# 20 Transfusion-Transmitted Infections (TTI) n=3 (1 confirmed, 2 probable)

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## Definition of a TTI:

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

- **The recipient 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 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**

**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 prolong 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.**

## Introduction

This chapter describes suspected transfusion-transmitted infection incidents investigated by the United Kingdom (UK) Blood Services and reported to the National Health Service Blood and Transplant (NHSBT)/Public Health England (PHE) Epidemiology Unit in 2018.

The risk of a TTI in the UK remains very low. During 2018 3 TTI were recorded as probable or confirmed. Investigations of these TTI have shown that none occurred due to errors in donor selection or testing.

## Summary of reports made to the NHSBT/PHE Epidemiology Unit in 2018

During 2018, UK Blood Services investigated 97 suspected bacterial cases and 8 suspected viral incidents (Figure 20.1). From these suspected cases, there has been:

- One confirmed transfusion-transmitted hepatitis E virus (HEV) incident reported by NHSBT
- One probable transfusion-transmitted *Staphylococcus epidermidis* incident reported by NHSBT
- One probable transfusion-transmitted hepatitis B virus (HBV) incident reported by NHSBT
- One late detection of *Staphylococcus aureus* incident reported by NHSBT (no evidence of a TTI)

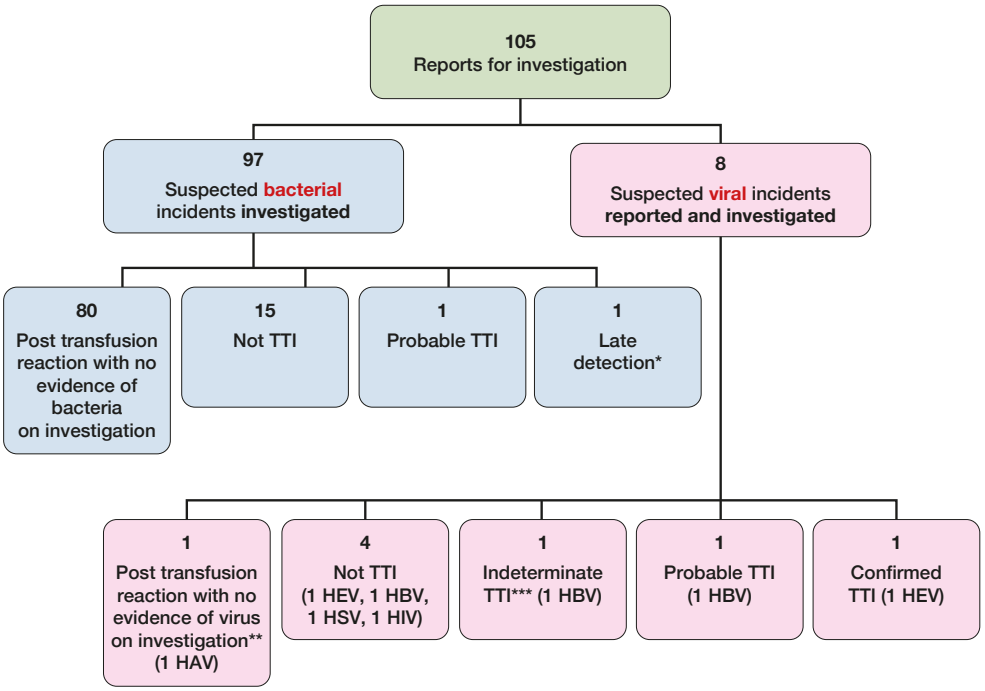


**Figure 20.1: Outcome of reports of suspected TTI made to the NHSBT/ PHE Epidemiology Unit in 2018**

*TTI=transfusion-transmitted infection; HAV=hepatitis A virus; HBV=hepatitis B virus; HSV=herpes simplex virus; HIV=human immunodeficiency virus; HEV=hepatitis E virus*

**The BacT/ALERT system flagged as positive after the associated platelets had been issued and transfused however no evidence of a TTI was found*

***Reported based on a clinical diagnosis of HAV, but this was not confirmed by further laboratory testing*

****Due to the time elapsed since transfusion archive samples were not available for half of the implicated donations*

## Death n=1

A patient with a probable case of transfusion-transmitted HBV died after being transfused in 2018 (Case 20.3).

## Bacterial TTI reports 2018

In 2018, no reported suspected bacterial TTI cases were confirmed, but 1 incident reported by NHSBT is assigned as probable. The four UK Blood Services all use the BacT/ALERT system for bacterial screening which has reduced the number of confirmed bacterial TTI since its introduction in 2011 (McDonald et al. 2017). Sampling methods vary slightly across the four countries, details of which are described in Table 20.1.

