Donor Haemovigilance

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Authors: Dr Lorna McLintock, Clinical Lead for Blood Donation, SNBTS
Dr Shruthi Narayan, SHOT Medical Director and Consultant in Donor Medicine, NHSBT
Dr Kathryn Maguire, Consultant in Transfusion Medicine, NIBTS
Dr Stuart Blackmore, Consultant in Donor Medicine, WBS
Sue Mackinnon, Lead Quality and Governance Nurse, WBS

With contribution from Dr Ibrahim Magzoub, NIBTS

Definition:

Donor haemovigilance refers to the systematic monitoring of adverse reactions and incidents during the blood donor's journey, with a view to improving donor experience and safety.

Serious adverse reaction: An unintended response in a donor or a patient associated with the collection or transfusion of blood or blood components that is fatal, life threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity (according to Article 3(h) of directive 2002/98/EC).

Key SHOT messages

- The overall incidence of serious adverse events of donation (SAED) remains low. The rate of SAED for 2020 in the United Kingdom (UK) was 0.22 per 10,000 donations
- Experience during the COVID-19 pandemic has shown that the UK Blood Services and the transfusion community work in an adaptive and collaborative way which is important in improving donation and transfusion safety
- Vasovagal events and bruising were more common in COVID-19 convalescent plasma (CCP) donors by both whole blood and plasmapheresis compared with regular whole blood and platelet donors

Abbreviations used in this chapter

ACE-2	Angiotensin converting enzyme 2
ACS	Acute coronary syndrome
AF	Atrial fibrillation
BP	Blood pressure
BSQR	Blood Safety and Quality Regulations
CCP	COVID-19 convalescent plasma
GP	General practitioner
JPAC	Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
RECOVERY	Randomised Evaluation of COVID-19 Therapy
REMAP-CAP	A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia
RTC	Road traffic collision
SAED	Serious adverse event of donation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SNBTS	Scottish National Blood Transfusion Service
UK	United Kingdom
VVR	Vasovagal reaction

NHSBT	NHS Blood and Transplant	**WB**	Whole blood
NIBTS	Northern Ireland Blood Transfusion Service	**WBS**	Welsh Blood Service
NICE	National Institute for Health and Care Excellence		

Recommendation

- The collection of a new blood component(s) requires a proactive adaptable whole system approach, including donor engagement and education, donor selection, donation process development and post-donation care procedure that includes adverse event recording and monitoring. Learning from the experiences during the pandemic must be incorporated to improve systems and processes

Action: United Kingdom (UK) Blood Services

Introduction

Blood donation is an uneventful experience for most donors, but as with any clinical intervention, there are associated risks. European legislation (European Blood Directives 2002/98/EC and 2005/61/EC) which has been subsequently transposed into UK law through the BSQR mandates that donors are made aware of these risks and that good governance processes exist to identify and mitigate risks, thus improving donor and donation safety. This chapter covers serious complications of blood donation reported in the UK in 2020 and, specifically, key aspects of CCP collections.

Serious adverse events of donation

UK Blood Services have implemented the 'Standard Surveillance of Complications Relating to Blood Donations' (Goldman et al. 2016) and individually record and monitor complications relating to blood donations referred to as adverse events of donation. SAED are those which either result in donor hospitalisation, interventions, significant disability/incapacity persisting for >1-year post donation or rarely death.

The UK Blood Services have ten reporting categories for SAED, and incidence rates are included in this chapter. The overall incidence of the SAED for the UK Blood Services from January to December 2020 was 0.22 per 10,000 donations, which has been stable for the last few years.

Assigning severity rating and imputability status (the strength of relation between donation and complication) is challenging, especially when information is incomplete, and some terms, such as long-term pain and/or disability, are subjective. There are currently no uniform objective criteria to separate levels of severity or imputability and there is considerable variation in how this is recorded (Land et al. 2018).

Recording imputability status for donor events, whilst not a mandatory requirement under BSQR, is assessed and documented for every SAED as follows:

- 3. Definite or certain link to donation
- 2. Probable or likely link to donation
- 1. Possible link to donation
- 0a. Link to donation unlikely
- 0b. Link to donation excluded

Occasionally, it is clear that the reported post-donation complication is unrelated or very unlikely to be related to the donation event itself. For example, a donor developing a complication relating to diverticulitis requiring admission within 24 hours of donation. Hence the risk of SAED in the UK is calculated using all reported cases in the first instance and in addition, the risk after excluding those that are clearly not related to donation, see Table 7.3.

