20 Transfusion-Transmitted Infections (TTI) n=0

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Definition:

A report was classified as a TTI if, following investigation:

- The recipient(s) had evidence of infection post transfusion with blood components, and there was no evidence of infection prior to transfusion, and no evidence of an alternative source of infection

and, either:

- At least one component received by the infected recipient(s) was donated by a donor who had evidence of the same transmissible infection

or:

- At least one component received by the infected recipient was shown to contain the agent of infection

These may be identified as a result of infection in the patient where transfusion is the suspected source or alternatively via lookback investigations. A lookback investigation is carried out if a donation is found to be positive for infection and retrospective testing finds a previous donation to also be positive at low levels below the detection level of screening.

Note that for the purposes of the European Union (EU) legislation, serious adverse reactions (SAR) are defined as any reactions in patients that are 'life-threatening, disabling or incapacitating, or which result in, or prolongs, hospitalisation or morbidity.' These must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) (a legal requirement). This includes all confirmed transfusion-transmitted infections.

Abbreviations used in this chapter

BSH	British Society for Haematology
DNA	Deoxyribonucleic acid
EIR	Emerging infection report
EU	European Union
FAIR	For the assessment of individualised risk
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HTLV	Human T cell lymphotropic virus
JPAC	Joint UKBTS Professional Advisory Committee
LGBTQ+	Lesbian, gay, bisexual, transgender and queer
MHRA	Medicines and Healthcare products Regulatory Agency
NAT	Nucleic acid testing
NHSBT	National Health Service Blood and Transplant
NIBTS	Northern Ireland Blood Transfusion Service
OBI	Occult hepatitis B virus (HBV) infection
PTR	Post-transfusion reactions
RNA	Ribonucleic acid
SaBTO	Advisory Committee on the Safety of Blood, Tissues and Organs
SACTTI	Standing Advisory Committee on Transfusion Transmitted Infection
SAR	Serious adverse reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

SNBTS	Scottish National Blood Transfusion Service	**vCJD**	Variant Creutzfeld Jakob Disease
TTI	Transfusion-transmitted infections United	**WBS**	Welsh Blood Service
UK	Kingdom	**UKHSA**	United Kingdom Health Security Agency

Key SHOT messages

- Any suspicion of a TTI should be reported to the appropriate UK Blood Service as soon as possible for it to be fully investigated
- The UK Blood Services store a sample from every blood donation for at least three years. Testing can be done on these samples during this time if a TTI is suspected
- All lookback investigations should be reported by the UK Blood Services to the infectious disease expert sitting on the SHOT working expert group
- It is important that all healthcare professionals consenting patients for blood transfusion have up-to-date knowledge of blood donation screening and the small potential for TTI

Introduction

This chapter describes TTI incidents investigated by the UK Blood Services and reported to the NHSBT/UKHSA Epidemiology Unit's surveillance scheme in 2021.

