anti-HBc test using a different technology is required to confirm reactivity.
- **Antibody to hepatitis B surface antigen – anti-HBs:** Appears in patients who clear HBV from their peripheral blood and appears following vaccination. Neutralising anti-HBs provides protection against HBV infection.

  Donations that have anti-HBc may be tested for anti-HBs using a quantitative assay. In the UK donations that have anti-HBs levels >100 IU/L may be accepted and the donor allowed to donate in future.

- HBsAg positive, anti-HBc positive: Individual is currently infected with HBV
- HBsAg negative, anti-HBc positive: Individual has had HBV infection but has cleared it from the bloodstream. Virus may still be present in liver.

Definition of Occult Hepatitis B Virus (HBV) Infection

For the purpose of this report, an individual with Occult HBV Infection (OBI) is defined as having undetectable levels of HBsAg in the blood but with the presence of HBV DNA and detectable levels of anti-HBc. Although individuals have been reported with OBI in the absence of anti-HBc (seronegative OBI) in countries where HBV is endemic, there is a scarcity of data about the prevalence of seronegative OBI in countries with low levels of HBV infection and the number is thought to be very low.

Residual risk of rate of a donation from an OBI donor reaching the blood supply has been estimated using two recent models hereby referred to as the Australian model (AUS)[1] and the Republic of South Africa model (RSA)[2]. The AUS model estimate was based on the rate of non-detection of HBV by NAT, the RSA model on the viral load of HBV in the blood of OBI donors.

Occult Hepatitis B and Blood Safety

It was shown over 30 years ago that HBsAg-negative and anti-HBc positive blood donors can transmit HBV. However, until very recently it was considered that infectivity of occult HBV carriers was generally low with several published studies reporting transmission rates of around 5%. It is now known, however, that most occult HBV cases are infected with a replication competent virus and that the true rate of transfusion-associated transmission of OBI likely approaches 60%.[3] Complicating systematic analysis of occult transmission is the frequent absence of markers detectable by standard HBV screening of blood donations, the absence of identifiable risk factors for HBV infection in the donors and finally by the frequent completely asymptomatic nature of HBV infections in blood recipients (around 50% of cases).

The minimum infectious dose that would transmit HBV was initially estimated at around 100 virus copies (corresponding to 20 IU)[4]. However, a published analysis of recently reported cases of OBI transmission contained a revised, substantially reduced estimate of the minimum infectious dose of 15 virus copies (3 IU)[3,5]. This level is far below the detection threshold of pooled HBV NAT currently used in the UK (33.6 IU/mL). To detect this amount

of HBV DNA, a PCR method able to detect as little as 0.015 IU/mL would be required. Although HBV DNA PCR can detect single DNA copies, an infectious dose of 0.015 IU/mL equates to 0.075 DNA copies/mL, necessitating DNA extracted from over 40 mL of donation-derived plasma for HBV DNA to be reliably detectable. Highly sensitive assays of this sort are not currently commercially available, nor are there practical methods available to extract and test DNA from such large volumes of samples. Although the majority of OBI cases can be identified by sensitive ID-NAT screening, it is acknowledged that around 5-10% of OBI cases will be missed by ID-NAT alone without anti-HBc antibody screening[6,7].

HBV Screening strategies

In the UK all blood donations are tested for HBsAg and for HBV DNA in mini-pools of 24 donations. Anti-HBc testing is only carried out on a small subset of donors with an enhanced risk of HBV (see below).

HBV testing strategies around the globe

A recent global survey was conducted on blood establishments[8] on the screening strategies they employ to reduce the risk of OBI to their blood supply. The survey provided data from 20 blood establishments in 19 countries; all countries including Germany, France, Netherlands, Republic of Ireland (ROI), the USA and Canada either test donations by individual donation nucleic acid testing (ID-NAT) or for anti-HBc to reduce the risk of HBV transmission from OBI donors. France and the ROI do both.
Some of these countries have published data on the outputs of their screening strategy, the number of anti-HBc positive donations, donor deferral rates and number of donors with OBI detected.

The Netherlands[9,10]

Testing for HBV DNA in mini pools of 6 (MP6) added to HBsAg screening in 2008; universal anti-HBc testing added in 2011. Between November 2008 and June 2011, a total of 2.3 million blood donations were tested and 16 OBI cases identified (7 per million donations). Through a thorough lookback, a low transmission rate of approximately 5% was documented.

USA[11]

A total of 34.4 million donations were tested between 2009–2015, with 583 OBI cases identified (17 per million donations), nearly 5 times as frequent as early acute window period donations. Most OBI cases were identified amongst first time donors. Median DNA load was 9 IU/mL, and the NAT strategy varied from ID-NAT to mini-pools of 6 donations. Testing for anti-HBc was universal so the authors were able to quote a seroprevalence for anti HBc as 0.23%.
A similar USA study[12] looked at 22.4 million donations between 2011-2015 tested by mini-pool NAT and anti-HBc and identified 404 donations from OBI donors (18 per million donations).

Germany[13]

70671 donations from a total of 31.5 million collected between 2006-2015 tested positive for anti-HBc and negative for HBsAg (0.22%). 82 donations were HBV NAT positive, 47 ID-NAT only. 54,203 of the anti-HBc positive donations were discarded as either having anti-HBs <100 IU/L or with no further testing (0.17% of total, 77% of anti-HBc positive, HBsAg negative donations).

Republic of Ireland (Niamh O'Flaherty unpublished information)
Between 2009-2018, the Irish Blood Transfusion Service collected 2.15 million donations, all tested by HBV ID-NAT and anti-HBc. 1664 donors were positive for anti-HBc (0.077%). 819 of these were confirmed as anti-HBc positive indicating resolved HBV infection HBV and 730 (43%) were false reactive for anti-HBc. 4 OBI donors had been detected in the period 2009-2018 giving an overall rate of 0.0002% (2 per million donations)

UK Blood Services
27 blood donors were identified with OBI between 2009 and 2018, 25 of them were identified by donation screening and the remaining two donors as a result of lookback investigations. Most donors were males (n=22, 81%), over 45 years of age (n=20, 74%) and repeat donors (n=18, 67%).

Exposure history was identified for 21 donors; 18 of them were born in countries where HBV is known to be endemic. These included Jamaica, Romania, Nigeria, Korea, Pakistan, Malta, Iran, Taiwan, Brazil, Bangladesh, Tunisia, Ghana, Somalia, India and Hong Kong. Other risk factors were identified for three donors. Risk factors were not identified for 6 blood donors, 5 of them known to be UK-born. In addition, 5 non-blood donors (two bone, one skin and two cord blood donors) were identified through ID-NAT screening.

All blood recipients of donors identified with OBI were followed up between 2009 and 2015. Investigations were limited in some cases due to difficulty in recipient follow-up.

- 16 donors with occult hepatitis B; 13 of them repeat donors
- 74 donations:
    - 33 recipients deceased
    - 33 tested negative for HBsAg and DNA
    - 2 had evidence of past HBV infections
    - 6 not followed up

Although the lookback data were reassuring, its collection is laborious and shows that transmission could easily be missed in circumstances when not all recipients can be contacted. Enhanced lookback was reintroduced during 2019.

Estimation of numbers of English donors with anti-HBc and donor deferral

As the UK currently only tests a small subset of donors for anti-HBc, the working group tried to estimate the number of donors who may be reactive if an anti-HBc strategy was introduced. Data was available for two donation intervals 2005-2007 and 2017-2019. In the period 2005-2007 donors were tested for anti-HBc if they gave a history of HBV infection, hepatitis, jaundice of unknown cause, having a high-risk partner or recent tattoos and body piercing. Following the SaBTO Donor selection criteria review in 2017 the requirement to test was withdrawn for body piercing and tattoos which led to a significant reduction in testing. The data for 2005-2007 are shown in figure 1 and for 2017-2019 in figure 2.

