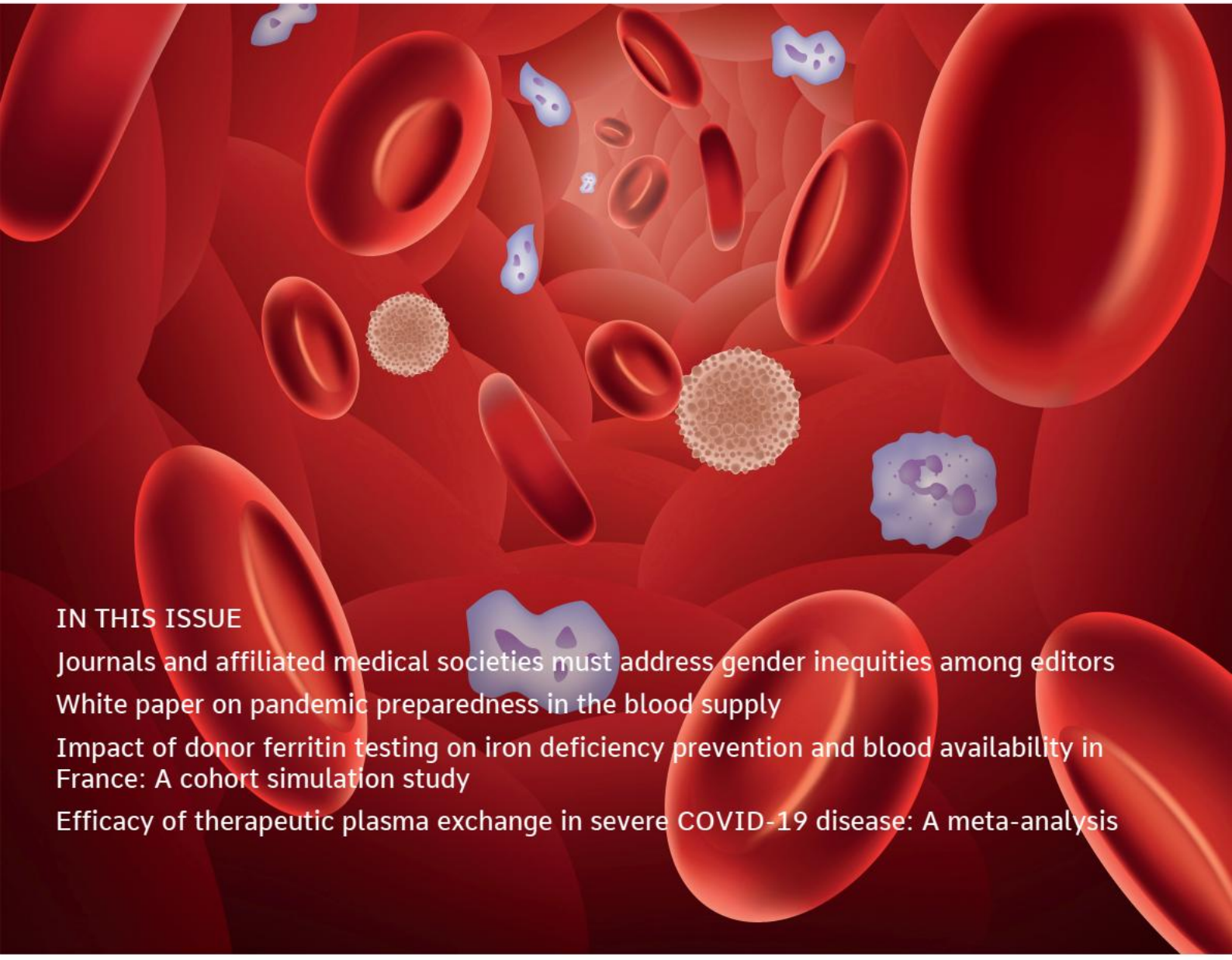
ISSN 0042-9007 (Print)
ISSN 1423-0410 (Online)

Volume 118 Number 12 DECEMBER 2023

Vox Sanguinis

The International Journal of Transfusion Medicine



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Official Journal of the International Society of Blood Transfusion

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Vox Sanguinis

International Journal of Blood Transfusion

Aims and Scope

Vox Sanguinis reports on all issues related to transfusion medicine, from donor vein to recipient vein, including cellular therapies. Comments, reviews, original articles, short reports and international fora are published, grouped into eight main sections:

1. Donors and Donations: Donor recruitment and retention; Donor selection; Donor health (vigilance, side effects of donation); Big data analysis and blood donation.
2. Blood Component Collection and Production: Blood collection methods and devices (including apheresis); Blood component preparation and storage; Inventory management; Collection and storage of cells for cell therapies; Quality management and good manufacturing practice; Automation and information technology; Plasma fractionation techniques and plasma derivatives.
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4. Transfusion Medicine and New Therapies: Transfusion practice, thresholds and audits; Transfusion efficacy assessment, clinical trials; Non-infectious transfusion adverse events; Therapeutic apheresis.
5. Haemovigilance: Near misses, adverse events and side effects throughout the transfusion chain; Monitoring, reporting and analysis of those adverse events and side effects; Activities aiming at increasing the safety of the whole transfusion chain; Standardization of the definition of adverse events and side effects.
6. Patient Blood Management: Caring for patients who might need a transfusion; Transfusion indication decision-making process; Search for the optimal patient outcomes; Study of transfusion alternatives; Autologous blood transfusion.
7. Immunohaematology: Red cell, platelet and granulocyte immunohaematology; Blood phenotyping and genotyping; Molecular genetics of blood groups; Alloimmunity of blood; Pre-transfusion testing; Autoimmunity in transfusion medicine; Blood typing reagents and technology; Immunogenetics of blood cells and serum proteins: polymorphisms and function; Complement in immunohaematology; Parentage testing and forensic immunohaematology.
8. Cellular Therapies: Cellular therapy (sources; products; processing and storage; donors); Cell-based therapies; Genetically modified cell therapies; Stem cells (sources, collection, processing, storage, infusion); Cellular immunotherapy (e.g., CAR-T cells, NK cells, MSC); Cell-based regenerative medicine; Molecular therapy; In vitro manufacturing of blood components.

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VOX SANGUINIS (Online ISSN: 1423-0410 Print ISSN: 0042-9007) is published monthly. Postmaster: Send all address changes to VOX SANGUINIS, Wiley Periodicals LLC, C/O The Sheridan Press, PO Box 465, Hanover, PA 17331, USA. For submission instructions, subscription and all other information visit: www.wileyonlinelibrary.com/journal/vox. Printed in the UK by Hobbs the Printers Ltd.

Vox Sanguinis (2023) **118**, 1025–1148

118/12/2023

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This journal is available online at *Wiley Online Library*. Visit wileyonlinelibrary.com to search the articles and register for table of contents e-mail alerts.

Received: 6 April 2023 | Revised: 1 August 2023 | Accepted: 17 August 2023

DOI: 10.1111/vox.13521

REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

Associated criteria used in investigating suspected septic transfusion reactions: A scoping review

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Funding information
Medical Affairs and Innovation, Héma-Québec, Montreal, Quebec, Canada; Mitacs Accelerate Program, Quebec, Canada, Grant/Award Number: IT17135

Abstract

Background and Objectives: Septic transfusion reactions (STRs) occur as a result of bacterial contamination of blood or blood products, resulting in sepsis. This scoping review aimed to identify, explore and map the available literature on the STR criteria triggering the investigation of STR.

Materials and Methods: Four electronic databases (MEDLINE, Web of Science, Science Direct, Embase) were searched to retrieve scientific literature reporting such criteria, published from 1 January 2000 to 5 May 2022. Grey literature was also searched from open web sources.

Results: Of 1052 references identified, 43 (21 peer-reviewed and 22 grey literature) met the eligibility criteria for inclusion and data extraction after full article screening. Of them, most (27/43, 62.79%) were found to report a single set of criteria, and only two reported four or more sets of criteria. The analysis of 66 sets of criteria collected from the selected references revealed 57 different sets. A few sets of criteria used only one sign and symptom (s/s) (12.12%, $n = 8$), whereas 16 sets used 7–15 s/s ($n = 16/66$; 24.24%). Of the total 319 occurrences of s/s associated with the 66 sets of criteria, post-transfusion hyperthermia, body temperature increase and hypotension were the most common s/s categories. Of all the literature available, only one study tested the diagnostic accuracy of the STR criteria.

Conclusion: This scoping review revealed a substantial variation in criteria used to identify suspected STR. Consequently, conducting further studies to enhance the diagnostic accuracy of these criteria, which trigger STR investigations, is imperative for advancing clinical practice.

Keywords

blood safety, criteria, risk factors, septic transfusion reactions, transfusion medicine

Highlights

- The criteria for triggering investigation of septic transfusion reactions (STRs) vary widely across the world.
- Post-transfusion hyperthermia, body temperature increase and hypotension were the commonly reported criteria that trigger the investigation of STRs.

Dilaram Acharya and Amaury Gaussen contributed equally to this work and share first authorship.

- Additional multi-centre studies are warranted to improve the diagnostic accuracy of the criteria for triggering STR investigations.

INTRODUCTION

Septic transfusion reactions (STRs) occur as a result of bacterial contamination of blood or blood products, resulting in sepsis. It remains one of the long-standing significant causes of transfusion-associated fatalities globally [1–3]. Recent data from North America, Europe, Africa and Oceania show that the transfusion-transmitted bacterial infection frequency ranged from 1:14,515 to 1:384,903 in transfused platelets, and from 1:96,850 to 1:3,448,275 in transfused erythrocytes in 2016 and 2017 [4]. In Canada, 0.8% (33/3957) of total adverse reactions reported following transfusion of blood or blood components between 2006 and 2012 were STRs [5].

Transfusion recipients can experience STRs even when well-known preventive measures such as appropriate donor selection, skin disinfection, diversion of initial blood collection, ongoing education and availability of up-to-date information regarding STRs to the related stakeholders are used [1, 6–8]. Control measures including sensitive screening tests, pre- and post-storage culture of blood components and post-transfusion culture of blood recipients have also contributed to confirming STR diagnosis but have limitations. STRs usually present a wide range of general clinical features such as fever, chills, generalized pain, tachycardia and hypotension and complicated conditions such as disseminated intravascular coagulation, shock and multi-organ failure leading to death [9]. Moreover, diagnosis and management of STRs have become difficult since many of these clinical presentations are also observed in several other diseases or non-infectious transfusion adverse reactions such as transfusion-related acute lung injury (TRALI), allergic/anaphylactic reactions, haemolytic transfusion and other infections [10–12]. Further, patient blood culture and blood component culture, when available, are usually carried out for passive reporting of suspected acute transfusion reactions, and in many cases, high rate of false-positive results are reported [10].

Varied criteria are employed to investigate STRs in different healthcare facilities, leading to the development of individual standards and procedures [10, 13]. This scoping review aimed to identify, explore and map the available literature on STRs. It is anticipated that the results of this review might be meaningful to policy makers, planners, researchers and other stakeholders to help identify precise STR criteria in the investigation of STR.

MATERIALS AND METHODS

Literature search strategy

Our study utilized electronic databases and grey literature searches. For scientific literature, we searched MEDLINE via PubMed, Web of Science, Science Direct and Embase via Ovid. Grey literature refers to scientific information not indexed in the mentioned databases. We conducted online searches on national or provincial health, blood, and haemovigilance authority websites. Additionally, we performed non-exhaustive internet searches using Google and Google Scholar search engines. Citations from scientific literature matching this definition were also explored. The search strategy was designed and executed during 3–4 November 2021, and updated twice: on 10 January 2022 and 5 May 2022. A further literature search was conducted from the reference list of all included studies. The following keywords were used to build queries launched on scientific databases: transfusion-associated; transfusion-transmitted; bacterial infection; contamination; septic transfusion reactions; sepsis; haemovigilance; signs; symptoms; prevalence; incidence; fever; temperature; chills; rigor; hypotension. Details of the literature search procedure are provided in Tables S1 and S2. In addition, the methodological details for this scoping review are available in our previously published study protocol [14].

Inclusion and exclusion criteria

We adhered to the Joanna Briggs Institute guideline for scoping reviews, using the population, concept and context definitions for inclusion. The population comprised subjects who underwent blood transfusion. The concept encompassed individual and collective criteria for investigating STRs, while the context included settings such as healthcare, haemovigilance and regional/provincial service facilities. We included all studies available in full text archived in electronic databases from 1 January 2000 to 5 May 2022, and grey literature from the same period, in English or French language, since analysis in both languages was possible in our team. Such a time frame was chosen arbitrarily for extensive literature collection while trying to limit gathering outdated data from older publications. The exclusion criteria were duplicate publications, studies without an outcome of interest, editorials, opinion pieces, letters and protocols.

Study selection and review management

We used the Preferred Reporting for Systematic Review and Meta-analysis-Scoping Review (PRISMA-SCR) [15] to compile the studies. Eligibility for inclusion was determined based on the topic, abstract and contents, with three authors (D.A., A.G. and A.L.) independently conducting the literature selection. In cases of disagreement, consensus was reached through discussion. To manage the search results, Endnote 20 (Clarivate Analytics, Philadelphia, USA) was employed. The study selection results based on inclusion and exclusion criteria are shown in the PRISMA flow chart (Figure 1).

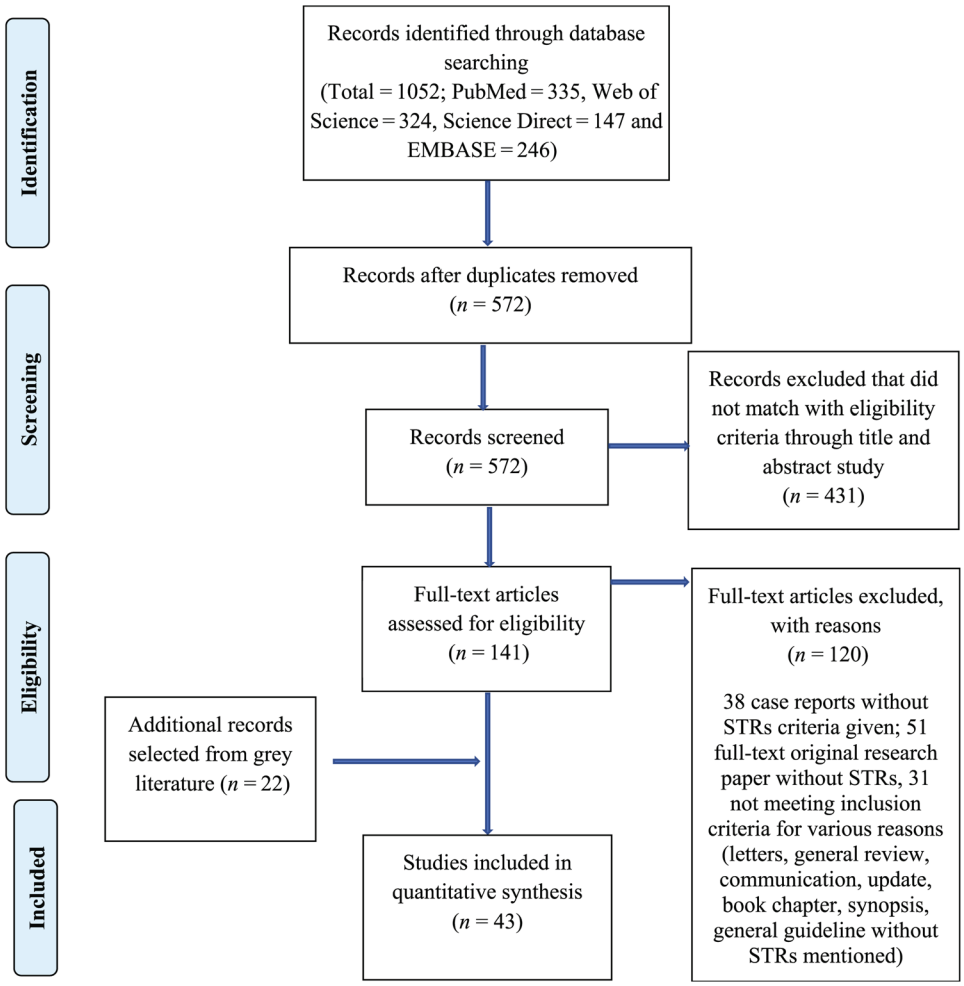

FIGURE 1 PRISMA flow chart for the selection of eligible studies on 5 May 2022. STRs, septic transfusion reactions.

Data extraction and presentation of the results

The descriptive information of each selected article has been included, such as author, study period, country of origin, population, blood components transfused, reported STRs, blood culture outcome and references. Data extraction was conducted logically and presented in the following order: (1) set(s) of criteria used in investigating STR; (2) occurrence of signs and symptoms (s/s) in each set of criteria; and (3) other characteristics of the selected literature (i.e., type and amount of blood components transfused, blood culture outcomes, reported incidence rates of STRs, and sensitivity and specificity of STR criteria and other relevant information based on the research questions). A reference, whether from grey or scientific literature, may list one or more sets of criteria. For example, two sets triggering culture for investigation could be (1) rise in temperature of 1°C or more and chills and rigours, or (2) hypotension and dyspnea. The number of sets of criteria per reference is given in Tables S6 and S7. The results of the included studies were provided in a tabular form with a narrative summary of all variables included as per the study objective and research question.

Criteria were translated using a Boolean algorithm triggering an investigation of STRs available from scientific and grey literature, as shown in Tables S3 and S4. Details of each of the criteria from scientific and grey literature, with the respective defining body, have been included in Tables S4 and S5, respectively.

RESULTS

Selection of scientific and grey literature

We retrieved 1052 scientific literature references, resulting in 572 hits after removing duplicates. From these, 431 articles were excluded based on title and/or abstract not meeting the eligibility criteria. The remaining 141 full-text articles were assessed, leading to the exclusion of 120 studies. Eventually, 21 scientific references from electronic databases and 22 additional records from grey literature were included based on the same criteria. In total, 43 records were included in this review (Figure 1).

Characteristics of selected studies

The detailed characteristics of the scientific literature are listed in Table S5. Of total of 21 articles, the majority originated from the United States ($n = 14$; 66.67%). The other references were from France ($n = 3$; 14.28%), Canada ($n = 2$; 9.52%), Iran ($n = 1$; 4.76%) and the United Kingdom ($n = 1$; 4.76%). Only one was in French language [16]. The reporting period of the STR criteria varied by article, the oldest being from 1987 to 1998 [17] and the latest in 2022 [18]. Red blood cells (RBC), packed red blood cells, granulocytes, platelets (single donor, pooled, apheresis, whole blood, pathogen reduced, and pre-storage pooled), plasma (fresh-frozen, cryoprecipitated, thawed) and reconstituted blood (RBC and plasma combined) were the transfused blood components reported in the selected literature. Out of 21 scientific studies, 12 (57.14%) reported blood components and recipients' blood culture concordance as a classification of definite STR imputability, but only Gauvin et al. detailed the s/s of a recipient with definite STR. Probable or possible STRs were reported in 10 references (i.e., 47.62%). Perez et al. [19] described the clinical presentation of cases of bacterial contamination associated with blood components but without distinguishing between possible and definite STR. Only one study reported the sensitivity and specificity of STR criteria [13]. Most scientific literature reported the incidence of STRs either in terms of rates or incidence rates per million events or both ($n = 16/21$; 76.19%) (Table S5).

Almost half of the references retrieved from the grey literature were from Canada and Australia ($n = 5/22$; 22.73% each), followed by France ($n = 4/22$; 18.18%) and the United States ($n = 3/22$; 13.64%) (Table S2). Of the references selected, 31.82% ($n = 7/22$) were in French.

Suspected STR criteria triggering investigation available from scientific and grey literature

Most of the selected references ($n = 27/43$; 62.79%) had a single set of criteria, defined as a single algorithm used to identify suspected cases of STR (Tables S3, S4, S6 and S7). Thirteen references ($n = 13/43$; 30.23%) reported two or three sets of criteria [17–29], whereas two references ($n = 2/43$; 2.33%) reported four or more different sets of criteria [13, 30]. Of the 43 references, 66 sets of criteria were counted. Several identical sets were identified among scientific and grey literature, resulting in the identification of 57 unique sets of criteria (Tables S6 and S7). The number of s/s in each set of criteria varied from 1 to 15, with only three sets including 10 or more s/s ($n = 3/66$; 4.55%), as shown in Table 1. Only 8 sets of criteria ($n = 8/66$; 12.12%) used only 1 s/s, whereas 16 sets used 7–15 s/s ($n = 16/66$; 24.24%). More than 62% ($n = 41/66$) of the sets used 1–5 s/s in their algorithm, which increased to more than 75% ($n = 50/66$) when the range was between 1 and 6 s/s. Nine sets of criteria included five or six s/s, representing the highest percentage (13.63%) (Table 1).

TABLE 1 Number of signs and symptoms associated with septic transfusion reaction by number of sets of criteria retrieved from electronic databases and grey literature.

Number of signs and symptoms	Number of set of criteria in scientific literature, *n* (%)	Number of set of criteria in grey literature, *n* (%)	Total number of set of criteria, *n* (%)
1	3 (10)	5 (13.89)	8 (12.12)
2	2 (6.67)	5 (13.89)	8 (12.12)
3	6 (20)	3 (8.33)	8 (12.12)
4	5 (16.67)	3 (8.33)	8 (12.12)
5	8 (26.66)	1 (2.78)	9 (13.63)
6	3 (10)	6 (16. 67)	9 (13.63)
7	1 (3.33)	5 (13.89)	6 (9.09)
8	1 (3.33)	4 (11.11)	5 (7.57)
9	0 (0)	1 (2.78)	1 (1.51)
10	1 (1.51)	0 (0)	1 (1.51)
>10	0 (0)	3 (8.33)	3 (4.54)
Total	30 (100)	36 (100)	66 (100)

The median number of s/s in references reporting only one set of criteria was 5, while it was 3 in references reporting two or more sets of criteria. The five most common s/s reported in the single set were hypotension-related s/s ($n = 27$ occurrences), rise in body temperature ($n = 24$), hyperthermia ($n = 22$), pulse-rate-related s/s ($n = 18$) and rigours ($n = 12$) (Tables S6 and S7). The three most common s/s reported in the references with two or more sets of criteria were also hypotension-related s/s ($n = 18$ occurrences), hyperthermia ($n = 18$) and rise in body temperature ($n = 15$), followed by dyspnea ($n = 12$), rigours ($n = 12$), chills ($n = 8$) and less commonly reported s/s including nausea/vomiting, syncope, headache, thoracic pain, back pain, digestive distress, abdominal pain, diarrhoea, myalgia, anxiety and other symptoms.

