# Hepatitis E virus transmission by blood transfusion - review of current screening effectiveness

8 December 2025

## Contents



## Executive summary

The Hepatitis E Virus (HEV) Working Group was established in October 2020 to re-examine the effectiveness of current HEV screening of blood and platelet (apheresis) donors and to advise on whether it provides sufficient mitigation of transmission risk. HEV screening is currently performed by nucleic acid testing (NAT) for HEV ribonucleic acid (RNA) in pools of 24 or 16 alongside NAT for human immunodeficiency virus (HIV) and hepatitis B and C viruses (HBV and HCV).

HEV testing is applied universally to all whole blood, platelet and plasma donations, as well as donors of organs and tissues. The effectiveness or otherwise of current HEV screening was reviewed in the light of a recent report of the death of an immunocompromised patient who became infected with HEV from transfusion of a platelet unit (see reference 1). The donation contained enough virus to be infectious but insufficient to be detected by current screening for HEV. Through donor lookback, further missed donations that were potentially infectious or demonstrated to be infectious were described.

The study group has discussed and reported back on the following areas requested in the remit for the working group provided by the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO):

- the testing or donor selection strategies that are available to reduce HEV transmission risk and whether they are feasible to implement?

- the residual risk of HEV transmission from red cells, platelets and plasma screened by current methodology

- the cost of introducing assays with increased sensitivity, and whether their use is cost effective by conventional health economic metrics

- to discuss and resolve each of these matters with the Working Group and make a recommendation to SaBTO on the benefit and value of changes to HEV testing strategy

The summary of the working group discussions and decisions is as follows.

Dietary exposure to HEV from uncooked pork is the primary source of HEV infection in the UK, including of blood and organ donors. There is little immediate prospect of HEV infection being reduced or removed from pork production in the UK or elsewhere.

With current screening, it was calculated that the proportion of donations with undetected HEV RNA per year was 0.004% (95% confidence interval (CI) 0.0025% to 0.0059%) for apheresis donations, and 0.003% (95% CI 0.0027% to 0.0034%) for whole blood donations.

The predicted infectivity of blood components depended on their residual plasma content. Plasma content was predicted to range from 33% (apheresis platelets) to 4% for red cells.

The health economic analysis was crucially dependent on several parameters that relate to the health impact of HEV transmission. In 2022 a review of outcomes of infections in recipients from 12 studies between 2014 and 2020 provided information on the proportion of recipients who might develop severe, life-threatening disease on infection and the extent to which persistent infections in the immunocompromised may be effectively treated (see reference 7).

It was estimated that approximately 6 platelet, plasma and red cell recipients are infected per year from donations missed by current screening, with an estimated impact of 5.9 quality-adjusted life years (QALYs) per year.

A QALY is a measure used to assess the value of medical interventions by combining the quantity of life with the quality of life.

A variety of donor selection and alternative testing strategies for HEV screening to reduce transmission risk were considered. The only practical methods available were to:

- increase sensitivity of HEV screening through testing of donation samples in smaller pools or individually
- use platelet additive solution (PAS) to reduce residual plasma volume in platelets

Individual NAT was considered capable of virtually eliminating current residual transmissions of HEV, but at a substantially increased additional testing cost when used for all donations.

The working group acknowledged the predicted benefit of individual NAT but acknowledged the high cost of doing so compared to other medical interventions.

## Recommendations for SaBTO

### Recommendation 1

The increased cost of testing individual donations for HEV (£11 million per year) was over 60 times greater than its calculated health economic benefit (£176,000) based on a QALY value of £30,000. This economic calculation shows that testing individual donations for HEV RNA is not conventionally cost-effective, and if decisions to implement changes in testing are based purely on this health economic metric, the working group does not recommend any change to current screening practice.

### Recommendation 2

The working group recognises the existence of less easily quantified factors such as reputational damage to the blood services if further incidents of HEV transmission occur with continuation of the less sensitive testing in ‘minipools’. Consequently, we advise that SaBTO evaluates risk tolerability as it applies to HEV screening and the extent to which conventional cost effectiveness calculations can be applied in the area of transfusion safety.

### Recommendation 3

SaBTO should develop a communications plan for the report, for example by writing to relevant royal colleges to raise awareness of HEV infection in the management of patients. Early diagnosis and initiation of appropriate treatment may substantially reduce HEV-associated morbidity and mortality. Some members of the HEV Working Group co-authored a review in 2023 on maintaining the microbiological safety of the UK blood supply (see reference 36) that may contribute to greater awareness of transfusion-transmitted infections.

**Recommendation 4**

Each year, SaBTO should review the reported incidence of HEV infections in the wider community using epidemiological data provided by the UK Health Security Agency (UKHSA), and NAT positivity rates in UK blood and platelet donors. Changes in HEV incidence can be evaluated against the economic model developed in this report and the QALY costs can be reviewed. Large increases in HEV incidence should prompt a re-evaluation of HEV testing strategies by the UK blood services - NHS Blood and Transplant (NHSBT), the Scottish National Blood Transfusion Service (SNBTS), the Welsh Blood Service (WBS) and the Northern Irish Blood Transfusion Service (NIBTS).

**Recommendation 5**

Evaluation of current testing should be mindful of donation testing strategies by blood services in other countries and their HEV transmission risk evaluations.

**Recommendation 6**

A review of the effect of potential changes in the parameters used in the current report should be undertaken in 5 years. Those changes might include:

- progress towards HEV elimination in pork production
- potential changes in NAT testing methods, pool sizes for other targets and associated costs
- the effectiveness of PAS in reducing the plasma content of apheresis platelets
- the development of pathogen inactivation (PI) technologies, their costs and potential use for red cell components
- increasing knowledge of the outcomes of HEV infection, better identification of susceptible individuals, potential improved antiviral treatments for HEV and greater clinical awareness by clinicians of HEV as a post-transfusion complication

# Background

The HEV Working Group was established in October 2020 to re-examine the effectiveness of current HEV screening of blood and platelet (apheresis) donors and to advise on whether it provides sufficient mitigation of transmission risk. The creation of the group was prompted by a recent report of the death of a recipient due to a transfusion-transmitted infection (TTI) of HEV from a platelet donation. This was later discovered during a review of previous donations (donation lookback) of an apheresis donor whose subsequent donation was detected as HEV NAT positive by minipool screening. The lookback

documented further donations that had been missed by current screening, prompting the question of its adequacy as a screening strategy.