Data

A total of 1,742,217 whole blood and component donations were collected by the 4 UK Blood Services in 2020. This is summarised in the Table 7.1 below:

Donations from 2020		NHSBT	SNBTS	NIBTS	WBS
Whole blood (including CCP from WB) donations	Donations from male donors	672,387	59,661	19,007	37,208
	Donations from female donors	699,770	76,349	19,821	43,745
	Donations from new donors	100,848	11,105	3, 201	9,433
	Donations from repeat donors	1,271,309	124,905	35,627	71,520
Apheresis (includes plateletpheresis and plasmapheresis)	Donations from male donors	88,823	6,945	3,340	2633
	Donations from female donors	11,115	621	343	449
	Donations from new donors	24,564	90	37	168
	Donations from repeat donors	75,374	7,476	3,646	2914
Total number of donations in 2020		**1,472,095**	**143,576**	**42,511**	**84,035**

Table 7.1: Cumulative donation data from the 4 UK Blood Services for the period January to December 2020

Table 7.2 summarises the number of SAED by category for all 4 UK Blood Services combined for period January to December 2020.

SAED category		Total number
01.	Death within 7 days of donation	0
02.	Hospital admission within 24 hours of donation	6
03.	Injury resulting in a fracture within 24 hours of donation (including fractured teeth)	10
04.	RTC within 24 hours of donation	2
05a.	Problems relating to needle insertion persisting for more than one year (this mainly includes suspected or confirmed nerve and tendon injuries)	17
05b.	Problems relating to needle insertion requiring hospitalisation/intervention (this mainly includes vascular complications)	0
06.	ACS diagnosed within 24 hours of donation	2
07.	Anaphylaxis	0
08.	Haemolysis	0
09.	Air embolism	0
10.	Other event	1
Total reported SAED in 2020		**38**

Table 7.2: SAED by category in 2020

Table 7.3 details the total number of whole blood and component donations and the total number of SAED reported for each of the 4 UK Blood Services for 2020. This equates to 0.22 SAED per 10,000 donations (irrespective of imputability) or 1 SAED per 45,848 donations. This is a very similar rate to the previous 4 years. Table 7.3 also gives a summary of total number of SAED excluding imputability scores of 0a, 0b for 2020.

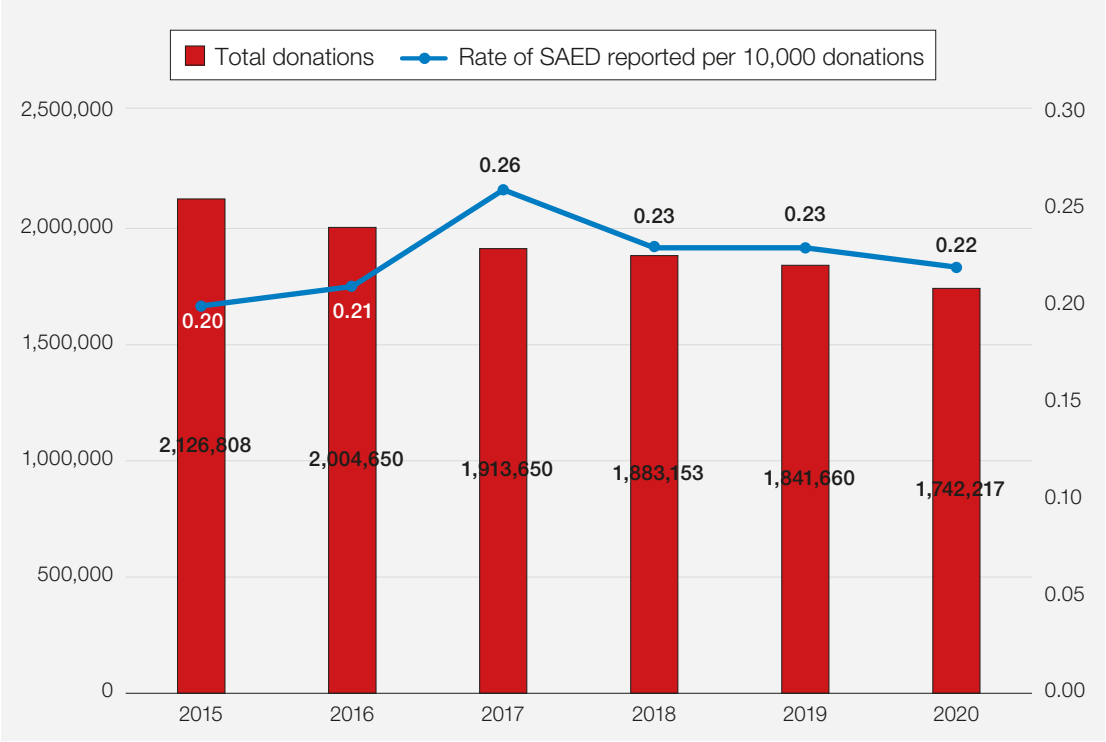
Table 7.3: Summary of total donations for the 4 UK Blood Services and total numbers of SAED for 2020

