

# Challenges for the maintaining the microbiological safety of the UK blood supply

Authors: James Neuberger,<sup>A</sup> Susan R Brailsford,<sup>B</sup> Gary Mallinson,<sup>C</sup> Michael F Murphy<sup>D</sup> and Peter Simmonds<sup>E</sup>

## ABSTRACT

The supply of blood, blood products and components in the UK, as elsewhere, is safe, although there is no cause for complacency. Use of blood, blood products and components is not without risk of morbidity and mortality. Transfusion-transmitted infections (TTIs) continue to occur and may severely affect the health and welfare of recipients. As indicated by recent and current inquiries, public interest in these TTIs is huge. The risk of TTI can be mitigated but not abolished. Measures to reduce risk include screening of donors, testing of donations and, where appropriate, treatment of donations. The introduction of newer screening tests might identify some infectious donations but come at a cost, which could exceed a justifiable limit. Thus, the recognition, detection, reporting and investigation of cases of possible TTIs need to be improved. Recipients of blood should understand that, although transfusion in the UK is safe, it is not free of risk and so should be provided with full information so that properly informed consent can be given.

**KEYWORDS:** blood transfusion, risk, transfusion-transmitted infection, consent, patient safety

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Providing a safe and adequate blood supply for transfusion should be an integral part of the healthcare policy and infrastructure of every country.<sup>1</sup> However, blood components and products are materials of human origin and, therefore, are inherently at risk of transmitting disease. There is a tension between the safety of blood and its availability: exclusion of potential donors on the basis of potential risk will reduce availability and could lead to a failure to meet the needs of patients.

**Authors:** <sup>A</sup>honorary consultant physician, Queen Elizabeth Hospital, Birmingham; <sup>B</sup>consultant in epidemiology and health protection, NHS Blood and Transplant, Charcot Road, Colindale, London; <sup>C</sup>SaBTO secretariat and lead scientist, Blood Safety Policy, Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC), NHS Blood and Transplant, Bristol; <sup>D</sup>professor of transfusion medicine, NHS Blood & Transplant, Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford; <sup>E</sup>professor of virology, University of Oxford, Oxford, UK

The UK has legal and regulatory requirements to ensure the blood supply is adequate and safe.<sup>2</sup> The Blood Safety and Quality Regulations 2005,<sup>3</sup> which transposed the EU Directives into UK law, have been superseded by The Blood Safety and Quality (Amendment) (EU Exit) Regulations 2019.<sup>4</sup> There is a non-mandatory framework to try to ensure that UK policy remains aligned. Blood safety is managed by several groups, including the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO)<sup>5</sup> and the Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC).<sup>6</sup>

Patients who receive a blood transfusion should, where clinically possible, be given full information about the risks and alternatives to transfusion so they can give fully informed consent.<sup>7</sup> When a patient has been given a transfusion, this should be recorded in the clinical records and the discharge summary, the patient informed and given verbal and written information about the implications, including the fact that they cannot donate blood in the future, and the low risk that they might have contracted a transfusion-transmitted infection (TTI), which might not manifest until years later.

Non-infectious complications continue to be the most common causes of transfusion-related deaths in the UK.<sup>8</sup> Delays in transfusion and pulmonary complications (mainly transfusion-associated circulatory overload) are the main causes of reported transfusion-related deaths. Although TTIs are a rare cause of morbidity and mortality, their impact can be catastrophic and public interest considerable, as amply demonstrated by the attention to the current Infected Blood Inquiry.<sup>9</sup>

## Maintaining and improving the microbiological safety of the blood supply

### Donor selection and donation testing

Ensuring blood safety depends on donor selection, safe venesection, and the storage, processing and testing of donations. Potential donors are screened to not only ensure that it is safe and appropriate for them to donate, but also to identify those behaviours that are associated with higher risk of infection with a transmissible agent. These include higher risk sexual behaviours, injecting drug use and potential exposure to infections through travel. If a potential donor is considered at risk, then they are deferred, either temporarily or permanently. In the absence of identified risk, blood samples from donors are tested for the presence of specific pathogens or antibodies. Blood components (red blood cells, platelets and plasma) might be subjected to

additional mitigations, such as leucocyte reduction, which became routinely applied to blood components in the UK in 1999 to minimise the risk of transmission of variant Creutzfeldt–Jakob disease (vCJD). The UK has moved toward a more individualised risk-based approach for donor selection, which keeps patient safety at the heart of any decision.<sup>10</sup> The rules are, wherever possible, evidence based on risk and behaviours and adapted in light of local epidemiological data. In other areas, the risks of TTIs have been further reduced by introduction of testing for hepatitis E virus (HEV) and improved testing of blood for hepatitis B virus (HBV) to reduce the risk of transfusion from those donors whose levels of circulating HBV DNA are below the limit of detection but might still infect the recipient.<sup>5</sup>