The terms of reference for the working group were to:

- review the potential risk to recipients of blood and blood products from the non-detection of HEV infection in donors under the current screening strategies employed by the UK blood services

- review the current screening strategy for HEV to determine if it is sufficiently sensitive to reduce the transmission risk to an acceptable level and consider the impact of any changes to the screening strategy for blood-borne infections recommended by the Occult Hepatitis B Infection Working Party

- conduct assessments for patient risk, operational impact and cost benefit for any proposed change to HEV screening

The group should take full account of the scientific evidence available regarding the risk to patients from HEV infection, including consideration of the work carried out by NHS Blood and Transplant (NHSBT) on donor lookback investigations into recent evidence of transmission. Current screening strategies employed by UK blood services should be compared with those by other blood services internationally.

## HEV screening in UK blood donors

The 2016 hepatitis E virus working group report for SaBTO (see reference 2) evaluated the cost-effectiveness of selective HEV screening of blood components for immunocompromised or otherwise susceptible recipients and of its extension to all donations. It contained an excellent review of the background of HEV infections, the dramatic increase in the incidence of HEV genotype 3 infections between 2005 and 2014 across Europe and the growing evidence for transmission through blood and platelet transfusion and organ transplantation in the UK and elsewhere over this period. While the authors acknowledge that dietary sources of HEV constitute the greatest risk for infection, the report authors were concerned that transfusion-related transmission and potential for chronic infection in immunocompromised individuals should be prevented. The analogy with hepatitis C virus (HCV) is helpful - injecting drugs is by far the most common route of HCV transmission but that does not remove the requirement to prevent its transmission through transfusion.

As evident from the terms of reference above, the current working group report does not seek to reinvestigate the decision to screen for HEV. Instead it will investigate the practicality and desirability of enhancing screening effectiveness to further reduce the small number of HEV transmissions that have occurred since the introduction of universal

screening of blood, platelets, organs and tissues in 2017, as described by Harvala H and others (see reference 1). The current report should therefore be read in conjunction with the 2016 working group report (see reference 2), which is summarised below, and concentrate on changes that have occurred since its publication.

Overall, both universal and selective testing strategies were shown in the 2016 working group report (see reference 2) to be cost-effective compared to not screening blood components. Economic costs of £1,662 per QALY for universal screening and £6,955 per QALY for selective screening of blood and platelet donations for transfusion into the immunocompromised recipients were calculated. Screening was cost-effective over a range of HEV infection incidences in donors, and an HEV RNA detection rate of 0.03% (2,392 from 9,348,602 donations screened - see table 2) between 2016 and 2021 lies within this range. The greater cost-effectiveness of universal screening was based on a reduction in the organisational costs of providing both screened and unscreened blood components.

Cost effectiveness calculations were based upon a benchmark figure of £90,000 per QALY as the threshold for an acceptable intervention cost at that time. However, the ethical principle of non-maleficence (avoiding doing harm to others), the 2001 Burton judgement (which ruled that hepatitis C infected blood was defective under product liability legislation) and the Penrose inquiry (which investigated the infection of individuals with hepatitis C and HIV through infected blood in Scotland, reporting in 2015) were considered to be further factors used to justify the recommendation to change to universal donor screening in 2017. The report did make the point, however, that the target group of immunocompromised patients that blood services seek to protect are at far greater risk of HEV infection from their diet. It is proposed that the Department for Environment, Food and Rural Affairs (DEFRA) and Food Standards Agency (FSA) should be asked what measures are being explored to reduce the risk of HEV through the food chain and what has been achieved in this area by DEFRA or other agencies since publication of the previous report by SaBTO in 2016.

## Morbidity and mortality from HEV infections

To inform decisions about possible changes in HEV screening to reduce transmission risk, we have reviewed the recent literature on outcomes of infections in recipients of blood components (red cells, fresh frozen plasma and platelets). HEV infections in immunocompetent individuals are transient, usually asymptomatic and are not associated with long-term conditions. In contrast, immunocompromised patients are the primary group at risk from acute and persistent infection and severe disease outcomes from HEV infection, including decompensated liver disease. For example, high rates of morbidity and mortality were reported in those receiving allogeneic hematopoietic stem cell transplants (see references 3, 4, 5 and 6). Infection outcomes in transplant recipients reported in 12

studies were comprehensively reviewed in 2022 (see reference 7) and combined data from this review, along with UK data (see reference 1), are summarised in table 1 below.

Table 1: outcomes of transfusion-transmitted HEV infections

| **Recipients with transfusion transmitted HEV** | **Numbers affected (Percentage of total)** |
|---|---|
| Recipients clearing infection spontaneously without medical intervention | 26 (51%) |
| Recipients clearing infection after reversing immunosuppression | 6 (10%) |
| Recipients clearing infection through treatment with ribavirin | 19 (33%) |
| Recipients with chronic infection | 2 (3%) |
| Recipient deaths | 4 (7%) |
| Total | 57 (100%) |

Source: Harvala H and others (see reference 1), and Cheung CKM and others, table 5 (see reference 7).

Serious disease outcomes were found in recipients with immunosuppression, leukaemias, lymphomas and other severe systemic illness. To identify susceptible recipients more inclusively, it was proposed that these might correspond to those listed in the Green Book. These include individuals needing to avoid live vaccines, neonates and patients who are on a transplant waiting list or are within 3 months of a planned elective transplant. By these criteria, 39% and 18% of recipients of red cells in England and Scotland respectively were categorised as immunocompromised, rising to 65% and 46% in platelet recipients (data based on publications from 2014 and 2012 (see references 8 and 9) and from the Scottish account for blood and acute, cancer, deaths and mental health from Scotland). Similar figures can be derived from a previous categorisation of blood, platelet and fresh frozen plasma (FFP) recipients by Wells and others in 2002 (see reference 10).

## Current HEV screening in the UK

The original recommendation from the working group and subsequently by SaBTO for the change to universal screening for HEV in 2017 was followed by England (by NHSBT), Scotland (Scottish National Blood Transfusion Service; SNBTS), Wales (Welsh Blood Service; WBS) and Northern Ireland (Northern Irish Blood Transfusion Service; NIBTS). Current testing is performed using broadly similar testing methodologies, as shown in table 2.

Table 2: summary of HEV screening by UK blood services between 2016 to 2021

| **Blood service** | **Pool size** | **Test method** | **Positive** | **Tested** | **Rate per 100,000 donations** |
|---|---|---|---|---|---|
| NHSBT | 24 | Roche COBAS | 2,085 | 7,859,085 | 26.5 |
| SNBTS | 16 | Grifols Procleix | 180 | 807,969 | 22.3 |
| WBS | 16 | Grifols Procleix | 101 | 446,320 | 22.6 |
| NIBTS | 16 | Grifols Procleix | 26 | 235,228 | 11.1 |
| Total (UK) | Not applicable | Not applicable | 2,392 | 9,348,602 | 25.6 |

Over the period from when screening for HEV began, HEV has been the most frequently detected blood-borne virus detected by NAT, with a total of 2,392 positive pools resolved to single donations within the current scheduled testing period (see table 2). NAT has been highly effective in identifying HEV RNA-containing donations and prompting their removal from the blood supply. Although the rate of HEV RNA positive donations has declined since 2016 (see reference 11), they remain substantial and fall within the cost-effective range calculated in the previous report.