**Case 20.1: Probable *Staphylococcus epidermidis* (Morbidity: moderate; imputability: 2-probable)**

*A young child received one standard unit of a 7-day old apheresis platelet. The child was receiving blood components due to ongoing chemotherapy for an underlying medical condition. Three hours prior to the platelet transfusion they had received a unit of red cells through a tunnelled central venous catheter with no adverse reaction. Within 5 minutes of the platelet transfusion being started the child experienced an anaphylactoid reaction including a rise in temperature to 40°C that lasted for 24 hours. This was treated empirically with intravenous antibiotics to cover the possibility of either a bacterial TTI or a central line infection. The patient made a good recovery and was discharged home within days to complete a week of antibiotics. Staphylococcus epidermidis was repeatedly isolated from recipient blood cultures and a transfusion reaction investigation was commenced by NHSBT.*

*Routine bacterial screening of the transfused platelet unit was negative but on return to the NHSBT national bacteriology laboratory Staphylococcus epidermidis was isolated from the index pack. This isolate was sent for typing along with isolates from the recipient's blood cultures and they were shown*

*to be indistinguishable. Associated components were recalled, however one associated 4-day old platelet unit had already been transfused into a patient in whom no adverse reactions were reported. It is possible that this does not represent a TTI, but rather a central venous catheter infection in the recipient. In this case, the isolate in the recalled index pack might represent contamination with blood from the recipient. However, the chronology of the presentation, the clinical picture and the lack of reaction during an earlier red cell transfusion make a bacterial TTI probable in this case. Donor investigations are ongoing.*

## Late detection: Staphylococcus aureus

An aerobic initial reactive bottle (IR) alert was issued on a unit of pooled platelets after one of the BacT/ALERT bottles flagged positive. Platelets are issued by NHSBT if bacterial screening remains negative after 6 hours' incubation (see Table 20.1), but the bottles remain incubated until the end of the platelet shelf-life (7 days). The IR flag came just over one hour after the pooled platelets had been issued but despite an immediate recall the platelets had already been transfused to a surgical patient in their 60s. However, three associated red cells units were returned and one discarded at the hospital to which it had been issued. *Staphylococcus aureus* was subsequently isolated from the IR bottle but could not be confirmed in the red cell units so a final result of indeterminate positive was concluded. Follow up with the local transfusion practitioner and NHSBT patient consultant revealed that the recipient had not experienced any transfusion reaction and had been discharged from hospital. They had not received any antibiotic therapy during their hospital admission.

There were four donors implicated in the donation, all of whom were followed up and asked to consent to take self-sampled nasal swabs. Three returned their swabs with nothing being received from the fourth donor despite agreeing to the sample, *Staphylococcus aureus* isolated from one swab. The isolate cultured from the bacterial screening bottles of the implicated donation and the isolate cultured from the donor swab were sent for molecular typing. On the basis of the typing results it seemed unlikely that this donor was the source of the platelet contamination, however, it was decided that the donor should be withdrawn.

## Bacterial TTI 1996 – 2018

Screening of platelet components cannot guarantee freedom from bacterial contamination. Packs are released for issue as 'negative-to-date', which may be before bacteria have multiplied sufficiently to trigger an initial screening reaction. There have been nine bacterial near misses, all but one in platelet components, reported to the unit between 2011 and 2018. 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 20.3) since reporting began.

Haemovigilance systems for bacterial TTI are passive and as such rely on clinical colleagues to report suspected TTI. Following the introduction of bacterial screening of platelets, colleagues were reminded that there was still the possibility of TTI occurring from both platelet and red cell transfusion and the number of reported suspected TTI has remained almost constant. Current British Society for Haematology (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 TTI become unwell very rapidly.

**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 |

**Screening methods in Wales changed mid-year from testing on day 1 and day 4 to testing on day 2 only*

*NIBTS=Northern Ireland Blood Transfusion Service; SNBTS=Scottish National Blood Transfusion Service; WBS=Welsh Blood Service*

## Viral TTI reports 2018

In 2018, there was 1 confirmed transfusion-transmitted HEV incident, 1 probable transfusion-transmitted HBV incident, and 1 indeterminate HBV incident.