	NHSBT	SNBTS	NIBTS	WBS
Whole blood donations	**1,372,157**	**136,010**	**38,828**	**80,953**
Apheresis donations including CCP	**99,938**	**7,566**	**3,683**	**3,082**
Total donations	**1,472,095**	**143,576**	**42,511**	**84,035**
	Total donations in the UK: 1,742,217			
Total number of SAED in the calendar year 2020	**31**	**6**	**0**	**1**
Total number of SAED excluding those cases unlikely or not related to blood donation	**29**	**6**	**0**	**1**
Rate of total SAED per 10,000 donations in UK for 2020 (all submitted reports irrespective of imputability)		**0.22**		
Rate of SAED per 10,000 donations in UK for 2020 excluding those cases unlikely or not related to donation		**0.21**		

Comparison of trends with previous years

The rate of SAED has remained stable the last few years.

Figure 7.1: Rate of SAED reported per 10,000 donations in the UK from 2015-2020



Impact of the COVID-19 pandemic on donor haemovigilance and collection of COVID-19 convalescent plasma (CCP)

The 4 UK Blood Services have worked collaboratively to initiate CCP collection to support randomised clinical trials of patients seriously unwell with COVID-19 (REMAP-CAP and RECOVERY) in line with guidance from the 4 UK Chief Medical Officers (issued April 2020). These trials showed no benefit from treatment with CCP and collection stopped in March 2021 (The RECOVERY Collaborative Group, 2021). Each Blood Service took a different approach to CCP collection. This is described in Table 7.4.

CCP donations from 2020	NHSBT	SNBTS	NIBTS	WBS
Total	33,301	4,227	593	1,242
Plasmapheresis	33,301	1,321	47	71
Whole blood (WB)	-	2,906	556	1,171
Donor sex	M/F	M/F	M/F	M
Pre-assessment	Telephone/email and info on web	Telephone	Telephone	Face to face
Donors questioned about long COVID	Relevant questions included later	yes	yes	yes
Total number of SAED in the calendar year 2020	1	1	0	0
Rate of total SAED per 10,000 donations in UK for 2020 (all submitted reports irrespective of imputability)	0.5 per 10,000, double that of overall rate, possibly reflecting the fact that despite satisfying the donor selection guidelines, these are still patients following a recent COVID-19 infection			

Table 7.4: COVID-19 convalescent plasma collection by Blood Service

** At NHSBT, CCP collection by WB was done only on the initial collections (<100) to validate and finalise the collection, manufacturing, and testing process*

Donor selection guidelines

Chapter 3 of Guidelines for the Blood Services in the UK (JPAC 2018) states that only persons in good health shall be accepted as donors of blood or components for therapeutic use. COVID-19 challenged donor selection practices balancing the need to supply whilst ensuring donor safety. Donor haemovigilance was particularly important given donors were recovering from an emerging illness.

Donor selection guidelines were reviewed and updated regularly based on evolving information on COVID-19 to allow the rapid implementation of collection of CCP.

Adverse events in CCP donors

Adverse event data from UK Blood Services demonstrated that

- Feeling faint was more common in CCP donors than non-CCP donors for both whole blood and plasmapheresis donations
- Bruising was more common in CCP donors than non-CCP donors (plasmapheresis compared to platelet apheresis)
- 2 SAED in CCP donors (one ACS, 1 severe VVR) equating to an SAED rate of 0.5 per 10,000 CCP donations

CCP collections by apheresis were started across NHSBT early in the pandemic to support the clinical trials (REMAP-CAP and RECOVERY). Apheresis collections avoid unnecessary red cell loss in the donor and optimise the volume of plasma that can be collected. Cumulative data from NHSBT showed that approximately 12% of CCP attendances resulted in at least one adverse event, reported within 7 days of attendance. Donors experiencing an adverse event were more likely to be first-time donors. The risk of having any adverse event falls from 15% for first-time donors to 7% for repeat donors.

As CCP was also collected through whole blood donations (4,077 donations from SNBTS and WBS), comparison was possible between adverse events in CCP and non-CCP donors following whole blood donation. VVR were more common in CCP donors (vasovagal rate in CCP donors from SNBTS was 27.87 vs 13.39 per 1,000 attendances in non-CCP whole blood donors). The age profile was the same in both groups although there were a higher number of first-time donors in the CCP donor cohort (SNBTS 24% vs 8%). This highlights there was something different about the CCP donors compared to non-CCP donors. Adverse event data relating to CCP reported from NIBTS were small and have not been included in the comparison between CCP and non-CCP whole blood donors here.