### Measures to minimise the risk of transfusion-transmitted infection

Currently, mandatory tests are performed on each blood donation for a variety of infectious agents (Table 1). Universal screening for antibodies to the HBV core protein (anti-HBc) to identify past or occult infections with HBV has recently been introduced. In addition, additional selective screening methods are used for new donors or for those who have recently travelled. However, for some infections, there are no appropriate tests; thus, reducing risk depends on excluding potential donors on the basis of screening questions and/or physical approaches, such as leucocyte reduction or pathogen inactivation technologies. Therefore, to reduce the risks of transfusion transmission of prion-associated diseases (for which there are no recognised appropriate tests available), screening criteria are used (Box 1), although these indications for deferral are being reviewed.

### Surveillance for transfusion transmitted infections

During 2020, of the 1.7 million blood donations screened in the UK, 176 were confirmed positive for HBV, hepatitis C virus (HCV), HIV, human T lymphotropic virus (HTLV) or treponemal antibodies, and were discarded.<sup>11</sup> Three-quarters were detected in donations from new donors. Of the donations, 458 tested positive for HEV and were discarded. Of the 44 donors with recent infections, 12 did not fully disclose deferrable risks at the time of donation.<sup>11</sup> Thus, donor screening will not identify all potential donors at risk of having a transmissible infection.

**Table 1. Infectious agents routinely screened for on all blood donations**

| Infectious agent                       | Test                      |
|--|---------------------------|
| Hepatitis B virus (HBV)                | HBsAg and anti-HBc*, NAT  |
| Hepatitis C virus (HCV)                | Anti-HCV and HCV NAT      |
| Hepatitis E virus (HEV)                | HEV NAT                   |
| HIV                                    | AntiHIV1 and 2 or HIV NAT |
| Human T cell lymphotropic virus (HTLV) | Anti-HTLV-1 and 2         |
| Syphilis                               | Treponemal antibodies     |
| Cytomegalovirus (CMV)                  | CMV antibodies            |

HBsAg = hepatitis B surface antigen; anti-HBc = antibodies to hepatitis B core antigen; NAT = nucleic acid technology. \*Currently being rolled out.

### Box 1. Reasons for excluding potential donors who are considered at risk of transmitting Creutzfeldt–Jakob disease

People who have received a blood transfusion, tissue or organ transplant from a donor since 1980.

Anyone who has received human pituitary-derived hormones, grafts of human dura mater or cornea, sclera or other ocular tissue.

Members of a family at risk of inherited prion diseases.

People who have been notified that they might be at increased risk of variant Creutzfeldt–Jakob disease because of possible exposure to an infected individual from surgical instruments, a blood product transfusion or transplant of tissues or organs, or that their blood or tissues have developed a prion-related disorder.

The UK operates an active haemovigilance scheme to monitor all adverse outcomes of transfusions (Serious Hazards of Blood Transfusion (SHOT)).<sup>8</sup> For TTIs, there is a legal duty to report cases to the Medicines and Healthcare Products Regulatory Agency (MHRA). In 2021, 2,194,215 units of blood components (1,607,174 red cells and 284,927 platelets) were issued to UK hospitals. During that time, the UK Blood Services investigated reports from hospitals of 115 suspected bacterial incidents and 10 suspected viral incidents: of the bacterial incidents, none were confirmed as TTIs and, of the viral TTIs, there were two cases of possible HCV. Between 1996 and 2021, 42 confirmed transfusion-transmitted viral infections were documented in the UK, involving 35 donors. Among these, HBV (n=12) and HEV (n=12) were the most commonly reported proven viral TTIs. All except two HEV transmissions were reported before HEV RNA screening was introduced in April 2017.