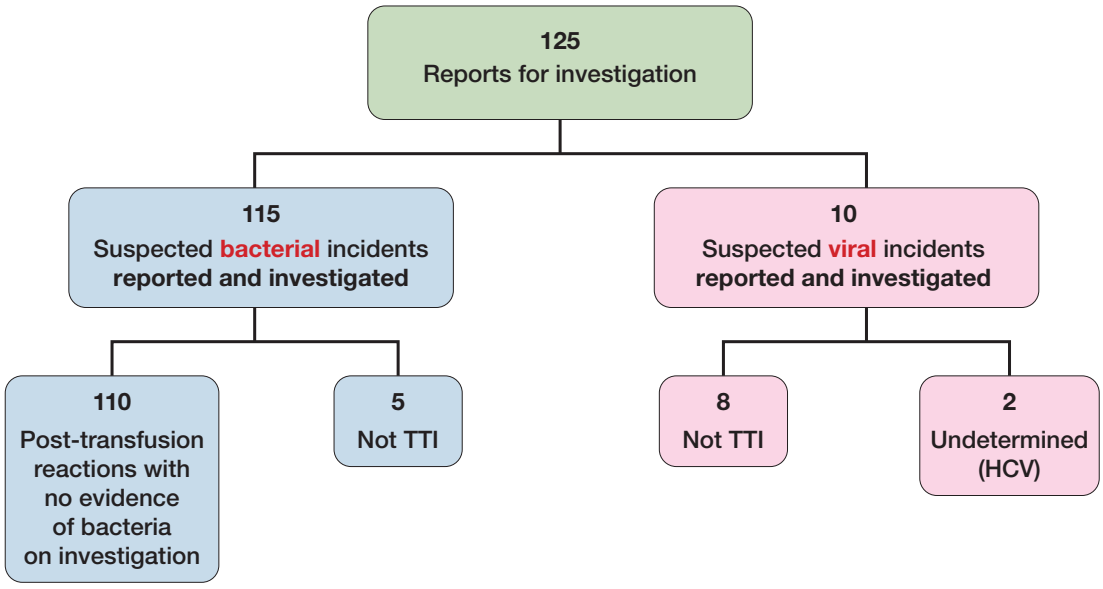
The risk of a TTI in the UK remains extremely low. During 2021, there were no reported TTI confirmed either viral or bacterial investigations.

Annual reports from the Epidemiology Unit surveillance schemes are available here: https://hospital.blood.co.uk/diagnostic-services/microbiology-services/epidemiology/

Summary of reports made to the NHSBT/UKHSA Epidemiology Unit in 2021

During 2021, UK Blood Services investigated 115 suspected bacterial incidents and 10 suspected viral incidents (Figure 20.1).

Figure 20.1 includes all investigations reported in 2021 in England, Northern Ireland, Scotland and Wales. In previous Annual SHOT Reports investigations in Northern Ireland, Scotland and Wales, concluded as bacterial PTR or not, were not included here.



TTI=transfusion-transmitted infection; HCV=hepatitis C virus

Figure 20.1: Outcome of reports of suspected TTI made to the NHSBT/UKHSA Epidemiology Unit in 2021 update

Please note:

- A **PTR** occurs when a blood transfusion recipient develops a reaction following a transfusion and bacteria were suspected. However, no bacteria were cultured in the recipient, units or donor(s); i.e. no evidence of any bacterial contamination
- A **confirmed TTI** is defined as in the above TTI definition with evidence that the virus/bacterium is indistinguishable on molecular typing between patient and donor/pack
- A **probable TTI** is classified as a TTI as in the above definition, but where molecular typing cannot be carried out to confirm this
- **Not a TTI** is defined as an investigation that concluded the infection in the recipient was NOT caused by transfusion, either as no infected donors identified (after all donors traced) or bacteria/virus identified in the recipient, but all units cleared (no bacteria/virus) in the unit and/or implicated donors
- A **near miss** is defined as either an infection was identified in the unit due to be transfused however the unit was NOT used in transfusion (e.g. bacterial growth seen in unit and returned to the bacteriology laboratory prior to transfusion for investigation) or an infected donor calls post donation, and the unit is recalled and infection found in unit before it is transfused

Deaths related to transfusion n=0

No patients with confirmed TTI were reported to have died after being transfused, following investigations in 2021.

Bacterial TTI reports 2021

In 2021, no reported suspected bacterial TTI investigations were concluded to be confirmed, probable or possible. All bacterial TTI investigations were concluded to be either a PTR with no evidence of bacteria in the implicated or associated products or in the recipient, or not a TTI, with evidence of bacteria in either the products or the recipient(s) but not both. In all cases where patient blood cultures were positive, the likely source was the patient's underlying condition.

The four UK Blood Services all use the BacT/ALERT system for bacterial screening which has been successful in reducing the risk of bacterial TTI (McDonald et al. 2017). Sampling methods have recently become more consistent across the four Blood Services, but some slight variation still exist, details of which are described in Table 20.1.