Differences were also observed in the timing of assessment of clinical triggers, ranging from 15 min or <24 h (Tables S3 and S4). A quarter of the sets of criteria mentioned s/s occurring until 24 h post transfusion ($n = 17/66$; 25.75%), whereas 34.85% had a time limit of 4 h or less ($n = 23/66$). Almost a third of the set of criteria ($n = 20/66$; 30.30%) did not mention such timing. Short observation periods, 90 min or less, were found in the references from 2001 to 2020. Observation periods until 24 h post transfusion were found in the references from 2005 to 2022.

We identified 62 formulations of s/s used to define the set of criteria associated with suspected STRs (Table 2). Hyperthermia was described in seven different ways from 38°C to more than 40°C. Body temperature increase was described in five different ways from more than 1°C to more than 2°C from baseline. Hypotension was mentioned with 15 different formulations and tachycardia with 6 different formulations. There were 320 s/s occurrences associated with STR criteria found from the selected references. Post-transfusion hyperthermia and rise in body temperature were the most common

TABLE 2 Signs and symptoms used to define set of septic transfusion reaction (STR) criteria associated with STR suspicion.

	Criteria occurrences in scientific literature		Criteria occurrences in grey literature		Total criteria occurrences	
Signs and symptoms	***n***	**%**	***n***	**%**	***n***	**%**
Hypothermia (<35°C)	0	0.00	1	0.52	1	0.31
Hyperthermia	15	11.63	27	14.14	42	13.13
>38°C	3	2.33	0	0.00	3	0.94
≥38°C	2	1.55	9	4.71	11	3.44
>38.5°C	0	0.00	1	0.52	1	0.31
≥39°C	7	5.43	9	4.71	16	5.00
>39°C	3	2.33	6	3.14	9	2.81
≥40°C	0	0.00	1	0.52	1	0.31
>40°C	0	0.00	1	0.52	1	0.31
Temperature increase	20	15.50	20	10.47	40	12.50
>1°C	5	3.88	1	0.52	6	1.88
≥1°C	5	3.88	8	4.19	13	4.06
2°C	0	0.00	2	1.05	2	0.63
≥2°C	6	4.65	6	3.14	12	3.75
>2°C	4	3.10	3	1.57	7	2.19
Hypotension-related signs and symptoms	23	17.83	27	14.14	50	15.63
Hypotension	11	8.53	14	7.33	25	7.81
Systolic blood pressure (SBP) 80 mmHg or lower	0	0.00	1	0.52	1	0.31
Decrease in SBP ≥ 30 mmHg	1	0.77	2	1.05	3	0.94
15%–25% or greater relative decrease from pre-transfusion SBP	0	0.00	1	0.52	1	0.31
Variation in arterial tension of ±30 mmHg	0	0.00	3	1.57	3	0.94
Decrease of blood pressure by 30 mmHg	2	1.55	0	0.00	2	0.63
Blood pressure increase or decrease of >30 mmHg	5	3.88	0	0.00	5	1.56
Variation of 30 mmHg in SBP within 4 h of transfusion	0	0.00	1	0.52	1	0.31
Isolated fall in SBP of 30 mmHg or more occurring during or within 1 h of completing transfusion	0	0.00	1	0.52	1	0.31
Fall in SBP of >30 mmHg	0	0.00	1	0.52	1	0.31
A SBP 80 mmHg or less in the absence of allergic or anaphylactic systems	0	0.00	1	0.52	1	0.31
Intervention required to maintain systolic blood pressure	0	0.00	1	0.52	1	0.31
Rise or fall in SBP	0	0.00	1	0.52	1	0.31
SBP < 80 mmHg and a drop ≥30 mmHg	1	0.77	0	0.00	1	0.31
(SBP ≤ 90 mmHg OR diastolic blood pressure ≤60 mmHg) AND (≥15% decrease in SBP OR diastolic blood pressure from pre-transfusion values)	2	1.55	0	0.00	2	0.63
Haemodynamic changes	1	0.77	0	0.00	1	0.31
Pulse-rate-related signs and symptoms	15	11.63	19	9.95	34	10.63
Tachycardia	4	3.10	5	2.62	9	2.81
Tachycardia: rise of >40 bpm (beats per minute) from pre-transfusion value	2	1.55	5	2.62	7	2.19
Tachycardia: rise of ≥40 bpm from pre-transfusion value	0	0.00	3	1.57	3	0.94
Tachycardia: ≥120 bpm from pre-transfusion value	0	0.00	2	1.05	2	0.63
Tachycardia ≥100 bpm and a 15% or more increase from the pre-transfusion value	1	0.77	0	0.00	1	0.31

(Continues)

TABLE 2 (Continued)

Signs and symptoms	Criteria occurrences in scientific literature		Criteria occurrences in grey literature		Total criteria occurrences	
	n	%	*n*	%	*n*	%
Tachycardia >120 bpm or a change of >40 bpm from pre-transfusion value	8	6.20	4	2.09	12	3.75
Respiratory-system-related signs and symptoms	5	3.88	18	9.42	23	7.19
Dyspnoea	5	3.88	11	5.76	16	5.00
Shortness of breath	0	0.00	1	0.52	1	0.31
Decreased oxygen saturation	0	0.00	4	2.09	4	1.25
SpO_2 (oxygen saturation) of 90% or less and a decrease of at least 5% from pre-transfusion	0	0.00	1	0.52	1	0.31
Intervention required to maintain SpO_2 (oxygen saturation)	0	0.00	1	0.52	1	0.31
General signs and symptoms	28	21.71	32	16.75	60	18.75
Chills	6	4.65	16	8.38	22	6.88
Rigours	14	10.85	11	5.76	25	7.81
Other general signs and symptoms (fever tremors on antipyretic medications or antibiotics; symptoms unspecified)	8	6.20	5	2.62	13	4.06
Neurological signs and symptoms (headache, anxiety, syncope)	1	0.77	5	2.62	6	1.88
Pain (abdominal pain, thoracic pain, back pain, myalgia, pain)	2	1.55	12	6.28	14	4.38
Gastrointestinal symptoms (nausea/vomiting digestive distress; diarrhoea)	6	4.65	10	5.24	16	5
End-stage signs and symptoms or other less commonly reported s/s	14	10.85	20	10.47	34	10.63
Cardiovascular collapse, haemoglobinuria/oliguria, renal failure, bleeding from IV sites, coagulation disorder, disseminated intravascular coagulation, hypertension	5	3.88	11	5.76	16	5
Shock	9	6.98	9	4.71	18	5.63
Total	129	100.00	191	100.00	320	100.00

categories of s/s (25.63%), followed by a cluster of general s/s, including fever, chills, rigours, tremors or patient on anti-pyretic medication with one of the listed s/s (18.75%) and hypotension-related s/s (15.63%). Those four categories accounted for 60% of all s/s occurrences. Less frequently occurring s/s associated with STR criteria were pulse-rate-related s/s (10.63%), such as tachycardia, and respiratory-system-related s/s (7.19%), such as dyspnea. The six most frequent single s/s were undefined hypotension (7.81%), rigours (7.81%), chills (6.88%), shock (5.63%), dyspnea (5%) and hyperthermia ≥39°C (5%).

DISCUSSION

This is the first review systematically mapping suspicion criteria for STRs from scientific and grey literature. Our research scope covered criteria defined by local and national health agencies, scientific societies and healthcare organizations in various countries, revealing the heterogeneity in criteria triggering an investigation of STR suspicion. This study uncovered that different healthcare settings and organizations have established and practiced their own sets of criteria with specific s/s used for investigating STR, resulting in a variety of protocols defined to trigger further investigations [10, 13, 21, 23, 27, 28, 31–33].

Interestingly, our search identified 66 (57 unique) sets of criteria used to suspect STR with associated s/s ranging from 1 s/s to a maximum of 15 s/s per set, leading to a total of 320 s/s occurrences associated with STR criteria. A wide range of s/s categories and formulations were found. This diversity exemplifies the possible complex combinations used to formulate an algorithm that is sensitive, specific and easy to use by the end users. The choice of only one set of criteria with several s/s (median of 5 s/s) or several sets with fewer s/s in each one (median of 3 s/s) can result in complex algorithms. When using only one set of criteria, the main pitfall is in possible too restrictive or too permissive algorithms depending on the selection of Boolean operators. Using different sets of criteria but fewer s/s enables the consideration of different categories of s/s but may result in complex formulations with potential confusion for healthcare service providers in clinical decision making.

The selection of the set of criteria is not free from limitations [13]. For instance, most of the criteria used are not validated, and their sensitivity and specificity are unknown. The lack of consensus on the definition or measurements of fever, hypotension or tachycardia may

explain the variety of s/s formulations [20]. Thus, some organizations have used or suggested criteria that lack quantitative definition, as already described [13], while others did not [18], with different impacts on culture rates. The nature of s/s was also highly variable, and criteria were selected inconsistently from hypo to hyperthermia, pulse rate as well as respiratory, neurological, gastrointestinal, general or end-stage-related s/s.

STR clinical triggers such as hyperthermia, increase in body temperature, hypotension, chills and rigours were the most common s/s. Changes in vital signs were characterized by dyspnea, shock and tachycardia (Tables 2, S6 and S7). A recent international survey conducted among 58 healthcare service providers from 39 countries reported that fever, tachycardia, rigours and hypotension were the most common clinical triggers of STR, which is in line with our review results [33]. Our work also revealed that some of the criteria reported in this review just showed only a single or two s/s. In the absence of specificity analysis, these sets of criteria may result in false-negative results. On the contrary, too broad criteria, represented by many optional s/s, may result in poor sensitivity if not appropriately selected and may give rise to increased false-positive results [34]. We also noted that out of the selected scientific papers, only one study reported the sensitivity and specificity of STR criteria to suspect STR caused by bacterial contamination of blood or blood products [13]. In that study, Shih et al. evaluated the sensitivity and specificity of American Association of Blood Bank (AABB) criteria triggering blood culture using a dataset aggregated from several partner hospitals but collating only one definite STR. Based on these results, they developed modified STR criteria to improve sensitivity, referred to as the Biomedical Excellence for Safer Transfusion (BEST) culture criteria when combined. BEST criteria tested against enriched datasets resulted in improved sensitivity compared to the AABB criteria but had less specificity. Previously, Hong et al. [10] evaluated the sensitivity and specificity of five sets of criteria, including the one selected by Centers for Disease Control and Prevention (CDC) [35], St. Jude Children's Research Hospital (SJCRH) [36], American Red Cross (ARC) [7, 37], Public Health Agency of Canada (PHAC) [28] and AABB [21] from STR data collected at the University Case Medical Center, Cleveland, OH, USA, between 2007 and 2013. AABB set of criteria gave the best results.

Another major highlight of this scoping review is about the period of observation for STR triggers, which was highly variable in the literature (between 15 min or less to a maximum of 24 h). Even though observation periods of less than 4 h were the most frequent (39%) among all periods reported, they were not exclusive to the oldest studies or bygone practices since they were also reported by recent studies. Short observation periods may be the cause of patients missing STR criteria if not associated with very specific s/s. Hong et al. already reported the importance of lengthy monitoring of patients receiving platelet transfusion [10].

Depending on the type of bacteria and the level of contamination of a blood product, the septic reaction of the recipient may manifest discreetly but could also lead to death. Since 1991, sepsis has been defined as generating a systemic inflammatory response syndrome (SIRS), and diagnostic criteria were expanded in 2001, but more than two decades later, the use of two or more SIRS criteria were considered inefficient to identify sepsis [38–40]. STR may be difficult to differentiate from non-infectious reactions. STR triggers overlap with many other ailments such as Febrile Non-Hemolytic Transfusion Reactions (FNHTR), allergic reactions, transfusion-associated circulatory overload, TRALI and febrile reactions [10, 41–44]. Furthermore, there are several factors to consider when deciding whether to culture blood components. Notably, a recent investigation carried out by Martin et al. [45] sheds light on further aspects that demand attention, encompassing the nature of the product, the patients' pre-existing medical condition and their reaction to the cessation of transfusion, among various other factors. Healthcare providers' clinical judgement for each individual case is therefore necessary with appropriate tools to trigger investigations and patient healthcare management. This makes a suspicion that STRs are not systematic. Moreover, STR reporting by passive surveillance has shown reduced efficiency compared to active surveillance [11], the former being less sensitive and specific than the latter [10]. Additionally, blood component culture is not done systematically even following the patient' blood culture. Patients under antibiotics can generate false-negative results, rendering STR confirmation more difficult. Therefore, definite STR, as defined by positive culture of the same pathogen from blood components and patient's blood, is very infrequent [13, 45–47]. As a consequence, STR may be underestimated by 10-fold [48] because of low detection and reporting. Many variables are thus likely to contribute to differences in STR incidence rates observed for one type of blood component.

Overall, it seems there is a discrepancy in the recognition and practices of STR triggers among clinicians and other related stakeholders [13, 45], which needs to be resolved with proven scientific criteria. Given the lack of consensus surrounding STR culture criteria in various healthcare settings globally, further evidence is essential to support supplementary recommendations. In this regard, an additional multi-centre follow-up study incorporating advanced statistical methodologies, such as mathematical modelling and Firth regression analysis, has the potential to enhance the diagnostic test accuracy of STR criteria. Such refined criteria would alleviate the burden of unnecessary additional investigations including culturing and specific intervention as well as the associated economic costs, while concurrently reducing instances of missed STR cases associated with poorly specified criteria and poor positive predictive values. Less underestimation of STR cases would focus attention and resources on the weakest links of the transfusion process to try to limit bacterial contamination.

Of the total 43 scientific and grey literature retrieved, most were from developed countries (Tables S2 and S5). While STRs are rarely reported, even in high-income countries the problems of quality of surveillance and reporting of STRs have been more challenging than in low- and lower middle-income countries due to deficiency in human resources, education, infrastructure, quality, standards and accreditation [49, 50]. Because active surveillance is a costly strategy for organizations, passive surveillance remains the best available option in the context of limited resources. While pathogen reduction technologies have successfully minimized the transmission of blood-borne pathogens during transfusions or through blood products, their application may be hard in resource-constrained settings. It is important to acknowledge

that these technologies are not suppressing risk, as highlighted by bacterial sepsis documented cases following pathogen-reduced platelet transfusion [51]. Ruby et al. have suggested not to generally culture pathogen-reduced platelets, with a goal to focus on investigation of transfusion reactions clinically significant and severe [18]. This balance between risks and the use of resources is a question of collective decision shared by all, but without a single answer applicable to all. Devising precise STR criteria may contribute to strengthening haemovigilance systems even in poor resource settings [52].

This study presents some limitations. Based on study methods, we have been able to map only the existing evidence but not provide a robust conclusion on which STR criteria is to be standardized. Owing to the range of scoping, from 2001 to 2022, we cannot exclude the possibility that some criteria reported in this review might no longer be in effect. However, this study has explored further research questions in the areas of STR and its management perspectives.

This scoping review showed that criteria triggering investigation of suspected STR vary widely. The most common STR clinical triggers were hyperthermia, an increase in body temperature and changes in vital signs characterized by hypotension, tachycardia and dyspnoea, with or without specific measurements. More general STR investigation triggers such as fever, chills and rigours were also frequent. The observation period for the clinical triggers of STR ranged from <15 min to 24 h. In addition, only one study reported the sensitivity and specificity of the clinical criteria associated with the suspicion of STR caused by bacterial contamination of blood or blood products. This study underscores the necessity of undertaking additional investigations focused on establishing more precise and standardized criteria, ultimately bolstering the diagnostic accuracy of STR. Such endeavours would effectively contribute to the detection of covert STRs, minimizing the need for superfluous culturing and the resulting costs incurred.

ACKNOWLEDGEMENTS

We are grateful and acknowledge the Medical Affairs and Innovation, Héma-Québec, Montreal, Quebec, Canada, and Mitacs Accelerate Programme, Quebec, Canada, for their support to this work. We would like to also extend our utmost appreciation to Dr. Nancy Dunbar for her invaluable feedback provided for this manuscript. This study received funding from Medical Affairs and Innovation, Héma-Québec, Montreal, Quebec, Canada, and Mitacs Accelerate Program, Quebec, Canada (# IT17135). T.G.P. is a member of the FRQS-funded CR-IUSMM.

D.A., T.G.P. and A.L. designed the study. D.A., A.G. and A.L. participated in the literature review process and wrote and edited the manuscript. All authors significantly contributed to the conception, writing and revision of the manuscript and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Acharya D, Gaussen A, Poder TG, Lambert G, Renaud C, Nawej K, et al. Associated criteria used in investigating suspected septic transfusion reactions: A scoping review. Vox Sang. 2023;118:1029–37.

Received: 24 August 2023 | Revised: 2 October 2023 | Accepted: 6 October 2023

DOI: 10.1111/vox.13548

COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

A norm for all seasons: Application of the ISO 14001 standard to manage the environmental impacts of transfusion

INTRODUCTION

The environmental crisis poses important risks to mankind, due to extreme weather events, famine and the expansion of infectious diseases [1]. These phenomena affect the transfusion community (TC), as they result in increased disease rates, requiring more blood, while hindering blood collection through the geographical spread of disease by pathogens, health impairment and mass migration [2–4].

The TC must adapt to this situation [5, 6], either from an ethical will to do its share in common challenges, as the healthcare sector is considered responsible for around 4.4% of global carbon dioxide emissions [7], or from self-interest: increasing energy and material costs, disruptions from natural catastrophes or supply chain breakdowns make adaptation to environmental change more profitable than ever.

While transitions to new work models can be cumbersome, in 2007, experts had already highlighted the economic benefits of climate adaptation and mitigation [8, 9].

Other environmental concerns exist, like the long-term toxic effects of chemical products used in transfusions. The European Union proposed regulation on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [10] to improve human health, preserve the environment from the risk posed by chemicals and support the competitiveness of Europe's chemical industry. Thus, one initiative will study the amount of DEHP (di (2-ethylhexyl) phthalate) released from plastics and degradation residues during the product's lifecycle and look for safer alternatives [11]. Transfusion waste products (i.e., discarded blood, especially when contaminated and improperly destroyed) are another concern as they pollute the ground and water sources. The WHO helped create a Biosafety and Waste Management for Blood Transfusion Guideline to address this problem [12].

Parallel to the urgency of this mission, the task of adapting to this challenge can be daunting because transfusionists have little experience here. To compound the problem, there is no specific, all-encompassing environmental legislation for transfusion.

Fortunately, ISO standards (International Organization for Standardization) can help manage the transition. ISOs are very useful for the TC as they help ensure patient safety, standardize practices, improve quality, regulatory compliance, manage risks, enhance traceability and foster international collaboration.

WHY ISO? WHY NOW?

ISO 9000 Standards for Quality Management Systems (QMS) implementation in the 80s–90s helped the TC navigate the HIV crisis [13]. Thanks to standardized QMS, technical improvements like HIV testing, molecular viral detection, leucocyte reduction, platelet photoinactivation and systems-wide digitalization were implemented seamlessly. Transfusion became safer, resilient and precise. This could be the case today for the ISO 14000 standard.

ISO 14000 is a family of standards designed to help organizations implement environmental management systems (EMS) for their operations [14] (see Data S1).

ISO 14000 is not a mandatory set of rules, but rather a collection of principles and actions to follow to implement thorough EMS. Once the implementation process ends, it can be certified by a third-party certification agency.

Put simply, environmental management relies on the three Rs: reduce, reuse and recycle. Obviously, this cannot be directly applied to transfusion and deserves deeper understanding and preparation.

Independent, self-reliant blood donation centres might be better suited to this adaptation. This does not mean that Hospital Transfusion Services cannot implement ISO 14000, but they might have to relate to a different kind of stakeholder and face an uphill road.

HOW ISO?

The process of ISO 14000 implementation resembles that of ISO 9000, being more straightforward if ISO 9000 is already implemented. Once the main stakeholders (board of directors, CEOs, etc.) approve the project, the implementation strategy usually starts by establishing a steering team and project leader. Their tasks include reviewing ISO 14000 and its applicability to the organization and the applicable environmental legislation.

Then, an environmental audit must be performed to identify environmental aspects of the transfusion process that could have an environmental impact or processes where environmental regulations are improperly followed.

Finally, a plan to manage environmental aspects and their impact, and to achieve environmental objectives, including corrective actions, must be established.

Environmental quality indicators must be defined, analysed and managed, introducing improvement initiatives. Ongoing risk monitoring is essential to ensure that potential issues are identified and addressed promptly. This includes identifying risks that could impact environmental quality objectives and developing plans to mitigate or manage those risks. An audit programme for indicators, objectives and EMS performance will be put in place, including management team audits to monitor compliance with the standard, internal policies and procedures related to EMS performance.

ISO 14000 relies on the continuous improvement cycle (Plan-Do-Check-Act). The organization must ingrain the standard into its operational culture, considering and managing the environmental impacts of its operations from then on.

Environmental objectives must be reviewed and redefined with each quality cycle. This is usually operated through expansion (increasing operational areas covered by the EMS), enrichment (increasing activities, processes, emissions, resources, etc., managed by the EMS) and upgradation (improving the EMS's structural and organizational framework, and knowledge accumulation in dealing with environmental issues).

Staff engagement is crucial, as they execute the environmental policy, are the best knowledge source on environmental aspects of operations, and spread culture change among blood donors, clinical users and suppliers.