UK blood services screen donations in small pools of either 16 or 24 samples of donations (see table 2). Selection of the pool size was calculated using the infectivity threshold calculated from a previous investigation of viral loads and transmission rate (see reference 12). Investigation of HEV infection in 60 recipients of unscreened blood revealed a minimum infectious dose of 2 x 104 international units (IU) of HEV RNA with no transmissions recorded below this level, contrasting with 18 of 33 transmissions of HEV from units above this level (55% transmission rate). Testing pools of samples with an assay with a minimum sensitivity (LOD95) of around 20 IU/ml (see 'Enhancing the sensitivity of NAT by reducing test pool size') would therefore intercept more than 95% of HEV-contaminated red cells. Red cells contain up to 25ml of residual plasma and therefore only pooled test plasma samples from the donation with a viral content of less than 12,000 IU (or 480 IU/ml) would be missed on minipool NAT. These missed donations would therefore be below the minimum infectious dose described by Hewitt and others. (see reference 12). However, minipool testing of apheresis platelets that possess a much greater residual volume of plasma (180ml) would admit donations with HEV amounts up to 4.5-fold above the minimum infectious dose (20 IU/ml x 24 (pool dilution factor) x 180ml = 9 x 104 IU). The selection of a pool size of 24 for HEV NAT screening was recommended by SaBTO in 2015. (See meeting minutes from the SaBTO meeting on 7 July 2015.)

The ability of HEV NAT screening to reduce HEV transmission by transfusion has been documented by the Serious Hazards of Transfusion (SHOT) haemovigilance scheme. Over 2,000 donors with HEV have been identified and their donations intercepted since the introduction of selective and then universal screening by the UK blood services in 2016 (see table 2). Despite this, HEV transmissions have been documented by SHOT, often with severe disease outcomes, listed in table 3 and consistent with previous observations (see reference 7). The last 5 patients listed were infected with HEV NAT screened components.

Table 3: transmissions of HEV in the UK reported by SHOT 2016 to 2021

| **SHOT Report Year** | **Component** | **Outcome of investigation** | **Patient outcome** |
|---|---|---|---|
| 2016 | Red cells | Confirmed TTI | Major morbidity, no other details |
| 2017 | Platelets | Probable TTI | Died from liver failure 2 months post-transfusion |

| SHOT Report Year | Component | Outcome of investigation | Patient outcome |
|---|---|---|---|
| 2017 | FFP | Confirmed | Severe liver disease, death |
| 2018 | Platelets | Confirmed TTI | Immunosuppressed, chronic infection, cleared with ribavirin |
| 2018 | Platelets | Unknown | Died from pre-existing illness |
| 2019 | Platelets | Confirmed | Pre-existing liver disease and aplastic anaemia, death from acute hepatitis |
| 2019 | Platelet | No infection | No evidence of transmission |
| 2020 | Red cells | Probable TTI | Initially HEV RNA positive, cleared without treatment |

Table notes: transmissions from platelets identified on donor lookback are described in detail in Harvala H and others (see reference 1). Publication year of the SHOT report - some transmissions described occurred in previous years. A probable TTI would be for an assessment in the absence of sequencing information to confirm the same strain of virus in the donor and recipient.

The transmissions were not the result of technical screening failures as implicated donation samples were verified as negative on repeat pool testing. However, they were positive on individual donation (ID) NAT. The 24-fold dilution of individual samples for minipool testing therefore resulted in an assay sensitivity that was too low to detect HEV in these samples.

The documented instances of transmission likely represent an underestimation of the true number for several reasons. In many cases, the recipient may have died of other causes or cleared infection before testing for HEV was possible. Secondly, viraemic donations of apheresis platelets below the minipool detection threshold can only be identified retrospectively following the detection of HEV viraemia in a subsequent donation. This method of detection has been possible because of the often short donation intervals between apheresis donations (as low as 2 weeks for some donors). Low level viraemia in

the much larger number of whole blood donations would not be detected by an equivalent process of donor lookback as there is a minimum 2 to 3-month donation interval. Thirdly, HEV infections in recipients may be clinically inapparent, particularly in those without immunodeficiencies or other co-morbidities. Even if infections were symptomatic, HEV infection may simply not be clinically suspected or diagnosed because the virus is not widely recognised as a transfusion transmissible infection and may not be considered as a differential diagnosis. Even when HEV infection is diagnosed, cases may be substantially underreported because a transfusion source may not be suspected.

The possibility that HEV transmissions may be substantially undetected is supported by residual risk calculations (see reference 1). The number of viraemic donations below the sensitivity threshold of minipool testing was predicted by an analysis of the incidence of HEV infections in blood and platelet donors and the duration of infectious window period for the HEV NAT assay (modelling at 7 and 14 days). Using this approach, the authors predicted that 11 apheresis and 177 whole blood donations positive for HEV RNA would not be detected over the study period (5 years) in England assuming a 7-day window period and double that for a 14-day window period. These relatively high numbers of undetected infections (nearly 40 per year) cannot be directly equated to actual numbers of transmissions. However, even if we estimate a relatively conservative frequency of 25% infectivity for viraemic donations, the annual number of predicted HEV transmissions would be around 10-fold greater than the number of transmissions reported by SHOT from minipool screened components (around one per year - see table 3). There may, therefore, be a substantially undiagnosed reservoir of infection in red cell, FFP and especially platelet recipients.

However, whether the large number of donations predicted to go undetected by current screening represents a substantial burden of morbidity and mortality is uncertain. Most blood recipients are immunocompetent and infections may therefore clear spontaneously without disease complications. Conversely, the subset of transmissions with severe outcomes would be much more likely to be recognised clinically and diagnosed. However, it is notable that the recipients of apheresis platelets who were infected by HEV (table 4 in Cheung and others (see reference 7)) were only identified once the donation had been identified as viraemic by NHSBT and the clinicians notified. There may be many other patients infected through transfusion that remain undiagnosed, even those potentially with severe disease. The uncertainty over disease impact from missed donations complicates the assessment of the incremental cost-effectiveness ratio (ICER) for interventions designed to increase the effectiveness of HEV screening.

