17 Transfusion-Transmitted Infections (TTI) n=1

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Definition of a TTI:

A report was classified as a transfusion-transmitted infection if, following investigation:

- **The recipient had evidence of infection following 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 the possible TTI 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 2017.

Summary of reports made to the NHSBT/PHE Epidemiology Unit in 2017

During 2017, UK Blood Services investigated 106 suspected bacterial cases and 8 suspected viral incidents (Figure 17.1). From these suspected cases, there has been:

- One confirmed transfusion-transmitted hepatitis A virus (HAV) incident reported by the Scottish National Blood Transfusion Service (SNBTS)
- One confirmed transfusion-transmitted hepatitis E virus (HEV) incident from NHSBT
- One probable transfusion-transmitted HEV incident from NHSBT
- One possible *Staphylococcus capitis* bacterial transfusion-transmitted incident from SNBTS

Further information about how and what to report can be found in 'SHOT Bite No. 7 Transfusion-transmitted infections' at www.shotuk.org/resources/current-resources/.

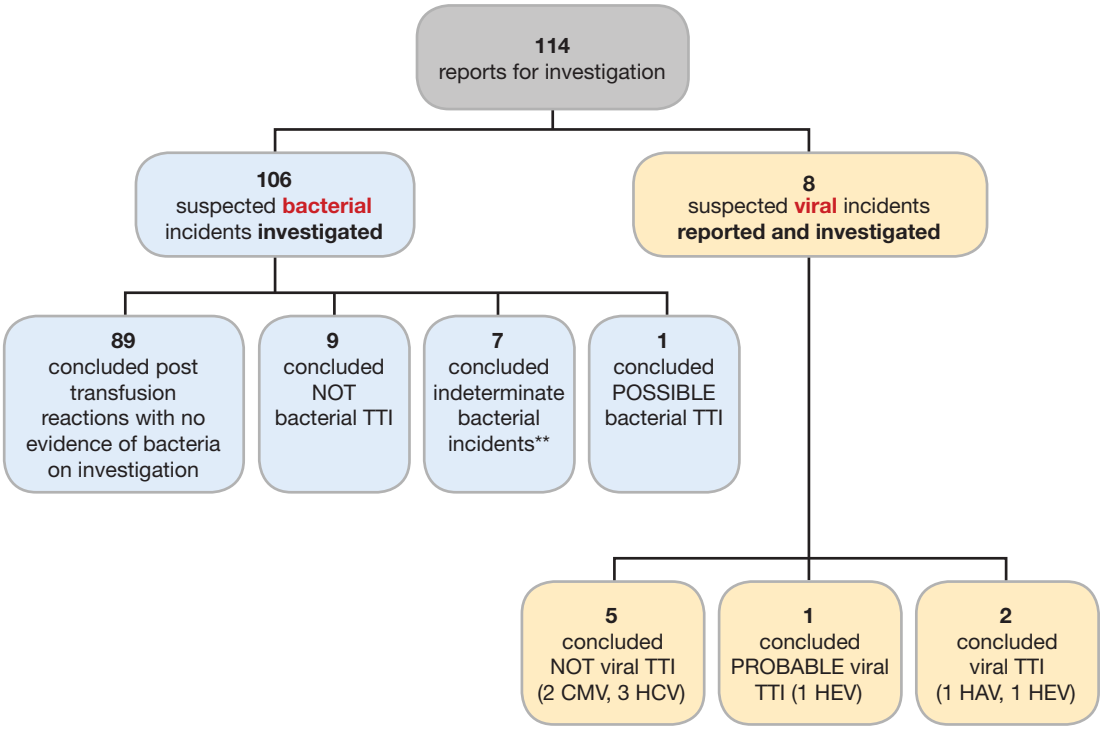

Figure 17.1: Outcome of reports of suspected TTI made to the NHSBT/PHE Epidemiology Unit in 2017*

**Hepatitis C virus (HCV) investigations where the transfusion was prior to screening are not included in the above figure (1 HCV incident reported in 2017, transfusion pre-1991)*

***No packs to test but investigation based on information received indicates unlikely to reflect a TTI*

TTI=transfusion-transmitted infection; CMV=cytomegalovirus; HEV=hepatitis E virus; HAV=hepatitis A virus

Major morbidity n=1

A patient with a confirmed case of transfusion-transmitted HAV suffered a serious reaction (Case 17.4) after being transfused in 2017.