Bacterial screening of platelet components as a risk-reduction measure by UK blood services identifies infection in 0.05% or less of those tested. These components are discarded and, over the past 5 years, there have been no reported and/or confirmed cases of TTI related to bacteria or malaria.<sup>12,13</sup>

Although these data are reassuring, there is no room for complacency. Collection of data through reporting of adverse events will miss infections that do not initially present symptomatically. Furthermore, we have seen even severe disease undiagnosed at the time because infections were not suspected clinically. Reported cases will inevitably be an underestimate of the true number of incidents because some cases will not be recognised, correctly attributed to the transfusion or reported.

### What are the current microbiological risks from blood donation?

Despite the comprehensive measures in place, a small number of infectious donations still reach the patient. Residual risk is the risk of an infected donation not being picked up by existing screening methods and potentially being transfused to recipients. This has been estimated for the UK per million donations for the period 2018–2022 as 0.81 for HBV, 0.04 for HIV and 0.02 for HCV; at 2020 UK donation levels, this equates to one infectious donation being detected every 8 months, 14 years, and 22 years respectively.<sup>8</sup> These residual risks are

primarily a result of donors being in the window period of their infection, that is, between infection and when the infection can be detected by a screening test. but might also relate to levels of sensitivity of the testing.

There is a residual risk for bacterial TTIs because, even with bacterial screening, near misses do occur, particularly with *Staphylococcus aureus*, but the components might be identified before issue by blood services or by hospital blood bank or clinical staff. The most recent confirmed transmission was in 2015.

New and emerging infections remain a constant cause for concern. These might be caused by new or previously undetected agents, as well as known agents that are re-emerging following a period of low incidence or those for which a disease association has not been previously recognised. One important cause is zoonotic infections.<sup>14</sup>

### Why do current approaches fail to remove all risk of TTI?

#### Human error

Evidence from the SHOT report<sup>8</sup> indicates that human error might be responsible for adverse events at all stages of the vein-to-vein journey from donor to patient. However, we are not aware of instances where human error has led to a TTI.

#### Accuracy of donor responses

Implicit for the safety of donation is that questions in the donor health check questionnaire are answered accurately. There are several reasons why the responses might not be accurate, but levels of intentional misrepresentation are thought to be low.<sup>15</sup> Evidence suggests that volunteer donors are good at assessing risk and do understand the importance of providing pre-donation information.<sup>10</sup> However, non-compliance with the questionnaire represents a significant proportion of those potential blood donors with potentially transmissible infections.<sup>16–19</sup> Some potential donors who are at risk of having a potential transmissible agent do not realise that their behaviour is considered a risk.<sup>20</sup> Thus, non-disclosure, for whatever reason, of relevant risk behaviour remains a small, but important cause of potentially infectious donations.

#### Testing does not identify all potentially infectious donation

Current testing strategies rely on a combination of approaches, using mini-pools for nucleic acid-based testing (NAT) and using individual donations for serological testing. Mini-pools allow a larger number of samples to be tested and might make such strategies more cost-effective. Current strategies do not always detect those donations in which the amount of infectious material is below the limit of detection using current techniques but might still transmit infection.

There are many other infections with the potential to be transmitted by transfusion, such as human parvovirus-19, human herpesvirus-8 and hepatitis A virus. With these viruses, the risk is low and, thus, testing might not be cost-effective in the UK, although it might cost-effective in other jurisdictions where the epidemiology is different. The rationale is varied and relates to the severity of disease, the epidemiology of the infection, the use of donor selection criteria and exclusion of those donations that are at risk,

the characteristics of the test and cost-effectiveness. Other causes of failure to identify potentially infectious donations include human and technical error, although reported cases are rare.<sup>21</sup>

#### Some infectious agents cannot be detected using currently available techniques

Some blood-borne infections, such as prions, cannot as yet be detected using validated technologies licenced for large volume use; thus, there is a reliance on the donor health check to identify and exclude higher risk donors.