### Testing for HEV by other blood services

Information on the screening practices for HEV RNA detection by other blood services helps put current UK screening (table 2) into a wider, international context (table 4). A previous review of HEV screening published in 2019 (see reference 13) indicated

substantial variability across EU countries (published information summarised in table 4). Of these, only 7 EU countries (Ireland, France, Netherlands, Germany, Spain, Austria and Luxembourg) and the UK were performing HEV RNA screening in 2019, while no screening was carried out in Denmark, Italy, Sweden, Poland, Portugal, Malta, Greece and Belgium. Internationally, HEV screening policies were similarly variable, with no screening being performed at that time in the USA, Canada (see references 14 and 15) and China, while ID-NAT had recently started in Japan (see reference 16).

A more recent survey of HEV screening in 2021 led by Ryanne Lieshout-Krikke (HEV Survey 2022, Emerging Infectious Disease (EID) Monitor Working Group of the European Blood Alliance) provided comparable data on HEV screening policies by different countries in 2021. The following countries reported universal donation testing: Austria, Germany, Ireland, Luxembourg, Netherlands, Switzerland and the UK, France reported performing selective screening for transfusion of susceptible patients. As of 2021, HEV screening was not routinely performed in Belgium, Denmark, Estonia, Finland, Greece, Italy, Malta, Portugal, Slovenia, Spain or Sweden, Outside Europe, HEV remained unscreened in Australia, Canada and the USA, as of 2021.

Table 4 also summarises available published data on HEV RNA detection in donors from different countries. The varying pool sizes used for screening (which affects test sensitivity) and variable date ranges of testing prevents exact comparison of rates of detection, but there is clearly a general comparability on HEV incidence between countries, in Europe in particular. Country-wide average detection frequencies after 2014 ranged from 0.007% (USA) to 0.08% (Germany). The combined rate of 0.02% (from 2 studies (see references 12 and 17) and blood service reporting in the UK) lies within this range. Apart from the low incidence of HEV RNA detection in the USA (where, as of 2024, no HEV screening is currently performed), there otherwise appears to be no association between HEV incidence in donors and national decisions on whether to screen donors for HEV RNA or not. Poland and Denmark do not screen for HEV despite reporting some of the highest rates of HEV detection in Europe at around 0.08%, while national screening is performed in Austria, which has a relatively low incidence of 0.02%.

Table 4a: published detection frequencies of HEV RNA in different countries between 2012 and 2018

| **Country** | **Years** | **Screened** | **Pool size** | **Positives** | **Rate** | **Frequency** |
|---|---|---|---|---|---|---|
| UK (references 12 and 17) | 2016 to 2017 | 3,515,304 | 16 to 24 | 787 | 1 in 4,466 | 0.0224% |

| Country | Years | Screened | Pool size | Positives | Rate | Frequency |
|---|---|---|---|---|---|---|
| Ireland (see reference 13) | 2016 to 2017 | 279,938 | 1 | 59 | 1 in 4,744 | 0.0211% |
| France (see reference 13) | 2012 to 2015 | 190,668 | 1 to 96 | 118 | 1 in 1,615 | 0.0619% |
| Netherlands (see reference 13) | 2013 to 2018 | 794,580 | 24 to 192 | 400 | 1 in 1,986 | 0.0503% |
| Germany (see reference 13) | 2015 to 2017 | 508,522 | 24 to 96 | 410 | 1 in 1,240 | 0.0806% |
| Spain (see reference 13) | 2017 to 2018 | 111,534 | 16 | 29 | 1 in 3,846 | 0.0260% |
| Austria (see reference 13) | 2016 to 2017 | 155,691 | 16 | 29 | 1 in 5,368 | 0.0186% |
| Japan (see reference 16) | 2014 to 2019 | 1,379,750 | 1 | 597 | 1 in 2,311 | 0.0433% |

Table 4b: detection frequencies of HEV RNA in different countries that are not currently screening

| Country | Years | Screened | Pool size | Positives | Rate | Frequency |
|---|---|---|---|---|---|---|
| Denmark (see references 18 and 19) | 2015 to 2017 | 44,374 | 1 to 24 | 34 | 1 in 1,305 | 0.0766% |

| Country | Years | Screened | Pool size | Positives | Rate | Frequency |
|---|---|---|---|---|---|---|
| Sweden (see reference 20) | No data | 95,835 | 24 to 96 | 12 | 1 in 7,986 | 0.0125% |
| Poland (see reference 21) | 2014 to 2015 | 12,664 | 1 | 10 | 1 in 1,266 | 0.0790% |
| USA (see references 14 and 15) | 2015 to 2016 | 69,553 | 1 | 5 | 1 in 13,910 | 0.0072% |

Table note: available data from multiple sources where available (such as the multiple studies listed in Boland F and others (see reference 13) were combined for calculation of detection frequencies.

## Potential improvements to screening of blood and platelet donors for HEV

The remit from SaBTO requests the working group to assess risk to patient safety, operational impact and cost-benefit for proposed changes to HEV screening designed to enhance its effectiveness. However, any proposed changes to NAT-based screening must be compatible with existing frameworks for NAT screening for HCV, HIV and HBV (currently performed using minipools). A proposed change to HEV screening would therefore need to acknowledge the cost impact of either a concomitant change in testing for these other viruses, or introduction of a parallel process stream for HEV screening. While a change to universal ID NAT for blood and platelet screening is an obvious strategy for enhancing screening sensitivity and prevention of transmissions, the working group conducted a comprehensive assessment of other means to reduce or eliminate HEV transmissions.

## 'Two-tier' blood component supply

Several measures to reduce potential HEV transmission risk and clinical harm reintroduce the strategy of selective screening. This was introduced originally by UK blood services to provide screened blood specifically for susceptible, immunocompromised recipients. This was replaced by universal screening for reasons of operational complexity and cost in

2017. However, a modified proposal could be considered for the continuation of minipool NAT for most donations, but the use of ID-NAT to screen components transfused to susceptible recipients such as the immunocompromised and/or for components with higher residual plasma volume such as platelets.

However, an indication of the difficulty and high costs associated in providing duplicate components and their targeting to the correct recipients required by a 2-tier supply is indicated in the SaBTO HEV Working Group Report from 2016 (see reference 2). The group has been advised by SaBTO members that its re-introduction would be highly problematic operationally and extremely expensive. As indicated in their previous cost analysis of selective versus universal screening, staff and logistic costs associated with managing separate inventories of selectively screened blood components were much greater than the associated reduction in laboratory screening costs, making universal screening around 3 times more cost effective than selective screening. While options for selective screening can be evaluated, the working group is unanimously of the opinion that strategies based on this principle should be avoided wherever possible.

## Options evaluated for improving blood component safety

The following were presented and discussed in varying level of detail and outcomes of the discussions summarised.