RESULTS AND CAVEATS

Several initiatives arise from ISO 14000 implementation:

1. Easy-to-implement initiatives with immediate results (e.g., installing efficient light bulbs) are generally easy to measure.
2. Changes in operations may have to be made (e.g., reshaping blood drives to optimize fuel usage or waste disposal changes).
3. Long-ranging initiatives are more difficult to achieve and require time to implement, like encouraging suppliers (utilities, manufacturers, etc.) to implement green policies.

Some caveats that will appear:

1. Some initiatives are limited and can only be established once (i.e., buying electric vans for blood drives).
2. Some initiatives will not be easily measured, (i.e., implementation of environmental standards by suppliers).
3. The benefits may not be reaped by the transfusion facility implementing the change, but by the structure or organization they belong to (e.g., donation network).

The most effective measure to manage the environmental impact of transfusion is to optimize its use. Patient blood management (PBM) is a multidisciplinary approach adopted to limit the use and need for allogeneic blood transfusion in patients, aiming to improve their clinical outcomes. Thus, PBM can be a key ally in environmental management [15].

Research on the specific environmental needs of the TC is needed [16].

CONCLUSION

Transfusionists must answer the menace posed by catastrophic climate change, both for moral and economic reasons. Standard ISO 14000 is designed to help organizations implement their environmental policy. Transfusionists will be familiar with the standard's implementation process because of their culture of process management. Environmental management outcomes are evident outside and within the organization, resulting in better resource use in relation to blood components and materials, and regulatory compliance. We expect our experience can help other colleagues in this endeavour.

ACKNOWLEDGEMENTS

The authors thank the staff of the Banco de Sangre y Tejidos de Cantabria for their continuous support and highest performance in environmental protection.

I.R. and J.L.A. contributed equally to the design and preparation of this work.

FUNDING INFORMATION

The authors received no specific funding for this work

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. They have not received any compensation, financial or otherwise, to write this paper from any public, private or non-profit entities.

DATA AVAILABILITY STATEMENT

Data from our experience can be shared with any interested researcher.

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This Commentary reflects the authors' environmental concerns and experience with the application of ISO 14000 in the transfusion industry.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Romón I, Arroyo JL. A norm for all seasons: Application of the ISO 14001 standard to manage the environmental impacts of transfusion. Vox Sang. 2023; 118:1038–40.

Received: 2 June 2023 | Revised: 15 August 2023 | Accepted: 17 August 2023

DOI: 10.1111/vox.13523

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Relevance of haemoglobin monitoring in apheresis plasma donors: A retrospective cohort study in Québec, Canada

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Abstract

Background and Objectives: Systematically measuring pre-donation haemoglobin (Hb) levels might be overly cautious for apheresis plasma donation, since plasmapheresis entails a small loss of red blood cells. We explored the association between the frequency of apheresis plasma donation and capillary blood Hb levels.

Materials and Methods: This retrospective cohort study included donors who gave apheresis plasma at least twice between 24 October 2020 and 23 October 2022 in Québec, Canada. Results were stratified by sex and analysed with linear repeated-measure mixed models with random intercepts.

Results: In total, 9535 men (mean age = 46.7 years) and 9409 women (mean age = 41.1 years) made ≥2, but no more than 16 apheresis plasma donations. Over an average of 9.2 months of observation, men maintained Hb levels well above the Hb deferral threshold, and their Hb levels decreased by only 0.17 g/dL between the 1st and 15th donation return ($p < 0.0001$). Over an average of 9.0 months of observation, women also maintained adequate Hb levels, and their Hb levels decreased by 0.08 g/dL between the 1st and 15th donation return.

Conclusion: The frequency of apheresis plasma donation was not associated with clinically meaningful changes in Hb levels, neither in men nor in women. This evidence questions the relevance of systematically monitoring Hb for apheresis plasma donation, at least for donation frequencies of ≤7–8 times per year. However, an adverse impact of plasmapheresis on Hb levels cannot be ruled out for individuals donating more frequently or for longer than ~9 months.

Keywords

deferral, eligibility criteria, frequency, haemoglobin, plasmapheresis, safety

Highlights

- This study observed 9535 men and 9409 women who made ≥2, but no more than 16, apheresis plasma donations.
- The frequency of plasma donation was not associated with clinically meaningful changes in capillary blood haemoglobin (Hb) levels, either in men or in women.
- These results call into question the relevance of measuring Hb levels at each plasma donation, at least for donation frequencies of ≤7–8 times per year. However, an adverse impact of plasmapheresis on Hb levels cannot be ruled out for individuals donating more frequently or for periods longer than ~9 months.

INTRODUCTION

In most jurisdictions, haemoglobin (Hb) levels are measured before each donation to protect whole blood donors from anaemia, and those who do not meet the acceptable threshold are temporarily deferred. In Québec (Canada), low Hb levels (i.e., below 12.5 g/dL in women and 13.0 g/dL in men) account for nearly a third of all blood donation deferrals [1].

However, the relevance of systematic Hb measurement is less obvious for apheresis plasma donations. On one hand, plasma can be donated much more frequently than whole blood [2, 3], and the amount of red blood cells (RBCs) lost at each apheresis plasma donation varies according to the collection systems and procedures used (e.g., with vs. without saline rinses). In Québec, this cumulative RBC loss may be further compounded by the small whole blood samples collected for serum electrophoresis at the start of an apheresis plasma donation and every eight donations thereafter. On the other hand, plasmapheresis (even when frequent) entails a much smaller loss of RBCs than whole blood donation (WBD) and might not, therefore, cause or worsen anaemia in donors.

To the best of our knowledge, only three studies have evaluated whether apheresis plasma donation impacts Hb levels. Two found that Hb levels or haematocrit (Hct) were similar between plasma donors and non-donors [4, 5], including one in which Hct did not correlate with plasma donation frequency [4]. Another study found higher Hb levels in donors relative to non-donors [3]. Importantly, two of these studies had a cross-sectional design [3, 5], which is sub-optimal to infer causality based on retrospectively collected data.

The relevance of low Hb measurement is therefore not firmly established for apheresis plasma donation. If this practice is overly cautious, rationalizing its use might yield significant gains in terms of time, human resources and financial resources. To fill this knowledge gap, we conducted a retrospective cohort study to explore the association between the frequency of apheresis plasma donation and Hb levels.

METHODS

Data source and setting

Internal data from Héma-Québec (HQ)—the sole blood operator in the province of Québec (Canada)—were used. In 2021–2022, HQ collected ~119,000 apheresis plasma donations. Per HQ's donor eligibility criteria, candidate donors are deferred from giving plasma if their Hb levels are below 12.5 g/dL (for women) or below 13.0 g/dL (for men). Hb levels are systematically measured at each plasma donation. This criterion applies to all types of donations, whether it is plasma, whole blood or platelets. The minimum interval between plasma donations and subsequent WBD depends on the estimated red cell loss in the past 56 days. If ≥200 mL red cell loss was estimated during plasma donations over the last 56 days, the donor is deferred for 56 days. After a WBD, the temporary deferral for all donation types is 56 days for men and 84 days for women. The other eligibility criteria pertain to donors' health, age (i.e., ≥18 years) and risks for the safety of the blood supply (see [6] for additional details).

Besides data on exposure (i.e., apheresis plasma donation) and outcome (i.e., Hb levels), data on the number of previous donations, other types of donations (e.g., WBD), the date of each donation and demographics (e.g., age, sex) were available. This study did not collect any identifying information and hence did not require approval by an internal review board. All included donors consented that their data may be used for research purposes as part of the general blood donation consent.

Study design and study population

This was a retrospective cohort study that assessed the association between the frequency of plasma donation and donors' Hb levels among regular plasma donors in Québec, Canada. The index date was the date of the second plasma donation during the 2-year study period (i.e., 24 October 2020–23 October 2022). During this period, apheresis plasma was collected with a PCS®2 plasma collection system (Haemonetics, Massachusetts, USA). A saline rinse was given at the end of plasma collection, but only in large-volume donations (i.e., ≥721 mL). For a typical donation, the loss of RBCs is estimated to be ≤20 mL without a saline rinse and ≤2 mL with a saline rinse. Moreover, only 0.9% of RBC returns by saline rinse are unsuccessful, mainly due to moderate or severe reactions to anticoagulant or vasovagal syncope. Transmissible disease testing is performed on plasma drawn from the collection bag. However, a 10-mL whole blood sample is collected every eight donations to perform serum protein electrophoresis.

Donors were observed from the index date up to the earliest among the following: the date of their 16th apheresis plasma donation (i.e., the 15th donation return) or 23 October 2022. The observation period covered the 1st to the 15th donation return (i.e., the 2nd to the 16th donation) owing to the expected small sample sizes for frequency groups above 16 donations.

All persons who donated plasma at least twice during the observation period were included, except those with missing data on baseline Hb levels. Donors with a history of WBD were not excluded, but statistical analyses controlled for this potential confounder (more details in the following).

Study outcome and statistical analysis

The study outcome was capillary blood Hb levels, as measured by a routine fingerstick test assayed by a portable haemoglobinometer (HemoCue Hb 301 [HemoCue AB, Angelholm, Sweden]) before plasma donation. This instrument has a bias of −0.54 g/dL (coefficient of variation <1%) when compared with a laboratory reference test [7]. Hb levels were reported as a continuous variable (i.e., mean ± standard deviation [SD]). All Hb levels recorded throughout the study

period were included in the analysis, whether or not the donor was deferred because of low Hb levels.

Analyses were stratified by sex, since an interaction was found between sex and baseline Hb levels. Changes in Hb levels were modelled with linear repeated-measure mixed models with random intercepts, based on a participant-level analysis with fixed effects that controlled for the following covariates: baseline Hb levels (at the first donation), age, number of previous donations, number of WBD during the study period and gap (in days) between plasma donations. Compound symmetry covariance matrix was used to model the within-patient variance–covariance errors with degrees of freedom controlled using a Satterthwaite approximation to account for inexact *F*-distributions of the fixed effects in the repeated-measure mixed model. Pairwise post hoc tests were estimated using Tukey–Kramer adjustment for multiple comparisons. All analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

During the study period, 9535 included men made 69,898 apheresis donations, and 9409 included women made 54,529 apheresis donations. Of these donors, 104 (1.1%) men and 84 (0.9%) women were excluded from the analysis because of missing data on baseline Hb levels.

On average, men were aged 46.7 years at the index date, and women were aged 41.1 years (Table 1). Men had made more donations than women at any time before the index date (median: 18.1 vs. 7.1 donations). The Hb levels measured at the time of the first donation were higher among men than women (mean: 15.5 g/dL vs. 13.9 g/dL).

On average ± SD, included men were observed during 9.2 ± 6.4 months and included women during 9.0 ± 6.5 months. The vast majority of men (9219 [96.7%]) and women (9113 [96.9%]) made no WBD during the study period.

In men, 597 (6.3%) donors (who made 751 [1.1%] donations) were deferred because of low Hb levels. The observed mean Hb levels remained above the deferral threshold for men throughout the observation period (Figure 1 and Table S1). The predicted Hb levels decreased by 0.17 g/dL between the 1st and 15th donation return (i.e., between the 2nd and 16th donation), and this reduction became statistically significant starting from the 10th donation return (i.e., the 11th donation) (all $p < 0.0001$; Figure 2 and Table S1). Although statistically significant, these differences were not clinically meaningful through the first 16 donations.

In women, 1810 (19.2%) donors (who made 2246 [4.1%] donations) were deferred because of low Hb levels. The observed mean Hb levels remained above the deferral threshold throughout the observation period (Figure 1 and Table S2). The predicted Hb levels

TABLE 1 Donor baseline characteristics.

	Men ($N = 9535$)	Women ($N = 9409$)
Age,[a] years, mean ± SD	46.7 ± 17.1	41.1 ± 16.3
Number of previous plasma donations,[b] median (Q1–Q3)	3 (0–19)	0 (0–7)
Number of previous plasma donations,[b] mean ± SD	18.1 ± 34.2	7.1 ± 17.0
Gap between donations, days, median (Q1–Q3)	14 (7–35)	18 (8–49)
Hb levels,[a] g/dL, mean ± SD	15.5 ± 1.1	13.9 ± 1.0

Abbreviations: Hb, haemoglobin; SD, standard deviation.
[a]At the time of the first donation.
[b]Number of donations recorded at any time before the index date.

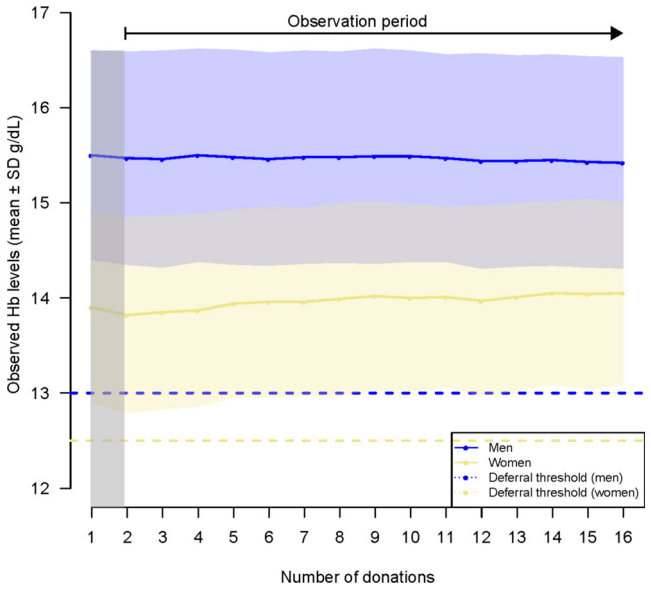

FIGURE 1 Observed haemoglobin (Hb) levels in men and women. SD, standard deviation.

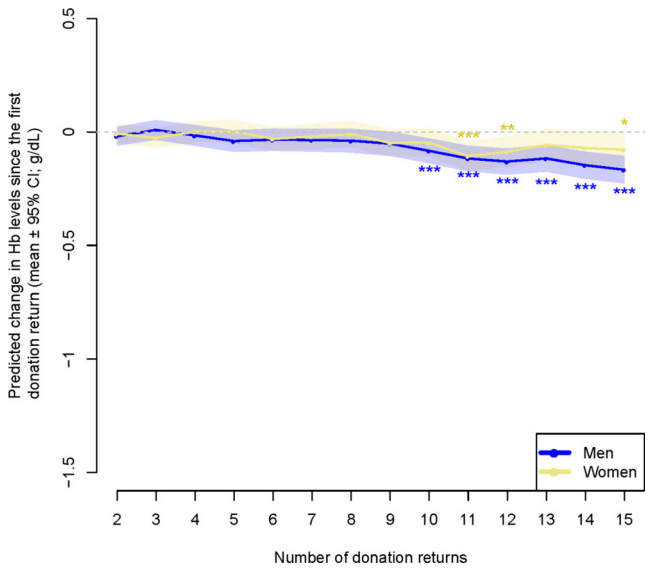

FIGURE 2 Association of plasma donation frequency with the predicted change in haemoglobin (Hb) levels since the first donation return, in men and women. CI, confidence interval. *$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.

decreased by 0.08 g/dL between the 1st and 15th donation return (i.e., between the 2nd and 16th donation) ($p < 0.05$), and the first statistically significant difference occurred at the 11th donation return (i.e., the 12th donation) ($p < 0.0001$; Figure 2 and Table S2).

DISCUSSION

In this large, retrospective cohort study, the frequency of plasma donation was not associated with clinically meaningful changes in Hb levels, at least for up to 15 return donations made over a 2-year period (i.e., 7–8 donations per year). In men, only ~1% of donations were deferred because of low Hb levels, and Hb levels modestly decreased with the frequency of apheresis plasma donation (albeit not to a level that may be clinically relevant). In women, more donations (i.e., ~4%) were deferred because of low Hb levels, but the reduction in Hb levels seemed too modest to underlie these deferrals.

These results build on those of other studies. In a retrospective cohort study ($N = 1254$) in the United States, Schreiber et al. found that mean Hct levels scarcely differed across plasma donation frequency groups [4]. Moreover, donation frequency and Hct levels were poorly correlated (i.e., $r < 0.03$) [4]. In a smaller ($N = 483$) cross-sectional study in Germany, Tran-Mi et al. found no clinically meaningful differences in Hb levels among non-donors and three plasma donation frequency groups (range across groups [mean]: 13.9–4.5 g/dL) [5]. In a cross-sectional study ($N = 43$ donors, $N = 5$ non-donors) in the United States, Li et al. found that plasma donors had higher Hb levels than non-donors (mean: 14.8 vs. 13.3 g/dL) [3]. However, this study had a small sample size and only included White, male donors aged 40–65 [3], which may limit the generalizability of these findings.

However, the donation frequencies analysed in our study (i.e., ~7–8 times/year) were much lower than those in the aforementioned studies. For example, in the Schreiber et al. study, donors in the high-frequency group had donated ≥70 times within a year [4]. Such donation frequency is possible in the United States (i.e., limit of twice every 7 days, or 104 donations per year) but not in Canada (i.e., limit of once every 6 days, or 61 donations per year) [8–10]. In the Tran-Mi et al. study, those in the SIPLA ('Study on Intensified Plasmapheresis') group had donated 35–38 times within a year [5]. Therefore, although plasma donation frequencies exceeding 7–8 times/year might also be safe with respect to Hb levels, such frequencies could not be explored in our study because of sample size limitations.

Based on our results and those of others, the relevance of monitoring Hb levels at each plasma donation appears questionable, at least for donation frequencies of ≤7–8 times per year. Because plasmapheresis impacts Hb levels only negligibly through the first 16 donations, it might be sufficient to monitor Hb levels occasionally. For example, Hb levels may be tested at the first plasma donation and every ~8 donations thereafter (i.e., at the same time as protein electrophoresis). Proceeding this way, an anaemic donor could be identified and deferred every eighth donation, and plasmapheresis would negligibly (if at all) impact any new-onset anaemia that could arise between two occasional tests. Such occasional testing could be carried out on the donation (i.e., after—and not before—blood collection), thereby allowing for a more robust laboratory measurement of Hb levels than what can be achieved with in-centre capillary Hb measurements [11]. In such a situation, the risk of collecting a plasma donation from an anaemic donor seems minimal and acceptable.

This study has several strengths. To begin, the sample size of our study (i.e., $N = 18{,}299$ when combining men and women) significantly exceeds those of previous studies (range: $N = 48$–1254) [3–5]. Moreover, our study accounted for the fact that many plasma donors also donate whole blood, and this variable was controlled for in the analysis. By contrast, most previous studies excluded whole blood donors [4, 5]. Furthermore, this was a cohort study in which each donor acted as its own control, which should better mitigate potential confounding than a cross-sectional study design.

However, our results must be interpreted in light of some limitations. To begin, the large sample size of our study was made possible by our study design, which allowed donors to give plasma or whole blood if and whenever they wanted to. However, this strength comes at the expense of a risk of confounding due to self-deferral. For example, some donors might self-defer from further plasma donations owing to symptoms of anaemia—in which case their Hb levels would not be captured by our study. However, because of the small RBC loss associated with plasma donation, this scenario appears unlikely. Another limitation is that our results might not be generalized to other centres that use different plasma collection systems and procedures, since blood loss varies based on the collection system and use of saline rinses (internal communication). Furthermore, the donation frequencies observed in our study were relatively low, and some individuals may donate regularly over much longer periods than just 9 months. Therefore, our results do not rule out the possibility that donating plasma more frequently and for longer might induce anaemia. Finally, as for any observational study, unobserved confounders may not be ruled out.

In conclusion, in this large, retrospective cohort study, the frequency of plasma donation was not associated with clinically meaningful changes in Hb levels, at least for moderate donation frequencies that did not exceed 7–8 times per year. This evidence questions the relevance of systematic Hb measurement for plasma donation, although an adverse impact of plasmapheresis on Hb levels cannot be ruled out for individuals donating more frequently or for longer than ~9 months.

ACKNOWLEDGEMENTS

This study was funded by Héma-Québec.

A.L. acquired, analysed and interpreted the data, wrote the manuscript and designed the study. A.L., M.G., C.R., N.R. and C.L. interpreted the data and reviewed the manuscript. Isabelle Rabusseau and Jessyka Deschêne assisted in the interpretation of the results. Medical writing assistance was provided by Samuel Rochette, an employee of Héma-Québec.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lewin A, Germain M, Renaud C, Robitaille N, Latour C. Relevance of haemoglobin monitoring in apheresis plasma donors: A retrospective cohort study in Québec, Canada. Vox Sang. 2023;118:1041–5.

Received: 25 July 2023 | Revised: 22 August 2023 | Accepted: 29 August 2023

DOI: 10.1111/vox.13530

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Insights into the diversity of blood donation practice across Asia: How blood collection agencies adapt donor criteria and processes to their population

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Funding information
Open access publishing facilitated by University of the Sunshine Coast, as part of the Wiley - University of the Sunshine Coast agreement via the Council of Australian University Librarians.

Abstract

Background and Objectives: Securing an adequate blood supply relies on accurate knowledge of blood donors and donation practices. As published evidence on Asian populations is sparse, this study aims to gather up-to-date information on blood donors and donation practices in Asia to assist planning and strategy development.

Materials and Methods: Ten blood collection agencies (BCAs) provided 12 months' data on donors who met eligibility criteria or were deferred, as well as details of their donation practices. Body mass index and blood volumes were calculated and analysed.

Results: Data on 9,599,613 donations and 154,834 deferrals from six national and four regional BCAs revealed varied donation eligibility and collection practices. Seven

used haemoglobin (Hb) criteria below the World Health Organization anaemia threshold. Seven accepted donors weighing <50 kg. Data collection on the weight and height of donors and on deferrals was inconsistent, often not routine. Deferred donors appear to weigh less, with corresponding lower estimated blood volume.

Conclusion: The diversity in eligibility criteria and donation practices reflects each BCA's strategy for balancing donor health with securing an adequate blood supply. Use of lower Hb criteria substantiate their appropriateness in Asia and indicate the need to define Hb reference intervals relevant to each population. We encourage routine gathering of donor weight and height data to enable blood volume estimation and local optimization of donation volumes. Blood volume estimation formulae specific for the Asian phenotype is needed. Information from this study would be useful for tailoring donation criteria of Asian donors around the world.