Bacterial TTI reports 2017

In 2017, no reported suspected bacterial TTI were confirmed, but 1 incident reported by the SNBTS is assigned as possible. The four UK Blood Services all use the BacTALERT system for bacterial screening which has had an impact on the number of confirmed bacterial TTI (McDonald et al. 2017). Each country uses slightly different sampling methods which are described in Table 17.1.

Case 17.1: Possible case: (Morbidity: Major; Imputability: 1-possible)

A 3-day old pooled platelet unit was transfused to a female patient in her 50s who was receiving a second cycle of chemotherapy for relapsed acute myeloid leukaemia (AML). She had a history of a perianal abscess and neutropenic fever, was reported as pyrexial prior to transfusion, and had been given antibiotic prophylaxis. Four hours post transfusion her condition worsened, she was found collapsed, confused, septic with a temperature of 40°C, hypoxic, and hypotensive with a tachycardia. She remained pyrexial over the following week and was treated with broad spectrum antibiotics; she continued to improve and recovered well. Bacterial screening signalled a reactive result after the pack had been transfused, and Staphylococcus capitis was isolated from the initial pouch sample and the anaerobic culture bottle, but the transfused unit was unavailable for culture. Blood cultures were taken from the patient but these results were not available to the Blood Service. The significant symptoms and persistent fever post transfusion resulted in the case being reported as a bacterial TTI although the symptoms may have been related to the patient's underlying condition. On the basis of these results this incident is reported as a possible TTI.

Bacterial TTI 1996–2017

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 8 bacterial near misses, all but 1 in platelet components, reported to the PHE Epidemiology Unit between 2011 and 2017. 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 17.3) 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 17.1: 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	48	2 x 8	Pre-split	6	Day 9
SNBTS	18	2 x 7	Pre-split	6	Day 7
WBS	16	2 x10	Pre-split	From start of screening	Day 7*

**Additional 10mL sample taken at day 4 to extend shelf-life from 5 to 7 days*

NIBTS=Northern Ireland Blood Transfusion Service; WBS=Welsh Blood Service

Time of sampling: time samples are taken from the pack for screening in hours after donation is made

Apheresis sample: two or three packs may be manufactured from one donation, NHSBT sample each pack i.e. 2 or 3 packs

Time at release: time bottles remain on the machine before packs are released as negative

Viral TTI reports 2017

In 2017, there was 1 probable transfusion-transmitted HEV incident, 1 confirmed transfusion-transmitted HEV incident and 1 confirmed transfusion-transmitted HAV incident.

Case 17.2: Probable viral HEV TTI case 1: (Morbidity: Major; Imputability: 2-probable)

A male patient in his 60s received a transfusion of one platelet pool and one apheresis platelet in mid-2015 prior to a prostate biopsy. Platelets were given due to the patient's low platelet count ascribed to significant alcohol intake. The patient developed acute hepatitis 2 months later and was found to have chronic liver disease with portal hypertension. Further investigations revealed hepatocellular carcinoma. The patient deteriorated due to liver failure and died 2 months after the transfusion. A blood sample which was taken a day prior to the patient's demise was confirmed to be anti-HEV IgM positive and IgG positive, indicating recent HEV infection.

Archive samples of the five donations (four donors from the platelet pool donation and one from the apheresis pool donation) were retrieved and tested for HEV ribonucleic acid (RNA). The four platelet pool donation samples were confirmed as HEV RNA-negative, but the apheresis platelet donation was HEV RNA-positive, with a viral load of 2044IU/mL. The associated platelet split had been transfused and the clinical team looking after this patient were informed of the potential risk of HEV transmission.

Since there was no remaining blood sample from the patient to refer for HEV RNA testing, it was not possible to prove conclusively that the recipient virus was identical to the donor virus. Therefore, it has been concluded that the infection was probably acquired through transfusion.