Figure 1: NHSBT discretionary anti-HBc testing data 2005-2007

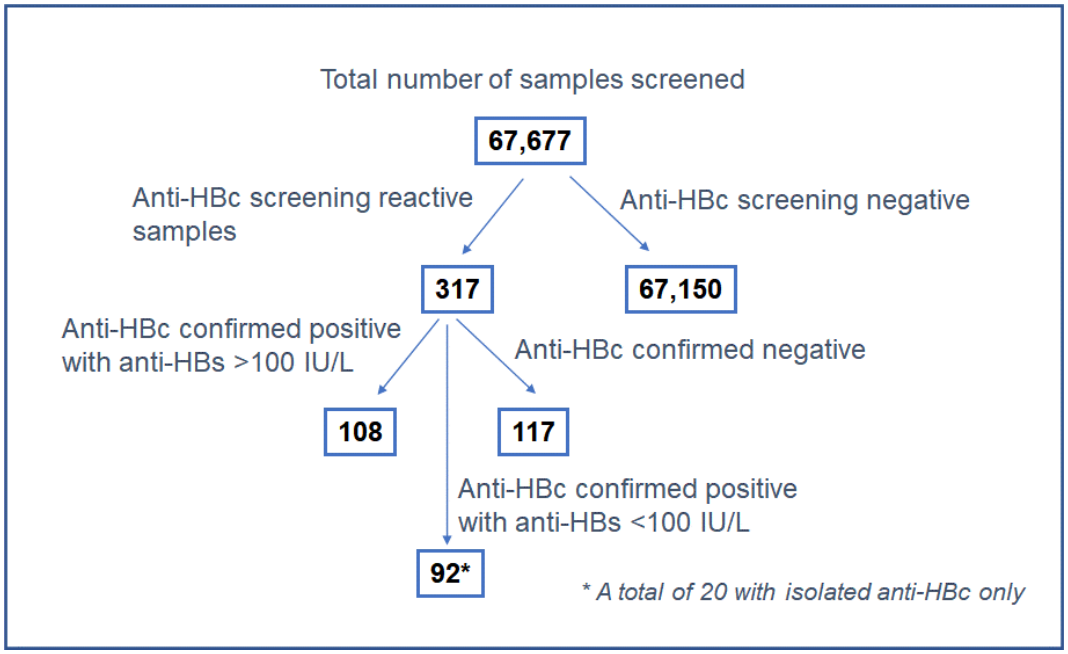
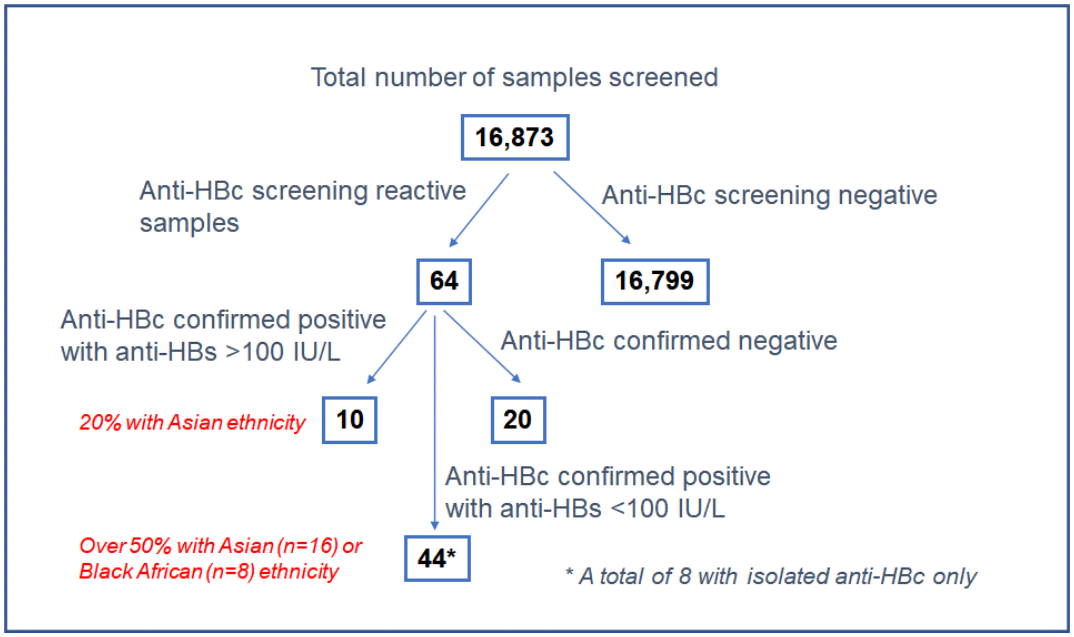


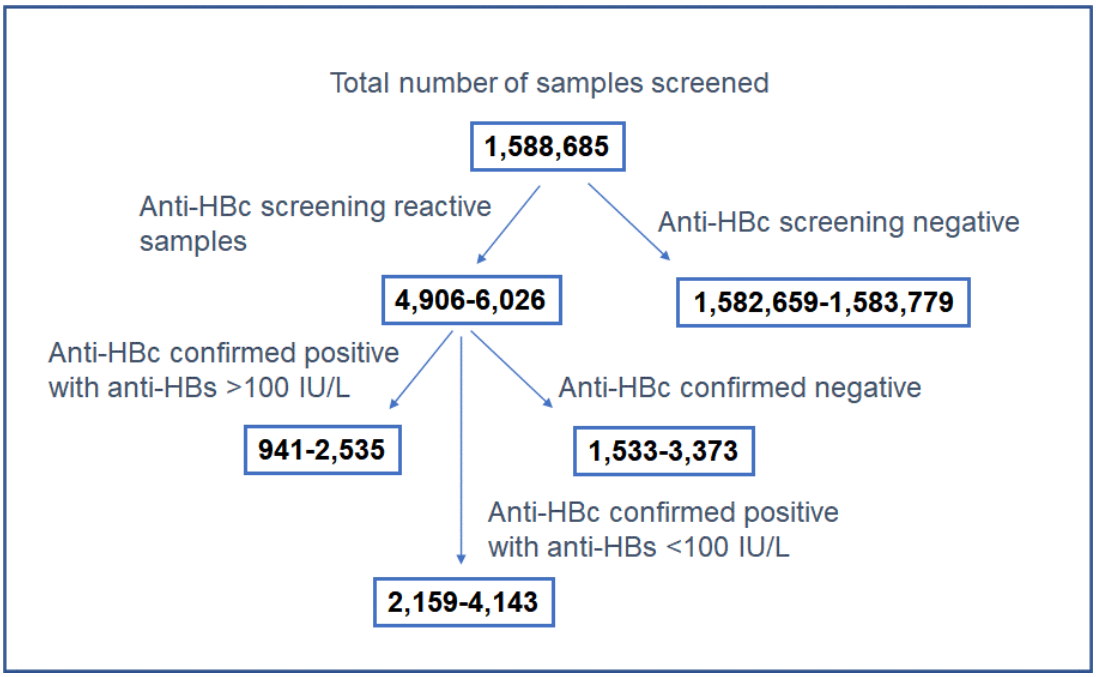
Figure 2: NHSBT discretionary anti-HBc testing data 2017-2019



The prevalence of confirmed anti-HBc positive donations was 0.30% (200/67,677) with 37% false positive for the 2005-2007 data set and 0.32% (54/16,873), 31% false positive, for the 2017-2019 data set. The prevalence is comparable to published data from Germany (0.22%), USA, (0.22%) and the Netherlands (0.77%) as detailed above. The data sets for both periods were small compared to the total number of donations and donations were selected for testing based on an enhanced risk for HBV. Therefore, the data may not be representative of the total NHSBT blood donor population.

Combining the two data sets it is possible to extrapolate the number of donors who would have HBc antibodies and the number of donors deferred in an average year if universal anti-HBc testing was implemented in England (figure 3).

Figure 3: NHSBT universal anti-HBc extrapolated from discretionary testing (per year)



The anticipated number of donations initially testing positive for anti-HBc would place a significantly increased burden on reference testing to investigate these donations to identify both false positives and also resolved infections in the donor which could be safely returned to the blood supply, thereby avoiding unnecessary donor deferral. The extrapolated data also indicate the likely scale of donor deferral (estimated at around 2000-4000 donors) with around 50% being from ethnic minority communities.

Estimation of number of OBI donors in the UK and residual risk from current testing strategies

The current residual risk for an HBV positive donation is estimated to be around 0.87/million in the UK✦. This is risk from a window period donation getting into the blood supply. The risk will depend on the sensitivity of the test being used. For mini-pool 24 HBV NAT the window period is estimated at 30 days. The residual risk does not take into account the risk from OBI donors.

Of note: the residual risk is not the same as the risk of transmission of infection. This is dependent on a number of factors:

- The component being transfused, components with a higher volume of plasma will have a higher risk.
- The amount of virus in the component may be below an infectious dose
- Not all components are transfused
- Recipients may die in the early period following transfusion

In addition, around 50% of HBV transmissions will be asymptomatic and the recipient will not be aware of having contracted HBV

To provide an estimate of the residual risk from donations from OBI donors in the UK, two published models were used, the RSA[2] and AUS[1] models using 2016-2018 UK data. The models use two different approaches to estimate risk; the RSA model extrapolates from known OBI detections using estimated viral load, whereas the AUS model extrapolates from known OBI detections using estimated screening sensitivity. The results are shown in Table 1[14].