Bacterial TTI 1996-2021

Screening of platelet components cannot guarantee the absence of bacterial contamination. Packs are released for issue as 'negative-to-date', which may be before bacteria have multiplied sufficiently to trigger detection on screening. There have been ten bacterial near misses, all but one in platelet components, reported to the unit between 2011 and 2021. Overall, out of a total of 44 bacterial transfusion-transmissions to individual recipients, 37 (34 incidents) have been caused by the transfusion of platelets, and 7 by red cells (Table 20.6) since reporting began in 1996.

Haemovigilance systems for bacterial TTI are passive and as such rely on clinical colleagues to suspect and report TTI. Current BSH guidance recommends that patients are advised to report any symptoms that occur within 24 hours of transfusion (BSH Tinegate et al. 2012) although our experience suggests that patients with confirmed bacterial TTI become unwell very rapidly, often during transfusion.

Table 20.1: Bacterial screening methods used by the UK Blood Services

	Time of sampling (hour)	Volume sampled (mL)	Apheresis sample	Time at release (hour)	Length of screening
NHSBT	≥36	2 x 8	Post-split	6	Day 7
NIBTS	≥36	2 x 8	Pre-split	6	Day 9
SNBTS	≥36	2 x 8	Pre-split	6	Day 7
WBS	≥36	2 x 8	Post-split	12	Day 7

Viral TTI reports 2021

In 2021, no reported possible TTI were confirmed.

Viral TTI 1996-2021

The year of transfusion may be many years before the year in which the incident is investigated and reported to SHOT due to the chronic nature, and possible late recognition, of some viral infections. Since 1996, 42 confirmed transfusion-transmitted viral infections have been documented in the UK, involving 35 donors. Among these, HBV (n=12) and HEV (n=12) were the most commonly reported proven viral TTI. For HBV, this is partly because the 'window period', where an infectious donation from a recently infected donor cannot be detected by the screening tests, is longer than for HCV or HIV, despite NAT screening of blood donations.

Evidence of transmission of OBI in the UK is emerging. Donors with this chronic form of HBV infection were thought to typically have a level of HBV DNA that was very unlikely to transmit, however 5 reports have been made of an HBV infection in recipients who had received components from donors with OBI in England; transmission could not be confirmed because of a lack of sequencing information.

All except two HEV transmissions were reported before the HEV RNA screening was introduced in April 2017 in the UK. The UK was one of the first Blood Services to introduce HEV screening; since implementation 2118 HEV RNA containing donations have been successfully identified by screening and removed from the blood supply (preliminary data as at 7/3/2022). The rate of HEV RNA detected among donors is greater than other viral infections because it is generally acquired through food, and there is no specific donor selection to minimise donations from those infected. This gives rise to an increased chance of non-detection of HEV RNA. Furthermore, as screening is performed in pools, it is recognised that donations containing a small amount of HEV RNA can be missed and potentially transmitted via blood transfusion.

Lookback investigations

Lookback investigations are considered when the UK Blood Services identify markers of infection in a donation from a repeat donor. This may be due to seroconversion or the introduction of a new test. The archive sample of their most recent screen-negative donation is requested for retrospective re-testing and if now identified as positive, the full clinical lookback will be instigated. For NHSBT, where donors are identified with occult HBV infection, donations given during the last three years are considered in lookback investigations regardless of the screening results. This is different to the other investigations reported here that are initiated due to a potential TTI in a recipient.

For lookbacks, the associated components are traced, recipients are identified, and advice given regarding follow-up and testing. Between 2019 and 2021, NHSBT identified 5 HEV and 12 syphilis infections in retrospective testing which were below the level of detection in routine screening, these donations were included in the lookback (Table 20.2). Furthermore, 14 previous donations from 4 donors with OBI were also subjected into lookback investigations. A total 46 of 55 components were transfused, and all 46 recipients identified. Of those recipients who were alive, 22 of 30 were tested and 2 were positive for markers of hepatitis B infection and 1 HEV. These infections in recipients were concluded as a probable HBV and a confirmed HEV transmission and were reported in SHOT 2020 and 2019 reports respectively. The remaining HBV infection was classified as a possible TTI, the recipient had markers of past HBV, but this could have been due to another source.