#### New and emerging infections

Many factors, including increasing travel and climate change,<sup>22–24</sup> mean that some TTIs, such as West Nile virus or Zika virus, currently rarely seen in the UK, are likely to become more prevalent in the UK population. Outbreaks of infections, including Ebola virus<sup>14</sup> and most recently monkeypox virus, have occurred where the potential transmission risk arises from the ability of the virus to establish a moderate and sustained viraemia during the prodromal asymptomatic stage of infection.<sup>25</sup>

#### Contamination of blood or products following collection

Acquired infectivity or contamination are possible during any stage of the journey of the blood from donor phlebotomy to recipient transfusion, although these events are rare. Stringent aseptic techniques and closed systems have removed much of the risk. Measures such as pathogen reduction technologies and/or bacterial sampling techniques could help remove these risks and reduce the risk to the recipients. Platelets are currently stored at 22°C to maintain optimum viability and, thus, present a greater risk of infection compared with blood (stored at 4°C).<sup>26</sup>

### How can the risks of new or emerging transfusion-transmitted infection be reduced?

There are several possible approaches to reduce the risk of TTIs.

#### Horizon scanning

SaBTO relies on the joint unit managed by NHS Blood and Transplant (NHSBT) and the UK Health Security Agency, which reports through JPAC to alert the Committee of emerging infections relevant to blood, tissues and organ donation safety. The unit monitors European and global updates on infections that pose a risk to the UK, including babesia, Chikungunya virus, Crimean-Congo haemorrhagic fever, dengue, malaria, pandemic and avian influenza, tick-borne encephalitis, West Nile virus and Zika virus.<sup>22</sup> Predicting the future is never easy (at least accurate prediction is rarely achievable) and, although this approach is necessary, it cannot be relied on to identify all emerging and new infections. Thus, warnings of a possible epidemic of monkeypox virus were not considered even though, with the benefit of hindsight,<sup>23</sup> outbreaks were postulated nearly a decade ago, as a consequence of the falling rates of smallpox vaccination. A further challenge is that the risk behaviour of blood donors might differ from that of the general population<sup>24</sup>; thus, simple extrapolation to the blood donor could give rise to misleading conclusions.

For those transfusion-transmissible viruses for which universal screening has been implemented, estimating transfusion risk is well established using models based on the incidence of infection in the donor population and the infectious window period. However, this approach is not applicable to emerging infectious agents because the incidence of infection in the donor population is not known and an assay window period is not applicable. Two models are available for estimating the risk: the Biggerstaff-Petersen model and the European Upfront Risk Assessment Tool (EUFRAT), with different strengths and limitations; thus, more work is needed to develop a robust model.<sup>14,25</sup>

Inevitably, some predictions will not be borne out: for example, xenotropic murine leukemia-related virus was reported to be associated with prostate cancer and chronic fatigue syndrome, and present in the blood of asymptomatic blood donors. It was later shown that the virus did not affect humans but was a laboratory contaminant from cell lines.<sup>25</sup>

### Enhanced recognition and reporting

There can be no doubt that the number of TTIs reported is an underestimate. Healthcare professionals must be continually reminded that TTIs should be considered and that reporting is mandatory.

### Improving donor questionnaires

Designing questionnaires for blood donors is problematic: there must be continuous review and, where appropriate, revision.

Language must be clear, and questions must be unambiguous, must not cause offence and must be available in formats that are appropriate for all potential donors. The need to avoid discrimination must be balanced with blood safety<sup>27</sup> but, in our view, the safety of the blood supply must take priority. Pre-donation computer-based questionnaires might be associated with increased compliance.<sup>28</sup>

### Improved laboratory detection

Improved detection of donations with potentially transmissible infections will reduce TTIs. Better use of current technologies and early introduction of new technologies both have a role. Currently, NAT testing is carried out on pooled samples to reduce cost. Introduction of individual testing could reduce the risk of missing potential infections but will increase cost and might have logistical implications. Similarly, reducing the cut-off points for defining positives will result in a trade-off between excluding infected samples and discarding non-infectious samples. New technologies, such as next-generation sequencing, allow potential identification of new infections and are under evaluation as a means to provide more comprehensive screening of a wider range of potential blood-borne viruses and bacteria in blood donations.