Case 17.3: Confirmed viral HEV TTI case 2: (Morbidity: Major; Imputability: 3-confirmed)

A male patient in his 60s received multiple plasma exchanges with fresh frozen plasma (FFP) as treatment for focal segmental glomerulosclerosis (FSGS) which he developed after renal transplant in November 2014. Between January and July 2015, he received 238 units of FFP. He was discharged to his home country.

In March 2017 the patient was noted to have developed ascites over 6 months and portal hypertension was diagnosed. On further investigation the patient was found to be HEV RNA-positive. A sample was referred to the Virus Reference Department at Public Health England which confirmed the HEV RNA result with a viral load of 1,500,000IU/mL, and a genotype 3 virus. The patient was also found to be HEV IgM positive and IgG positive. Testing of stored patient samples confirmed that the HEV infection was present at completion of, but not prior to, the plasma exchange therapy. The patient had therefore developed chronic HEV infection, dating from at least August 2015, on a background of immunosuppression following a renal transplant. The patient subsequently developed multi-organ failure and died.

Patient samples predating each cycle of plasma exchange were tested for HEV RNA; it was found that all samples up to mid-March were HEV RNA-negative, whereas those from May 2015 were HEV RNA-positive. An investigation was therefore carried out into the 59 units of FFP transfused in late March. Archive samples were retrieved and tested: 57 were HEV RNA-negative, one sample was insufficient for testing and one was identified as HEV RNA-positive, IgM- and IgG-negative, indicating early acute HEV infection in the donor at the time of donation. Sequence analysis indicated that the viruses in the donor and recipient samples (both genotype 3c) were likely to be linked and therefore this case is confirmed as a TTI.

An associated red cell pack from the same donation did not result in transmission, probably due to low levels of virus in the pack.

This case has been added to the number of confirmed TTI for 2015 in Table 17.3.

Case 17.4: Confirmed viral HAV TTI case 3: (Morbidity: Major; Imputability: 3-confirmed)

Hepatitis A is usually transmitted by contaminated food and water, although other routes have been identified including sexual transmission and blood transfusion. Outbreaks of hepatitis A were identified during 2017 in adults across the UK, including one associated with a bakery in Scotland. The last confirmed report of hepatitis A transfusion transmission was in 2005.

An apheresis platelet donor felt unwell 2 days prior to donation but recovered and attended to donate. The following day the donor again felt unwell and developed dark urine but no jaundice. A week after donation the donor was hospitalised with acute hepatitis A infection. On investigation, it was found that the donor had visited the bakery linked to a hepatitis A outbreak.

Investigation of the issued platelet doses was carried out. One recipient, a female in her 50s with renal cancer, neutropenic sepsis and a low platelet count, was transfused with one apheresis platelet unit. Post transfusion, the patient had evidence of hepatitis A immunity (HAV IgG, but no HAV IgM detected), with transient HAV RNA positivity. Sequence analysis indicated that the viruses in the donor and recipient samples were likely to be linked and therefore this TTI is confirmed. Sadly, the patient died of her underlying disease.

Health Protection Scotland and SNBTS worked together to ensure that no other donors potentially affected by the outbreak donated for a 6-month period, and sessions were cancelled in the areas affected by the HAV outbreak. The Public Health services in England and Scotland have modified their hepatitis A questionnaire for patients and contacts to ask an additional question about recent blood donation. Public health teams will notify their Blood Service if patients answer ‘yes’ to this question to allow appropriate actions to be taken.

Update on viral TTI reports investigated in 2016

Of the 2 pending HEV cases in 2016, 1 case was found to be probable viral HEV TTI and 1 was a confirmed viral HEV TTI.

Case 17.5: Probable HEV viral TTI 2016 case 1: (Morbidity: Major; Imputability: 2-probable)

A male patient in his late teens received blood transfusions between December 2013 and January 2014 in association with a liver transplant. He received four units of red cells, 12 units of FFP, two units of apheresis platelets and two platelet pool donations, equivalent to 26 donor exposures. In 2015, the patient developed persistent transaminitis and tested HEV RNA-positive in October 2015.