Keywords

Asia, blood volume, donor eligibility criteria, donor height, donor weight, donors and donation

Highlights

- There is diversity in donor eligibility criteria and donation practices across the 10 Asian blood collection agencies (BCAs) studied. Each BCA has tailored donor eligibility criteria and donation strategies to balance donor health with securing an adequate blood supply.
- We suggest that BCAs consider capturing weight and height routinely to facilitate local customization of donor eligibility criteria, thereby ensuring the health of blood donors, and to facilitate effective planning to meet blood supply demands.
- Further research is needed to determine haemoglobin reference values and blood volume estimation formulae specifically for Asians and subsequently for different Asian population groups.

INTRODUCTION

The World Health Organization (WHO) estimates that each year 117.4 million blood donations are collected globally [1]. Blood collection is shaped by wealth, as high-income countries collect 42% of donations though they comprise only 19% of the world's population [2]. Older adults often make up the largest blood user group in high-income countries, while anaemic children or pregnancy-related complications are the ones requiring transfusions in low-income countries. Advances in health care, reduced mortality at a younger age and economic prosperity have led to increases in both the proportion and the absolute number of older people in many populations. Thus, growing populations combined with longer life expectancy will place increased demands on blood supply [3]. Although there are global efforts to promote the judicious use of blood through patient blood management, this is still in its infancy [4].

In the Asian region, there are few published studies on blood donor characteristics as well as blood collection practices. Most of the published information is obtained from European, North American and Australian cohorts. A recent study in Japan has predicted a shortfall of blood availability if current donation behaviours continue [5], while another study has identified the need to increase donation frequency per donor to meet the demand [6]. In addition, as Asian people generally have a smaller body frame compared to Caucasians, they are likely to have a smaller blood volume (BV), which may impact donation practices [7–9]. This underscores major knowledge gaps on blood donors and donation practices in the Asian region, which accounts for 59.7% of the global population and where the population is also ageing. To address this knowledge gap, our objective is to gather accurate and current blood donor and donation data to support an evidence-based approach to meet blood sufficiency challenges in the Asian region. This study will also support recruiting practices for blood donors from immigrant Asian populations in other countries.

METHOD

An invitation to participate in this retrospective cross-sectional study of blood donor and donation practices was sent to 16 blood collection agencies (BCAs) across Asia. BCAs were asked to provide data for a

12-month period (2017–2020) prior to the COVID-19 pandemic. An Excel spread sheet was designed to capture the data for the study. The spread sheet was reviewed, tested and optimized by two well-established BCAs (Japan and Hong Kong) prior to being issued. The University of the Sunshine Coast Human Research Ethics Committee approved this study (A201359).

The analysed data are presented by mean, 95% confidence intervals, numbers and percentages as appropriate. Data were analysed in R version 4.0.3 (2020-10-10). Mean differences were analysed using analysis of variance (ANOVA) with post hoc Tukey honest significant difference ($\alpha = 0.05$). Donor height and weight were used to calculate the body mass index (BMI) (BMI = mass [kg]/height^2 [m]). Estimations on BV were generated using a web-based omni calculator [10] that applied the Lemmens, Bernstein and Brodsky formula [11], with the mean value for indexed BV in normal-weight adults being 70 mL/kg for males, and 65 mL/kg for females. This BV formula was selected because it accommodates a wide weight range. The estimated BV was compared with the WHO recommendation that the volume of blood donated should not exceed 13% of the total BV [12].

RESULTS

A total of six national BCAs (Hong Kong, Japan, Korea, Mongolia, Singapore, Taiwan) and four regional BCAs (Chandigarh in India [Chandigarh], University Malaya in Malaysia [Uni Malaya], the Eight Blood Collection Centre in Nakhonsawan Province, Thailand [Thai 8BC] and Sardjito Hospital in Yogyakarta, Indonesia [Yogyakarta]) participated in this study. All collected information on voluntary, non-remunerated donations. The range of data collected and subsequently provided by each BCA was varied.

Data on 9,599,613 donations and 154,834 deferrals were gathered from the 10 participating BCAs (Table 1). In 2020, five BCAs were classified as high-income, two as upper middle-income and three as low-to-middle income countries [13]. According to the human development index (HDI), seven BCAs were considered to have very high HDI (>0.800); Mongolia and Indonesia had high HDI and India had medium HDI [14]. The national male-to-female ratio was approximately 1:1 in all populations studied, but the sex distribution of blood donors in the BCA was different [15]. The age distribution of donors varied between sexes. Although close to 40% of Korea's national population is aged 50 years or more, it had the youngest cohort of donors with over 50% of both male and female donors aged under 30 years. Japan had the highest proportion of donors aged 50 years or more, followed by Taiwan and Thai 8BC. In Japan, Korea, Singapore, Taiwan, Chandigarh and Yogyakarta, the majority were male donors; only Mongolia had more female donors (62.6%).

Donor deferrals

Only seven BCAs had data on the age of donors who were deferred; the rate of deferrals ranged from 0.16% to 14.96% (Table 1). Over 70% of deferrals were female donors, with the exception of Taiwan (63.9%), and over 80% of female deferrals were aged under 50 years. Only 50% of BCAs comprehensively recorded the haemoglobin (Hb) of deferred donors, and as expected, the mean Hb of deferred donors was lower than that of those who donated (Table 2). The mean Hb of male donors in nine BCAs decreased gradually with age, with the exception of Mongolia. In contrast, in Hong Kong, Japan, Taiwan and Yogyakarta, the mean Hb of female donors increased around the fifth decade.

During the study period, Hong Kong deferred 15,878 females and 406 males, and collected some weight and height data (56.4% and 53.4%, respectively) (Figure 1a). In Taiwan, the Hb of whole blood (WB) donations was primarily assessed by the copper sulphate method and occasionally by a full blood count (FBC). Plateletapheresis donations were all assessed by FBC. Taiwan deferred 5.41% (111,707) of individuals attending donation venues based on low Hb. Complete data on Hb, height and weight were available on 340 female and 2109 male deferred donors in Taiwan, which enabled BMI and BV determinations (Figure 1b). Individuals, particularly females, who were deferred had lower body weight, BMI and estimated BV in both Hong Kong and Taiwan. Height and weight data from Japan, Hong Kong and Taiwan were used to calculate BMI and estimate BV (using the Lemmens, Bernstein and Brodsky equation [10]) (Table 3).

Donation practices

All BCAs were accredited by either national or international bodies (Table 4). The total number of tests conducted to minimize the risk of transfusion-transmissible infections (TTIs) ranged from 7 in Yogyakarta to 15 in Japan. All BCAs conducted the WHO-recommended screening for human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B surface antigen (HBsAg), hepatitis C and syphilis [12]. The next most common TTI test was human T lymphocyte virus (HTLV)-1/2 antibody ($n = 4$) and bacterial screening ($n = 4$). The five high-income national BCAs (Hong Kong, Japan, Korea, Singapore and Taiwan) conducted 10 or more TTI tests.

All BCAs collected WB and nine conducted plateletapheresis, but only five conducted plasmapheresis procedures. Details on the donation criteria of each BCA are provided in Table 5.

DISCUSSION

To our knowledge, this is the largest cross-sectional study of blood donors and donation practices in Asia with the participation of 10 BCAs. The data from over 9.5 million donations and 0.15 million donation deferrals of blood donors has provided us with a picture of the 'Asian blood donor phenotype' [9] (Table 1). The observed variability in donor eligibility criteria and blood donation practices across the 10 BCAs reflects the strategy each BCA has adopted to secure a safe and sufficient blood supply for their population.

TABLE 1 National statistics and age and sex distribution of donors who donated and those who were deferred.

World Bank income category[a]		Hong Kong HI	Japan HI	Korea HI	Mongolia LMIC	Singapore HI	Taiwan HI	India LMIC	Malaysia UMIC	Thailand UMIC	Indonesia LMIC
HDI[b]		0.949	0.923	0.922	0.745	0.939	0.923	0.642	0.806	0.802	0.709
National population (million)[c]		7.62	126.30	51.78	3.39	6.11	23.92	1416.00	33.37	70.36	280.69
Male (%)		47.30	48.70	50.10	49.40	50.40	49.90	51.60	50.70	49.10	49.90
Female (%)		52.70	51.30	49.90	50.60	49.60	50.10	48.40	49.30	50.90	50.10
National age distribution (%)	<20 years	10.34	5.53	16.97	13.28	5.94	5.29	3.12	11.94	11.01	4.98
	20–29 years	21.97	14.95	13.46	32.74	27.96	19.71	39.13	39.29	25.95	44.44
	30–39 years	23.58	16.81	13.91	21.12	28.31	23.92	34.03	25.99	22.66	22.97
	40–49 years	23.53	27.60	16.01	20.41	20.90	24.06	17.51	15.01	23.43	18.09
	50–59 years	16.61	25.31	16.58	12.14	13.39	19.97	5.78	6.99	16.12	9.26
	60+ years	3.97	9.79	23.06	0.30	3.49	7.05	0.41	0.78	0.84	0.25
		National BCA						Regional BCA			
Blood collection agency		Hong Kong	Japan	Korea	Mongolia[d]	Singapore	Taiwan	Chandigarh	Uni Malaya	Thai 8BC	Yogyakarta
Total donations (*n*)		234,495	4,812,307	2,435,210	25,889	125,102	1,833,310	49,795	21,591	41,504	20,410
Male donations (%)		50.99	71.87	73.63	37.39	67.65	62.83	97.39	59.90	44.53	78.67
Female donations (%)		49.01	28.13	26.37	62.61	32.35	37.17	2.61	40.10	55.47	21.33
Deferral (%)[e]		6.49	NAv	NAv	3.11	12.2	11.17	NAv	8.13	4.73	NAv
Male deferrals (%)[f]		2.49	NAv	NAv	29.81	10.76	36.07	NAv	5.34	10.54	NAv
Female deferrals (%)[f]		97.51	NAv	NAv	70.19	89.24	63.93	NAv	94.66	89.46	NAv
Male donation (%)	<20 years	8.03	4.46	16.80	4.40	4.41	3.88	3.10	9.36	10.70	4.08
	20–29 years	18.10	13.01	37.25	31.40	25.32	17.96	39.20	35.12	26.08	40.36
	30–39 years	24.35	16.88	17.61	27.83	29.32	24.80	34.13	28.54	20.68	25.12
	40–49 years	25.87	28.77	17.64	23.41	22.14	26.16	17.42	17.56	22.74	19.94
	50–59 years	18.80	26.43	9.08	12.51	14.76	20.35	5.73	8.36	18.53	10.22
	60+ years	4.85	10.44	1.61	0.44	4.06	6.86	0.40	1.06	1.26	0.29
Male deferrals (%)	<20 years	7.39	NAv	NAv	10.48	1.48	5.61	NAv	3.92	1.84	NAv
	20–29 years	16.50	NAv	NAv	33.06	18.03	19.52	NAv	15.69	10.60	NAv
	30–39 years	17.73	NAv	NAv	28.63	24.37	21.97	NAv	25.49	18.89	NAv
	40–49 years	27.09	NAv	NAv	21.77	22.21	23.93	NAv	26.47	26.73	NAv
	50–59 years	22.91	NAv	NAv	6.05	24.49	20.66	NAv	19.61	40.55	NAv
	60+ years	8.37	NAv	NAv	0.00	9.42	8.32	NAv	8.82	1.38	NAv

(Continues)

TABLE 1 (Continued)

Blood collection agency		National BCA						Regional BCA			
		Hong Kong	Japan	Korea	Mongolia[d]	Singapore	Taiwan	Chandigarh	Uni Malaya	Thai 8BC	Yogyakarta
Female donations (%)	<20 years	12.75	8.26	27.78	18.59	9.16	7.67	3.77	15.80	11.25	8.31
	20–29 years	26.00	19.93	34.42	33.54	33.50	22.68	36.85	45.51	25.84	59.51
	30–39 years	22.78	16.63	15.25	17.12	26.22	22.44	30.46	22.19	24.24	15.04
	40–49 years	21.09	24.60	14.64	18.62	18.30	20.51	20.69	11.19	23.99	11.28
	50–59 years	14.33	22.46	6.87	11.91	10.52	19.33	7.46	4.95	14.18	5.72
	60+ years	3.05	8.13	1.04	0.22	2.31	7.36	0.77	0.36	0.50	0.14
Female deferrals (%)	<20 years	12.77	NAv	NAv	18.32	10.20	9.25	NAv	10.07	8.03	NAv
	20–29 years	27.79	NAv	NAv	33.73	37.53	25.99	NAv	48.67	21.93	NAv
	30–39 years	24.90	NAv	NAv	19.18	26.72	25.65	NAv	24.00	26.11	NAv
	40–49 years	24.69	NAv	NAv	19.69	18.44	22.92	NAv	13.88	30.62	NAv
	50–59 years	8.36	NAv	NAv	9.08	6.06	12.01	NAv	3.10	13.08	NAv
	60+ years	1.49	NAv	NAv	0.00	1.05	4.18	NAv	0.28	0.22	NAv

Abbreviations: BCA, blood collection agency; HDI, human development index; HI, high income; LMIC, low-to-middle-income country; NAv, data not available; UMIC, upper middle-income country.

[a]Country Classification by Income FY 2021–2022 from World Bank (WB) accessed on 25 August 2022 [13].

[b]HDI from United Nations Human Development Reports accessed on 15 August 2023 [14].

[c]National population statistics from Countrymeter accessed on 14 June 2022 [15].

[d]In Mongolia, 35 female and 47 male donors were in their 60th year.

[e]Deferrals as percentage of all donors who attempted to donate.

[f]Deferrals by sex as percentage of all deferrals.

TABLE 2 Mean haemoglobin (Hb) (g/dL) level of donors who donated and those who were deferred by gender and age decade.

			Hong Kong	Japan	Korea	Mongolia	Singapore	Taiwan	Chandigarh	Uni Malaya	Thai 8BC	Yogyakarta
Male Min Hb (g/dL)			13.00	13.00	12.50	12.50	12.50	13.00	12.50	12.50	13.00	12.50
Mean Hb (g/dL)	Donations	All age groups	14.83	14.89	14.99	14.21	14.95	14.82	14.44	NAv	15.44	15.00
		<20 years	15.09	15.20	15.22	13.81	15.37	15.23	14.83	NAv	15.62	15.18
		20–29 years	14.96	15.17	15.14	13.91	15.21	14.99	14.51	NAv	15.62	15.06
		30–39 years	14.86	14.99	14.98	14.20	15.01	14.95	14.40	NAv	15.55	15.03
		40–49 years	14.77	14.89	14.77	14.38	14.83	14.84	14.21	NAv	15.35	14.93
		50–59 years	14.69	14.76	14.56	14.49	14.62	14.73	14.32	NAv	15.11	14.78
		60+ years	14.63	14.56	14.28	14.50	14.39	14.61	13.40	NAv	14.91	14.73
	Deferrals	All age groups	10.92	NAv	NAv	11.82	NAv	12.52	NAv	11.57	12.36	NAv
		<20 years	10.86	NAv	NAv	11.49	NAv	12.80	NAv	11.78	11.98	NAv
		20–29 years	10.94	NAv	NAv	11.68	NAv	12.42	NAv	11.34	12.33	NAv
		30–39 years	10.88	NAv	NAv	11.96	NAv	12.52	NAv	11.31	12.36	NAv
		40–49 years	10.98	NAv	NAv	11.98	NAv	12.54	NAv	11.56	12.42	NAv
		50–59 years	10.86	NAv	NAv	11.98	NAv	12.54	NAv	11.87	12.36	NAv
		60+ years	10.98	NAv	NAv	None	NAv	12.50	NAv	12.02	11.83	NAv
Female Min Hb (g/dL)			11.50	12.50	12.50	12.00	12.50	12.00	12.50	12.50	12.50	12.50
Mean Hb (g/dL)	Donations	All age groups	13.01	13.34	13.40	14.11	13.44	13.30	13.80	NAv	13.76	13.50
		<20 years	13.07	13.23	13.41	13.74	13.45	12.88	Few	NAv	13.70	13.42
		20–29 years	12.96	13.28	13.40	14.06	13.42	13.26	Few	NAv	13.77	13.46
		30–39 years	12.97	13.26	13.38	14.13	13.46	13.08	Few	NAv	13.77	13.55
		40–49 years	12.98	13.30	13.36	14.02	13.43	13.11	Few	NAv	13.76	13.59
		50–59 years	13.14	13.48	13.48	14.33	13.49	13.38	Few	NAv	13.76	13.67
		60+ years	13.17	13.49	13.44	13.00	13.47	13.57	Few	NAv	13.77	13.85
	Deferrals	All age groups	10.77	NAv	NAv	11.49	NAv	11.43	NAv	11.45	11.90	NAv
		<20 years	10.72	NAv	NAv	11.21	NAv	NAv	NAv	11.30	11.91	NAv
		20–29 years	10.81	NAv	NAv	11.32	NAv	11.38	NAv	11.48	11.92	NAv
		30–39 years	10.76	NAv	NAv	11.67	NAv	11.50	NAv	11.47	11.89	NAv
		40–49 years	10.72	NAv	NAv	11.73	NAv	11.36	NAv	11.31	11.88	NAv
		50–59 years	10.81	NAv	NAv	11.81	NAv	11.62	NAv	11.74	11.95	NAv
		60+ years	11.00	NAv	NAv	None	NAv	11.33	NAv	12.04	11.83	NAv

Note: Hb data was not available from Uni Malaya because Hb screening for donors was conducted by the copper sulphate method. Hb on deferred donors was not available from Japan, Korea, Singapore, Chandigarh and Yogyakarta.

Abbreviations: Few, mean not calculated because of small cohort (<100); Min, minimum; NAv, data not available.

Recent studies or reports on Asia give the anticipated challenges to meet future blood supply needs [16–19]. Indeed, these blood supply challenges are not restricted to Asia but are world-wide [3] and can be compounded by health endemics such as COVID-19. The recruitment and retention of eligible blood donors are central to meeting the demand, and this is impacted by global immigration

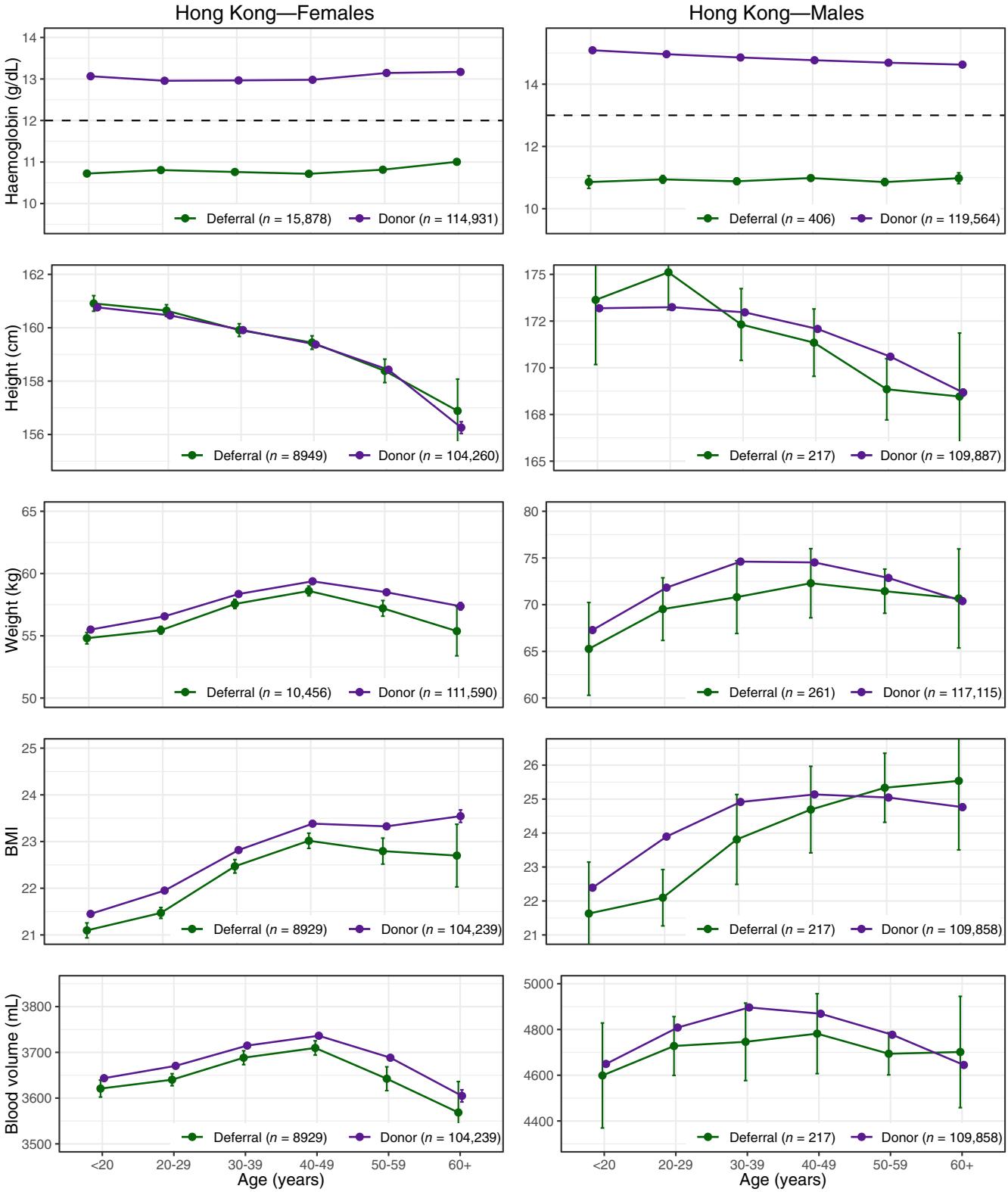

FIGURE 1 Haemoglobin (Hb), height, weight, body mass index (BMI) and blood volume estimates (mean and 95% confidence intervals) of (a) Hong Kong donors and (b) Taiwan donors who donated and those who were deferred due to low Hb. The means have been offset for easy visualization.