### The potential effect of HEV testing due to reductions in HEV incidence

Proposals in this category revolved around postponing decisions about HEV screening until trends in its natural epidemiology became clearer, perhaps consequent to possible reductions of HEV contamination in UK sourced or imported pork.

Viewing the current available data from blood donor screening and surveillance by UKHSA there is no evidence for a sustained reduction in HEV incidence in the UK. The UKHSA surveillance indicates that there have been fluctuations in the risk of acquiring HEV but what influences these risks is not known. At present, pigs appear to be almost uniformly infected with HEV with consequent high rates of pork and pork product contamination throughout Europe. Furthermore, the UK is not self-sufficient in pork production and will continue to import not just from Europe but also from low and middle income countries that may lack the resources and motivation to eliminate HEV. There appears to be little prospect for the future introduction of manufacturing changes to reduce infectivity of pork products, such as irradiation.

SaBTO is unlikely to be able to influence DEFRA policies on pork production. However, a cross government working group for HEV has been established which brings together DEFRA, FSA, APHA and public health agencies such as UKHSA and PHS. The group is

developing programmes of work to reduce the prevalence of viraemia in pigs at slaughter in the UK and also aims to engage and work collaboratively with other European countries to control the virus through food consumption.

There is a programme of public health advice on how to cook pork properly so that infectivity of HEV and of other infectious agents is removed, although these do not apply to cured, uncooked pork products that may retain residual HEV infectivity. Those who are immunosuppressed will receive advice to avoid consumption of uncooked pork, but such programmes would likely prove less effective and too diffuse if they were to be extended to blood, platelet and organ donors.

**Identification of risk factors for HEV infection in donors independent of screening**

Pork is ubiquitously present in the diet of most donor demographic groups and pork consumption cannot be made into a donor exclusion criterion, nor would a request to desist from eating pork 4 or more weeks pre-donation be remotely practical or enforceable. Substantial amounts of pork blood is widely used in the manufacture of unrelated foods, such as smoked salmon, making avoidance even more difficult. Vegetarians and certain ethnic groups could conceivably be recruited as a means to provide blood and platelets with a reduced (but not zero) risk of HEV contamination but would require the creation of a 2-tier supply with its attendant costs (see above). Such donors would furthermore likely supply an insufficient quantity of lower HEV risk blood components to serve the full transfusion needs of identified susceptible recipients, particularly of platelets.

**Identification of surrogate markers for HEV infection or HEV infection risk**

Cytopathic infection of the liver releases liver-specific enzymes such as alanine aminotransferase (ALT). Acute infections are associated with abnormal ALT and other liver function test (LFT) metrics but the use of LFTs as surrogate markers of infection is limited for several reasons. Firstly, elevation of ALT is non-specific and may occur independently of viral infection, and the test has a measurable non-specificity and will lead to unnecessary deferral of donors. Finally, and most problematic, ALT elevation is generally a late manifestation of acute HEV infection - donations collected in the early stages of infection typically may have normal ALT levels and other LFTs (see references 22 and 23). As most of the donations with low viral loads that are missed by NAT screening are collected in this early period, the addition of LFT testing will serve little purpose.

The working group is not aware of any other demonstrated or hypothesised surrogate markers for active HEV infection that could supplement current NAT screening.

**Modifications to blood and platelet processing to reduce infectious plasma content**

Residual donor plasma is considered to represent the primary source of infectious HEV in donations. Standard red cells are estimated to contain up to approximately 25ml of

residual plasma while apheresis platelets contain approximately 220ml and consequently present an 8-fold greater risk of HEV transmission. Consideration should be given to suspending apheresis platelets in PAS to reduce the final volume of plasma present from 220ml to around 80ml. Pooled platelets recovered from whole blood donations are currently suspended in approximately 80ml of plasma and 190ml PAS, with plasma derived in equal proportions from each of the 4 contributing donations. For these, an average effective residual volume of 20ml could be used in infectivity calculations from each donor. The largest plasma volumes (approximately 250ml) are present in FFP.

While PAS is used as a diluent for pooled platelets, and should be encouraged for apheresis platelets, in both cases a substantial volume of donor plasma is still required to stabilise and prolong the shelf-life of platelets (around 30% of final volume). This precludes any further reduction of donor plasma volume in the final product. It is impractical to further reduce the residual plasma volume in standard red cells.

## Pathogen inactivation (PI) of platelets

There are licensed methods for inactivation of pathogens in platelets and plasma, with a likely future extension to red cell components. The effectiveness of currently used PI methods varies for different viruses and different inactivating technologies and is substantially reduced for non-enveloped DNA viruses such as parvoviruses. However, the working group reviewed the evidence that at least some methods, such UV-C irradiation (as used for example by THERAFLEX with a 3.5 log reduction in infectivity (see reference 24)) would likely be effective for samples with the low viral loads that are missed by current minipool testing for HEV. However, it may not be fully effective at inactivating HEV in very high viral load plasma from some donors (greater than 105 IU/ml; see figure 1 in reference 1). Indeed, plasma treated by the photoreactive amotosalen and UV light (INTERCEPT) showed residual infectivity in recent trials (see references 25 and 26). Any proposed future use of PI would therefore not remove the requirement to continue with minipool NAT for HEV.

The adoption of PI has been considered previously by the blood services and formally reviewed by SaBTO in 2014. The working group concluded that its use by the UK blood services for platelets was not cost-effective as a means to prevent bacterial contamination and transmission, for elimination of defined pathogens (HCV, HBV and HIV) missed by current screening (including donors with occult HBV for which anti-HBc screening has been recently introduced), or as a means to guard against harm from currently unscreened emerging and potentially pathogenic agents, such as tick-borne encephalitis virus and other arboviruses. These conclusions were endorsed in a re-review of the evidence and cost by SaBTO in 2021 to 2022. The value of PI in preventing HEV transmission from low viral load samples missed on minipool screening was considered by the working group to be insufficient to change this decision.

## Consideration of non-NAT screening methods for HEV

Before considering possible changes to NAT screening to enhance sensitivity, the working group discussed what other approaches might exist to intercept infectious donations or remove their infectivity.

### Reverse serology

By analogy with screening adopted by some blood services for parvovirus B19, donations could be tested for anti-HEV antibody and only those that were IgG antibody positive used for transfusion to susceptible recipients. The rationale for this is that those who were seropositive from previous infection would now be immune and non-viraemic. There is a catalogue of problems with this approach that can be briefly summarised. Firstly, the rate of seropositivity for HEV in the general population is low (13% in 2009 (see reference 27)) and unlikely to be substantially higher now. Seropositive donation might then only fill the transfusion needs for only a fraction of patients. Their production would furthermore introduce a requirement for 2-tier blood component supply. Secondly, antibody seroconversion occurs during the period of acute infection and viraemia and minipool NAT would still have to be continued to identify acute seropositive donors. Thirdly and unlike B19V, longitudinal studies reveal frequent re-infection of seropositive individuals by HEV (see references 28 and 29) and paradoxically regular reinfections may be required to maintain IgG antibody levels to HEV. As reinfections are also associated with viraemia, seropositivity does not therefore guarantee non-infectivity in donors.