One HEV lookback investigation was undertaken by SNBTS in 2021, following a donation positive for HEV RNA (HEV IgG and IgM negative). Their most recent donation 35 days prior to index donation was identified to contain HEV RNA in retrospective testing. Three components from positive donation were transfused, testing was not possible for one of these recipients, who was deceased, although this was unrelated to the transfusion. This individual had no clinical signs of HEV, and liver function tests remained normal. Testing of the two transfused components were found to be negative for markers of HEV infection

Table 20.2: Summary of lookback investigations in England, 2019-2021

	Number		
	Occult HBV	HEV	Syphilis
Donors with a previous donation identified as positive in retrospective testing	**4**	**5**	**12**
Donations by these donors considered here	**14**	**5**	**13**
Total components from these donations	**26**	**10**	**19**
platelets	4	10	5
cryoprecipitate	3	0	2
red cells	14	0	11
FFP	5	0	1
Components reported as transfused	**19**	**10**	**17**
Recipient identified but deceased	5	4	7
Recipient identified and alive	14	6	10
Recipients tested	**11**	**6**	**5**
Recipient tested positive	2	1	0
Recipients tested negative	9	5	5
Recipients not tested	**3**	**0**	**5**
Clinical decision made not to test	0	0	2
No response from GP or patient	2	0	0
Testing outstanding	1	0	3
	probable transmission - reported in the 2020 Annual SHOT Report, **possible transmission** - one patient with evidence of past HBV infection	**confirmed transmission** - reported in the 2019 Annual SHOT Report	

Residual risk of HBV, HCV, or HIV

The risks of a potentially infectious HBV, HCV or HIV window period donation not being detected on testing in the UK are very low at less than 1 per million donations tested (Table 20.3) (JPAC 2021). The window period is the time very early in the course of infection when tests in use do not detect the virus but there may be sufficient to transmit. The calculations are made annually, but for HBV only consider the risk of non-detection of acute infections and not the risk of non-detection of an OBI.

Table 20.3: The estimated residual risk (and 95% confidence interval) that a donation made in the HBV, HCV and HIV infectious window period is not detected on testing UK: 2018-2020

	HBV	HCV	HIV
Number per million donations	0.81	0.02	0.04
95% confidence interval	*(0.28-1.75)*	*(0.00-0.14)*	*(0.01-0.10)*
At 1.9 million donations per year, testing will miss a potentially infectious window period donation every:	6 months	22 years	14 years

Far fewer TTI are observed in practice than the estimated risks in Table 20.3 indicate, partly because the estimates have wide uncertainty and the model used to calculate risk is based on the risk in all donations tested. The model does not incorporate pack non-use, recipient susceptibility to infection, or under-ascertainment/under-reporting, for example due to recipients dying from an

underlying medical condition before a chronic asymptomatic viral condition is identified, or, in the case of HBV, an asymptomatic acute infection.

Blood donation screening process

Every blood donation in the UK is screened for HBV, HCV, HEV, HIV and syphilis. HTLV is screened for in donations from new blood donors and other infections such as malaria are screened for depending on travel history of the donor. A separate bacterial screening process is also in place for platelets as the storage of platelets at 22°C encourages bacterial growth.

At the time of blood donation, separate blood samples are collected for screening purposes. For the screening of viral nucleic acids (RNA or DNA) the blood samples are pooled together in a batch of six, 16 or 24 prior to screening. If RNA/DNA is detected in that pool, then individual samples known to be in that pool are re-tested separately in order to identify a positive sample. All antibody and/or antigen testing is done using individual blood samples. If RNA/DNA is detected, or antibody result is repeatedly positive suggesting an infection then the donation is discarded, and the sample is sent to a reference laboratory for further testing to confirm the result. If a positive result is confirmed the donor will be notified, offered an opportunity to discuss these results in detail and referred to the appropriate medical care as necessary.