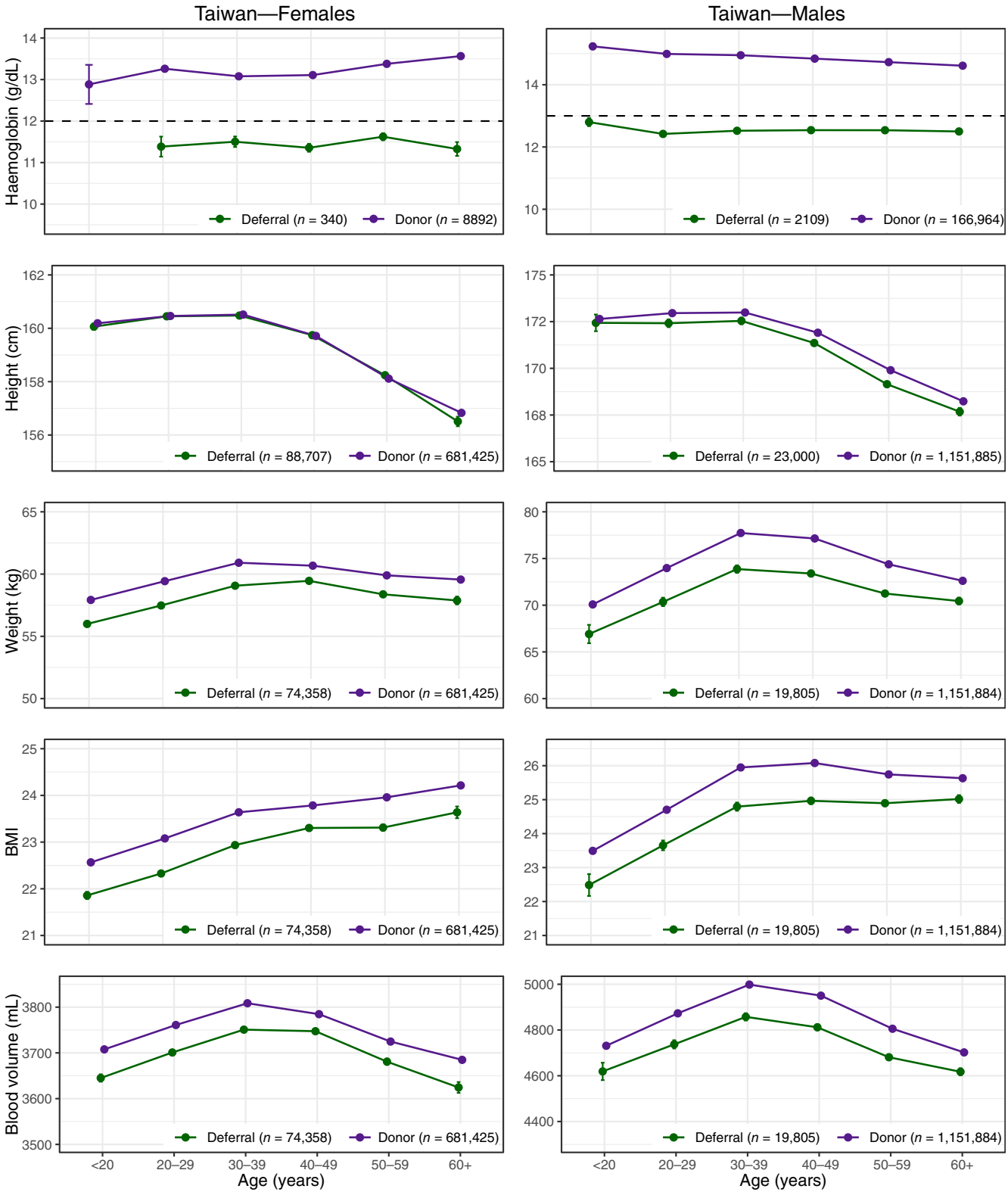

FIGURE 1 (Continued)

and travel, which have altered the ethno-racial characteristics of many populations. A number of European countries and the United States have recognized the difficulty of recruiting blood donors from immigrant populations, termed the 'missing minorities' [20] or 'minority donors' [21]. Thus, all BCAs must continually review their approaches to dynamically adapt their collection approaches to meet the current and future blood supply needs. The detailed donor and donation criteria information from the 10 BCAs (Table 5) allow other

TABLE 3 Comparing body mass index and blood volume of donors and deferrals.

Mean (SD)	Male				Female			
	Japan Donors	Hong Kong Donors	Deferrals	Taiwan Donors	Deferrals	Japan Donors	Hong Kong Donors	Deferrals	Taiwan Donors	Deferrals
Height (cm)	171.16 (5.78)	172.20 (6.10)	171.57 (6.57)	171.73 (5.85)	170.69 (6.06)	158.68 (5.24)	159.78 (7.34)	160.03 (5.57)	159.58 (5.33)	159.88 (5.30)
Weight (kg)	70.13 (10.76)	72.96 (11.46)	70.74 (12.48)	75.57 (11.54)	71.91 (11.20)	56.67 (8.61)	57.73 (9.70)	56.77 (9.40)	60.00 (9.89)	58.40 (9.29)
BMI	23.91 (3.29)	24.58 (4.54)	24.03 (4.04)	25.60 (3.50)	24.67 (3.49)	22.51 (3.29)	22.60 (3.62)	21.48 (3.43)	23.56 (3.70)	22.15 (3.48)
BV (mL) based on mean height and mean weight	4698 (447)	4820 (469)	4724 (488)	4893 (467)	4744 (458)	3635 (326)	3691 (367)	3629 (353)	3760 (360)	3669 (345)
BMI										
<20 years	22.21 (3.30)	22.39 (3.92)	21.63 (3.14)	23.49 (4.09)	22.49 (4.03)	21.54 (2.62)	21.45 (3.21)	21.10 (3.09)	22.57 (3.67)	21.86 (3.18)
20–29 years	23.27 (3.57)	23.90 (7.72)	22.10 (2.45)	24.70 (3.81)	23.65 (3.76)	22.01 (3.12)	21.95 (3.50)	21.47 (2.98)	23.08 (3.94)	22.33 (3.43)
30–39 years	24.06 (3.54)	24.92 (3.53)	23.81 (4.19)	25.95 (3.63)	24.79 (3.79)	22.70 (3.66)	22.82 (3.83)	22.47 (3.45)	23.64 (4.02)	22.94 (3.69)
40–49 years	24.29 (3.31)	25.14 (3.29)	24.69 (4.71)	26.08 (3.35)	24.97 (3.46)	22.80 (3.54)	23.38 (3.60)	23.02 (3.73)	23.78 (3.59)	23.30 (3.45)
50–59 years	24.08 (3.04)	25.05 (3.12)	25.33 (3.69)	25.74 (3.00)	24.89 (3.13)	22.68 (3.18)	23.33 (3.36)	22.80 (3.66)	23.96 (3.18)	23.31 (3.04)
60+ years	23.74 (2.70)	24.76 (3.97)	25.54 (3.36)	25.63 (2.87)	25.02 (2.99)	22.96 (2.93)	23.54 (3.42)	22.70 (3.13)	24.21 (3.05)	23.64 (3.17)

Abbreviations: BMI, body mass index; BV, estimated blood volume (using the Lemmens, Bernstein and Brodsky equation) [11]; WHO, World Health Organization.

Asian BCAs to compare and assess their own donor eligibility criteria. This information is also valuable where there is a desire or need to enhance recruitment of Asian blood donors in predominantly non-Asian populations.

The volume of blood that can be safely donated is directly related to the donor's BV, leading the WHO to state that the volume of WB donated or apheresis procedures (plasma, platelets or red cells collected) should not exceed 13% of the donor's BV [12]. Accurate BV measurements are difficult and invasive, requiring the infusion of an indicator (e.g., ^{51}Cr isotopes). This has led to the wide use of BV estimations such as Nadler's [22]. However, when traditional BV estimations such as Nadler's (1962) was compared with ^{99m}Tc red cell volume (RCV) measurements, the results showed that the traditional BV formula overestimated RCV because the BMI of the American population had increased [23]. The challenge to accurate BV estimation for Asians is further compounded by the fact that Asians have 3%–5% higher body fat than Caucasians [24]. As fatty tissue is relatively poorly perfused compared with lean tissue, this means that the use of such formulae on Asians will lead to an overestimation of their BV.

Factors determining BV include height, weight, body surface area and body composition [25]. Given the ease and feasibility of measuring weights, all BCAs have a minimum weight eligibility criterion. Data on donor height and weight (Table 3) enabled BV estimation, which found that generally donors are donating <13% of their BV [12]. Notwithstanding questions about the overestimation of calculated BV especially for the Asian phenotype, we tested the Lemmen's indexed BV estimation [11] on a scenario based on some Hong Kong parameters (Table 3). A female donor of mean height (160 cm) and minimum weight (41 kg) would have an estimated BV 3123 mL. If she donated 480 mL (450 mL WB and 30 mL samples), she would be donating 15.36% of her BV, which is above the WHO-indicated 13% [2]. Conscious of the lighter weight of some of its donors, Hong Kong collects a smaller volume of 380 mL (350 mL WB and 30 mL samples) from donors weighing 41–50 kg (Table 5). Similarly, in Japan females weighing 40–50 kg and males weighing 45–50 kg donate only 200 mL of WB, whereas Taiwan routinely collects 250 mL of WB and permits only donors weighing over 60 kg to donate 500 mL (Table 5).

Indeed, all 10 BCAs in this study have multiple strategies to safeguard donor BV, to avoid anaemia and create a positive donation experience which is crucial to securing repeat donations. In 80% of BCAs, lighter weight donors donate smaller volumes, 90% of BCAs limit the number of donations permitted annually and 4% also limit the total volume donated annually (Japan, Korea, Taiwan and Uni Malaya). These actions suggest that if BCAs could more accurately determine the BV of each donor, they would have the information to optimize blood donation volumes or even customize donation volumes. Hence, there is a need to establish BV estimation formulae specific to the populations in Asia, to enable a more precise definition of donor weight eligibility criteria.

A recent WHO report has revealed that low weight causes more deferrals in low-income countries, whereas low Hb is the main cause of deferral in high, upper-middle and low-middle income

TABLE 4 Screen positive rates (%) for transfusion-transmitted infections and accreditation bodies.

	National BCA						Regional BCA			
	Hong Kong	Japan	Korea	Mongolia	Singapore	Taiwan	Chandigarh	Uni Malaya	Thai 8BC	Yogjakarata
Number of tests (*n*)	11	15	10	8	10	10	8	7	9	7
HBs antigen	0.10	0.04	0.03	1.00	0.05	0.19	0.50	0.03	0.31	1.04
HBc antibody		0.21								
HBs antibody		0.11								
HCV antibody	0.01	0.09	0.10	0.70	0.01	0.08	0.50	0.09	0.20	0.47
HIV-1/2 antibody	0.00	0.06	0.10	0.00	0.01	0.06	0.05	0.02	0.08	0.16
HTLV-1/2 antibody	0.00	0.13	0.02			0.02				
HBV NAT	0.02	0.007	0.03	0.16[c]	0.06	0.102[c]	0.07	0.03	0.10	1.26
HCV NAT	0.01	0.002	0.00	0.01[c]	0.01	0.015[c]	0.025	0.09	0.00	0.18
HIV-1/2 NAT	0.00	0.001	0.00	0.00[c]	0.01	0.002[c]	0.0006	0.02	0.00	0.45
HEV NAT		0.079[a]							No data[d]	
West Nile virus NAT					0.00					
Zika virus NAT	0.00				0.005				No data[d]	
Cytomegalovirus	0.00	No data[d]								
Human parvovirus B19 Ag		0.10								
Treponema pallidum Ab	0.03	0.24	0.01	1.70	0.02	0.14	0.00	0.16	0.20	0.44
Trypanosoma cruzi Ab		0.017[b]								
Malaria (serology)			0.06				0.00			
ALT (liver enzyme)		0.68	0.85			0.33				
Bacterial screening	0.00[c]			2.08	0.02	0.009				
Accreditation body	AABB	GMP accreditation by Japan Pharmaceutical and Medical Devices Agency	Ministry of Health and Welfare & Ministry of Food and Drug Safety	Structural and Operational Standard of the National Center for Transfusion Medicine MNS 6647:2017; Laboratory Standard ISO 15189:2015; ISO 9001:2015 Standards of Quality management system; OHSAS 18001:2012 'International standard for occupational health and safety management systems'	AABB	ISO 9001:2015 (SGS UK Ltd); ISO 15189 (Taiwan Accreditation Foundation); PIC/S GMP (Ministry of Health and Welfare, Executive Yuan, Taiwan)	National Accreditation Board for Hospitals & Healthcare Providers, Quality Council of India	ISO 9001, MSQH	Management System Certification Institute (Thailand) and Bureau of Laboratory Quality Standard	Indonesian Ministry of Health

Note: Single testing with the exception of the following pooled testing: HBV, HCV, HIV-1/2 NAT in Mongolia and Taiwan; bacterial testing in Hong Kong and Singapore. Blank boxes indicate testing not conducted in the BCA.
Abbreviations: AABB, Association for the Advancement of Blood and Biotherapies; ALT, alanine aminotransferase; BCA, blood collection agency; GMP, good manufacturing practice; HBc, hepatitis B core; HBs, hepatitis B surface; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HTLV, human T lymphocyte virus; MSQH, Malaysian Society for Quality in Health; NAT, nucleic acid test.

[a]Data on only 5 months.

[b]Based on a small number of donors who met specific criteria.

[c]Pooled samples.

[d]Testing had begun but no data was available at the time of analysis.

TABLE 5 Donation criteria for whole blood, plateletapheresis and plasmapheresis.

		National BCA											
		Hong Kong		Japan		Korea		Mongolia		Singapore		Taiwan	
		M	F	M	F	M	F	M	F	M	F	M	F
Whole blood	Min age (year)	16		16		16		17		16		17	
	Max age (year) first donation	66		NA		64		NA		60		65	
	Max age (year) repeat donation	76		69		69		60		75		69[a]	
	Min weight (kg)	41		45		50		50		45		50	45
	Hb Min or range (g/dL)	13.0–18.0	11.5–16.5	13[b]	12.5[c]	12.5		12.5	12	12.5–18.5	12.5–16.5	13	12
	Systolic BP (mmHg)	160		90–190		90–180		ND		100–180		90–160	
	Standard vol. (mL)	450		400		400		400		450		250	
	Other vol. (mL)	41–50 kg small vol. 350 mL		45–50 kg small vol. 200 mL	45–50 kg small vol. 200 mL	<17 years small vol. 320 mL	<17 years or <50 kg small vol. 320 mL	First time, 17–19 years, ≤50 kg 350 mL	First time, 17–19 years, ≤45 kg 350 mL	45–49 kg small vol. 350 mL	45–49 kg small vol. 350 mL	>60 kg large vol. 500 mL	>60 kg large vol. 500 mL
	Max no. donated/year	5	4	3	2	5	5	6	4	5	5	NA	NA
	Max vol. donated/year (mL)	NA		1200	800	2160		NA		NA		1500	1000
Plateletapheresis	Min age (year)	18		18		17		18		18		17	
	Max age (year)	65		69	54	59		55		65		69[d]	
	Min weight (kg)	60		45	40	50	45	55	50	50		50	
	Systolic BP (mmHg)	160		90–180		90–180		ND		100–180		90–160	
	Hb Min or range (g/dL)	13.0–18.0	11.5–16.5	12	12	12	12	12.5	12.5	12.5–18.5	12.5–16.5	13.0–18.5	12.0–16.5
	Min platelet count ($\times 10^9$/L)	200		150		150		180		150		Single 150, double 250	
	Vol. collected (mL)	500		600		250		4–6 units		500		1–2 doses	
	Max no./year	24		12		24		12		12		24 (12 for 66–69 years)	
Plasmapheresis	Min age (year)	18		18		17		18		18			
	Max age (year) first donation	65		69		69		55		65			
	Min weight (kg)	60		45	40	50	45	55	50	50			
	Systolic BP (mmHg)	160		90–180		90–180		NA		100–180			
	Min Hb (g/dL)	13.0–18.0	11.5–16.5	12	12[e]	12		12.5	12	12.5–18.5	12.5–16.2		
	Vol. collected (mL)	500		600		500		500–600		600			
	Max no./year	24		24		26		16		12			

TABLE 5 (Continued)

		Regional BCA							
		Chandigarh		Uni Malaya		Thai 8 BC		Yogjakarta	
		M	F	M	F	M	F	M	F
Whole blood	Min age (year)	18		17		17		17	
	Max age (year) first donation	60		65		NA		NA	
	Max age (year) repeat donation	65		70		70		60	
	Min weight (kg)	45		45		45		50	
	Hb Min or range (g/dL)	12.5		12.5		13	12.5	12.5	
	Systolic BP (mmHg)	100–140		160		100–160		170	
	Standard vol. (mL)	450		450		450		350	
	Other vol. (mL)	45–59 kg small vol. 350 mL	45–59 kg small vol. 350 mL	NA		45–49 kg small vol. 350 mL	45–49 kg small vol. 350 mL	NA	
	Max no. donated/year	4	3	4	4	5	5	6	4
	Max vol. donated/year (mL)	NA		1800		NA		NA	
Plateletapheresis	Min age (year)	18		17				17	
	Max age (year)	60		65				60	
	Min weight (kg)	50		55				50	45
	Systolic BP (mmHg)	100–140		160				170	
	Hb Min or range (g/dL)	12.5	12.5	12.5	12.5			12	12
	Min platelet count ($\times 10^9$/L)	150		150				150	
	Vol. collected (mL)	3.0×10^{11}		4.8×10^{11} (double)				3.1×10^{11}	
	Max no./year	24		20				24	

Abbreviations: BCA, blood collection agency; BP, blood pressure; $CuSO_4$, copper sulphate; F, female; Hb, haemoglobin; M, male; Max, maximum; Min, minimum; NA, not applicable; ND, not done; RBC, red blood cells; vol., volume.

[a]65–69 years donate only 250 mL.

[b]Hb 12.5 < 13.0 g/dL donate 200 mL.

[c]Hb 12.0 < 12.5 donate 200 mL.

[d]Donors >65 years only single dose.

[e]Minimum Hb 11.5 if RBC indices are normal.

countries [26]. The age distribution of deferrals was different between females and males, with deferred donors being predominantly females (Table 1). Singapore's deferral rate is unusually high because donors with borderline low Hb levels are allowed multiple visits till they meet the Hb criteria. Generally, although the proportion of females who donated and those who were deferred are comparable under 50 years of age, the incidence of deferrals in older female donors is much lower. The data are consistent with a post-menopausal Hb increase, which explains the lower incidence of deferrals among older female donors. These results support our previous report that identified the potential contribution of older female donors to blood supply in ageing populations [27]. However, studies are needed to assess their iron profile to ensure that they have adequate iron stores. Conversely, data from among the six BCAs reveal that among male donors the number of deferrals peaks in the fifth decade (Table 1).

It is worth noting that six BCAs had male Hb thresholds below the WHO-recommended anaemia threshold of 13.0 g/dL, which is based on Caucasian populations (Table 2) [28]. The reasons for the lower donation Hb criteria are varied. In Mongolia, Chandigarh, Yogyakarta and Korea, 12.5 g/dL is required by the national policy of the respective Ministry of Health. Being Association for the Advancement of Blood and Biotherapies (AABB) accredited, the Singapore Blood Service followed its criterion of 12.5 g/dL. There is some recent information on Hb reference levels in the region. A 2014 Malaysian study defined a Hb reference interval of 13.5–17.4 g/dL for males aged <60 years and suggested that males wanting to donate with Hb < 13.5 g/dL should be disqualified [29]. Recently, a large Korean retrospective study of 1.7 million male participants, who were screened with exclusion criteria covering most causes of anaemia, clearly showed a decline in Hb among men after 30 years, similar to our observation in older male donors. The authors questioned the accuracy of the current lower cut-off at least for the Korean population, and they advocated for age-related reference intervals [30]. Collectively, this suggests that it might be time for BCAs to review their Hb criterion for blood donation using local and current haematology data.

Detailed data of deferred donors from Hong Kong and Taiwan allowed comparison with individuals who donated, and provided a valuable and unique insight (Figure 1a,b). Although there was no obvious height difference between individuals who donated compared with those who were deferred, there was a significant weight difference, and this difference was consistent across the age decades. This is significant because individuals with lower weight will have a lower BMI and BV. This highlights the importance of defining a population-appropriate minimum weight eligibility criterion for both male and female donors in each BCA. As a result, seven participating BCAs had minimum weights below 50 kg, unlike the 50-kg requirement of most Caucasian countries [31]. The fact that many of the donation criteria among the Asian BCAs do not align with those of the European Directorate for the Quality of Medicines and HealthCare of the Council of Europe [32] confirms the physiological differences between the Asian and non-Asian donor.

We know that blood collection is determined by the wealth of a country [2]. The HDI provides a more sophisticated measure, as it considers longevity, education and income. Countries with higher HDI often also have higher ageing rates. For example, high-HDI Japan has decreasing birth rates and increased ageing, hence the number of people requiring blood transfusion is increasing while the number of people who can donate is decreasing. In 2021, 65.8% of Japan's donors were aged 40+ years and only 18.4% were aged 20 or under. As a consequence, there is always a risk of blood shortage. As a result, donor recruitment in most developed countries is focused on younger donors, especially teenagers, because there is data showing that people who experience blood donation at a younger age tend to become repeat donors [33].