### New technologies for HEV testing

A range of new technologies are under development that exploit the greater specificity and affinity of CRISPR/Cas probes for target detection (for example, SHERLOCK, DETECTR; (see references 30 and 31)). Methods described in these initial studies lack the absolute sensitivity of PCR (by 2 logs), but ongoing development may provide rapid, potential point of care testing with single copy target sensitivity without the requirement for laboratory equipment or specialised testing facilities. While it is possible that such methods may ultimately replace PCR and allied NAT methods for donor screening and wider diagnostics, the timescale for their development lies far beyond the action period of the current working group’s remit and cannot be considered further at this stage.

HEV pre-neutralisation. The working group were unaware of any approved anti-HEV mono- or polyclonal neutralising antibodies that could be added to NAT-screened blood components pre-transfusion to eliminate any residual infectivity. Such an intervention may be classed as a therapeutic and would be outwith the scope of the advisory group.

## Enhancing the sensitivity of NAT by reducing test pool size

The remaining identified option for the working group to evaluate was to enhance the sensitivity of NAT screening for HEV RNA, ideally to make it sufficiently sensitive to identify HEV within the platelet, blood and FFP components associated with documented transmissions (see table 3 and reference 1). The working group was presented with 4 possible ways to enhance test sensitivity:

### Use a screening test with a greater analytical sensitivity

The UK blood services use either Roche COBAS or Grifols Procleix NAT assays for screening (see table 2). Despite the different analytical sensitivities stated by the manufacturers, independent evaluation using the NIBSC HEV RNA International Standard demonstrated similar assay sensitivities. Limit of detection values for 95% of replicates (LOD95) for the Roche COBAS PCR assay in 2 studies of 22 IU/ml (95% confidence intervals 17 to 32) (see reference 32) and 12 IU/ml (95% CI: 9 to 19) (see reference 33) were comparable to those of the Grifols Procleix isothermal assay in 3 studies - 24 (95% CI: 19 to 33) IU/ml (34), 8 IU/ml (95% CI: 7 to 10) (see reference 35) and 13 IU/ml (95% CI, 9.47 to 20.01) (see reference 33). There appear to be no other assays available for HEV NAT screening in the UK and their approximately equal sensitivities does not favour one over the other. In the event that HEV testing is multiplexed with NAT for HCV, HBV and HCV, then test selection will be primarily determined by a wider consideration of assay performance and cost for these other viruses. This is beyond the remit of the HEV working group.

### Increase test volume

Some assays, such as Altona, achieve high analytical test sensitivities by amplifying extracted nucleic acid from a much larger sample volume (5 to 10ml) than is typically used for NAT. However, increasing test volumes for use in the Roche COBAS or Grifols Procleix assay is precluded by their assay protocols (set at 885 µl and 525 µl respectively), and by restrictions arising from their automation of sample extraction. There is additionally a similar non-independence from NAT screening for other viruses, as extracted RNA for HEV testing would be also used for HBV, HCV and HIV NAT in assays that impose their own requirements.

### Reducing pool size

It can be assumed provisionally that ID NAT for HEV would enhance assay sensitivity by 24- or 16-fold depending on current pool size selected. As demonstrated (see reference 1), this step would have prevented all 6 transmissions of HEV reported by SHOT (see

table 3 and footnote a). Set against that are the increased testing costs of ID NAT (estimated to BE 6-fold greater) and the potential requirement to extend the laboratory space required for screening with associated infrastructure costs (currently undefined and not costed into the economic calculations).

### Selective screening of apheresis platelet donors

Apheresis donors are a select group who may donate at frequent and regular intervals for the provision of platelets. Although their processing and microbiology testing are ultimately combined with workflows used for the much larger number of whole blood donations, there may be greater scope for these to be separately identified for screening purposes and potentially reserved for susceptible recipients. All platelet recipients with reported HEV morbidity and/or mortality (see table 3) would have fallen into the susceptible category, and the adoption of ID NAT specifically for apheresis platelet screening would have prevented these transmissions.

While potentially simpler to implement logistically than the previous 2-tier testing of all donations, there remains a question of whether current numbers of apheresis donations would be sufficient to meet the demands of platelet recipients considered to be susceptible. While we understand the reluctance of the blood services to consider 2-tier testing and component issue on costs and logistics grounds, this option was considered for comparative cost-benefit purposes with universal ID NAT by formal economic analysis (see below).

To conclude this section, the working group has identified no practical or organisationally viable options for preventing residual HEV transmissions other than by reducing test pool sizes for HEV NAT or by reducing residual plasma volume using PAS. Accordingly, ICERs and the cost effectiveness of this change were evaluated by formal health economic analysis to inform the working group of the desirability of this potential change to HEV screening.

## Health economic analysis

A simple health economic analysis was performed to investigate the potential benefit of switching to NAT testing of individual donations instead of the current 24- or 16-minipool

[a] Without wishing to complicate discussions unduly here, in many cases PCR positivity in originally missed donations of platelets by subsequent donor look back after they seroconverted is intrinsic to the study design and not a finding. As described (see reference 1), a total of 9 HEV-positive samples from platelet donors were identified on testing previous samples from 89 seroconverting apheresis donors. These were the subject of lookback to investigate transmission. However, the study did not investigate possible HEV transmission from the much larger number of previous donations that were PCR negative on ID NAT. It is possible this might have identified further transmissions missed by ID NAT too, although no such instances have been identified by recipient lookback to date.

screening or using PAS in the preparation of apheresis platelets to reduce residual plasma volume. Estimates of the additional costs for performing ID NAT were used to calculate an overall cost-effectiveness of such changes and to determine whether these approached acceptable QALY costs for interventions used in the NHS (see table 5). For the purposes of this calculation, we have used costs of HEV testing in minipools provided by the blood services and their estimates of increases cost if donations were to be tested individually or PAS used. We have not included any costs (or cost benefit) of individual donation NAT testing for HIV, HCV and HBV, nor incorporated other benefits of PAS independent of its effect on reducing HEV infectivity.