The higher rate of VVR in these donors is likely to be multifactorial. Reasons for this may include increased donor anxiety or reduced nutrition following COVID-19. Other factors such as vasodilation,

vascular dysregulation, or subclinical cardiac dysfunction secondary to recent COVID-19 infection may be contributory. SARS-CoV-2 (the virus causing COVID-19) binds to the ACE-2 receptor, a key component of the renin angiotensin aldosterone system which regulates fluid and electrolyte balance, systemic vascular resistance, and blood pressure. ACE-2 is expressed on respiratory and gut epithelial cells but also on vascular endothelial cells where blockade (or downregulation) will cause vasodilation. Hypotension due to vascular dysregulation may result and could explain increased VVR rates.

The phenomenon of 'long-COVID' and evidence of persisting subclinical cardiac dysfunction in a proportion of patients may explain the higher incidence of post-donation hypotension in CCP donors irrespective of known confounding factors such as gender, new/repeat and collection method. Given that COVID-19 is increasingly recognised as a multisystem disease with cardiac, neurological and renal sequelae that can give rise to fatal vasoplegia in some people, it seems reasonable to hypothesise that something similar is happening in the systemic circulation resulting in increased rates of VVR.

The following caveats need to be considered when interpreting adverse events in CCP donors:

- While there was significant collaboration between the UK Blood Services, recruitment, donor assessment and collection methods differed between services and changed over time
- Staff familiarity and experience with CCP collection may have been limited initially but will have increased during the pandemic
- There is a higher proportion of new and returning donors amongst CCP donors, but this has changed with time
- The incidence of adverse events in CCP donors may be artificially high due to the low total number of donations compared to non-CCP donors

Case 7.1: Acute coronary syndrome in a new CCP donor

A first time CCP donor in his 50s who had last donated blood in 1993. The donor donated CCP by plasmapheresis 4 months after he was diagnosed and hospitalised with COVID-19. The donation was uneventful but the next day the donor experienced a brief episode of very sharp central chest pain and felt sweaty and 'not right' following exercise. He was admitted to hospital and diagnosed with acute coronary syndrome and sinus bradycardia. Aspirin, clopidogrel, ramipril, isosorbide mononitrate and simvastatin were commenced. The donor developed further similar symptoms while awaiting coronary angiogram. This demonstrated coronary artery disease for which angioplasty and stenting were performed. All symptoms subsequently resolved. The donor has been withdrawn from further donations.

Cardiac complications can occur in donors with pre-existing heart disease stressing the need for careful donor selection and a robust pre-donation assessment to identify risk factors. Around 20% of hospitalised COVID-19 patients have underlying cardiovascular disease (Zou et al. 2020). Acute myocardial injuries in patients with COVID-19 include acute coronary syndromes, arrhythmias, cardiac arrest, cardiogenic shock, cardiomyopathy, heart failure, myocarditis, pericarditis, and pericardial effusion (NICE 2020a). Common cardiovascular symptoms of ongoing symptomatic or post COVID-19 syndrome include chest tightness, chest pain and palpitations (NICE 2020b). A study of patients with COVID-19 (49% with mild or moderate COVID-19) showed 78% had evidence of cardiac involvement on biochemical or imaging markers and 60% of ongoing myocardial inflammation at 2-3 months independent of pre-existing conditions, severity or overall course of illness (Puntmann et al. 2020).

Careful assessment of donors recovering from COVID-19 is required, including consideration of cardiac symptoms, and is reflected in JPAC guidance recovery from coronavirus (JPAC n.d.).

Case 7.2: Delayed vasovagal reaction resulting in damage to donor teeth

A female donor in her 40s who had previously donated 20 times uneventfully had a delayed vasovagal reaction (faint) several hours post donation in the middle of the night when she got up. The donor had consumed alcohol and reported feeling 'quite tipsy' when going to bed. She had fainted whilst downstairs and was found by a family member with front two teeth damaged significantly needing

emergency dental surgery the following week. She was withdrawn from future donations.