Blood use is the key determinant of blood sufficiency. Conscious of the global disease burden of iron deficiency, anaemia, blood loss and bleeding disorders, the WHO has advocated for the urgent implementation of patient blood management (PBM) as a vital framework to facilitate judicious use of transfusion only when clinically indicated [4]. PBM implementation among the participating BCAs is variable. For example, PBM was introduced to public health care in Hong Kong in 2018 but its practice is still inconsistent. Although National BCAs support PBM, they often have limited influence on PBM policy making or implementation because that is controlled by the hospital or heath authorities. In addition, BCAs are constantly looking for ways to secure adequate supply, for example, by increasing the donation age limit, increasing donation volume and increasing donation frequency. The donation criteria presented in Table 5 allows BCAs to identify possibilities of changes to in their own criteria. However, because most BCAs operate under and are stringently regulated by some form of governmental or legislative authority, any change has to be carefully substantiated. Therefore, for example, Asian BCAs seeking to increase the maximum donation age may benefit by consulting the Hong Kong and Singapore BCAs, which have higher upper age limits.

A key limitation of this study is that it is retrospective in nature. As the type and range of donor data routinely collected by each BCA is varied (e.g., four BCA did not routinely collect Hb data on deferred donations), this prevented a comprehensive comparison. Since there was limited capacity and no resources to collect additional data, this was considered a reasonable compromise for this study. These data gaps have, however, revealed the value of expanding donor and donation data collection so that each BCAs has evidence to review and refine their recruitment and collection strategies. It would be interesting to investigate the incidence of iron deficiency among donor deferrals; however, this was not possible because none of the BCAs routinely measured ferritin.

In conclusion, to our knowledge this is the first large multi-centre study to record and report on the diversity of donor eligibility criteria and blood collection practice among BCAs in Asia. Although there was 100% compliance with WHO recommendations for transfusion-transmitted agent testing, many BCAs did not apply the WHO anaemia definition [12] nor the Council of Europe guidelines [32]. The diversity of donor eligibility criteria suggests that over time, each BCA has defined criteria tailored to their donor population. This corroborates the reality of not a single 'Asian phenotype' but rather a range of different 'Asian phenotypes'. It highlights the need to define Hb

reference values and BV estimation formula specifically for Asians and subsequently for different Asian population groups. This study has shown that easily obtainable data such as weight and height are invaluable for BMI and BV determination. Therefore, we suggest that BCAs consider capturing this information routinely. These basic parameters are essential to enable BCAs to better determine donor eligibility criteria to ensure the health of blood donors and to effectively plan to meet their growing blood supply demands. This study lays the foundation for prospective blood donation cross-sectional studies across different regions of the world. Importantly, the knowledge generated by this study has global applications, as it provides evidence for BCAs in predominantly non-Asian populations wanting to recruit Asian donors to develop more ethnically appropriate donor eligibility criteria.

ACKNOWLEDGEMENTS

Y.L.F. conceptualized the study, supervised the project, curated and analysed the data, wrote the first draft and conducted final editing prior to submission. S.Y.K., C.K.L. and N.H.T. conceptualized the study and acquired data. R.D. developed the methodology and helped write early drafts. L.B.C. managed, curated and conducted data analysis. R. M.A., S.B., J.W.C., Y.Y.C., P.K., V.S.N., E.N., T.O., R.R.S., R.S., S.S., S. T. and T.T. acquired the data. All authors reviewed and edited the manuscript. Open access publishing facilitated by University of the Sunshine Coast, as part of the Wiley - University of the Sunshine Coast agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Fung Y-L, Alcantara RM, Cavalli LB, Chen J-W, Chen Y-Y, Donkin R, et al. Insights into the diversity of blood donation practice across Asia: How blood collection agencies adapt donor criteria and processes to their population. Vox Sang. 2023;118:1046–60.

Received: 4 June 2023 | Revised: 18 August 2023 | Accepted: 17 September 2023

DOI: 10.1111/vox.13541

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Physiological and psychological stress response of blood donors during the blood donation process

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Blood donation can be a potentially stressful event, leading to the activation of an acute stress response. Knowing and identifying potential stressors could help in optimizing the donation experience. The present study aimed to measure the physiological and psychological stress changes before, during and after blood donation.

Materials and Methods: Physiological and psychological stress response was assessed in 70 blood donors. To evaluate physiological stress response, pulse rate, respiratory rate, blood pressure (BP), beat-to-beat BP and lead II electrocardiogram were recorded. Baroreflex sensitivity was calculated using the available software. Psychological stress response was assessed using the State–Trait Anxiety Inventory scale.

Results: A significant increase in systolic blood pressure, diastolic blood pressure and mean arterial pressure was observed in the pre-donation period ($p < 0.001$). Among the time-domain parameters, SDSD (standard deviation of differences between adjacent respiratory rate intervals) and RMSSD (root mean square of the successive differences) were significantly lower during the post-donation period ($p < 0.005$, $p < 0.007$, respectively). Among the frequency-domain parameters, LF nu (relative power of the low-frequency band in normalized units), HF nu (relative power of the high-frequency band in normalized units) and LF% (relative power of the low-frequency band in percentage) were significantly lower before donation compared to during donation ($p < 0.001$, $p < 0.001$ and $p < 0.012$, respectively). LF nu, LF% and LF/HF ratio were also significantly lower during donation compared to after donation ($p < 0.05$, $p < 0.016$ and $p < 0.042$, respectively). Baroreflex sensitivity was also statistically higher during the pre-donation period. State score was significantly higher among the blood donors during the pre-donation period.

Conclusion: Physiological and psychological stress is experienced by blood donors during the pre-donation period. A pre-donation informative conversation should be carried out with each blood donor and potential stressors should be identified in each.

Keywords

blood donation, physiological stress, psychological stress

Highlights

- A physiological stress response was observed in blood donors. In the pre-donation period, there was an increase in systolic and diastolic blood pressure, an increase in baroreflex sensitivity and a decrease in frequency-domain parameters. In the post-donation period, a decrease in time-domain parameters was observed.
- A psychological stress response, namely a significantly higher state score on the State–Trait Anxiety Inventory Scale, was also observed among the blood donors.
- Some differences were observed between first-time donors (FTD) and repeat donors (RD): in the pre-donation period, the state anxiety score was significantly higher in FTD ($p < 0.001$). In the post-donation period, pulse rate was significantly higher in FTD compared with RD.

INTRODUCTION

Blood donation is a safe procedure and is mostly associated with positive feelings of satisfaction and wellbeing. The volume of blood lost during donation leads to activation of baroreceptors in the aortic arch and carotid arteries, leading to the stimulation of the sympathetic nervous system. This results in increase in heart rate (HR) as well as the contraction of veins and arterioles in the muscles and skin bed. This compensatory physiological response helps in maintaining the cardiac output following blood donation.

At times, blood donation can be a potentially stressful event for the donor, leading to the activation of acute stress response. Investigating the physiological and psychological stress responses can help us to understand and reduce side effects to a minimum as well as formulate targeted risk reduction strategies. Physiological stress responses comprise an increased HR or pulse rate (PR) and increased systolic blood pressure (SDP) and diastolic blood pressure (DBP). Heart rate variability (HRV), pulse rate variability (PRV) and baroreceptor reflex are often used to determine the autonomic activity during physiological stress [1]. HRV can be further analysed in the time domain or the frequency domain. Baroreceptor reflex plays an important role in the maintenance of circulatory haemostasis. Quantification of baroreceptor reflex as baroreflex sensitivity (BRS) is a validated tool for assessing autonomic function [2].

Because of the unfamiliarity of situations and various other factors, blood donors can also experience psychological stress, which includes feelings of emotional stress such as increased levels of anxiety, fear or tension. Stress levels are known to increase immediately before venipuncture [3]. Anxiety related to blood donation can be assessed using the State–Trait Anxiety Inventory (STAI-Y), a 40-item scale. It allows the self-reporting of the state anxiety levels, with total scores ranging from 20 to 80 [4].

Studies have been conducted in the past to investigate the physiological and psychological stress response in individuals undergoing blood donation but with variable results [5–8]. We hypothesized that physiological and psychological stress levels vary in different phases of blood donation, that is, before donation, during donation and after donation. Thus, in the present study we aimed to measure the physiological and psychological stress changes before, during and after blood donation. We also compared these changes among first-time donors (FTD) and repeat donors (RD) of blood.

MATERIALS AND METHODS

This prospective observational study was conducted in a tertiary care hospital from March 2021 to August 2022 after approval from Institutional Ethics Committee (GMCH/IEC/2020/537/101). Blood donors who approached the blood centre for in-house blood donation and were eligible to donate whole blood as per the donor selection criteria laid down by the National Regulatory Authority were included in the study [9]. Blood donors donating blood in outdoor blood donation camps and all in-house allogeneic whole blood donors who were hypertensive, were diabetic, had hypo/hyperthyroidism or were on medication for the above or for anxiety disorders were excluded from the study. A total of 70 blood donors were enrolled using purposive sampling after obtaining informed consent. Depending on the donation frequency, blood donors were divided into FTD and RD. Donor demographic details and detailed donor history were recorded on a pre-structured proforma.

Data acquisition

Physiological stress response

For assessment of physiological stress response, blood donors were directed to a separate quiet room. They were asked to rest in a lying-down position for at least 15 min. Subsequently, PR and blood pressure (BP) measurements were performed using a manual sphygmomanometer. Beat-to-beat BP and lead II electrocardiogram (ECG) were recorded for 10 min before donation, during blood donation and was continued for 10 min after blood donation. Beat-to-beat BP was recorded non-invasively by the 'volume clamp' method of Penaz with finger plethysmography using a Finometer (Finapres Medical Systems, The Netherlands). Graphical waveforms of brachial arterial pressure on a beat-to-beat basis were obtained. Lead II ECG was recorded using the Lab Chart Pro 7 software (AD Instruments, Australia) at a sampling rate of 1 kHz and a band-pass filter between 0.5 and 35 Hz.

For all blood donors, 350 mL double blood bags (Terumo Penpol, Thiruvananthapuram, India) were used to collect whole blood.

Psychological stress response

For assessment of psychological stress response, each eligible blood donor was administered the STAI-Y scale twice, that is, before the start and at the end of donation. The initial scale was administered before the blood donor was shifted to the quiet room, and for post-donation assessment the scale was applied 10 min after donation. The scale consists of 40 self-report items on a 4-point Likert scale and measures both the temporary condition of 'state anxiety' and the more general and long-standing quality of 'trait anxiety'. Each type of anxiety has its own scale based on 20 different questions that are scored. Scores range from 20 to 80, with higher scores meaning greater anxiety [4].

Figure 1 provides a detailed overview of the study procedure.

Analysis of data

Heart rate variability

Short-term HRV was analysed using a 5-min lead II ECG recorded while the subjects were at rest. Lab Chart Pro 7 software was used to analyse the ECG signals and extract the respiratory rate interval (RRI) data. Nevrokard software was used to calculate the different parameters of HRV in the time and frequency domains. In the time domain, the mean value of time intervals between successive pulse peaks (RRIs) was calculated, which was further used to determine the RR interval, standard deviation (SDRR), the standard deviation of differences between adjacent RR intervals (SDSD), root mean square of the successive differences (RMSSD) and percentage of RR50 (pRR50; i.e., the number of adjacent RR intervals that differed by more than 50 ms). RMSSD reflects short-term HRV. RMSSD is inversely related to the PR and stress [6]. The lower the levels of RMSSD, the higher will be the PR, reflecting more stress.

Frequency-domain analysis of HRV was performed by power spectral density analysis of tacho-grams (graphical representations of RRI data with respect to time) by fast Fourier transform. Power spectral distribution in the low (LF; 0.04–0.15 Hz) and high (HF; 0.15–0.40 Hz) frequency bands was calculated in terms of absolute power (LF μs^2, HF μs^2) and normalized unit (LF nu, HF nu). The normalized unit represents the absolute power of the respective band proportional to the total power in the very low frequency band. The LF/HF ratio was calculated as a ratio of LF power to HF power. The HF component reflects the parasympathetic nervous activity, whereas the LF component assesses sympathetic efferent activity. The more the stress, the lower will be the levels of HF and LF [5].

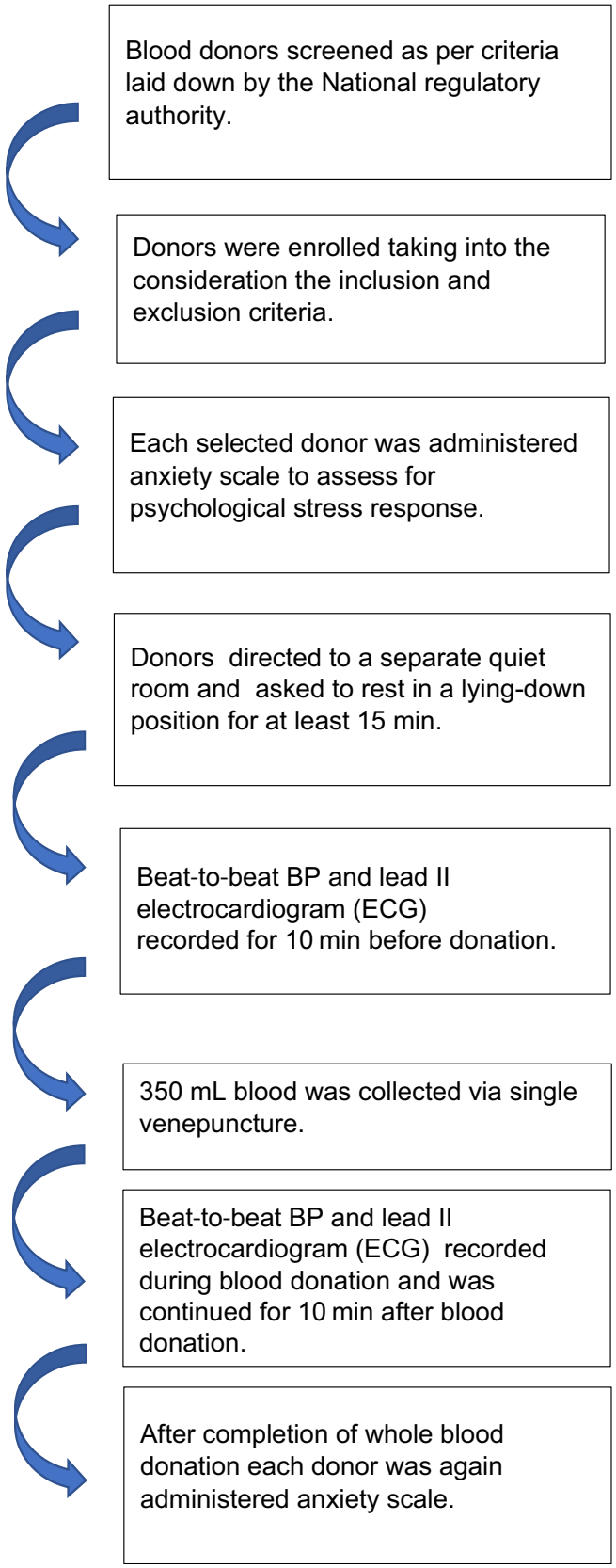

FIGURE 1 Detailed overview of the study procedure.

Baroreflex sensitivity

Beat-to-beat BP and RRI signals were analysed by fast Fourier transform to determine BRS by a spectral method. The coherence between power spectral densities of RRI and BP in low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.40 Hz) bands was computed. The baroreflex gain was calculated by dividing the amplitude of RR oscillations by the amplitude of the corresponding

oscillations in systolic, mean and diastolic BP in the low- and high-frequency bands. These were referred to as α-LF and α-HF in their respective frequency bands. Both α-LF and α-HF are expressed as ms/mmHg.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize all the variables. The distribution of all parameters was tested using standard normality tests (D'Agostino–Pearson omnibus normality test, Kolmogorov–Smirnov test and Shapiro–Wilk test). Data with normal distribution are expressed as mean ± standard deviation (SD) and data with non-parametric distribution are expressed as median with interquartile range. To compare the mean or median of different parameters during baseline and conditional probability table (CPT), the paired *t*-test or the Wilcoxon matched paired test was performed depending upon the distribution of data. Depending upon the parametric and non-parametric distribution of data, the association between two parameters was evaluated using Pearson's or Spearman's rank correlation coefficient. A *p*-value <0.05 was considered significant. Analysis was conducted using IBM SPSS Statistics (version 22.0).

RESULTS

The study included 69 (97.1%) male and 1 (2.9%) female whole blood donors. Thirty-five were FTD while 35 had donated blood earlier and were considered RD. The mean age of the donors was 35 ± 4.5 years. The mean age of FTD (30.4 ± 7.7 years) and RD (33.2 ± 8.4 years) was comparable. Four (5.7%) blood donors, two from each group, had occupation-related stress.

Physiological stress response was analysed before, during and after donation; it was also compared among FTD and RD.

Physiological stress response among blood donors before, during and after donation ($n = 70$)

Haemodynamic values of SBP were significantly higher during the pre-donation period compared to during donation ($p < 0.014$). SBP, DBP and mean arterial pressure (MAP) were also higher in the pre-donation period compared to the post-donation period, and all values were statistically significant ($p < 0.001$ for all three values). PR was comparable during all three periods of blood donation (Table 1).

Values of the time-domain parameters, namely SDSD and RMSSD, were significantly lower during the post-donation period as compared to the pre-donation period ($p < 0.005$, $p < 0.007$, respectively). In the frequency domain, the parameters LF nu, HF nu and LF% were significantly lower during the pre-donation period compared to during donation ($p < 0.001$, $p < 0.001$, $p < 0.012$, respectively). LF nu, LF% and LF/HF ratio were also significantly lower during the pre-donation period compared to the post-donation period ($p < 0.05$, $p < 0.16$, $p < 0.042$, respectively). BRS was also statistically higher during the pre-donation period compared to the post-donation period ($p < 0.001$) (Table 1).

Physiological stress response among first-time ($n = 35$) and repeat donors ($n = 35$) before donation, during donation and after donation

Haemodynamic values among FTD and RD before donation, during donation and after donation were comparable except for PR, which was significantly higher in FTD compared with RD in the post-donation period ($p < 0.03$). Time-domain and frequency-domain parameters were comparable, except for LF nu (a frequency-domain parameter), which was significantly raised in FTD during donation compared with RD (Table 2).

Psychological stress response among blood donors before and after donation ($n = 70$)

The state anxiety score was significantly higher among blood donors before donation compared to after donation ($p < 0.001$), while the trait anxiety score was comparable during the two periods (Table 3).

Psychological stress response before and after donation in first-time ($n = 35$) and repeat ($n = 35$) blood donors

Before donation, the state anxiety score was significantly higher in FTD compared with RD ($p < 0.001$), while the trait anxiety score was comparable (Table 4).

DISCUSSION

Blood donation is of the most precious contribution that a person can make towards society. Blood donors may experience psychological stress during the donation because of fear of the needle, anxiety or worry. Blood lost during blood donation can also cause a physiological stress response in the form of increased levels of nor-adrenaline and cortisol in the donors [7]. Evaluation of the stress response during different phases of the blood donation process can help us in optimizing the donation experience for the donor. To the best of our knowledge, this is first study, in a developing country like ours, where the physiological and psychological stress responses are studied before, during and after blood donation.

Only male blood donors constituted the study population, as very few female blood donors were able to donate blood because of low haemoglobin and low weight [10].

TABLE 1 Parameters of physiological stress among blood donors before, during and after donation ($n = 70$).

Parameters	Before donation (mean ± SD)	During donation (mean ± SD)	After donation (mean ± SD)	*p*-Value (pre-donation vs. during donation)[a]	*p*-Value (pre-donation vs. post-donation)[a]
Pulse rate (beats/min)	77.7 ± 7.3	76.0 ± 7.3	76.8 ± 6.9	0.170	0.454
Systolic blood pressure (mmHg)	121.7 ± 5.4	119.3 ± 6.0	113.8 ± 6.9	0.014	<0.001
Diastolic blood pressure (mmHg)	79.0 ± 4.6	77.2 ± 8.9	72.4 ± 8.6	0.135	<0.001
Mean arterial pressure (mmHg)	92.6 ± 3.7	91.6 ± 4.8	86.1 ± 5.3	0.169	<0.001
Heart rate variability: Time-domain parameters					
Average RR	763.8 ± 156.9	777.6 ± 169.2	740.3 ± 211.1	0.617	0.318
Median RR	764.4 ± 158.3	749.9 ± 201.1	723.8 ± 219.2	0.636	0.869
SDRR	57.8 ± 28.3	52.1 ± 21.0	49.8 ± 20.9	0.178	0.656
SDARR	2.1 ± 6.9	1.8 ± 11.6	3.9 ± 10.7	0.852	0.218
CVRR	0.07 ± 0.03	0.09 ± 0.3	0.09 ± 0.1	0.579	0.090
Average rate	77.9 ± 11.3	76.1 ± 12.8	76.4 ± 11.7	0.379	0.374
SD rate	5.2 ± 1.8	5.1 ± 2.7	4.4 ± 1.3	0.796	0.973
SDSD	46.2 ± 25.7	38.9 ± 22.6	34.8 ± 21.2	0.076	0.005
RMSSD	46.2 ± 25.6	41.4 ± 27.6	35.1 ± 21.2	0.287	0.007
pRR50%	17.9 ± 18.7	16.1 ± 18.0	13.4 ± 16.4	0.562	0.132
Heart rate variability: Frequency-domain parameters					
Total power (μs^2)	2816.9 ± 2053.1	2820.3 ± 2265.1	2246.2 ± 1627.6	0.992	0.071
LF μs^2	774.8 ± 620.7	769.5 ± 660.2	805.1 ± 618.4	0.961	0.772
HF μs^2	872.8 ± 1141.2	707.7 ± 926.3	596.3 ± 618.4	0.349	0.077
LF/HF ratio	1.5 ± 1.1	2.2 ± 3.1	1.9 ± 1.2	0.077	0.042
LF%	28.1 ± 10.5	33.1 ± 12.7	32.8 ± 12.3	0.012	0.016
HF%	29.0 ± 25.2	25.5 ± 15.2	25.5 ± 15.2	0.321	0.322
LF nu	52.3 ± 16.9	69.6 ± 12.7	57.7 ± 16.4	<0.001	0.057
HF nu	44.9 ± 16.6	57.2 ± 13.7	42.3 ± 17.6	<0.001	0.370
Baroreflex sensitivity	14.6 ± 2.9	14.0 ± 2.7	12.1 ± 5.1	0.207	<0.001

[a]Calculated using the paired *t*-test.