Table 1: OBI UK residual risk with pool sizes of 24 estimated using the South African and Australian risk models

Model	Total risk (derived)	Detected (observed)	Residual risk (estimated)
	Rate per million donations		
South African	9.5	1.6	7.9
Australian	42.9		41.3

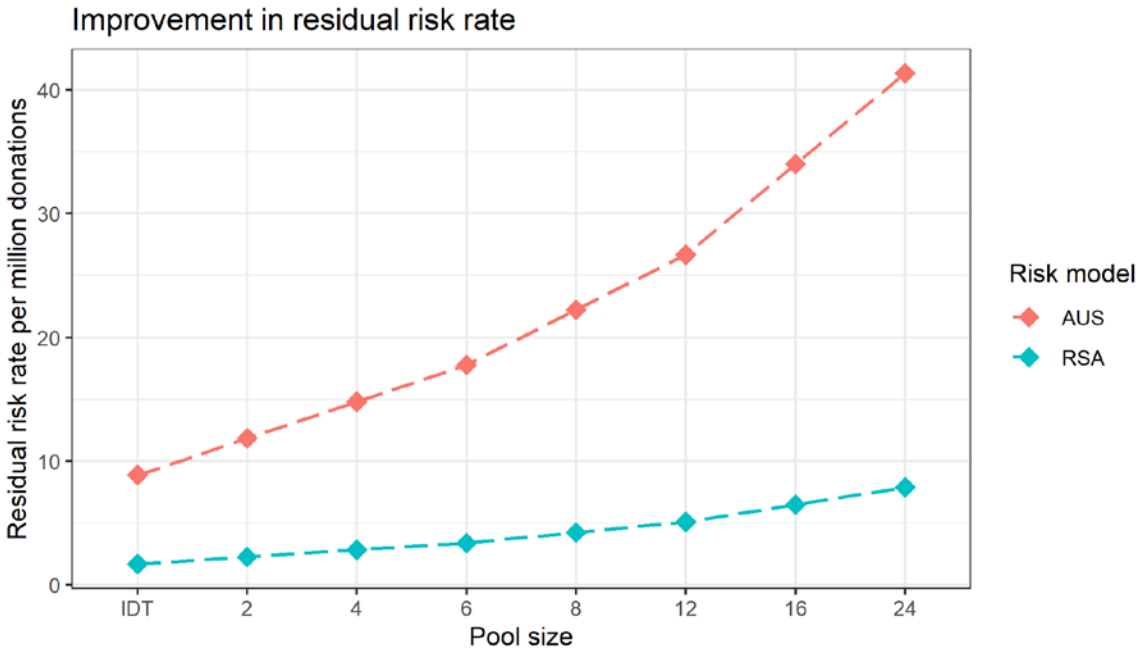
The table shows the estimated total risk, the number of OBI donors who would be detected by NAT in mini-pools of 24 donations and the estimated residual risk of a donation being missed by current testing. The residual risk was estimated to be 7.9/million donations for the RSA and 41.3/million donations for the AUS. These rates were similar to published OBI detection rates from other blood services (see above).

For the purpose of further analysis, neither model was considered to be more robust than the other and both were based on small numbers of donations with OBI and have considerable uncertainty. Therefore, the outputs from both risk models provided separate inputs into the economic analysis and it was assumed that any recommendation to SaBTO must be acceptable under both risk scenarios.

✦ JPAC Position Statement - The estimated residual risk that a donation made in the infectious window period is not detected on testing: risks specific for HBV, HCV and HIV in the UK, 2017-2019.

Enhanced screening strategies are expected to minimise the residual risk of OBI. The RSA model provides the predicted improvement in detections (and remaining residual risk) per million donations for different NAT pool sizes. We mapped the RSA predicted improvements proportionally to the AUS model, as the AUS model does not explicitly estimate this. For NAT, residual risk lessens as pool sizes decrease and we would expect to detect an additional 6.2 (RSA) or 32.4 (AUS) cases of OBI for every million donations screened with ID-NAT compared to pool sizes of 24.
Figure 4 shows the estimated improvement in OBI detections for reduced NAT pool sizes.

Figure 4: Improvement in OBI detection per million donations for reduced NAT pool sizes compared to pool sizes of 24; estimated using the South African and Australian risk models



The improvement of residual risk of HBV from OBI donations does not apply to an anti-HBc testing strategy as we are assuming that almost all OBI individuals would be anti-HBc positive thereby reducing residual risk to close to zero. For practicality in the modelling, we have assumed residual risk will be effectively zero.

Options appraisal

Modelling of residual risk indicated that the risk from OBI donors was considerably higher than the risk from window period infections for HBV of 0.87 (0.35-1.70) per million donations.

The group conducted an appraisal of options to reduce this residual risk by changing the testing strategy for HBV. Options considered were:

- Reduction in the pool size for NAT testing
- Expansion of anti-HBc testing for all donations in the first instance, then only from new and returning donors

An appraisal of more sensitive assays for HBsAg was considered but rejected as not practicable at the present time as these assays are untested for mass screening by Blood Services. This may change and would be kept under review.

Analysis of blood screening strategies to reduce risk of Occult Hepatitis B transmission

Background

Economic modelling was carried out on options for enhanced detection of OBI donations. The aim of this analysis was to model the costs and benefits of two possible OBI testing strategies: (i) reduced pool Nucleic Acid Testing (NAT) and (ii) HBV core antibody (anti-HBc) testing, to appraise the value of each strategy.

Methods

Overview

This analysis assesses the value of screening options via estimating the costs and benefits of each strategy. We estimate the total costs to UK blood services covering testing, operational requirements and donor loss. We estimate benefits via the number of additional OBI detections and remaining residual risk (number of non-detections of OBI). Costs and benefits are combined to estimate the cost per additional OBI detection with each strategy. The analysis does not propose an acceptable threshold for the cost per additional OBI detection

Screening strategies

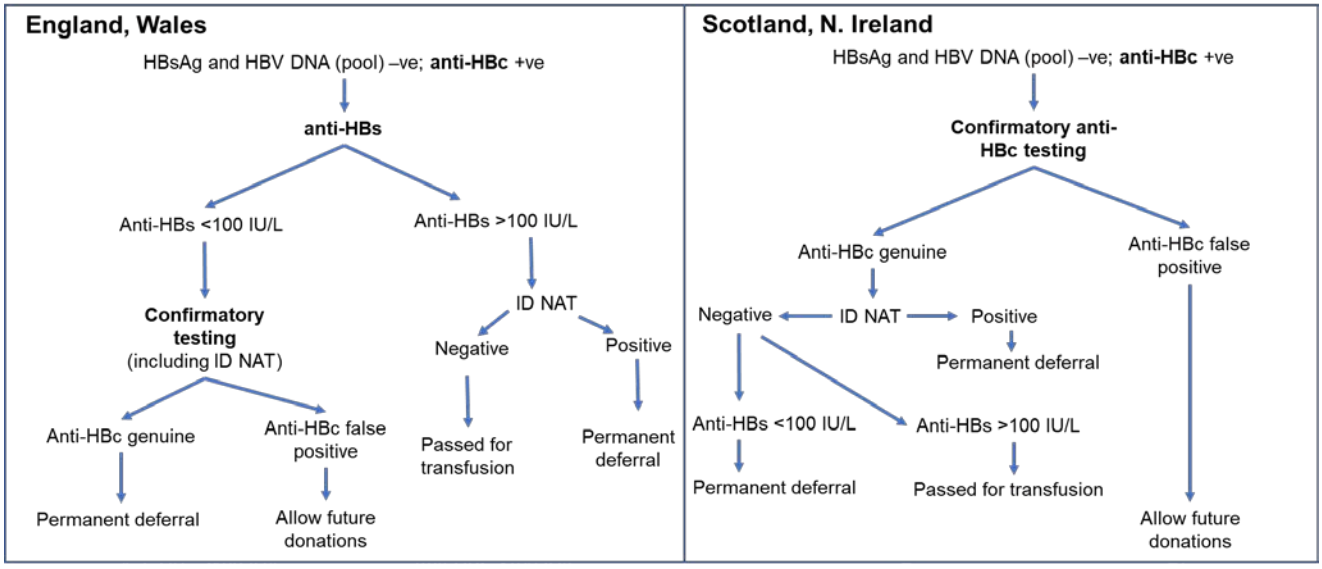
Existing screening includes testing for HBV DNA using pooled NAT, with pools of 24 donations. To accommodate scenarios from multiple manufacturers who offer different pool sizes, we used NAT medium pool sizes (12-24) as the baseline scenario. We modelled two different strategies against the baseline over a ten-year timeframe: reduced pool NAT and anti-HBc testing. These strategies are summarised in Table 2.

Table 2: Summary of modelled OBI screening strategies

Strategy	Details	Frequency over 10 years
Reduced pool NAT	• Pool sizes: individual (ID-NAT; 1), small (4-8)	All donations annually
Anti-HBc screening	• Universal anti-HBc screening as an additional screening test. • Involves a testing algorithm to confirm anti-HBc (repeat testing and reference testing). • Specific testing algorithms differ across blood services.	All donors once: • Initially all donors then only new and lapsed donors (2+ years since donation) in subsequent years. • It takes two years to cover all existing donors as some repeat donors donate every 1-2 years.