Testing and selection of donors

The HBV and HEV screening processes are currently under review by SaBTO (Harvala et al. 2021).

From summer 2021, the FAIR (For the Assessment of Individualised Risk) blood donation policy was implemented across the UK Blood Services. The same questions are now asked of all donors and allows anyone who has not had anal sex with new and/or multiple partners in the last 3 months to give blood if other donation safety criteria are met. Donors are no longer asked about sex between men, questions are gender neutral. As soon as these changes were implemented, routine surveillance was adapted to ensure timely monitoring of positive donors and close review of those with recently acquired infections. To date, there is no evidence that FAIR has impacted on recent viral infections, and no TTI have been reported. While syphilis in donors has continued at a higher rate in 2021, this is not thought to be because of FAIR but reflects the sustained higher level among the general population. In addition, recommendations to withdraw the questions relating to partners who have had sex in parts of the world where HIV is endemic were approved.

Parasitic TTI

There were no reported parasitic infections for investigation in 2021.

Emerging infections

The Emerging Infections Report (EIR) produced by the NHSBT/UKHSA Epidemiology Unit is distributed monthly. A range of sources are checked for relevant infection issues relating to patient safety and/or blood and tissue availability in the UK and collated into a monthly listing. Sources include outbreak alerts, various regular outbreak surveillance reports, journals, websites and online news resources, listed in more detail below.

The EIR is sent to the chair of SACTTI. The chair of SACTTI also receives early warning communications or other reports deemed urgent as they arise.

These monthly listings, alongside other sources of information are reviewed by SACTTI and may lead to further risk assessment and changes to the donor selection guidelines, or other blood safety measures, where necessary.

Currently west nile virus and usutu virus are spreading in Europe, with usutu virus presenting in birds in the UK. The current situation is being monitored carefully and all blood donors from endemic regions are screened for both viruses.

SARS-CoV-2

Any blood units obtained from donors subsequently diagnosed with SARS-CoV-2 (within 5 days for infection) are re-called and discarded. We have retrospectively investigated whether donations obtained

from these donors with SARS-CoV-2 infection with wild-type virus, Delta or Omicron variant contained SARS-CoV-2 RNA. Although a small number of donations containing SARS-CoV-2 RNA were identified, none of these units were transfused and hence did not pose a risk to a recipient. There were no known cases of transfusion-transmitted SARS-CoV-2 infections reported to the Blood Services in 2021 and there is still no evidence that SARS-CoV-2 is a TTI.

Variant Creutzfeld Jakob Disease (vCJD) 2021

There were no vCJD investigations in 2021.

vCJD 1996-2021

Three vCJD incidents (Table 20.4) took place prior to the introduction of leucodepletion and other measures taken by the UK Blood Services to reduce the risk of vCJD transmission by blood, plasma and tissue products. All these measures have been reviewed and endorsed by SaBTO (SaBTO 2013).

One of these measures, the provision of imported plasma for individuals born on or after 1st January 1996, was withdrawn in September 2019. This followed a recommendation by SaBTO based on evaluation of the risk of transmission of vCJD. Other risk-reduction measures, such as leucodepletion, remain in place (SaBTO 2019).