**Case 20.2: Indeterminate viral HBV TTI case 1: (Morbidity: minor; imputability: N/A)**

*In 2011, a man in his 40s received multiple blood transfusions over the course of 3 months, amounting to three units of pooled platelets and four units of apheresis platelets. The transfusions were given during treatment for Hodgkins lymphoma. Many years later in mid-2018 the patient was tested for HBV following a prolonged period of raised alanine aminotransferase (ALT) and was found to have HBV markers for chronic infection (HBsAg positive, HBeAg positive, core antibody positive, IgM negative). Following this an investigation was launched into blood components as a possible source of the infection.*

*Given the time period, there were no index samples available for testing, but 16 donors were identified that related to the seven units the patient received. Half of these donors had donated in the past three years and so had a recent archive sample available for testing, all of which had negative results for HBV. The other eight donors had not recently donated due to personal choice or medical reasons (unrelated to hepatitis B) and so no samples were available for testing for them. Of these seven had returned at least once since the implicated donation. This meant NHSBT were unable to ascertain whether transfusion was the source of this patient's HBV infection and a classification of indeterminate was therefore assigned.*

**Case 20.3: Probable viral HBV TTI case 2: (Morbidity: major - death; imputability: 2-probable)**

*After being admitted to hospital in late 2017, a woman in her 70s received two units of red cells in response to a low haemoglobin level of 83g/L. She had multiple medical conditions including liver cirrhosis due to non-alcoholic steatohepatitis (NASH). Approximately 6 months later she was re-admitted to hospital with acute hepatitis and diagnosed with acute hepatitis B infection. She developed acute-on-chronic liver failure and unfortunately died about 5 weeks after the HBV diagnosis. The patient had tested negative for HBV infection in late 2016 and further samples from the patient were deemed to be consistent with a recent HBV infection (anti-HBcore IgM antibodies detected and anti-HBcore antibody avidity results compatible with a recent HBV infection). The virus was identified as genotype D2. Investigations external to NHSBT took place which looked at the hospital and lifestyle as possible sources of infection, these were excluded as possible sources. Blood transfusion was therefore the only risk factor identified and an investigation was launched by NHSBT.*

*The two donors associated with the units transfused to the patient were identified. One was a repeat donor who had an archive sample from the implicated unit and another archive sample for a subsequent donation; both tested negative for HBV. The other donor was a new donor, the archive sample from the implicated donation was retrieved and tested positive for anti-HB core antibodies with anti-HBs of 9.60 mIU/mL but negative for HBV deoxyribonucleic acid (DNA) using singleton nucleic acid testing (NAT). The donor kindly provided a large volume sample which was concentrated and then tested. In this concentrated sample, HBV DNA was detected at a level below the level of detection of our routine screening tests, and even if singleton testing had been used in screening it is unlikely DNA would have been detected. The concentrated sample was sent for confirmatory testing but unfortunately this was unable to detect HBV DNA and unable to perform sequencing. Investigations confirmed that this donor had an occult HBV infection and he had likely had a completely asymptomatic HBV infection as a child, as he was born in HBV endemic country. For these reasons, this infection could not have been picked up by donor questionnaire or by testing. It was noted that this donor was born in a region where genotype D2 HBV infection is prevalent.*

*Since it was not possible to sequence the sample, transmission cannot be confirmed. However, since no other risk factors were identified in the recipient, despite extensive investigations, and because the virus found in the recipient had a genotype prevalent in the donor's country of birth, it is was concluded probable that the blood transfusion was the route of HBV transmission.*

**Case 20.4: Confirmed viral HEV TTI case 3: (Morbidity: major; imputability: 3-confirmed)**

*In late 2018, as part of routine screening, NHSBT identified a regular apheresis platelet donor who tested positive for HEV ribonucleic acid (RNA), indicating an acute HEV infection, and this donation was discarded. The donor had donated in the previous month and following the usual lookback process an archive sample from this previous donation was tested and found to be HEV RNA positive with a very low viral load. This previous donation had been tested for HEV in a pool of 24 donations, as per normal screening procedures, and was issued as screen negative at the time. The low viral load detected in individual screening would have been below the level of quantification in the pooled screening, hence the screen negative result. Based on previous work this viral load was thought to be very unlikely to transmit by transfusion (Tedder et al. 2017). Both platelet packs from the previous low-level HEV-positive donation had been issued and the hospitals were contacted and recipients identified.*

*One recipient had died shortly after the transfusion from their underlying conditions. The other platelet recipient was a haematology patient undergoing chemotherapy at the time of the transfusion. The patient was informed and a blood sample was taken 11 weeks post transfusion, this tested positive for HEV RNA. Samples from the donor and recipient were sequenced and the hepatitis E virus isolated was found to be identical at the nucleotide level therefore making this a confirmed TTI. Testing of a follow-up sample from the donor indicated that they had cleared the infection and, at the time of writing, the recipient had not experienced symptoms of HEV infection, but they continue to be monitored. This is the first recorded case of an HEV TTI since universal screening was introduced in April 2017.*

## Viral TTI 1996 – 2018

The year of transfusion may be many years prior to the year in which the case is investigated and reported to SHOT because of the chronic nature, and therefore late recognition, of some viral infections. Since 1996, 34 confirmed incidents of transfusion-transmitted viral infections have been documented, involving 41 recipients. HBV is the most commonly reported proven viral TTI in the UK. 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.