For the anti-HBc testing strategy we included the additional anti-HBs, ID-NAT and confirmatory testing required to reduce donor deferral. The test strategy would be slightly different for the screening and reference services in England and Scotland, shown in figure 5.

Figure 5: Anti-HBc testing strategies for the UK blood services, including additional tests to reduce donor deferral



Costs and benefits

Modelled costs and benefits are based on data collected from UK blood services and screening test manufacturers and residual risk estimates calculated from published OBI risk models. Table 3 shows a summary of variables and data points used in the model.

Note: These strategies are indicative and do not include additional tests which may be carried out on anti-HBc reactive samples. All anti-HBc reactive samples with anti-HBs >100 IU/L must be HBV ID-NAT negative before the component can be released for transfusion.

Table 3: Costs and benefits included in the model

	Variable		Data points	
			NAT	Anti-HBc
Costs	**Testing**	Tests	• Annual donations (2019, blood services) • Price/test (2020, manufacturer)	• Donor profiles: new, repeat, lapsed (2019, blood services) • Anti-HBc testing data (2015, NHSBT) • Price/test (2020, blood services)
	Operational	Staffing requirements for additional testing	• Number of machines (2020, manufacturer) • Staff required to operate machinery (2020, blood services) • AfC pay scales (2020)	• Staff required (blood services) • AfC pay scales (2020)
		Space requirements	• Space required: general lab, ambient, cold, frozen (2020, manufacturer) • Cost for new lab space (2021, NHSBT)	-
	Donor loss	Recruitment costs to replace donors	• OBI detections via risk models (see benefits) • Recruitment cost (2021, NHSBT)	• True positive anti-HBc via anti-HBc testing data (2015, NHSBT) • Recruitment cost (2021, NHSBT)
Benefits	**Detections**	Additional OBI detections	• OBI residual risk models: South African (RSA)[1] and Australian (AUS)[2]	

Benefits

The model includes benefits via the number of additional detections. We calculate the number of additional detections based on two distinct residual risk estimates. This is because there are two different OBI risk models in the literature: South African (RSA) and Australian (AUS) models. The RSA and AUS models estimate the current UK residual risk to be 7.9 and 41.3 OBI cases per million donations based on NAT pool sizes of 24 donations.

We are assuming that almost all OBI individuals would be anti-HBc positive thereby reducing residual risk to close to zero. For practical purposes for the modelling, we have assumed residual risk to be effectively zero.

Costs

The modelling captures costs from testing, operational changes and donor loss. Testing refers to the direct costs of tests required for each strategy. NAT involves a single test for all donations. Anti-HBc screening involves multiple tests: repeat anti-HBc tests, HBV surface antibody (anti-HBs) tests (for NHSBT and the Welsh Blood Service (WBS) only due to their

[1] Weusten J, van Drimmelen H, Vermeulen M, Lelie N. A mathematical model for estimating residual transmission risk of occult hepatitis B virus infection with different blood safety scenarios. Transfusion 2017;57:841-9.
[2] Seed CR, Kiely P. A method for estimating the residual risk of transfusion-transmitted HBV infection associated with occult hepatitis B virus infection in a donor population without universal anti-HBc screening. Vox sanguinis 213;105:290-8.

testing algorithm) and subsequent reference testing including ID-NAT (and anti-HBs at this stage in Scotland). To calculate anti-HBc testing costs, we estimated the number of donors screened in each year and the numbers of tests required. We calculated the number of donors based on donor profiles: new, repeat (within year), repeat (1-2 years), lapsed (2+ years). Initially all donors are screened, then only new and lapsed donors in subsequent years. See Table 4 for a breakdown of donor screening over ten years. We calculated the numbers of tests required for the number of donors using NHSBT 2015-16 testing data on outcomes from anti-HBc screening.

Table 4: Anti-HBc screening strategy, 10-year breakdown of donor types included in screening

Year	New	Repeat (within year)	Repeat (1-2 years)	Lapsed (2+ years)
1	Screened	Screened	Screened	Screened
2	Screened		Screened	Screened
3-10	Screened			Screened

Operational costs include additional space and staffing requirements. These are based on the expected operational changes proposed by manufacturers and UK blood services. For reduced NAT, manufacturers provided estimates of the numbers of machines and lab space required. Based on steer from blood services, we estimated the number of staff required relative to number of machines and calculated staffing costs. We additionally calculated cost of lab space using NHSBT price estimates based on the new NHSBT Barnsley lab. For anti-HBc testing, we did not model any additional space requirements. Operational costs were therefore purely based on expected staffing requirements provided by blood services for initial screening, reference testing and further clinical work.

Donor loss captures the cost of replacing any donors identified by each testing strategy. In NAT this includes any additional OBI detections. We have used the AUS risk model for this calculation to provide a more conservative estimate of donor loss. In anti-HBc screening donor loss includes anyone identified with a positive anti-HBc test. For both strategies, we estimate the cost to replace a donor as a flat rate of £70 and this does not incorporate any further granularity, for instance BAME donor loss.

We combined testing, operational and donor loss costs to estimate the total cost for each strategy and the additional cost of enhanced screening compared to baseline (medium pool sizes). For NAT testing, we calculated additional costs within-manufacturers. In other words, we did not use an average cost for the medium pool size group as a single baseline in this calculation. Instead for pool sizes smaller than 12, we calculated the additional costs relative to the respective medium NAT pool from the same manufacturer. This is to ensure that our inferences are not biased by differences between manufacturers. For NAT, results are subsequently summarised into pool size groups: ID-NAT and small (4-8) with only aggregate results presented to preserve anonymity for test kit manufacturers (see Limitations).

Outside model scope

The following areas are beyond the scope of this analysis:

- **Health impacts** of the transmission of HBV from OBI cases, due to the uncertainty in estimating which OBI detections lead to transmission.
- **Cost-effectiveness** of each strategy, as it is not possible to evaluate cost-effectiveness without including health impacts of transmission.
- **Wider detection benefits from reduced pool NAT**, including reduced residual risk of HIV and HCV, as this was not the focus of the analysis.
- **Wider societal costs and benefits**, such as the reputational benefit of reduced residual OBI risk. We excluded these to maintain a proportionate scope as there are challenges in estimating broader, less tangible costs and benefits.
- **Wider operational impacts** to blood services (for example changes of manufacturing supplier for NAT or contracting out anti-HBc screening in Year 1 for anti-HBc screening), as these are challenging to robustly estimate. We justify the included operational impacts as proportionate to allow SaBTO to make a recommendation.
- **Tests not currently on the market**. Future developments are likely to provide more competitive prices which could affect which screening strategy is preferable. However, until any new tests are approved by regulators, we cannot include them in our analysis or decision-making.

Key assumptions

The modelling makes the following key assumptions:

- **Results are indicative**: many data points feed into the model and there is uncertainty associated with several inputs. Results are indicative as our best estimates.
- **Donations are constant over time**: the number of donations (new, repeat, lapsed) are the same in each year.
- **Donor profiles are constant over time**: risk of prior HBV infection and immunisation status for HBV are the same in each year.
- **Anti-HBc residual risk**: screening for anti-HBc reduces residual risk to approximately 0.
- **Anti-HBc testing data**: NHSBT 2015-16 anti-HBc testing data is adequately representative of expected results of testing for the UK population.
- **Anti-HBc space requirements**: each blood service needs no further lab space for the anti-HBc testing strategy.
- **Anti-HBc reference testing:** NHSBT and the Scottish National Blood Service (SNBTS) will conduct reference testing for Welsh Blood Service (WBS) and Northern Irish Blood Transfusion Service (NIBTS), respectively. We take this into account when estimating the costs to each blood service.

Limitations

The analysis has several limitations that SaBTO should consider when interpreting results. These are summarised as follows:

Test kit manufacturers shared data with DHSC under a non-disclosure agreement (NDA). To anonymise commercially sensitive information, NAT pool sizes are categorised into ID-NAT, small (4-8) and medium (baseline; 12-24) with only summary results presented. SaBTO should be aware that there were differences in data reported between manufacturers reflecting the differences in testing products and operational requirements.

Therefore, we emphasise that results for NAT pool size groups are indicative summary measures and do not reflect precise costs.

Manufacturer data reported for NAT also contained costs for Hepatitis B virus (HEV) testing which was not possible to disaggregate. As this was the case for all manufacturer data, by using a baseline and comparing strategies, we to some extent remove HEV costing from results. However, there were some inconsistencies on HEV pool sizes in reported costs. Therefore, we caveat our results as including some costs of HEV testing. We do not expect our overall inferences to change because of this limitation.

Upon implementation of either strategy there may be efficiencies and economies of scale for each blood service. We do not capture these within the modelling. This is because we do not necessarily know where and to what extent efficiencies might fall. Additionally, we have opted for a more conservative approach to avoid under-estimating costs.