**Parameters used in the model**

The following parameters and assumptions were used:

- components currently screened for HEV NAT comprise whole blood and apheresis donations. Screening of other donation types (for example, organs and tissues) was excluded from the analysis

- separate analyses were performed for red cells, FFP, platelets derived from apheresis or recovered from whole blood (combined into pools of 4)

- the numbers of transfusions of each component each year in the UK was derived from the 2021 SHOT Report

- the proportion of donations that would be missed by MP NAT followed calculations of 11 apheresis and 177 whole blood donations over the 5 year study period based on a proposed 7 day window period before infection and positivity in the MP assay (see reference 1). Estimates were doubled for a 14-day window period. For the analysis, a mid-point estimate between these 2 window periods was used

- the likelihood of transmission from a window period donation is difficult to calculate although the data from donor lookback (see table 5 in reference 1) indicated that approximately one-third of apheresis platelet recipients that were MP NAT negative, ID NAT positive became infected (2 from 7). As the amount of infectious virus depends on the volume of residual plasma in the donation, transmission risk from other components can be scaled by ratios of residual volumes (red cells: 25 of 220; pooled whole blood derived platelets 80 of 220; FFP: 250 of 220)

- a 13% fatality rate from HEV infection in immunocompromised recipients was based on summary values from 13 studies of infection outcomes in transfusion recipients (see references 1 and 7)

Tables summarising the health economic calculation are set out below.

Table 5a: parameters used in the health economic calculation (see note 1)

| **Parameter** | **Value** |
|---|---|
| Proportion missed by MP NAT but detected by ID NAT (see note 2) | 100% |
| Proportion of platelets from apheresis (see note 3) | 0.5 |
| Cost of NAT (per donation; NHSBT) (see note 4) | [redacted] |
| Increased cost of ID NAT (NHSBT data) | [redacted] |
| QALY value (see note 5) | £30,000 |

Table 5b: number of cases of undetected HEV in 5-year study (see note 6)

| **Blood Component** | **Number of cases** |
|---|---|
| Platelets | 16 |
| Whole blood | 177 |

Table 5c: economic cost (central estimate for missed donations)

| **Parameter** | **Value** |
|---|---|
| Total QALY impact of undetected HEV (see note 7) | £176,000 |
| QALYS saved | 5.9 |
| Cost per QALY | £2,089,000 |

Note 1: the likelihood of transmission from a window period donation is difficult to calculate

although the data from donor lookback in Table 5 indicated that approximately one third of apheresis platelet recipients that were MP NAT negative, ID NAT positive became infected (2 from 7). As the amount of infectious virus depends on the volume of residual plasma in the donation, transmission risk from other components can be scaled by ratios of residual volumes (red cells: 25/220; pooled whole blood derived platelets 80/220; FFP: 250/220).

Note 2: the number of patients becoming infected with HEV.

Note 3: a 32.5% fatality rate from HEV infection in immunocompromised recipients was based on summary values from 13 studies of infection outcomes in transfusion recipients (see references 1 and 7).

Note 4: the proportion of HEV chronic infections in immunocompromised recipients

Note 5: this represents the average number of years of life lost from HEV infection, using the age ranges of recipients.

## Cost calculations

Economic calculations for screening donations individually or by using PAS to reduce platelet residual plasma volume have been carried out. A health-associated cost of around £176,000 per year could be calculated to be incurred as a result of the current minipool screening strategy (central estimate) based on a QALY valuation of £30,000 per year). The use of PAS for apheresis donations would reduce cost to £99,000 per year based on a 65% reduction in infectivity of apheresis platelets.

To estimate the cost effectiveness of introducing ID NAT for HEV, the estimated QALY gain was compared to the increased cost of ID NAT screening. A separate calculation was performed in which the alternative strategy of screening only apheresis platelets by ID NAT and continuing MP NAT for whole blood donation screening. Apheresis platelets could then be specifically targeted towards immunocompromised recipients. This cost calculation does not account for additional blood service and hospital costs associated with separately supplying and stocking these for immunocompromised recipients, which might however be substantial.

The following assumptions and parameters have been used:

- a NAT cost of [redacted] per sample for HEV minipool NAT
- an increased cost of ID NAT compared to MP NAT was estimated to be [redacted] (NHSBT figure) not 24-fold greater because of economies of scale

- an assumption that all infectious donations missed by MP NAT would be detected by ID NAT

- an estimate of the additional cost of detecting each currently contaminated component missed by minipool NAT is based on the calculation that 11 platelet and 177 whole blood donations can be predicted to be missed by minipool NAT over 5 years

- the additional cost of preventing the estimated 6 transmissions of HEV per year by ID NAT was calculated in terms of economic cost

Based on these parameters it could be calculated that it would cost an additional £9.6 million (based on estimated or modelled cost data) to detect and exclude donations calculated to be currently missed by minipool NAT if ID NAT were to be introduced. Based on the current modelled 6 transmissions per year with current MP-NAT, the additional cost of ID-NAT would be £1.6 million per prevented transmission.

To represent actual health costs, the cost effectiveness of universal ID NAT for HEV would be low - £2.1 million per QALY. The cost effectiveness of PAS in in reducing HEV infectivity of apheresis platelets (estimated 2.2 transmissions per year) would be £160,000 per QALY.

An alternative strategy of screening apheresis platelets only would have a cost effectiveness of £410,000 per QALY. However, this estimate does not take into account differences in estimated costs for performing ID-NAT between the different blood services.

Collectively, overall cost-effectiveness estimates are all beyond the standard intervention cost where QALYs are valued at £30,000. While the options to screen apheresis platelets by ID NAT or using PAS to reduce infectivity shows a greater cost-effectiveness, their implementation fails to address the problem of ongoing transmission of HEV by other components. As the patients who would receive ID NAT screened or PAS treated platelets are relatively restricted, elimination of transmission in this group removes less than half of the overall harm caused by HEV in blood component recipients.

# Conclusions and working group recommendations

## Summary of findings

Follow-up of recipients of apheresis platelets and other components that were missed on MP screening for HEV (SHOT report and (see reference 1)) described substantial morbidity and mortality from transfusion-acquired HEV infections that should be of considerable concern medically. The root cause of HEV infection in the UK is primarily

dietary and the direct result of farming practices for pigs that have led pork production worldwide to be extensively contaminated with HEV. While the UKHSA has requested that the cross government working group on HEV includes the impact to transfusion and/or transplantation safety in its future discussions, the current problem of HEV transmission through transfusion and transplantation will unfortunately remain for some time. Blood services will therefore need to maintain screening or other preventative measures to minimise infection risk in recipients.