### Pathogen reduction/inactivation technologies (PITs)

These technologies primarily target nucleic acids and, therefore, can inactivate viruses, bacteria, and parasites in plasma and platelets. There are several commercially available technologies for

**Table 2. Approaches to improving blood safety**

| Area for improvement             | Aspects for improvement   | Responsibilities                                      |
|----------------------------------|---|---|
| Haemovigilance                   | Improve recognition and reporting of TTIs   | All healthcare professionals                          |
|                                  | Better awareness and greater ease of reporting processes  | All healthcare professionals and managers             |
| Donor screening                  | Review and revision of donor questionnaires to ensure they remain effective in identifying higher risk potential donors. Where possible, questions should be evidenced based and non-discriminatory   | SaBTO, blood services, patient groups                 |
|                                  | New testing procedures and technologies must be evaluated promptly and, where appropriate, implemented in a timely fashion. However, changing established procedures and introducing new technologies might not only be costly, but could also lead to errors   | SaBTO, Blood services, commissioners                  |
| Horizon scanning                 | Some emerging infections have been missed and others incorrectly identified as a risk to blood safety; incorrect predictions do not invalidate the need for, and importance of, horizon scanning  | Epidemiologists, microbiologists                      |
| Prescribe blood only if required | Some patients undergo transfusions when other options are indicated (eg iron or erythropoietin prescription)  | Healthcare professionals                              |
| Patient awareness                | Recipients must be informed that, although blood, its components and products are safe, they are not free from risk and their right to decline a transfusion respected. Guidelines have been issued for ensuring that patients are given full information and are able to give valid informed consent. <sup>34</sup> Patient groups will have a key role in ensuring the messaging is appropriate and available | Healthcare professionals, patients and patient groups |
| Oversight                        | Effective regulation and resources to monitor safety, review current practice, and review and react to new and emerging infections and provide regular feedback to healthcare professionals   | Department of Health, regulators, professional bodies |

SaBTO = Advisory Committee on the Safety of Blood, Tissues and Organs.

platelet inactivation.<sup>29</sup> These technologies can inactivate a range of microbial infections and, thus, could offer some benefit from both known and unknown infections. PITs might also minimise the risk of transfusion-associated graft-versus-host disease and avoid the need to provide irradiated blood components for patients at risk. There are concerns that PITs might affect the haemostatic quality of platelets. An alternative measure for reducing the risk of bacterial contamination of platelets is the use of cold storage at 4°C, as for red cell units. There is considerable interest in the enhanced haemostatic effectiveness of such platelets in patients with major haemorrhage.

### Keeping prescribing to the minimum clinically needed

It is axiomatic that the best way to avoid the risks of transfusion is not to give a transfusion where it is not needed or where safer alternatives are available.<sup>30</sup> For example, some patients are given a transfusion to improve haemoglobin levels for whom oral iron would be as effective,<sup>6</sup> and the use of tranexamic acid reduces major bleeding and need for transfusion in surgery.<sup>31</sup> Other examples include the inappropriate use of fresh-frozen plasma or platelets in an attempt to improve clotting where these are not indicated.<sup>32</sup> Thus, clinicians should ensure the use of blood, blood products and components is kept to the minimum that is clinically indicated.

### What level of risk is acceptable?

Given that it will not be possible to abolish the risk of TTIs, then risk must be mitigated. The level of risk acceptable to recipients might differ from that acceptable to commissioners, the public or other interested parties, but acceptance of the currently published residual risks suggests that current levels are reasonable. The Alliance of Blood Operatives<sup>33</sup> has developed a risk-based decision-making framework that emphasises the need to allocate resources in proportion to the magnitude and seriousness of the risk and the effectiveness of the intervention to reduce that risk as well as ensuring the adequacy of the blood supply. Conventional measures, such as cost/Quality Adjusted Life Year, can be used but, in practice, estimating these figure is not easy because they would be based on many assumptions; thus, the confidence limits are very broad. Social and ethical issues will require that thresholds for improvements in blood safety should not be based on those adopted for the introduction of new therapies. Introduction of new measures to reduce risk further will usually have a cost and could result in reduced donations, leading to a shortage of blood and its components.

### Conclusions

Transfusion is safe but still carries risks, even in the UK. Transfusion-associated circulatory overload and delayed transfusion remain the major causes of death. Although there are several measures in place to reduce risk, transfusion remains associated with a small risk of TTI, which varies depending on the TTI but can be fatal. Many healthcare professionals have a role in reducing these risks and, thus, levels of morbidity (Table 2). ■

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**Address for correspondence: Dr James Neuberger, Honorary consultant physician, Queen Elizabeth Hospital, Birmingham B15 2TH, UK.**  
**Email: jamesneuberger@hotmail.co.uk**