A full cost-effectiveness analysis was beyond model scope and therefore we do not evaluate any strategy against a standard cost-effectiveness threshold. Typically, we would calculate an Incremental Cost-Effectiveness Ratio (ICER) using £15,000 per Quality Adjusted Life Year (QALY) as our threshold. There would be benefit in future modelling estimating this for each strategy to further inform decision making using a standard cost-effectiveness framework. This would allow greater comparison between proposed strategies and other interventions across the health system.

Results

We present results in the following three sections:

- Costs of enhanced screening
- Cost per additional OBI detection
- Summary and key insights

Costs

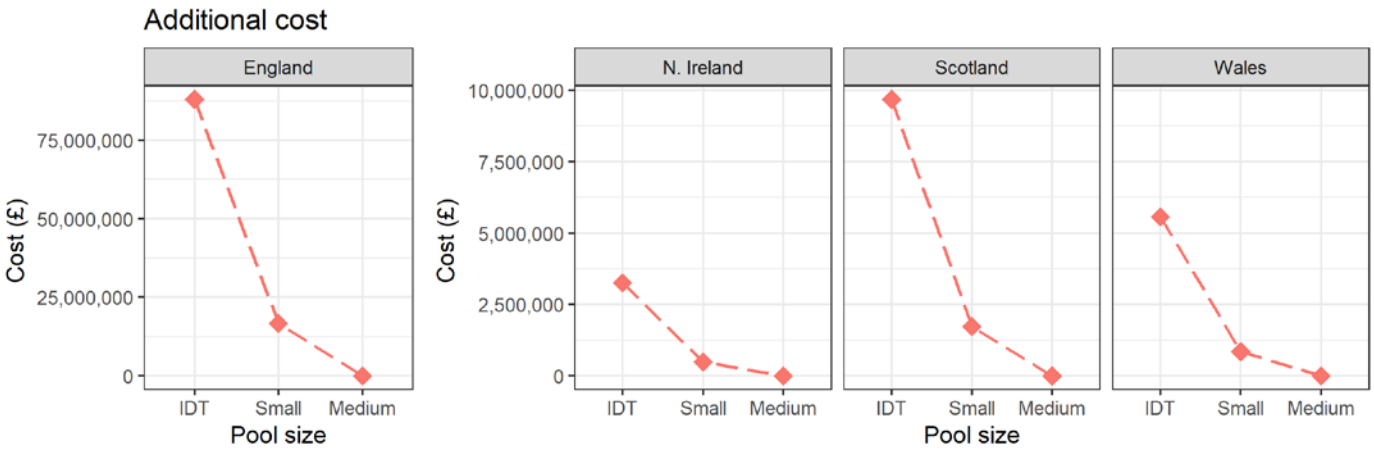
We have estimated the total costs over ten years for each testing strategy. As highlighted in the Limitations, please note that for reduced pool NAT we have grouped data from multiple manufacturers into categories: ID-NAT, small (4-8) and medium (12-24). Results are therefore indicative summary measures not precise costs. Average baseline costs for NAT medium pool sizes (12-24) are shown in Table 5.

Table 5: Average baseline costs for ten years, medium NAT pool sizes (12-24)

Country	Baseline cost (£)
England	45,851,392
N. Ireland	2,076,103
Scotland	5,158,464
Wales	3,505,565

We estimate this to be approximately £46 million for England. The additional costs for reduced pool NAT are shown in **Error! Reference source not found.**.

Figure 6: Additional costs over ten years for reduced pool NAT compared to baseline (medium pool sizes 12-24)



For all blood services, smaller NAT pool sizes have increasing costs compared to baseline, based on the higher numbers of tests and machines required. This increase is most notable for ID-NAT which is approximately three times the cost of baseline, whereas the difference between baseline and small pool sizes is much lower. For instance, the additional costs for England are £17 million and £88 million for small and ID-NAT pool sizes, respectively. Note that these costs are over a ten-year period, however annual costs are the same each year

since the strategy involves testing all donations every year. We do not provide a further breakdown of costs in line with the NDA.

Total costs for Anti-HBc screening over ten years are shown in Table 6. We estimate this at approximately £6 million for England. Table 7 shows the breakdown of costs by year. For all blood services, there are greater costs in Years 1 and 2. This reflects the testing strategy itself, which requires greater initial investment to cover the entire donor population. From Year 3 onwards only new and lapsed donors are screened and the cost is substantially lower, at less than one quarter of Year 1 costs. There is some variation in costs across blood services other than from expected variation from the size of each blood service. This is due to different donor populations, operational requirements and confirmatory testing algorithms for anti-HBc.

Table 6: Anti-HBc screening costs over ten years

Country	Test costs (£)	Staff costs (£)	Donor replacement costs (£)	Total costs (£)
England	4,753,435	1,175,817	245,235	6,174,487
N. Ireland	199,031	57,627	8,956	265,615
Scotland	553,390	94,637	24,903	672,930
Wales	321,494	88,745	16,586	426,826

Table 7: Anti-HBc screening costs by year

Country	Year	Test costs (£)	Staff costs (£)	Donor replacement costs (£)	Total costs (£)
England	1	1,631,069	301,529	84,149	2,016,747
England	2	568,928	117,609	29,352	715,889
England	3-10	319,180	94,585	16,467	430,232
N. Ireland	1	67,788	48,526	3,050	119,364
N. Ireland	2	23,781	9,101	1,070	33,952
N. Ireland	3-10	13,433	0	604	14,037
Scotland	1	214,238	70,890	9,641	294,769
Scotland	2	68,206	23,746	3,069	95,021
Scotland	3-10	33,868	0	1,524	35,392
Wales	1	114,364	45,873	5,900	166,137
Wales	2	38,807	4,764	2,002	45,572
Wales	3-10	21,040	4,764	1,086	26,890

Cost per additional OBI detection

We calculated the cost per additional OBI detection for each strategy. Figure 7 shows this for reduced NAT pool sizes and figure 8 for anti-HBc screening.

Figure 7: Cost per additional OBI detection for reduced pool NAT pool compared to medium pools, pool size groups are ID-NAT(1), small (4-8), medium (12-24)

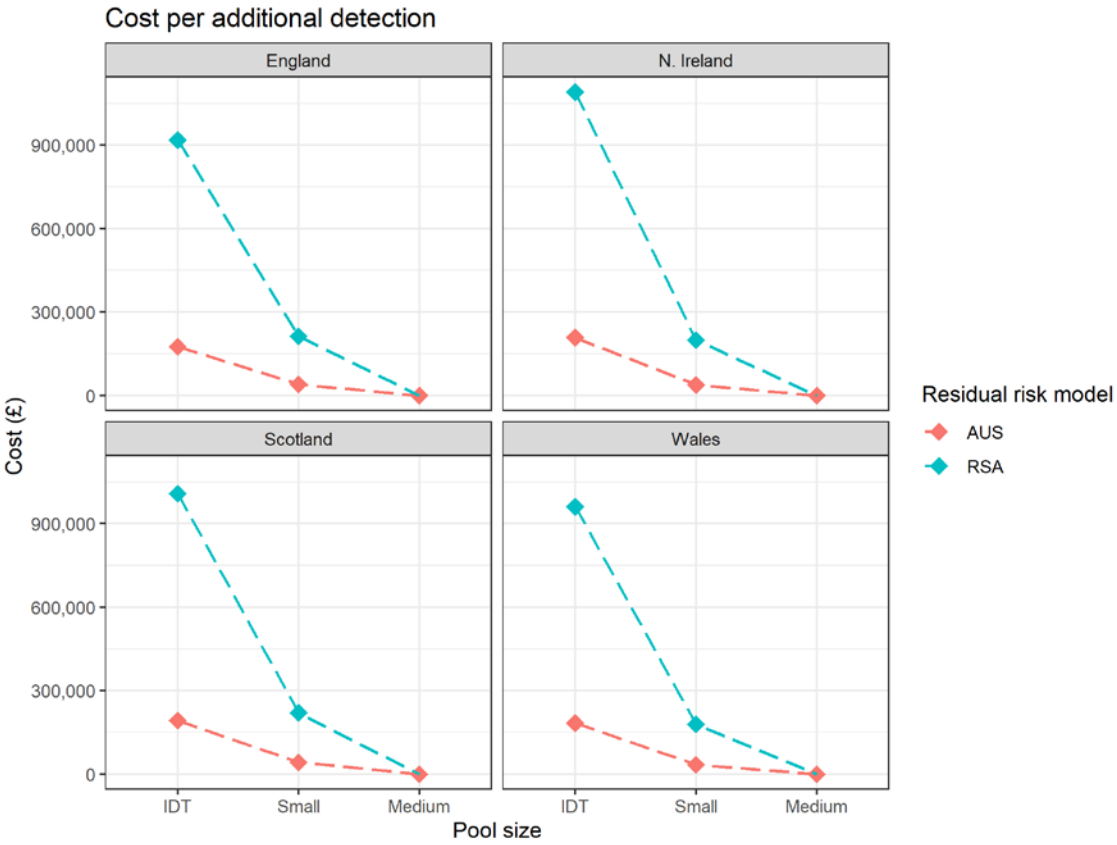
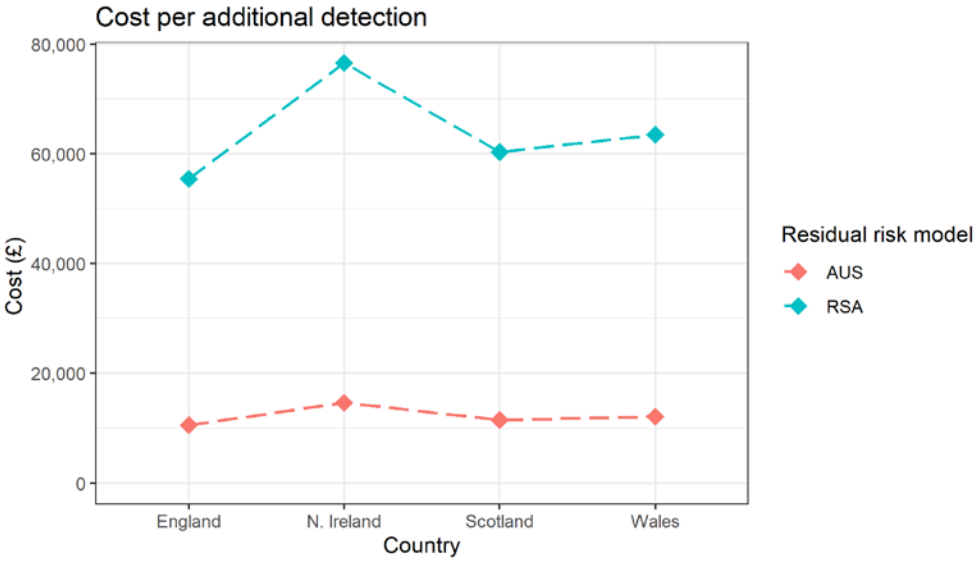