After review of a range of possible methods to reduce transmission (listed and discussed under ‘Potential improvements of screening of blood and platelet donors for HEV'), the working group identified improvements in NAT screening test sensitivity and the use of PAS to reduce residual plasma volume in platelets as the only practical or achievable means to reduce HEV transmission (see ‘Enhancing the sensitivity of NAT by reducing test pool size’). Of the various ways to improve the sensitivity of screening, only reduction in the test pool size was considered practical. The logistics and laboratory processes required for NAT screening and the health economic analysis of a change from minipool NAT to ID NAT for HEV was accordingly calculated.

Using a simple health economic model, it was found that reduction in pool size for HEV testing (along with HIV, HBV and HCV) had a very low cost-effectiveness, with a calculated cost of over £2.2 million per QALY for universal ID NAT and £410,000 per QALY for apheresis platelet ID NAT (see table 5), both substantially above the £30,000 per QALY threshold for cost effective interventions. The use of PAS was similarly not conventionally cost effective as a measure to prevent HEV transmission, with estimated reductions in transmission costing substantially more than the health benefit obtained. While the working group acknowledges the potential benefit of testing blood and platelets donations individually or using PAS in preventing transmissions, it acknowledges the high cost of doing so compared to other medical interventions.

It additionally recognises that individual blood services may use their own costings rather than a national average for their specific evaluations of interventions such as ID-NAT.

## Application of health economic model

The working group recognises that continuation of HEV screening in minipools may perpetuate the occurrence of a small number of HEV transmissions each year that would be preventable by the adoption of individual NAT testing for HEV RNA. These infections may have potentially severe disease outcomes and mortality as described in the previous analysis of HEV transmission (see reference 1). Using a standard health economic analysis, the cost of such transmission was estimated at around £176,000 per year, based on the current NICE evaluation of £30,000 for each QALY lost. Set against this, the additional cost of screening donations individually would be greater than £9.6 million per

year, making the intervention not cost-effective by standard health economic assessments (amounting to a calculated £2.1 million per QALY). While we acknowledge that many of the parameters used in the economic analysis are estimates, these have tended to over-estimate both transmission risk and recipient susceptibility to severe disease. Greater awareness of HEV transmission risk from platelets following the recent report (see reference 1) may additionally enable better diagnosis and provide scope for earlier treatment interventions. The true health cost may therefore be lower than used in the calculation, as would the corresponding cost-effectiveness metric.

## Recommendations and qualifications

Although we acknowledge the existence of less easily quantified factors such as reputational damage to the blood services and the allied often cited special case of blood transmission risk, the calculation of HEV risk and costs in isolation using the current model provides no justification for the introduction of individual NAT testing of donors for HEV RNA. While PAS has the potential to reduce HEV transmission by 60 to 70% and its use may be associated with other benefits, its cost is similarly well beyond standard metrics of cost-effectiveness as a measure to purely reduce HEV transmission.

The working group is therefore not in a position to recommend any change to current screening practice, although we acknowledge that some blood services may incur lower costs and possess greater organisational practicality for performing ID-NAT for apheresis platelets than the average costs used in the economic model. While SaBTO advised that continuing with minipool NAT provides an acceptable level of transfusion safety, decisions to use ID-NAT or PAS are at the discretion of the individual blood services and lie within their area of responsibility.

We welcome advice from the wider SaBTO committee on risk tolerability and the extent to which conventional cost effectiveness calculations can be applied in the area of transfusion safety.

We should further acknowledge that it is simply not possible to completely eliminate HEV transmission risk in transplantation or transfusion and even the adoption of ID NAT for HEV may fail to prevent some transmissions. It should further be acknowledged that current HEV infection risk using minipool testing is orders of magnitude lower than the risk of infection with HEV from dietary sources. Related to that, patient consent for transfusion or transplant explicitly acknowledges that there are always going to be unavoidable risks, both microbiological and non-microbiological, but these are outweighed by the benefits of transfusion or transplant.

In a broader context, we should also recognise that blood services in the UK have been proactive in the introduction of HEV screening, following the pioneering work of Pat Hewitt, Richard Tedder and colleagues in documenting HEV transmission through transfusion

(see reference 12). While decisions on UK screening should be primarily based on nationally collected data and risk assessments, current policies for HEV testing by blood services in other countries and their HEV transmission risk do provide some context for decisions made. For example, apart from Ireland, no other European country has adopted ID-NAT. Many others have not adopted any HEV testing despite several showing much higher incidences for HEV infection in donors - donor detection frequencies in Germany, Denmark and Poland of around 0.08% are 4 times higher than in the UK (0.02% - see table 4).

The HEV Working Group makes the following recommendations:

**Recommendation 1**

The increased cost of testing individual donations for HEV (£11 million per year) was over 60 times greater than its calculated health economic benefit (£176,000) based on a QALY value of £30,000. This economic calculation shows that testing individual donations for HEV RNA is not conventionally cost-effective, and if decisions to implement changes in testing are based purely on this health economic metric, the working group does not recommend any change to current screening practice.

**Recommendation 2**

The working group recognises the existence of less easily quantified factors such as reputational damage to the blood services if further incidents of HEV transmission occur with continuation of the less sensitive testing in minipools. Consequently, we advise that SaBTO evaluates risk tolerability as it applies to HEV screening and the extent to which conventional cost effectiveness calculations can be applied in the area of transfusion safety.

**Recommendation 3**

SaBTO should develop a communications plan for the report, for example by writing to relevant royal colleges to raise awareness of HEV infection in the management of patients. Early diagnosis and initiation of appropriate treatment may substantially reduce HEV-associated morbidity and mortality. Some members of the HEV Working Group co-authored a review in 2023 on maintaining the microbiological safety of the UK blood supply (see reference 36) that may contribute to greater awareness of transfusion-transmitted infections.

**Recommendation 4**

Each year, SaBTO should review the reported incidence of HEV infections in the wider community using epidemiological data provided by UKHSA, and NAT positivity rates in UK blood and platelet donors. Changes in HEV incidence can be evaluated against the

economic model developed in this report and the QALY costs can be reviewed. Large increases in HEV incidence should prompt a re-evaluation of HEV testing strategies by the UK blood services.

**Recommendation 5**

Evaluation of current testing should be mindful of donation testing strategies by blood services in other countries and their HEV transmission risk evaluations.

**Recommendation 6**

A review of the effect of potential changes in the parameters used in the current report should be undertaken in 5 years. Those changes might include:

- progress towards HEV elimination in pork production
- potential changes in NAT testing methods, pool sizes for other targets and associated costs
- the effectiveness of PAS in reducing the plasma content of apheresis platelets
- the development of PI technologies, their costs and potential use for red cell components
- increasing knowledge of the outcomes of HEV infection, better identification of susceptible individuals, potential improved antiviral treatments for HEV and greater clinical awareness by clinicians of HEV as a post-transfusion complication

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