Abbreviations: CVRR, coefficient of variance of RR interval; HF μs^2, absolute power of the high-frequency band; HF nu, relative power of the high-frequency band in normalized units; HF%, relative power of the high-frequency band in percentage; LF μs^2, absolute power of the low-frequency band; LF nu, relative power of the low-frequency band in normalized units; LF%, relative power of the low-frequency band in percentage; pRR50%, percentage of successive differences; RMSSD, root mean square of successive differences; RR, respiratory rate; SDARR, standard deviation of the average RR interval; SDRR, standard deviation of RR interval; SDSD, standard deviation of differences between adjacent RR interval.

In our study, SBP was significantly higher before donation as compared to during donation. SBP, DBP and MAP were also significantly higher immediately before donation compared to after donation. The stress response was mainly evidenced by an increase in SBP at needle insertion and a decrease thereafter. This response pattern is mainly in line with the literature showing an overall decrease from pre- to post-donation values [6, 11]. In a study carried out on 43 blood donors, all the haemodynamic parameters, namely HR, SBP, DBP and MAP, were significantly higher before donation compared to after donation [6, 11]. In another study, a significant increase in SBP, DBP and MAP was observed when haemodynamic parameters were compared before and after donation [6].

PR usually shows a U-shaped response pattern: that is, an increase in PR occurs before and after donation while it decreases during donation [12]. In addition, stress-related anticipatory HR acceleration might increase the PR during the pre-donation period [5]. In our study, no change in PR was observed in any of the periods for all the blood donors ($n = 70$). The recording was done in a separate quiet room where the donor was allowed to rest for 15 min, which could have resulted in the non-increase in PR before the donation. Moreover, half of our blood donors were RD who were well-versed with the process of whole blood donation and were therefore less anxious.

Among all the parameters studied for HRV in the time domain, only SDSD and RMSSD were significantly lower during the post-donation period as compared to the pre-donation period. In a study carried out on 48 blood donors, RMSSD was also significantly decreased during the post-donation period as compared to the pre-donation period [6]. Withdrawal of blood during blood donation results in vagal withdrawal and sympathetic activation, which exhibit as a decrease in RMSSD [5].

In our study, HRV in the frequency-domain parameters, namely LF nu, HF nu, and LF%, was significantly lower before donation

TABLE 2 Parameters of physiological stress response among first-time ($n = 35$) and repeat donors ($n = 35$) before, during and after donation.

	Before donation			During donation			After donation		
Parameters	**FTD**	**RD**	***p*-Value[a]**	**FTD**	**RD**	***p*- Value[a]**	**FTD**	**RD**	***p*-Value[a]**
Pulse rate	77.9 ± 7.6	77.4 ± 7.2	0.778	77.2 ± 7.6	76.6 ± 7.1	0.733	79.1 ± 7.0	75.7 ± 7.1	0.047
Systolic blood pressure	121.7 ± 6.2	121.7 ± 4.2	1.00	119.7 ± 5.1	119.7 ± 5.1	1.00	114.3 ± 6.5	114.0 ± 6.5	0.847
Diastolic blood pressure	78.6 ± 3.6	79.4 ± 5.4	0.468	78.0 ± 4.1	78.3 ± 5.7	0.243	73.4 ± 5.4	73.1 ± 5.3	1.00
Mean arterial pressure	92.1 ± 2.6	93.1 ± 4.4	0.251	91.5 ± 4.1	92.1 ± 5.0	0.584	86.4 ± 5.3	86.2 ± 5.3	0.987
RR	16.8 ± 1.4	16.7 ± 1.2	0.749	16.9 ± 1.0	17.1 ± 1.4	0.855	16.9 ± 1.1	16.7 ± 1.0	0.897
Heart rate variability: Time-domain parameters									
Average RR	782.2 ± 110	745.4 ± 192.7	0.330	796.1 ± 113.7	777.6 ± 168.1	0.591	779.9 ± 160.6	719.5 ± 219.1	0.192
Median RR	782.7 ± 111.9	745.9 ± 194.0	0.334	769.0 ± 159.3	749.8 ± 199.9	0.658	727.7 ± 221.9	719.6 ± 220.8	0.879
SDRR	60.6 ± 26.4	54.9 ± 30.2	0.403	53.2 ± 20.9	51.5 ± 20.3	0.731	51.4 ± 19.5	47.1 ± 22.0	0.389
SDARR	2.2 ± 7.7	2.1 ± 6.0	0.952	1.1 ± 6.4	0.0 ± 0.0	0.312	5.8 ± 12.9	1.2 ± 5.8	0.058
CVRR	0.07 ± 0.0	0.07 ± 0.0	1.00	0.06 ± 0.0	0.06 ± 0.0	1.00	0.09 ± 0.1	0.09 ± 0.1	1.00
Average rate	78.7 ± 11.0	77.2 ± 11.7	0.584	77.3 ± 10.7	76.8 ± 11.9	0.853	76.2 ± 11.0	77.3 ± 12.3	0.694
SD rate	5.6 ± 1.6	4.8 ± 1.9	0.061	4.9 ± 1.6	4.6 ± 1.3	0.392	4.7 ± 1.2	4.2 ± 1.3	0.099
SDSD	46.7 ± 24.0	45.7 ± 27.6	0.872	37.8 ± 19.7	40.7 ± 24.7	0.587	34.9 ± 17.8	34.6 ± 24.3	0.953
RMSSD	46.7 ± 23.9	45.6 ± 27.6	0.845	37.8 ± 19.6	40.6 ± 24.6	0.600	34.8 ± 17.8	35.1 ± 24.3	0.954
pRR50%	16.8 ± 16.4	19.0 ± 20.9	0.625	14.6 ± 15.9	15.5 ± 17.9	0.824	13.6 ± 15.9	12.8 ± 17.2	0.841
Heart rate variability: Frequency-domain parameters									
Total power μs^2	3074.1 ± 2118.9	2559.6 ± 1982.1	0.298	2738.2 ± 2341.2	2906.2 ± 2212.6	0.758	2279.5 ± 1622.3	2198.1 ± 1658.2	0.836
LF μs^2	816.1 ± 606.6	733.5 ± 640.8	0.582	787.7 ± 706.5	753.2 ± 617.8	0.828	757.6 ± 534.6	839.3 ± 700.5	0.583
HF μs^2	796.9 ± 771.2	948.7 ± 1427.0	0.582	648.8 ± 831.7	766.7 ± 1021.0	0.598	606.4 ± 648.7	711.6 ± 1031.8	0.517
LF/HF ratio	1.6 ± 1.1	1.4 ± 1.1	0.449	1.8 ± 1.3	1.9 ± 1.6	0.775	2.1 ± 1.3	1.8 ± 1.2	0.319
LF%	28.9 ± 11.4	27.3 ± 9.6	0.527	32.9 ± 12.3	32.8 ± 12.6	0.973	32.9 ± 11.2	36.3 ± 10.5	0.195
HF%	29.9 ± 31.8	28.1 ± 16.5	0.767	24.2 ± 13.9	26.4 ± 16.5	0.548	20.9 ± 11.6	33.8 ± 53.8	0.170
LF nu	54.3 ± 16.9	50.3 ± 17.1	0.328	82.5 ± 14.5	56.4 ± 17.9	<0.001	62.6 ± 13.7	59.8 ± 15.7	0.429
HF nu	42.9 ± 17.1	46.8 ± 16.2	0.331	39.2 ± 14.2	41.8 ± 17.2	0.492	36.9 ± 12.2	38.8 ± 14.1	0.548
Baroreflex sensitivity	14.8 ± 2.9	14.5 ± 2.9	0.666	14.1 ± 2.7	14.2 ± 2.9	0.8331	12.5 ± 3.9	11.6 ± 2.2	0.094

[a]Calculated using the paired *t*-test.

Abbreviations: CVRR, coefficient of variance of RR interval; HF%, relative power of the high-frequency band in percentage; HF μs^2, absolute power of the high-frequency band; HF nu, relative power of the high-frequency band in normalized units; LF%, relative power of the low-frequency band in percentage; LF μs^2, absolute power of the low-frequency band; LF nu, relative power of the low-frequency band in normalized units; pRR50%, percentage of successive differences; RMSSD, root mean square of successive differences; RR, respiratory rate; SDARR, standard deviation of the average RR interval; SDRR, standard deviation of RR interval; SDSD, standard deviation of differences between adjacent RR interval.

compared to during donation ($p < 0.001$, $p < 0.001$, $p < 0.012$, respectively). LF nu, LF% and LF/HF ratio were also significantly lower during the pre-donation period as compared to the post-donation period ($p < 0.05$, $p < 0.16$, $p < 0.042$, respectively). A study on human autonomic responses to blood donation also reported lower levels of both LF and HF in the pre-donation period as compared to the post-donation period. LF is a sensitive indicator of parasympathetic control over the peripheral circulation, while HF governs the strength of respiratory variation [5]. During the pre-donation period, at the time of needle prick, the donor withholds the breath for a few seconds. The drop in HF in the pre-donation period might be due to the lowered breathing, indicating a short-term stress response. BRS was also statistically higher in our study during the pre-donation period compared to the post-donation period, which also reflects an increase in sympathetic activity and a reciprocal decrease in parasympathetic activity. In another similar study, BRS was also found to be statistically higher during the pre-donation period as compared to the post-donation period [5].

As a subgroup analysis, we also compared the physiological stress response parameters among FTD and RD before, during and after donation. All the parameters were comparable except PR and LF nu. PR was significantly higher in FTD compared with RD in the post-donation period. LF nu was significantly raised in FTD compared with RD during the donation. Both increased PR and LF nu indicate more stress among the FTD. Literature also reports stress reactions to be directly related to the number of prior blood donations [8, 13, 14]. Several studies have also reported that inexperienced blood donors show significantly higher levels of stress-related reactions than more experienced blood donors [15, 16]. Moreover, it is also known that FTD exhibit a higher number of adverse reaction than RD [17].

Because of the unfamiliarity of situations and various other factors, blood donors can also experience psychological stress during donation. In our study, we assessed psychological stress related to blood donation using the STAI-Y 40-item scale [4]. It allows for the self-reporting of state and trait anxiety levels. State anxiety score reflects the apprehension levels, while trait anxiety score reflects the personality of an individual. In our study, the state anxiety score was significantly higher among the blood donors before donation compared to after donation, while trait anxiety score was comparable during the two periods, which indicates the blood donors were anxious during the pre-donation period. Further, the two scales were compared between FTD and RD. In FTD also, the state anxiety score was significantly higher during the pre-donation period compared to the post-donation period, while the trait anxiety score was comparable in both the groups. In a previous study, where several character traits were compared in 45 plasmapheresis donors, the authors observed that donors with negative feelings about plasma donation had higher stress levels before plasma donation. Informative conversation with such donors before the donation can help them to decrease their stress and anxiety [16]. In another recent study investigating the association between fear of blood and various donor outcomes, the authors found that fear among blood donors was associated with higher pain perception, post-donation anxiety and vasovagal reactions. The researchers also found that providing positive reinforcement through brochures about blood donation, along with a tailored conversation with the donor, was associated with less pain at the venipuncture site [18]. A study reported that the Trait Anxiety Inventory score was higher in FTD compared to regular blood donors [19]. However, in our study, no such difference in trait anxiety score was observed in FTD and RD, as the trait score is more related to the blood donor's perception and personality [20].

Our study highlights that blood donors experience both physiological and psychological stress in the pre-donation phase. Therefore, blood donors should be educated and pre-informed about the blood donation process. All doubts should be dispelled and the donor should be made comfortable. In our study, a significant increase in SBP was observed in pre-donation period, stressing the need of monitoring BP, especially in first-time, anxious and hypertensive blood donors.

To conclude, stress response does occur in blood donors during whole blood donation. A pre-donation informative conversation should be done with each blood donor, and potential stressors should be identified. However, the study population included in this study was only confined to in-house blood donors, and females constituted only 2.9% of the study population. Our study was also not powered enough for subgroup analysis of first-time and regular blood donors.

TABLE 3 Parameters of psychological stress response before donation and after donation ($n = 70$).

Variables	Overall ($n = 70$)		
	Before donation (mean ± SD)	After donation (mean ± SD)	p-Value[a]
State scale score	45.6 ± 4.7	29.6 ± 2.5	<0.001
Trait scale score	30.1 ± 4.6	29.6 ± 4.9	0.587

[a]Calculated using the paired t-test.

TABLE 4 Parameters of psychological stress response before donation and after donation in first-time and repeat blood donors.

Variables	Before donation			After donation		
	FTD ($n = 35$) (mean ± SD)	RD ($n = 35$) (mean ± SD)	p-Value[a]	FTD ($n = 35$) (mean ± SD)	RD ($n = 35$) (mean ± SD)	p-Value[a]
State anxiety	47.3 ± 5.8	43.9 ± 2.3	0.001	29.6 ± 2.7	29.7 ± 2.3	0.868
Trait anxiety	31.5 ± 4.3	31.1 ± 4.3	0.698	28.9 ± 4.9	30.1 ± 4.9	0.309

[a]Calculated using the paired t-test.
Abbreviations: FTD, first-time donor; RD, repeat donor.

Another limitation of our study was that the blood donation process and recordings for physiological stress response were performed in a separate quiet room rather than in the blood donation complex, which could have impacted the donor anxiety and stress levels. A larger cohort study performed in a common blood donation room might provide us with an even better understanding of the true incidence of physiological and psychological stress responses. It will also help us to understand and reduce side effects to a minimum and thus help make the blood donation process safer.

ACKNOWLEDGEMENTS

A.K., R.K. and T.S. were involved in planning of the study, data collection, data acquisition, data analysis and manuscript development, A.M. and P.A. were involved in planning of study and data acquisition and K.M., P.K. and G.K. reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Kaur A, Kaur R, Sood T, Malhotra A, Arun P, Mittal K, et al. Physiological and psychological stress response of blood donors during the blood donation process. Vox Sang. 2023;118:1061–8.

Received: 24 May 2023 | Revised: 21 September 2023 | Accepted: 22 September 2023

DOI: 10.1111/vox.13545

ORIGINAL ARTICLE

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Two-phase Bayesian latent class analysis to assess diagnostic test performance in the absence of a gold standard: COVID-19 serological assays as a proof of concept

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Funding information
COVID-19 Immunity Task Force (CITF); Public Health Agency of Canada (PHAC)

Abstract

Background and Objectives: In this proof-of-concept study, which included blood donor samples, we aimed to demonstrate how Bayesian latent class models (BLCMs) could be used to estimate SARS-CoV-2 seroprevalence in the absence of a gold standard assay under a two-phase sampling design.

Materials and Methods: To this end, 6810 plasma samples from blood donors who resided in Québec (Canada) were collected from May to July 2020 and tested for anti-SARS-CoV-2 antibodies using seven serological assays (five commercial and two non-commercial).

Results: SARS-CoV-2 seroprevalence was estimated at 0.71% (95% credible interval [CrI] = 0.53%–0.92%). The cPass assay had the lowest sensitivity estimate (88.7%; 95% CrI = 80.6%–94.7%), while the Héma-Québec assay had the highest (98.7%; 95% CrI = 97.0%–99.6%).

Conclusion: The estimated low seroprevalence (which indicates a relatively limited spread of SARS-CoV-2 in Quebec) might change rapidly—and this tool, developed using blood donors, could enable a rapid update of the prevalence estimate in the absence of a gold standard. Further, the present analysis illustrates how a two-stage BLCM sampling design, along with blood donor samples, can be used to estimate the performance of new diagnostic tests and inform public health decisions regarding a new or emerging disease for which a perfect reference standard does not exist.

Keywords

Bayesian latent class analysis, blood donors, COVID-19 serological testing, diagnostic accuracy, SARS-CoV-2, seroprevalence

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Highlights

- Bayesian latent class models with a two-stage sampling design might help estimate the performance and interpret the results of newly developed serological assays for SARS-CoV-2, as none currently qualifies as a reference standard.
- The seroprevalence of SARS-CoV-2 was estimated at 0.71% during the early phase of the pandemic; the cPass surrogate neutralization assay and the non-commercial assay developed by Héma-Québec had the lowest and highest sensitivity, respectively.
- The reported seroprevalence may be affected by the availability of testing, sociodemographic characteristics and other factors; serosurveillance is still needed to quantify the trajectory of population immunity to inform public health policy.

INTRODUCTION

The SARS-CoV-2 pandemic has exposed how blood services can help inform public health decisions [1, 2]. Blood services have participated in serosurveys [3], clinical trials (i.e., convalescent plasma) [4] and even helped develop tools to better understand SARS-CoV-2 immunity [5].

Early in the pandemic, several private and public organizations developed SARS-CoV-2 antibody detection assays, with more than 80 approved by the US Food and Drug Administration as of December 2021 [6]. These assays proved essential to further knowledge of the immune response to SARS-CoV-2 and to study population-level immunity through serosurveys [7]. However, this progress exposed many challenges associated with the interpretation of such assays amid a new or emerging pathogen.

First, existing SARS-CoV-2 serological assays are imperfect, with no individual assay clearly standing out as the reference standard (with perfect sensitivity and specificity). However, they collectively provide complementary information on SARS-CoV-2 humoral immunity, in part because they detect different antibodies [8, 9]. Indeed, a testing strategy that combines an anti-spike or anti-RBD assay with an anti-nucleocapsid assay can discriminate vaccine- from infection-induced immunity [10]. Furthermore, some assays exclusively detect immunoglobulin G (IgG), whereas others also detect immunoglobulin A (IgA) or immunoglobulin M (IgM) that have different kinetics than IgGs [11].

Second, the lack of a reference standard assay for the detection of SARS-CoV-2 antibodies made it difficult to assess diagnostic accuracy. While polymerase chain reaction-confirmed infection has been used as reference sample, the composition of this reference sample can influence sensitivity and introduce bias. Sensitivity seemingly decreases when reference samples are collected early in the recovery phase of infection, before seroconversion in some individuals [12], or if they include samples from immunocompromised individuals, or asymptomatic and mildly symptomatic infections [12]. Conversely, an over-representation of individuals with severe COVID-19 and asymptomatic SARS-CoV-2-negative controls will overestimate diagnostic accuracy due to a spectrum bias [13].

Third, because a new or emerging infection initially has a low community prevalence, a given assay would need a near-perfect specificity to yield a satisfactory positive predictive value [14, 15]. Earlier in the pandemic, the Centers for Disease Control and Prevention (CDC) recommended a specificity target of 99.5%, a threshold since revised to 95% amid increasing prevalence [16]. Therefore, disease prevalence is a key parameter to consider when interpreting serologic assay results.

Bayesian latent class models (BLCMs) are increasingly used to address the above limitations to estimate disease prevalence and assay sensitivity and specificity in the absence of an established reference standard [17]. With BLCMs, the true infection history of patients (i.e., serologic status) is assumed to be unobserved (or 'latent'), and pre-existing information regarding assays at stake and disease prevalence is used to infer plausible values for test accuracy and disease prevalence, given the observed test results [18]. In other words, this technique can infer test sensitivity and specificity, and disease prevalence without a priori knowledge on the true serologic status, as it combines prior information on these parameters with the observed results of several imperfect tests. While most published BLCMs assume all tests are performed on every sampled individual, the model presented in this paper is suited for a two-phase sampling design, that is, when testing information is available only for a subset of individuals.

This proof-of-concept study aims to show how BLCMs can be used to infer the seroprevalence of SARS-CoV-2, as well as the sensitivity and specificity of several SARS-CoV-2 antibody detection assays, in the presence of two-stage sampling designs.

MATERIALS AND METHODS

Study population

Study participants were residents of Québec, Canada, who donated blood during the first SARS-CoV-2 pandemic wave (25 May 2020–09 July 2020) at one of Héma-Québec's (HQ) donation centres. Donors were required to be (1) eligible for blood donation per HQ eligibility criteria and (2) free of SARS-CoV-2-related symptoms in the preceding 14 days. A total of 6812 plasma samples were collected and tested for SARS-CoV-2 antibodies.

Serological assays

This study investigated seven serological assays, including two non-commercial and five commercial assays. The non-commercial assay

(i.e., the 'HQ assay') was an enzyme immunosorbent assay (ELISA) developed at HQ [19, 20]. This assay detects all antibody sub-classes (i.e., IgA, IgG and IgM) that target the receptor-binding domain (RBD) of spike [21]. The other non-commercial assay (i.e., the 'academic assay') was a SARS-CoV-2 IgG ELISA chemiluminescent assay that targets the full-length spike glycoprotein, the RBD and nucleocapsid [22].

Commercial assays included (1) the Abbott SARS-CoV-2 IgG chemiluminescent microparticle immunoassay (CMIA) from Abbott Laboratories (i.e., the 'Abbott assay'), performed on the Architect i2000sr platform, which detects IgG against the SARS-CoV-2 nucleocapsid protein [23]; (2) the Elecsys Anti-SARS-CoV-2 quantitative electrochemiluminescence immunoassay (ECLIA) from F. Hoffmann-La Roche AG (i.e., the 'Roche assay'), performed on the Roche e601 platform, which detects all nucleocapsid-targeting antibodies [24]; (3) the Ortho Clinical Diagnostics VITROS Immunodiagnostic assay (i.e., the 'Ortho assay'), performed on the VITROS XT7600 platform, which detects all spike-targeting antibodies [25]; (4) the Meso Scale V-Plex COVID-19 Coronavirus Panel 2 test from Meso Scale Diagnostics (MSD; i.e., the 'MSD assay'), performed on the Meso QuickPlex SQ120 instrument, which detects IgG targeting the spike, nucleocapsid and RBD antigens [26]; and (5) the cPass surrogate neutralization assay (i.e., the 'cPass assay'), performed using the cPass SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript), which detects antibodies of any subclass that block the interaction between the RBD and angiotensin-converting enzyme (ACE)-2 [27].

Assays were performed and their results were interpreted following the instructions supplied by the manufacturers or academic investigators. Unlike other single-antigen assays, the interpretation of the MSD assay was based on the number of antigens with signals above a pre-specified antigen-specific threshold, with ≥2/3 antigens showing a positive test result required to establish positivity.