Figure 8: Cost per additional OBI detection, Anti-HBc screening



For both strategies, we see a similar trend across blood services, with some minor variation due to expected differences in economies of scale and operational requirements. In contrast, we see significant differences in the cost per additional OBI detection between the RSA and AUS risk models.

For reduced pool NAT, the cost per additional OBI detection increases as pool sizes decrease. Across blood services, the cost per additional detection is approximately £1 million

(RSA) and £200,000 (AUS) for ID-NAT, and £250,000 (RSA) and £45,000 (AUS) for small pool sizes. The increasing cost per detection highlights that as pool sizes decrease, the increase in cost outweighs the additional OBI detections. As with the additional costs, this is most applicable for ID-NAT which has a much greater cost per additional detection. Additionally, the difference between risk models is stark with the RSA cost per additional detection approximately five times greater than the AUS model for both pool sizes.

For anti-HBc screening, the cost per additional OBI detection is similar across blood services. This is approximately £60,000 (RSA) and £15,000 (AUS), which is notably lower than those estimated for reduced pool NAT. Again, we observe stark differences between the RSA and AUS estimates.

Donor loss

We calculated the expected donor loss with each testing strategy compared to baseline. This is shown in Table 8.

Table 8: Estimated donor loss for each testing strategy compared to medium pools; pool size groups are ID-NAT (1), small (4-8), medium (12-24)

Country	Reduced pool NAT		Anti-HBc screening			
	ID-NAT All years	Small All years	Year 1	Year 2	Years 3-10	All years
England	445	300	1,202	419	235	3,503
N. Ireland	14	9	44	15	9	128
Scotland	45	30	138	44	22	356
Wales	27	18	84	29	16	237

Donor loss is greater for anti-HBc screening than reduced pool NAT, estimated at an additional 3,503 donors compared to 300 (small) and 435 (ID-NAT) over ten years for England. This is because anti-HBc donor loss captures all anti-HBc positive donors, whereas reduced pool NAT includes only the additional OBI cases. The breakdown of donor loss over time also differs between strategies. Reduced pool NAT donor loss will be consistent over time, with the same number of additional OBI detections identified each year. However, anti-HBc testing screens more donors in Years 1 and 2 to initially cover the full donor pool. As a result, greater donor loss is expected in the earlier years of the testing strategy.

The ethnic profile of donor loss from anti-HBc testing has been extrapolated from NHSBT data from 2017 which was the last year that selective anti-HBc testing was carried out (Table 9).

Table 9: Estimated donor loss for anti-HBc screening by ethnicity

Country	Ethnicity	Year 1	Year 2	Years 3-10
England	Asian	117	41	23
	Black	117	41	23
	Mixed and other	29	10	6
	Not known	59	20	11
	White	880	307	172
N. Ireland	Asian	4	1	1
	Black	4	1	1
	Mixed and other	1	0	0
	Not known	2	1	0
	White	32	11	6
Scotland	Asian	13	4	2
	Black	13	4	2
	Mixed and other	3	1	1
	Not known	7	2	1
	White	101	32	16
Wales	Asian	8	3	2
	Black	8	3	2
	Mixed and other	2	1	0
	Not known	4	1	1
	White	62	21	11
Total All countries		**1466**	**505**	**281**

The estimate shows that donor loss is split roughly between white and other ethnic backgrounds. However, as the number of donors from ethnic backgrounds is a much lower percentage of total donors compared to white donors, anti-HBc will have a disproportionate effect on donations from ethnic minority donors. Important caveats are that the extrapolated numbers are based on small numbers of donors tested and this was targeted at donors with an enhanced risk of hepatitis B and may not accurately reflect testing of the entire donor pool.

Summary of cost benefit analysis

In this section, we provide a summary table of results for each UK nation. Each table contains data on: (1) baseline residual risk levels; (2) improvements in OBI detections and residual risk for enhanced screening; (3) costs of enhanced screening; and (4) cost per additional OBI detection. This aims to provide a holistic view of the analysis to aid decision making.

Key insights

Key insights from this analysis have been summarised below:

Minimal variation across blood services

- Across blood services, the scales of cost and OBI risk differs, largely due to differences in population size for each UK nation. However, the overall trends, particularly for the summary metric (cost per additional OBI detection) are similar across blood services.

Uncertainty and robustness

- Estimates for reduced pool NAT hold a higher degree of uncertainty than anti-HBc screening estimates. This is because NAT cost estimates are based on speculative data from test kit manufacturers not concrete agreements.
- Additionally, differences between manufacturers mean that the summary cost estimates presented reflect approximate estimates which are not necessarily accurate representations of the entire group.

Residual risk

- We estimate baseline (medium pool sizes; 12-24) residual risk as 7.2 (RSA) and 37.7 (AUS) non-detections per million donations.
- Anti-HBc screening reduces OBI residual risk to close to 0, whereas the residual risk rate remains at best 1.7 (RSA) and worst 8.7 (AUS) OBI non-detections per million donations for ID-NAT.

Costs

- We estimate that costs for anti-HBc screening will be lower than using reduced NAT pool sizes. For England, we estimate total costs as £6 million (anti-HBc) compared to £17 (NAT small) or £88 million (NAT ID-NAT) over ten years.

Cost per additional detection

- The analysis does not provide a definitive recommendation or propose an appropriate threshold for additional cost per OBI detection.
- We estimate the cost per additional OBI detection to be significantly lower for anti-HBc screening than for the reduced pool NAT groups considered. This reflects the higher numbers of OBI cases detected and the smaller costs for anti-HBc screening.
- For England, the cost per additional detection for anti-HBc screening is £55,000 (RSA) or £10,000 (AUS). The other UK blood services have similar results.