Records of all donors were examined; all except two had donated at least once since the donation transfused to the patient. An archive sample of a follow-up donation from each of the 24 returning donors was retrieved: 18 tested HEV IgG-negative and six were HEV IgG-positive, indicating prior HEV infection. For two of these donors the index archive was available and tested HEV RNA-negative. Given the time elapsed since the transfused donations there was no index archive sample available for the other four donors whose follow-up sample was HEV IgG positive, nor for the two donors who did not re-attend. Therefore, it was possible to eliminate 20 of the 26 donors as a source of HEV infection. Five of the six remaining donors contributed FFP and the final one contributed platelets as part of a platelet pool. Due to lack of archive samples for these six donors it was not possible to assess when the four donors known to have become HEV IgG-positive may have acquired their hepatitis E infection, nor confirm if they were the source of the hepatitis E infection in the patient, however it was assessed that this was likely to be a probable transfusion-transmitted infection.

Case 17.6: Confirmed HEV viral TTI 2016 case 2: (Morbidity: Major; Imputability: 3-confirmed)

A male in his 60s diagnosed with myelodysplastic syndrome (MDS), had an allogeneic stem cell transplant, and received blood transfusions from late 2014 to mid-2015. A deterioration in liver function test results in early 2016 led to HEV testing; the patient was HEV IgM-positive, IgG not detected. The patient received 66 units of red cells, 33 units of apheresis platelets and 14 platelet pools during this time, with 155 donor exposures. Archive samples of all the donations were retrieved and tested for HEV RNA. One donation was identified as HEV RNA-positive with a viral load of 2,000,000IU/mL. The platelets and plasma from this donation were used in preparation of a platelet pool which was transfused to the patient. Sequence analysis indicated that the viruses in the donor and recipient samples were likely to be linked and therefore this TTI is confirmed. The associated red cell unit was transfused to an immunocompetent patient; the clinical team looking after this patient was informed of the HEV status of the donation.

This case has been added to the number of confirmed TTI for 2015 in Table 17.3.

Viral TTI 1996–2017

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, 33 confirmed incidents of transfusion-transmitted viral infections have been documented, involving 40 recipients. Hepatitis B virus (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 human immunodeficiency virus (HIV), despite nucleic acid (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 17.2) (PHE 2016).

	HBV	HCV	HIV
Number per million donations	0.47	0.010	0.06
95% confidence interval	*0.08-1.06*	*0.00-0.05*	*0.02-0.12*
At 2.3 million donations per year testing will miss a potentially infectious window period donation every:	1.02 years	46 years	7 years

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

Table 17.2: The estimated risk of a potentially infectious HBV, HCV or HIV window period* blood donation not detected on testing, UK 2014-2016

Far fewer TTI are observed in practice than the estimated risks in Table 17.2 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 update: 2017

SNBTS began 100% HEV screening of donations from 1 March 2017. NHSBT implemented 100% screening of blood donations from 10 April 2017, followed by the other Blood Services. HEV screening for non-blood donors (stem cell, tissues and organs) went live in NHSBT on 2 October 2017.

NHSBT changed human T-cell lymphotropic virus (HTLV) screening from universal to selective (new donors and donations that will be used for non-leucodepleted blood components) in January 2017.

Parasitic TTI

There were no reported parasitic infections for investigation in 2017. There have been two proven malaria TTI reported to SHOT, the last in 2003 (Table 17.3). Malaria antibody testing according to information supplied at donation was not applicable at the time, and the donor selection guidelines were updated after these incidents to minimise the risk of further malaria TTI (Kitchen et al. 2005). The current selection guidelines on deferral and additional testing for malaria can be accessed at the UK transfusion guidelines web pages at http://www.transfusionguidelines.org.uk/red-book.

Variant Creutzfeld-Jakob Disease (vCJD) 2016

There were no vCJD investigations in 2016.

vCJD 1996-2017

Three vCJD incidents (Table 17.3) 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) (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 17.3: 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 2017 (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	-	-
Number of incidents	**41**	**4**	**12**	**2**	**10**	**2**	**2**	**1**	**2**	**3**	**79**					
Number of infected recipients	44	4	14	2	13	4	2	1	2	4	**90**	**36**	**27**	**19**	**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	8	4	2	1	1	1§	**65**					
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	-	1	-	-	-	-	-	**19**					
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, HTLV, 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.

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