Table 20.4: Number of confirmed TTI incidents, by year of transfusion and infection in the UK, reported to SHOT between October 1996 and December 2021 (Scotland included from October 1998)

Year of transfusion	Bacteria	HAV	HBV	HCV	HEV	HIV	HTLV	Parvovirus (B19)	Malaria	vCJD or prion	Total
Pre 1996	0	0	1	0	0	0	2	0	0	0	3
1996	0	1	1	1	0	1(3)	0	0	0	1	5 (7)
1997	3	0	1	1	0	0	0	0	1	2	8
1998	4	0	1	0	0	0	0	0	0	0	5
1999	4	0	2 (3)	0	0	0	0	0	0	0 (1)	6 (8)
2000	7	1	1	0	0	0	0	0	0	0	9
2001	5	0	0	0	0	0	0	0	0	0	5
2002	1	0	1	0	0	1	0	0	0	0	3
2003	3	0	1	0	0	0	0	0	1	0	5
2004	0	0	0	0	1	0	0	0	0	0	1
2005	2	1	1	0	0	0	0	0	0	0	4
2006	2	0	0	0	0	0	0	0	0	0	2
2007	3	0	0	0	0	0	0	0	0	0	3
2008	4 (6)	0	0	0	0	0	0	0	0	0	4 (6)
2009	2 (3)	0	0	0	0	0	0	0	0	0	2 (3)
2010	0	0	0	0	0	0	0	0	0	0	0
2011	0	0	1 (2)	0	1 (2)	0	0	0	0	0	2 (4)
2012	0	0	1	0	1	0	0	1	0	0	3
2013	0	0	0	0	0	0	0	0	0	0	0
2014	0	0	0	0	2 (3)	0	0	0	0	0	2 (3)
2015	1	0	0	0	4 (5)	0	0	0	0	0	5 (6)
2016	0	0	0	0	1	0	0	0	0	0	1
2017	0	1	0	0	0	0	0	0	0	0	1
2018	0	0	0	0	1	0	0	0	0	0	1
2019	0	0	0	0	1	0	0	0	0	0	1
2020	0	0	0	0	0	0	0	0	0	0	0
2021	0	0	0	0	0	0	0	0	0	0	0
Total number of incidents (recipients)	**41 (44)**	**4**	**12 (14)**	**2**	**12 (15)**	**2 (4)**	**2**	**1**	**2**	**3 (4)**	**81 (92)**

Year of transfusion	Red blood cells	Pooled platelets	Apheresis platelet	Fresh frozen plasma	Cryoprecipitate	Total
Pre 1996	3	0	0	0	0	**3**
1996	5	1	0	1	0	**7**
1997	6	1	1	0	0	**8**
1998	2	1	2	0	0	**5**
1999	5	3	0	0	0	**8**
2000	1	5	3	0	0	**9**
2001	0	4	1	0	0	**5**
2002	2	1	0	0	0	**3**
2003	1	1	3	0	0	**5**
2004	1	0	0	0	0	**1**
2005	1	3	0	0	0	**4**
2006	0	1	1	0	0	**2**
2007	2	1	0	0	0	**3**
2008	0	2	4	0	0	**6**
2009	1	0	2	0	0	**3**
2010	0	0	0	0	0	**0**
2011	2	0	0	2	0	**4**
2012	2	0	0	1	0	**3**
2013	0	0	0	0	0	**0**
2014	1	0	0	2	0	**3**
2015	0	3	1	1	1	**6**
2016	1	0	0	0	0	**1**
2017	0	0	1	0	0	**1**
2018	0	0	1	0	0	**1**
2019	0	0	2	0	0	**2**
2020	0	0	0	0	0	**0**
2021	0	0	0	0	0	**0**
Total number of recipients	**36**	**27**	**22**	**7**	**1**	**93**

Table 20.5: Number and type of implicated components from confirmed TTI recipients, by year of transfusion in the UK, reported to SHOT between October 1996 and December 2021 (Scotland included from October 1998)