Table 10: Summary of OBI economic modelling for England

ENGLAND		Baseline NAT medium pool sizes (12-24)	
Estimated baseline residual risk over 10 years	**Number of non-detections**	111.3	582.3
	Residual risk rate (per million donations)	7.2	37.7

ENGLAND	NAT Reduced pool sizes, all donations				Anti-HBc Donor screening	
	ID-NAT		**Small**			
Improvement in number of OBI detections from additional screening	85	444.8	58.7	307.3	111.3	582.3
Residual risk: number of non-detections with additional screening	26.3	137.5	52.6	275	0	0
Residual risk rate (per million donations) with additional screening	1.7	8.9	3.5	18.3	0	0
Total cost of additional screening (£)	133,877,863		54,768,856		6,174,487	
Cost of additional screening compared to baseline (£)	88,026,471		16,712,045		6,174,487	
Cost per additional OBI detection (£)	1,035,277	197,887	247,563	47,320	55,472	10,607

Risk model key: RSA, AUS

Table 11: Summary of OBI economic modelling for N. Ireland

N. IRELAND		Baseline NAT medium pool sizes (12-24)	
Estimated baseline residual risk over 10 years	**Number of non-detections**	3.5	18.1
	Residual risk rate (per million donations)	7.2	37.7

N. IRELAND	NAT Reduced pool sizes, all donations				Anti-HBc Donor screening	
	ID-NAT		Small			
Improvement in number of OBI detections from additional screening	2.6	13.9	1.8	9.6	3.5	18.1
Residual risk: number of non-detections with additional screening	0.8	4.3	1.6	8.6	0	0
Residual risk rate (per million donations) with additional screening	1.7	8.9	3.5	18.3	0	0
Total cost of additional screening (£)	5,333,635		1,994,818		265,615	
Cost of additional screening compared to baseline (£)	3,257,532		485,696		265,615	
Cost per additional OBI detection (£)	1,229,763	235,062	230,946	44,144	76,598	14,647
Risk model key: RSA, AUS						

Table 12: Summary of OBI economic modelling for Scotland

SCOTLAND		Baseline NAT medium pool sizes (12-24)	
Estimated baseline residual risk over 10 years	**Number of non-detections**	11.1	58.3
	Residual risk rate (per million donations)	7.2	37.7

SCOTLAND	NAT Reduced pool sizes, all donations				Anti-HBc Donor screening	
	ID-NAT		Small			
Improvement in number of OBI detections from additional screening	8.5	44.6	5.9	30.8	11.1	58.3
Residual risk: number of non-detections with additional screening	2.6	13.8	5.3	27.5	0	0
Residual risk rate (per million donations) with additional screening	1.7	8.9	3.5	18.3	0	0
Total cost of additional screening (£)	14,842,854		5,746,214		672,930	
Cost of additional screening compared to baseline (£)	9,684,390		1,731,519		672,930	
Cost per additional OBI detection (£)	1,137,077	217,345	256,069	48,946	60,356	11,541
Risk model key: RSA, AUS						

Table 13: Summary of OBI economic modelling for Wales

WALES		Baseline NAT medium pool sizes (12-24)	
Estimated baseline residual risk over 10 years	**Number of non-detections**	6.7	35.2
	Residual risk rate (per million donations)	7.2	37.7

WALES	NAT Reduced pool sizes, all donations				Anti-HBc Donor screening	
	ID-NAT		**Small**			
Improvement in number of OBI detections from additional screening	5.1	26.9	3.5	18.6	6.7	35.2
Residual risk: number of non-detections with additional screening	1.6	8.3	3.2	16.6	0	0
Residual risk rate (per million donations) with additional screening	1.7	8.9	3.5	18.3	0	0
Total cost of additional screening (£)	9,069,274		3,400,163		426,826	
Cost of additional screening compared to baseline (£)	5,563,709		847,590		426,826	
Cost per additional OBI detection (£)	1,083,959	207,192	207,992	39,756	63,523	12,147
Risk model key: RSA, AUS						

Comments on anti-HBc testing as a blood testing strategy for OBI

Introduction of anti-HBc testing will be more cost effective than reducing HBV NAT pool size in reducing the residual risk from OBI donations. It has the additional benefit of reducing the additional risk to effectively zero whereas even individual donation testing by HBV NAT is predicted to fail to detect some OBI donations.

However, there is considerable uncertainty in the prevalence of OBI in blood donors in the UK, the number of donors with antibodies to HBc which will include donors who have a resolved HBV infection with high levels of anti-HBs who can continue to donate, and the false positive rate of anti-HBc tests.

Two important issues were discussed by the working group which required consideration if an anti-HBc testing strategy was introduced:

- Donor deferral policy for anti-HBc reactive donors. Deferral of all such donors could result in significant donor loss and could add significant costs not fully considered in the cost benefit analysis.

- Lookback protocols for previous donations of anti-HBc reactive donors.

Deferral of anti-HBc reactive donors

The working group considered whether it would be reasonable to recommend deferral of all donors found to be anti-HBc positive, irrespective of the results of testing for other markers of HBV infection.

Anti-HBc positivity is a marker of past or current active HBV infection; any individual who has had past HBV infection may harbour viral DNA in their hepatocytes for their lifetime; such virus may replicate and result in release of infectious viral particles into the blood stream. Introduction of anti-HBc testing would, therefore, identify ALL donors who might be at risk of transmitting occult HBV infection.* This conclusion is reflected in the calculations made by the group on costs and of residual risk should any of the proposed interventions considered be introduced – for anti-HBc testing the residual risk of an occult-infected donation being missed by screening was assumed to be zero.

Anti-HBc testing therefore provides the most effective way of reducing risk – introduction of individual NAT testing does not reduce risk to zero because the infectious dose of occult HBV is thought to be lower than the lower limit of detection of the assay.

It would therefore be a reasonable approach to introduce anti-HBc testing and defer all positive donors. However, it should be noted that not all anti-HBc positive individuals will be suffering from occult infection at the time of donation. Such a blanket deferment policy would therefore maximise patient safety but at the expense of losing valuable donors. It could be argued that loss of ethnic minority donors, who would be disproportionately affected by a blanket deferral could, itself, be detrimental to some patients from a similar background if this led to a shortfall of the most suitable blood components for their needs.

* with the caveat that the literature does contain reference to OBI individuals who have no markers of HBV infection at all (i.e., are anti-HBc negative). However, this is controversial, and there would be no possible way of eliminating such donors, if indeed they exist, from the donor pool.

The group were concerned at the potential loss of donors, especially within the first year of introduction of such a policy, and the ability to replace them at the same rate and considered a number of ways of “retrieving” anti-HBc positive donors whose donations are highly likely to be safe but would be lost under a blanket deferral. There is evidence in the literature that high levels of anti-HBs are associated with a considerably reduced risk of transmission of occult HBV. The principle of accepting anti-HBc positive donors who have anti-HBs levels exceeding 100 IU/L is already in place in some transfusion services; the group therefore agreed it would be reasonable to extend that principle and allow such donors to continue to donate.

In summary, the group were AGREED that:

1) A policy of blanket deferment of all anti-HBc positive donors is a sensible approach if blood transfusion services wish to adopt such a policy.

2) The downside of such an approach is the greater number of donors who would be deferred; if an individual BTS felt this would be a problem, then the group recommended a supplementary set of tests that would allow anti-HBs positive donors with levels of anti-HBs > 100 IU/L to donate, provided that they are HBV DNA negative by ID-NAT.

Recipient lookback investigations

The working group were asked to consider recommendations on recipient lookback protocols for anti-HBc reactive donors. The working group have assumed that all such donors would undergo further testing to confirm anti-HBc positivity and further investigate the risk of transmission of HBV to recipients. This would include individual donation nucleic acid testing (ID-NAT) and anti-HBs titration.

Donations which are confirmed anti-HBc positive would fall into 4 categories dependant on anti-HBs titre and HBV DNA status after ID-NAT. These categories also stratify the risk of transmission of OBI, with category one being the highest, 4 the lowest.

1. HBV DNA detected, anti-HBs <100 IU/L
2. HBV DNA detected, anti-HBs >100 IU/L
3. HBV DNA not detected, anti-HBs <100 IU/L
4. HBV DNA not detected, anti-HBs >100 IU/L

Unless a blanket deferral policy is enacted, donors in group 4 would be allowed to continue to donate. A recipient lookback would not be required as the anti-HBs titre would be assumed to have remained at a high level in previous donations. As anti-HBs levels decline slowly over time the group recommends that the anti-HBs titre is retested at least every two years. The group recognises that it may be operationally easier for blood services to monitor anti-HBs levels each time the donor donates.

It is also important to note that the donor may have a recent history of vaccination for HBV which could have boosted otherwise low levels of anti-HBs and there may have been recent anti-HBc seroconversion indicating intercurrent acute HBV infection.

For donors who fall into the remaining groups 1-3 the working group recommends that lookback investigations should be considered for all components for a minimum period of 3 years.

The group recommends that all archived samples retrieved as part of lookback are tested by ID-NAT. As levels of circulating HBV DNA can vary it is possible that one or more archived samples will be HBV DNA positive. Lookback should be prioritised for recipients of all previous donations from any donor for whom any residual sample (including the index donation at which anti-HBc positivity was identified) is found to be HBV DNA positive (i.e., groups 1 and 2 donors above).

Group 3 donors are likely to be the most numerous. In order to help prioritise which, if any, of these donors should be subjected to lookback, the working group identified that higher anti-HBc titres have been associated with an increased risk of HBV DNA positivity. Thus, we suggest that monitoring of anti-HBc titres, together with anti-HBs titre, may allow prioritisation of the donors with the highest risk of HBV transmission.

Data collected during the pilot phase of anti-HBc testing would be very useful in determining the number of donors in each category, their transmission risk and the scale of lookback investigations.