## 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 20.2) (PHE 2017).

**Table 20.2: The estimated risk of a potentially infectious HBV, HCV or HIV window period* blood donation not detected on testing, UK 2015-2017**

| | HBV | HCV** | HIV |
|---|---|---|---|
| Number per million donations | 0.46 | 0.00 | 0.051 |
| 95% confidence interval | 0.11-1.14 | 0.00-0.00 | 0.02-0.10 |
| At 2.3 million donations per year testing will miss a potentially infectious window period donation every: | 1.0 years | N/A | 9.3 years |

**The window period is the time at the start of an infection before the tests can detect it*

***Risk cannot be calculated as there were no HCV seroconversions between 2015 and 2017*

Far fewer TTI are observed in practice than the estimated risks in Table 20.2 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.

### Testing and guideline update: 2018

In November 2017, the blood donor selection guidelines for men who have sex with men (MSM) were changed in England, Wales and Scotland from a 12-month deferral since last sex with a man to a 3-month deferral. Similar changes were made for other donor selection criteria related to higher risk sexual behaviours. Since this change, no possible, probable, or confirmed TTI reported to UK Blood Services have related to the changes in the selection guidelines. No changes to virology testing procedures occurred in 2018 but minor changes to the bacterial screening process have been noted in Table 20.1.

## Parasitic TTI

There were no reported parasitic infections for investigation in 2018.

## Emerging infections

The Epidemiology Unit produces the Emerging Infection Report (EIR), a monthly horizon scanning list of emerging infections with potential to affect the UK blood and tissue supply. The Standing Advisory Committee on Transfusion Transmitted Infection (SACTTI) then risk-assesses the EIR and highlights whether further action is required by the Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC).

## Variant Creutzfeld-Jakob Disease (vCJD) 2018

There were no vCJD investigations in 2018.

### vCJD 1996-2018

Three vCJD incidents (Table 20.3) 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 the Advisory Committee on the Safety of Blood, Tissues and Organs (SABTO 2013).

Risk assessment and research into vCJD continues. Currently there is no suitable blood test available for screening blood donations for vCJD.

More information can be found here: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/407681/measures-vcjd.pdf

**Table 20.3: Number of *confirmed* TTI incidents*, by year of transfusion** with total infected recipients and outcomes (death, major morbidity, minor morbidity) in the UK between October 1996 and December 2018 (Scotland included from October 1998)**