A VVR is a general feeling of discomfort and weakness with anxiety, dizziness, and nausea, which may progress to loss of consciousness. Syncope, or transient loss of consciousness, is the major cause of immediate morbidity of medical significance during blood donation and is the most severe of a spectrum of VVR, which range from mild pre-syncopal symptoms to severe reactions involving syncope. VVR is associated with hypotension and relative bradycardia. VVR can result in an unexpected fall which can lead to injuries. The overall prevalence of VVR in whole blood donors is estimated to be between 1.4 and 7% (moderate reactions) and between 0.1 and 0.5% (severe reactions) (Amrein et al. 2012). VVR have significant implications not only for the welfare of donors but also staff time and training, the management of donor sessions and perhaps more crucially on the retention of donors and security of the blood supply (France et al. 2004).

Several factors, both physiologic and psychological can contribute to VVR. The reaction is generated by the autonomic nervous system and further stimulated by psychological factors and the volume of blood removed, relative to the donor's total blood volume. VVR that occur after the donor has left the donation session are of concern, due to the potential for the donor to come to harm (Kamel et al. 2010). These are delayed reactions and are a poorly understood complication of blood donation. They are thought to occur because of failure of the donor's normal compensatory reflexes to respond to the volume loss associated with donation. Inadequate fluid intake post donation, prolonged standing and high environmental temperature are recognised factors increasing the risk of a delayed VVR.

Many studies have shown that female gender is associated with VVR, both immediate and delayed, highlighting the gender differences in incidences of adverse reactions (Garozzo et al. 2010). Gender differences in autonomic functions are associated with differences in BP. There are also gender differences in the renin angiotensin system and the effects of bound angiotensin II type 2 receptor on renal vascular resistance. Renal sympathetic nervous activity is the main cause of vascular resistance in the evaluation of BP in female subjects.

Unlike immediate VVR, the risk of a delayed reaction is not significantly higher in first time, inexperienced and younger donors compared to experienced, regular, and older donors. It is possible that experienced donors become complacent about following advice to increase their fluid intake following donation, thereby increasing their risk of a delayed reaction.

Post-donation information must be provided to all donors. This should include the risk of delayed reactions and advice on maintaining post-donation fluid intake, and avoidance of known precipitating factors such as overheating and prolonged standing. The mechanism for delayed VVR remains poorly understood. Understanding the physiological basis of such reactions may lead to the development of appropriate interventions to reduce their likelihood.

Prevention is important as blood donors who experience VVR are less likely to give blood again (Eder et al. 2012). Reducing adverse events improves donor retention. Therefore, it is important to understand and prevent adverse events related to blood donation and to improve blood donation safety.

Case 7.3: Irregular pulse detected at a routine pre-donation check in a regular platelet donor

A male platelet donor in his 30s, with no history of cardiac issues, was found to have an irregular pulse rate on a routine pre-platelet donation check. The donor had donated upward of 25 whole blood and platelet donations uneventfully. He was not accepted for donation and was deferred pending further investigation. A preliminary diagnosis of AF was made by the GP and he was referred to a cardiologist.

AF is characterised by a rapid, irregular heartbeat and is the most common heart rhythm irregularity. The irregular cardiac rhythm can cause the formation of blood clots which increases the risk of stroke by fivefold (NICE 2019). The risk of a serious adverse event is also significantly increased should a donation take place whilst a donor is experiencing AF.

JPAC guidance states that, as a minimum, the pulse must be taken on entry to the apheresis programme (JPAC 2018). Pulse checks are undertaken prior to apheresis donations due to potential adverse cardiac effects of citrate. Following cardiology review it was concluded that the irregular pulse was due to sinus arrythmia and AF was ruled out, the donor was reinstated.

This case has been included to highlight the precautionary approach in selecting donors and the proactive approach taken in the UK Blood Services to ensure donor safety- this is especially relevant in the case of CCP donors who may have silent cardiac effects following COVID-19. A pre-apheresis donation pulse check on donors is a simple, cost-effective safety measure which identifies potential issues so that further specialist investigation and intervention can take place, thus protecting donor health and preventing serious adverse events.

Conclusion

The implementation of CCP collection increased collaboration across the UK Blood Services with regular reviews and shared learning. The identification of increased adverse events in CCP donors and emerging evidence on ongoing and post COVID-19 symptoms ('long-COVID') led to the expansion of the JPAC donor selection guidance 'recovery from coronavirus infection' in an attempt to defer donors with 'long-COVID'. It should be highlighted that these questions apply to all donors recovering from COVID-19 and not just CCP donors. A good donor haemovigilance system is vital in helping improve donor and donation safety. Effective public awareness campaigns on the importance of maintaining an adequate national blood supply, the continuing need for blood donors and safety of the donation process should be disseminated continuously, using different communication platforms to reach all segments of the population (WHO 2021).

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Figure 7.2: Serious Adverse Events following Blood Donation reported to the UK Blood Services in 2020