The working group considered whether it would be appropriate to retrieve samples from lapsed donors (i.e., who had not donated in the last two years) in order to determine which were anti-HBc positive, and thereby initiate lookback for recipients of previous donations from those donors. Lookback is thought to be appropriate for current donors noted to be anti-HBc positive because such individuals may have inadvertently transmitted HBV infection to their recipients despite appropriate HBV screening at the time of donation. The same risk will also apply to any anti-HBc positive donor who no longer donates.

However, the group also NOTED that:

1) Institution of such a policy would be completely without precedent. In particular, no such exercise in tracking down lapsed donors was carried out when prospective screening of blood donors for evidence of HBV, HIV, HCV or HTLV was introduced. The risk of serious adverse outcomes following transmission of any of those viruses is likely to be far higher than that posed by receipt of an occult HBV infected donation.
2) It is not clear what the yield of any lookback exercise for anti-HBc positive donors will be, in terms of the numbers (percentages) of recipients still alive who might have acquired HBV infection from an occult infected donor, and for whom medical intervention may be beneficial i.e., individuals with chronic HBV at risk of developing liver cirrhosis and cancer.
3) Lookback exercises also have the propensity to do harm; in this instance, such harm might arise in donors, who will be informed that unbeknownst to them, they might have been suffering from HBV infection during their history of donations and who might therefore become anxious about the effect of that on their own health (likely to be minimal) and also experience guilt at possibly transmitting infection to others. Recipients who are contacted and asked to be tested for evidence of HBV infection will experience concern and anxiety up to the point when their laboratory results are available. The diversion of considerable resources within transfusion services to this exercise might impact adversely on other functions of the service.
4) Samples archives were not designed for mass retrieval of samples for testing. There would be a risk of compromising other lookback investigations by using up samples for testing, thaw/freezing samples etc.

Lookbacks on lapsed donors would require testing of tens of thousands of samples for each service and would add considerably to workload. There may not be the capacity to do this, especially while conducting investigations on current donors.

In the absence of being able to quantify either the potential benefits of lookback or the potential for harm, and in the knowledge that such an exercise would consume a considerable amount of resources at a considerable cost, the group did not feel it appropriate to recommend such retrospective identification of anti-HBc positive donors in order to initiate lookback on their previous donations.

The group recommends that this be reviewed at a later date with appropriate data allowing more accurate estimates of the scale and costs of such a policy, along with better estimates of the likely benefits and harms which might arise from it. Clearly, data derived from the planned lookback for donors prospectively identified as anti-HBc positive will generate relevant data that can be considered.

Future research

The working group is aware of significant gaps in data which will inform the decision to continue anti-HBc testing beyond the initial 12-month pilot phase. These include easily collectable data such as the number of OBI donors identified, the number and ethnicity of donors deferred, the ID-NAT status of anti-HBc positive donors throughout their donation history, and the monitoring of anti-HBs titres in repeat donors to estimate the risk of donors developing OBI. Additional data from a research perspective which would be extremely helpful includes titration of anti-HBc reactivity, and the use of larger plasma volumes (e.g., 5mL) for nucleic extraction prior to ID-NAT testing from donors prospectively identified as anti-HBc positive. This would increase the sensitivity of detection of HBV DNA and give a truer picture of the frequency of DNAemia in such donors. The working group will continue to meet and monitor both routinely collected data and any research data following the introduction of anti-HBc testing over the 12-month time frame.

Conclusions and Recommendation to SaBTO

After modelling the estimated residual risk of infection of HBV from OBI donors, the group considered that the risk was unacceptable and that an options appraisal of changes to the HBV testing strategy was required.

A cost/benefit analysis was conducted on reduction of the mini-pool size or testing by individual donation for HBV NAT. This was compared to the introduction of anti-HBc testing, initially on donations from all donors then only for new and lapsed donors. The analysis considered costs of tests, space for additional equipment, and additional staff for clinical work and confirmatory testing. However, the group did not consider the full economic cost of recipient lookbacks due to lack of data to estimate the scale of these lookbacks and the operational aspects which will differ for each service.
For the introduction of anti-HBc testing consideration was also given to anti-HBs testing required to allow donations with anti-HBs>100 IU/L to be accepted, donor loss and additional costs to recruit replacement donors.

Introduction of anti-HBc testing will be more cost effective than reducing HBV NAT pool size in reducing the residual risk from OBI donations. It has the additional benefit of reducing the additional risk to effectively zero whereas even individual donation testing by HBV NAT is predicted to fail to detect some OBI donations.

However, there is considerable uncertainty in the prevalence of OBI in blood donors in the UK, the number of donors with antibodies to HBc which will include donors who have a resolved HBV infection with high levels of anti-HBs who can continue to donate, and the false positive rate of anti-HBc tests.
The working group agreed the following recommendations:

- The UK blood services introduce an anti-HBc testing strategy to reduce the number of OBI donations reaching the blood supply. This would be done once on all current donors, subsequently only on new donors or donors who have not donated within the previous two years.

- Given the uncertainties in the data used to provide a cost/benefit analysis, the group recommends that the strategy is reviewed after 12 months of implementation when additional will be available, including the number of donations that are anti-HBc positive, the anti-HBc false positive rate, the proportion of anti-HBc positive donors with anti-HBs levels >100 IU/L, the number of anti-HBc positive donors with HBV DNA detectable by ID NAT, the number and characteristics of donors deferred and data from lookback studies. This information will be used to provide a revised residual risk estimate and a more complete economic appraisal.
- All anti-HBc reactive donations should undergo confirmatory testing; confirmed anti-HBc positive donations must be tested by ID-NAT and anti-HBs levels determined.

- Donations which are anti-HBc positive with an anti-HBs titre greater than 100 IU/L can be accepted and the donor may continue to donate although this is at the discretion of individual blood services. If these donors are allowed to donate, they must remain HBV DNA negative by ID-NAT at each subsequent donation, their anti-HBs titre must be retested at least every two years and remain greater than 100 IU/L.

- Lookback investigations should be conducted on previous donations of current donors who are anti-HBc positive, ID-NAT positive and/or have an anti-HBs titre less than 100 IU/L going back a minimum period of 3 years. All archived samples should be tested for HBV DNA by ID-NAT. Blood services have well established lookback protocols and will operationally determine the extent and how best to conduct these investigations. Priority for lookback should be given to donors found at any time in their donation history to be HBV DNA positive by ID-NAT.

- Lookback investigations on lapsed donors are not recommended at this time; this will be reviewed during the initial testing phase as data on existing donors is gathered to allow a more informed risk assessment.

- Lookback policy and recommendations should be reviewed after 12 months. Additional data which can then be considered will include: the distribution of anti-HBc positive donors between risk stratification groups; frequency and stability of ID-NAT positivity in anti-HBc positive donors, the scale of lookback required; the results of 12 months lookback in terms of recipient morbidity identified and the results of further research.

- As an anti-HBc testing strategy is likely to impact disproportionately upon donors and, potentially, recipients from ethnic minority groups, SaBTO should conduct a health impact assessment to minimise unanticipated consequences during the 12-month test period.

The group did not consider every operational aspect of anti-HBc testing, for example management of donors who have a current or former sexual partner who has or had recovered from hepatitis B infection at time of last sexual contact. The group considered that the UK Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) should consider the implications of these recommendations for donor deferral policies.

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Appendices

Remit & Terms of Reference for the Occult Hepatitis B Infection working group

Remit

The working group will:

- Review the potential risk to recipients of blood and blood components from the non-detection of occult hepatitis B infection in donations
- Develop options for screening strategies for hepatitis B virus (HBV)
- Conduct assessments for patient risk, operational impact and cost/benefit for different options for screening strategies for HBV including changes to pool size and detection of HBcore antibodies
- Produce a final report with recommendations for the SaBTO committee.

Terms of Reference

In formulating its recommendations, the working group will:

- Take full account of the scientific evidence available regarding the risk to patients from occult hepatitis B infection
- Examine screening strategies for detection of HBV carried out by blood services internationally to detect occult hepatitis B infection in donors
- Develop workstreams to conduct the risk assessments.

Way of working

- The working group will meet on at least three occasions in person or by teleconference during the review.
- A smaller sub-group or groups may be required (in person or by teleconference) to conduct analysis or assessments and draft papers for consideration for the full review group
- Administrative issues will pass to the SaBTO Secretariat who will also maintain a document library.

- **For Information**
- Travelling expenses are payable for attendance at meetings in line with DH rates for individuals who serve on committees.
- Members of the Working Group are asked to use public transport and to travel at standard rates.
- Receipts must be submitted with claims.

Members of the Occult Hepatitis B Infection working group

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Prof Will Irving	Member of SaBTO Professor of Virology, University of Nottingham
Members	
Dr Su Brailsford	Member of SaBTO, Consultant in Epidemiology & Heath Protection NHS Blood and Transplant/Public Health England
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