	Bacteria	HAV	HBV	HCV	HEV	HIV	HTLV I	Parvovirus (B19)	Malaria	vCJD or prion	Total
Death due to, or contributed to, by TTI	11	0	0	0	3	0	0	0	1	3	**18**
Major morbidity	29	3	14	2	9	4	2	1	1	1	**66**
Minor morbidity	4	1	0	0	4	0	0	0	0	0	**9**
Red blood cells	7	1	11	2	4	2	2	1	2	4	**36**
Pooled platelets	21	2	1	0	2	1	0	0	0	0	**27**
Apheresis platelets	16	1	1	0	4	0	0	0	0	0	**22**
Fresh frozen plasma	0	0	1	0	5	1	0	0	0	0	**7**
Cryoprecipitate	0	0	0	0	1	0	0	0	0	0	**1**

Table 20.6: Outcome of confirmed TTI incidents and implicated components by infection in the UK, reported to SHOT between October 1996 and December 2021 (Scotland included from October 1998)

Accompanying notes for Table 20.4, 20.5 and 20.6:

- Where applicable, number of recipients are included in brackets
- No screening has been ever in place for vCJD, HAV or parvovirus B19
- HTLV screening began in 2002
- HEV screening was not in place at the time of the documented transmissions
- In both malaria transmissions, malaria antibody testing was not applicable at the time according to information supplied at donation
- HCV investigations where the transfusion was prior to screening are not included in the above figure
- The year of transfusion may be prior to year of report to SHOT due to delay in recognition of chronic infection
- The 2 HIV incidents were associated with window period donations (anti-HIV negative/HIV RNA positive) before HIV NAT screening was in place. A third window period donation in 2002 was transfused to an elderly patient, who died soon after surgery. The recipient's HIV status was therefore not determined and not included
- In 2004 there was an incident involving contamination of a pooled platelet pack with *Staphylococcus epidermidis*, which did not meet the TTI definition because transmission to the recipient was not confirmed, but it would seem likely. This case was classified as 'not transfusion-transmitted'
- The vCJD case in 1999 was found to have the same blood donor as one of the 1997 transmissions and has therefore been counted as the same incident. Please note this was counted as two separate incidents in previous reports
- A further prion case died but transfusion was not implicated as the cause of death. The outcome was assigned to major morbidity instead because although there was post-mortem evidence of abnormal prion proteins in the spleen the patient had died of a condition unrelated to vCJD and had shown no symptoms of vCJD prior to death

For further information or alternative breakdown of data please contact the National Coordinator for Transfusion Transmitted Infections via the NHSBT/UKHSA Epidemiology Unit at epidemiology@nhsbt.nhs.uk

References

BSH Tinegate H, Birchall J, Gray A, et al. Guideline on the investigation and management of acute transfusion reactions. Prepared by the BCSH Blood Transfusion Task Force. *Br J Haematol.* 2012;**159(2)**:143-153.

Harvala H, Reynolds C, Gibney Z et al. Hepatitis B infections among blood donors in England between 2009 and 2018: Is an occult hepatitis B infection a risk for blood safety? *Transfusion.* 2021;**61(8):**2402-2413. doi: 10.1111/trf.16543.

JPAC. Position Statement: The estimated residual risk that a donation made in the infectious window period is not detected on testing: risks specific for HBV, HCV and HIV in the UK, 2018-2020 (2021). https://www.transfusionguidelines.org/document-library/documents/jpac-position-statement-residual-risks-2021-for-website2-pdf [accessed 05 May 2022].

McDonald C, Allen J, Brailsford S et al. Bacterial screening of platelet components by National Health Service Blood and Transplant, an effective risk reduction measure. *Transfusion.* 2017;**57(5)**:1122-1131. doi:10.1111/trf.14085.

SaBTO. Measures currently in place in the UK to reduce the potential risk of transmitting variant Creutzfeldt-Jakob disease via blood (2013). https://www.gov.uk/government/publications/current-measures-to-reduce-the-risk-of-vcjd-transmission-by-blood [accessed 08 May 2022].

SaBTO. Importation of plasma and use of apheresis platelets as risk reduction measures for variant Creutzfeldt-Jakob Disease (2019). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/829906/SaBTO_PC_report.pdf [accessed 08 May 2022].