| Year of transfusion** | Number of incidents (recipients) by infection | | | | | | | | | | | Implicated component | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bacteria | HAV | HBV | HCV*** | HEV | HIV | HTLV I | Parvovirus (B19) | Malaria | vCJD/prion | Total | RBC | Pooled platelet | Apheresis platelet | FFP | Cryo |
| Pre 1996 | - | - | 1 (1) | - | - | - | 2 (2) | - | - | - | **3 (3)** | 3 | - | - | - | - |
| 1996 | - | 1 (1) | 1 (1) | 1 (1) | - | 1 (3) | - | - | - | 1 (1) | **5 (7)** | 5 | 1 | - | 1 | - |
| 1997 | 3 (3) | - | 1 (1) | 1 (1) | - | - | - | - | 1 (1) | 2 (2) | **8 (8)** | 6 | 1 | 1 | - | - |
| 1998 | 4 (4) | - | 1 (1) | - | - | - | - | - | - | - | **5 (5)** | 2 | 1 | 2 | - | - |
| 1999 | 4 (4) | - | 2 (3) | - | - | - | - | - | - | ‡ (1) | **6 (8)** | 5 | 3 | - | - | - |
| 2000 | 7 (7) | 1 (1) | 1 (1) | - | - | - | - | - | - | - | **9 (9)** | 1 | 5 | 3 | - | - |
| 2001 | 5 (5) | - | - | - | - | - | - | - | - | - | **5 (5)** | - | 4 | 1 | - | - |
| 2002 | 1 (1) | - | 1 (1) | - | - | 1 (1)† | - | - | - | - | **3 (3)** | 2 | 1 | - | - | - |
| 2003 | 3 (3) | - | 1 (1) | - | - | - | - | - | 1 (1) | - | **5 (5)** | 1 | 1 | 3 | - | - |
| 2004 | †† | - | - | - | 1 (1) | - | - | - | - | - | **1 (1)** | 1 | - | - | - | - |
| 2005 | 2 (2) | 1 (1) | 1 (1) | - | - | - | - | - | - | - | **4 (4)** | 1 | 3 | - | - | - |
| 2006 | 2 (2) | - | - | - | - | - | - | - | - | - | **2 (2)** | - | 1 | 1 | - | - |
| 2007 | 3 (3) | - | - | - | - | - | - | - | - | - | **3 (3)** | 2 | 1 | - | - | - |
| 2008 | 4 (6) | - | - | - | - | - | - | - | - | - | **4 (6)** | - | 2 | 4 | - | - |
| 2009 | 2 (3) | - | - | - | - | - | - | - | - | - | **2 (3)** | 1 | - | 2 | - | - |
| 2010 | - | - | - | - | - | - | - | - | - | - | **-** | - | - | - | - | - |
| 2011 | - | - | 1 (2) | - | 1 (2) | - | - | - | - | - | **2 (4)** | 2 | - | - | 2 | - |
| 2012 | - | - | 1 (1) | - | 1 (1) | - | - | 1(1) | - | - | **3 (3)** | 2 | - | - | 1 | - |
| 2013 | - | - | - | - | - | - | - | - | - | - | **-** | - | - | - | - | - |
| 2014 | - | - | - | - | 2 (3) | - | - | - | - | - | **2 (3)** | 1 | - | - | 2 | - |
| 2015 | 1 (1) | - | - | - | 4 (5) | - | - | - | - | - | **5 (6)** | - | 3 | 1 | 1 | 1 |
| 2016 | - | - | - | - | 1 (1) | - | - | - | - | - | **1 (1)** | 1 | - | - | - | - |
| 2017 | - | 1 (1) | - | - | - | - | - | - | - | - | **1 (1)** | - | - | 1 | - | - |
| 2018 | - | - | - | - | 1 (1) | - | - | - | - | - | **1 (1)** | - | - | 1 | - | - |
| **Number of incidents** | **41** | **4** | **12** | **2** | **11** | **2** | **2** | **1** | **2** | **3** | **80** | - | - | - | - | - |
| Number of infected recipients | 44 | 4 | 14 | 2 | 14 | 4 | 2 | 1 | 2 | 4 | **91** | 36 | 27 | 20 | 7 | 1 |
| Death due to, or contributed to, by TTI | 11 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 3 | **16** | | | | | |
| 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** | | | | | |
| **Implicated component** | | | | | | | | | | | | | | | | |
| RBC | 7 | 1 | 11 | 2 | 4 | 2 | 2 | 1 | 2 | 4 | **36** | | | | | |
| Pooled platelet | 21 | 2 | 1 | - | 2 | 1 | - | - | - | - | **27** | | | | | |
| Apheresis platelet | 16 | 1 | 1 | - | 2 | - | - | - | - | - | **20** | | | | | |
| FFP | - | - | 1 | - | 5 | 1 | - | - | - | - | **7** | | | | | |
| Cryoprecipitate | - | - | - | - | 1 | - | - | - | - | - | **1** | | | | | |

*Note: Numbers in brackets refer to recipients, and probable incidents are excluded.*

** No screening was in place for vCJD, human T cell lymphotropic virus (HTLV), hepatitis A virus (HAV), HEV or parvovirus B19 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*

*** Year of transfusion may be prior to year of report to SHOT due to delay in recognition of chronic infection*

**** HCV investigations where the transfusion was prior to screening are not included in the above figure.*

*† The two 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'*

*‡ Same blood donor as one of the 1997 transmissions so counted as the same incident; note: 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/PHE Epidemiology Unit at epidemiology@nhsbt.nhs.uk.

## References

BSH Tinegate H, Birchall J, Gray A, et al. (2012) 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.

McDonald C, Allen J, Brailsford S, et al. (2017) 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.

PHE (2017) NHSBT/PHE Epidemiology Unit: Safe Supplies: A year of change. Annual Review from the NHS Blood and Transplant / Public Health England Epidemiology Unit, 2017. London, July 2018. https://www.gov.uk/government/publications/safe-supplies-annual-review [accessed 06 June 2019].

SaBTO (2013) Current measures to reduce the risk of vCJD transmission by blood. https://www.gov.uk/government/publications/current-measures-to-reduce-the-risk-of-vcjd-transmission-by-blood [accessed 31 May 2019].

Tedder R, Ijaz S, Kitchen A, et al. (2017) Hepatitis E risks: pigs or blood-that is the question. *Transfusion* 2017;**57(2)**:267-272. doi:10.1111/trf.13976.