Test results were gathered in two phases. In phase 1, all samples ($N = 6810$) were tested using the non-commercial (HQ) and Abbott assays (the 'phase-one assays'). In phase 2, the five other assays (i.e., Roche, Ortho, MSD, cPass and non-commercial [academic], or 'phase-two assays') were performed on a subset of 387 samples, which included all samples that tested positive using phase-one assays and randomly selected samples that tested negative.

BLCM specification

Most published BLCMs assume all tests are performed on every sampled individual. Here, we propose a model suited for two-phase sampling designs, such as the one used in this study, where testing procedure unfolds in two phases involving different assays. This type of design is routinely used to reduce costs or save time when the disease prevalence is low [28]. When a two-phase sampling design is used, statistical methods must be adapted to avoid biased estimates [29].

This two-phase setting can be treated under a missing data framework. The results of phase-two assays are considered 'missing' for the set of individuals involved only in phase 1. Formally, following the 'Selection model factorisation' framework of Little and Rubin [30], let $T = (t_{i,j}), i \in \{1,\ldots,n\}$ and $j \in \{1,\ldots,7\}$ denote the data matrix assuming no missing values, where $t_{i,j}$ encodes individual i's result for Test j, with $j = 1,2$ denoting phase 1 assays, and $j = 4,\ldots,7$ phase 2 assays. Let $M = (m_{i,j})$ denote the fully observed missingness indicator matrix, that is, $m_{i,j} = 0$ if $t_{i,j}$ is missing and $m_{i,j} = 1$ if $t_{i,j}$ is observed. When $m_{i,j} = 1$, $t_{i,j} = *$, meaning that $t_{i,j}$ can take any value in $\{0,1\}$. In our setting, the assumed sampling mechanism ensures that the probability distribution of M only depends on the sub-matrix $T^{(l)}$ of T formed by the first two columns of T, which are fully observed, since phase-two selection probabilities depend on phase-one test results only. Hence, the missingness mechanism is 'ignorable', meaning that the likelihood of T is proportional to

$$\Pi_{i=1}^{n} p(t_{i,1}, t_{i,2}, d_i)^{(1-m_{i,3})(1-m_{i,4})(1-m_{i,5})(1-m_{i,6})(1-m_{i,7})} \times \Pi_{i=1}^{n} p(t_{i,1},\ldots,t_{i,7}, d_i)^{m_{i,3}m_{i,4}m_{i,5}m_{i,6}m_{i,7}}$$

where d_i denotes the unobserved true infection history of individual i, with $d_i = 0$ if they were never infected and 1 otherwise. From there, parametrizing the factors $p(t_{i,1}, t_{i,2}, d_i)$ and $p(t_{i,1},\ldots,t_{i,7}, d_i)$ in terms of accuracy parameters of assays at stake and of seroprevalence will conclude the model specification. This is done by reasoning about conditional dependence between test results. See Supporting information 1 for more information regarding conditional dependence.

Setting priors for accuracy and prevalence parameters is required in BLCMs and is especially important when dealing with non-identifiable models. It is also important when strong prior information is available, enabling real scientific knowledge to be integrated into the analysis. Here, the model's identifiability is ensured by the inclusion of seven assays, the ignorable nature of the missingness mechanism (given our two-phase sampling design), and the assumption of conditional independence. Additionally, the availability of published sensitivity and specificity estimates for the study assays prompted us to include a scenario with informed priors.

We determined the prior distributions of proportions with a plausible range by assigning a beta distribution, matching the centre of the range with the mean of the beta distributions and minimizing the squared distance between the endpoints of the range and the quantiles of order 2.5% and 97.5% of the beta distribution [31]. The selected ranges (i.e., 95% confidence intervals [CIs]) of plausible prior values ('informed priors') for sensitivity, specificity and prevalence parameters were based on a literature review and on clinical opinions (see Table 1). Beta distributions associated with 95% CI = [0.5–0.99] were used as 'neutral priors' to assess the impact of informative priors on final estimates.

Data analysis

We estimated the seroprevalence of SARS-CoV-2 and the sensitivity and specificity of each assay using the specified BLCM.

TABLE 1 Ninety-five percent confidence intervals used for informed prior distributions of model parameters.

Parameter	Assay	95% CI (%)	Detected Ab isotype(s)	References
Prevalence	-	0.5–3.1	-	[19, 32, 33]
Sensitivity	Non-commercial (HQ)	96.8–100.0	IgA/IgG/IgM	[20]
	Abbott Diagnostics Inc.	95.8–100.0	IgG	[26]
		82.8–98.7	IgG	[24]
	Ortho Clinical Diagnostics Inc.	76.9–96.0	IgA/IgG/IgM	[26, 34]
		70.9–85.0	IgA/IgG/IgM	[35]
	Roche Diagnostics	99.4–99.6	IgA/IgG/IgM	[26]
		64.8–88.5	IgA/IgG/IgM	[36]
	MSD	95.1–99.6	Indirect IgG (Spike)	[37, 38]
		89.1–96.8	Indirect IgG (NP)	
		95.1–99.6	Indirect IgG (RBD)	
	cPass	77.0–100.0	IgA/IgG/IgM	[27]
	Non-commercial (academic)	88.7–97.3	IgG (Spike)	[39]
		84.1–93.5	IgG (RBD)	
		74.1–83.2	IgG (NP)	
Specificity	Non-commercial (HQ)	95.5–100.0	IgA/IgG/IgM	[26]
	Abbott Diagnostics Inc.	99.0–99.9	IgG	[26]
		92.5–98.9	IgG	[24]
	Ortho Clinical Diagnostics Inc.	99.1–100.0	IgA/IgG/IgM	[26, 40]
		99.4–100.0	IgA/IgG/IgM	[35]
	Roche Diagnostics	99.7–100.0	IgA/IgG/IgM	[26]
		99.0–100.0	IgA/IgG/IgM	[36, 41]
	MSD	97.2–100.0	Indirect IgG (Spike)	[37, 38]
		98.2–100.0	Indirect IgG (NP)	
		95.7–99.7	Indirect IgG (RBD)	
	cPass	95.0–100.0	IgA/IgG/IgM	[27]
	Non-commercial (academic)	97.9–98.4	IgG (Spike)	[34]
		99.3–99.7	IgG (RBD)	
		97.9–98.4	IgG (NP)	

Abbreviations: CI, confidence interval; Ig, immunoglobulin; MSD, Meso Scale Diagnostics; NP, nucleocapsid protein; RBD, receptor-binding domain.

A Markov chain Monte Carlo (MCMC) algorithm (i.e., a Gibbs sampler, Supporting information 2) was used to approximate 95% credible intervals (CrI) from simulations of the posterior joint distribution (100,000 iterations). The first 10,000 iterations were discarded (i.e., 'burn-in'), and the remaining 90,000 were used for posterior inference [42]. To reduce MCMC-induced autocorrelation, thinning was performed every 10 iterations. Convergence was assessed using diagnostic plots [43]. As a sensitivity analysis, we ran several two-phase BLCMs for all possible combinations of 2, 3 and 4 assays with the non-commercial (HQ) and the Abbott assays (i.e., the two assays involved in phase-one were always included in the model). This sensitivity analysis provided a deeper insight into the specified model's robustness in capturing essential information when different combinations of assays are employed in the second phase. Models were implemented using the R statistical software version 4.1.1 (R Core Team, 2021).

Ethics statement

All donations were made after donors provided a written informed consent to participate in a seroprevalence study. The Research Ethics Boards of Héma-Québec and the Research Institute of the McGill University Health Centre approved this study.

RESULTS

Overview of test results

In phase 1, 2.2% and 1.0% of the plasma samples tested positive using the HQ and Abbott assays, respectively. Of the 387 samples in the phase 2 subset, all phase-1-positive samples were used, and 10%–13% tested positive with the other assays (Table 2).

Negative controls comprised 210 randomly selected samples that tested negative with the HQ and Abbott assays. The other specimens included 40 samples that tested positive with the HQ and Abbott assays; 29 that tested negative with the HQ assay and positive with the Abbott assay; and 108 that tested positive with the HQ assay and negative with the Abbott assay. Most of the samples that tested positive with a single phase 1 assay had a negative test result with all five phase 2 assays. More detailed results can be found in Table 3.

Estimation of SARS-CoV-2 seroprevalence

Our BLCM estimated the seroprevalence of SARS-CoV-2 at 0.71% (95% CrI = 0.53%–0.92%) with informed priors and at 0.69% (95% CrI = 0.52%–0.91%) with neutral priors (Table 4).

Assay sensitivity and specificity

The sensitivity of the non-commercial (HQ) assay was the highest irrespective of the type of priors considered. Its 95% CrI ranged between 97.0% and 99.6% for informed priors and between 86.3% and 98.9% for neutral priors. The cPass assay had the lowest sensitivity estimate (95% CrI = 80.6%–94.7%) for informed priors, while the Abbott assay had the lowest sensitivity for neutral priors (95% CrI = 72.2%–92.0%). Results obtained with the informed and neutral prior models were similar, as most CrIs overlapped (Table 4). For the sensitivity parameter of the Abbott assay, the CrI computed from the informed prior model did not overlap with the one obtained from the neutral prior model, with a 1% separation between them.

All assays were highly specific (lower CrI bound > 94%). For informed priors, the Roche and MSD assays had the highest (95% CrI = 99.7%–99.9%) and lowest (95% CrI = 96.7%–98.9%) specificities, respectively. For neutral priors, the Abbott and the non-commercial (academic) assays were the most specific (95% CrI = 99.3%–99.7%) and least specific assays (95% CrI = 94.1%–98.0%), respectively. The CrIs obtained with neutral priors were slightly larger (Table 4). The average widths of the 95% CrIs for sensitivity were 6.7% and 16.4% with the informed and neutral priors, respectively, whereas those for specificity were 0.9% and 2.0%, respectively.

Sensitivity analysis

Parameter estimates were similar across the assay combinations used in the model for both informed and neutral priors, although the CrIs narrowed with the number of assays involved (Supporting information 3).

DISCUSSION

In this study, we used BLCM to estimate the seroprevalence of SARS-CoV-2 among blood donors and the performance parameters of seven serological assays. The estimated seroprevalence during the period of

TABLE 2 Test results of study assays conducted on the first and second phase samples.

	Overall sample (phase 1) ($N = 6812$)		Phase 2 subset ($N = 387$)	
Test	**Positive**	**Negative**	**Positive**	**Negative**
Non-commercial (HQ)	148 (2.2%)	6662 (97.8%)	148 (38.4%)	239 (61.6%)
Abbott	69 (1.0%)	6741 (99.0%)	69 (17.8%)	318 (82.2%)
Ortho	-	-	44 (11.4%)	343 (88.6%)
Roche	-	-	39 (10.1%)	348 (89.9%)
MSD	-	-	49 (12.7%)	338 (87.3%)
cPass	-	-	39 (10.1%)	348 (89.9%)
Non-commercial (academic)	-	-	52 (13.4%)	335 (86.6%)

Abbreviations: HQ, Héma-Québec; MSD, Meso Scale Diagnostics.

TABLE 3 Number of positive tests by Héma-Québec (HQ) and Abbott results in phase 1.

		Phase 2 results						
	Phase 1 results	Number of positive tests by *n* other assays						
	n	0 assays	1 assays	2 assays	3 assays	4 assays	5 assays	*n*
HQ+/Abbott+	40	2	0	1	0	6	31	40
HQ+/Abbott−	108	91	10	1	2	3	1	108
HQ−/Abbott+	29	25	4	0	0	0	0	29
HQ−/Abbott−	6633	206	4	0	0	0	0	210

TABLE 4 Prevalence, sensitivity and specificity estimates for informed and neutral priors models.

Parameter	Assay	Informed priors, median (95% CrI)	Neutral priors, median (95% CrI)
Prevalence	-	0.71 (0.53–0.92)	0.69 (0.52–0.91)
Sensitivity	Non-commercial (HQ)	98.7 (97.0–99.6)	94.9 (86.3–98.9)
	Abbott Diagnostics Inc.	96.0 (93.0–98.0)	83.8 (72.2–92.0)
	Ortho Clinical Diagnostics Inc	92.1 (85.4–96.5)	92.1 (83.2–97.3)
	Roche Diagnostics	97.9 (96.3–99.0)	86.2 (75.4–93.6)
	cPass	88.7 (80.6–94.7)	86.1 (75.2–93.5)
	MSD	96.4 (93.6–98.2)	88.0 (77.9–95.0)
	Non-commercial (academic)	93.7 (89.5–96.6)	90.9 (82.0–96.6)
Specificity	Non-commercial (HQ)	98.4 (98.1–98.7)	98.4 (98.1–98.7)
	Abbott Diagnostics Inc.	99.5 (99.3–99.6)	99.5 (99.3–99.7)
	Ortho Clinical Diagnostics Inc	99.6 (99.2–99.8)	99.0 (97.6–99.7)
	Roche Diagnostics	99.8 (99.7–99.9)	99.3 (98.1–99.9)
	cPass	99.2 (98.1–99.8)	99.3 (98.0–99.8)
	MSD	98.0 (96.7–98.9)	96.8 (94.6–98.3)
	Non-commercial (academic)	98.1 (97.9–98.4)	96.4 (94.1–98.0)

Abbreviations: CrI, credible interval; HQ, Héma-Québec; MSD, Meso Scale Diagnostics.

specimen collection was 0.71% (95% CrI = 0.53%–0.92%) with informed priors and 0.69 (95% CrI = 0.52%–0.91%) with neutral priors. Our findings suggest that the non-commercial (HQ) and Roche tests have the highest sensitivities, and that the Roche and Abbott assays have the highest specificities.

Although most of them overlapped, the CrI estimates of the accuracy parameter often differed whether they were derived from informed versus neutral priors, indicating that the data do not fully support the information encoded in the informed prior. In such a situation, the decision to draw conclusions from either of these two approaches hinges on an individual's confidence in the prior information relative to their trust in the data's capacity to improve the current understanding of the research question at hand.

Seroprevalence estimates can vary greatly depending on the choice of prior parameter estimates [44], although this was not the case in our study. The CrIs obtained with informed and neutral priors were almost identical, which suggests that the data collected for this study support a seroprevalence of ~0.5%–0.9% during the first wave of the pandemic. Further, when used as a stand-alone test (in phase 1), the non-commercial (HQ) assay estimated the seroprevalence at 2.2%, which is three times as high as the estimate obtained by the two-phase BLCM. Therefore, without an established reference standard, choosing a single stand-alone assay is an arbitrary and suboptimal mean to estimate seroprevalence. Besides, evidence of specific differences in overall agreements were found between the two types of assays [39], suggesting a complementarity in urgent public health crises. Indeed, during the COVID-19 waves, both types of assays were important for prompt testing, monitoring and understanding the spread of the virus [40].

As mentioned in the result section, the CrI estimates of sensitivity obtained for the Abbott assay were statistically different when considering informed versus neutral priors. This variation illustrates the impact of prior distributions on diagnostic accuracy estimates. Bayesian model estimates typically balance prior knowledge and information gathered from collected data and are therefore subject to yield slight gaps in CrIs obtained with different prior assumptions.

The prevalence of SARS-CoV-2 was previously estimated at 0.7% (95% CrI = 0.5%–1.1%) during the first pandemic wave, based on a BLCM analysis of 8999 samples tested with four assays (including three in-house IgG ELISAs—the same academic assays used herein) [34]. In our study, 6810 samples were considered along with seven assays in a two-phase Bayesian model, and a slightly narrower CrI for prevalence was obtained. Although the higher accuracy achieved might have been due to the dataset itself, it could also be due to the larger number of tests, suggesting that the use of more assays can sometimes balance smaller sample sizes in terms of accuracy, even in a two-phase design. The plausibility of the conditional independence hypothesis has been checked using two posterior predictive check approaches. This is also supported by supplementary analyses in which a two-phase BLCM was run over all possible combinations of 2, 3 and 4 assays involved in phase 2. These analyses (Supporting Informations 3 and 4) yielded consistent estimates across assay combinations, and the CrIs narrowed as the number of assays increases. In addition, we have used donors' serologic status as a proxy for having a true history of infection. However, seronegative donors may have had a recent history of infection given the time needed for seroconversion to occur. In other words, the model considers that all individuals who had contracted SARS-CoV-2 had anti-SARS-CoV-2 antibodies at the time of donation. This oversimplification was necessary to assess seroprevalence. Additionally, only the HQ and Abbott assays were used to test the whole study sample ($N = 6810$), whereas the other assays were used to test only a subset ($N = 387$). This can be seen as a limitation, since it makes the phase 2 results dependent on those of phase 1, especially when prevalence is low.

However, the relatively small sample size involved in phase 2 was likely offset by the large number of assays considered. Assays targeting various SARS-CoV-2 antigens provide different and complementary biological information that likely improves the accuracy of parameter estimates.

Our analysis also highlights the usefulness of blood donors in health research. Despite its large sample size (i.e., nearly 7000 donors) and number of assays tested, the experimental part of our study was completed within only 2 months. Furthermore, costs were minimized because the personnel and infrastructure were already in place, and no additional recruitment efforts were necessary beyond those routinely deployed by our blood service. Blood services also maintain robust quality-control services that ensure samples are handled appropriately. Lastly, blood donors are broadly representative of the healthy adult population and are therefore an appropriate data source in public health research. Given these advantages, blood services are poised to have an increasing role in the conduct of studies similar to the one presented herein.

The SARS-CoV-2 pandemic has exposed the risks associated with new or emerging pathogens. Such events threaten public health, and so early efforts to limit disease spread may involve imperfect diagnostic tests. This analysis, which used routinely collected blood donor samples, shows that BLCMs can be used to estimate prevalence and the performance of diagnostic tests when a new or emerging disease rapidly spreads. The approach was reliable even with a two-phase sampling design, which can be useful to reduce costs and operating time. From a practical standpoint, two-phase BLCMs are especially relevant when prevalence is low and testing procedures are imperfect, costly and/or time-consuming. BLCM-derived estimates of diagnostic accuracy can also be used to adjust serosurvey results and better estimate seroprevalence, identify high-risk groups and inform public health decisions. Importantly, our analysis emphasizes that choosing a single stand-alone test is an arbitrary and suboptimal mean to estimate these parameters. This two-stage sampling design BLCM addresses these limitations by aggregating measures from several tests, thereby limiting potential biases that may emerge when a given test is considered as the reference standard [45]. While informative, our results could not be used directly to recalibrate the cut-off of an assay, except for our prevalence estimate.

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ACKNOWLEDGEMENTS

The project is entirely funded by the COVID-19 Immunity Task Force (CITF), which is supported by the Public Health Agency of Canada (PHAC). The views expressed herein do not necessarily reflect the views of the PHAC.

A.L., J.P., F.C.L., S.H.H. and C.P.Y. conceived and designed the study, A.L., J.P., C.P.Y., M.K., B.D.M., R.C., K.C., C.M., M.M., A-C.G. and C.C. collected the data, F.C.L., S.H.H. and A.L. analysed the data, with input from J.P. and C.P.Y. C.C., R.C., C.R. and M.P.C. helped interpret the results, A.L., S.H.H. and F.C.L. drafted the manuscript, and C.C., M.P.C., R.C., C.R., C.P.Y., M.K., K.C., A-C.G., B.D.M., M.M., A.J. and J.P. critically revised it for important intellectual content. All authors approved the final version to be published.

CONFLICT OF INTEREST STATEMENT

J.P. has received honoraria from Merck and Astra-Zeneca, is a site investigator for trials by MedImmune and Merck, and is a member of the National Advisory Committee on Immunization, all unrelated to the current work. A-C.G. has received research funds from a research contract with Providence Therapeutics Holdings, Inc for other projects. M.K. has received contract funding paid to his institution from Roche, Hologic and Siemens unrelated to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Camirand Lemyre F, Honfo SH, Caya C, Cheng MP, Colwill K, Corsini R, et al. Two-phase Bayesian latent class analysis to assess diagnostic test performance in the absence of a gold standard: COVID-19 serological assays as a proof of concept. Vox Sang. 2023;118:1069–77.

Received: 12 May 2023 | Revised: 5 September 2023 | Accepted: 25 September 2023

DOI: 10.1111/vox.13546

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Degree of blood safety of voluntary non-remunerated versus replacement blood donations: A multi-centre study of the large cohort of blood donors from two provinces of Pakistan

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Voluntary non-remunerated blood donors (VNRBDs) are recognized as being crucial for the safety and sustainability of national blood supplies. Systems based on replacement donors (RDs) pose high risks of transfusion transmissible infections (TTIs). Currently, only 10%–13% of blood donations are voluntary in Pakistan. No large-scale studies have been conducted to objectively evaluate the impact of the mode of donation on the frequency of TTIs, a gap this study aimed to fill.

Materials and Methods: The study was conducted at the Indus Hospital, Karachi. Data from a total of 591,820 blood donations were included from 1 October 2017 to 30 May 2021 and evaluated for type of donations and results of TTI testing, primarily performed on Architect i2000SR (Abbott). The TTIs tested include hepatitis B virus, hepatitis C virus, human immunodeficiency virus, syphilis and malaria.

Results: A total of 477,938 (80.7%) RDs and 113,882 (19.3%) VNRBDs were screened. Among these, 53,590 (9.06%) were positive for TTIs. There were 10.2% positive RDs (10.08–10.25 95% confidence interval [CI]) while 4.4% in VNRBDs (4.29–4.53 95% CI). Co-infections were observed in 2367 (0.4%) RDs, while 159 (0.02%) in VNRBDs. Geographically, the highest frequency of TTIs was observed in semi-urban areas of Sindh (11.2%) and Punjab (9.6%). A site-wise comparison of TTIs in RD versus VNRBD showed significant differences (p-value 0.00).

Conclusion: RDs are associated with higher frequencies of TTIs, compared with VNRBD. However, the study was unable to assess whether the significant difference was related to individual risk or repeat/first time status of the donors. Other important variables affecting frequency are the catchment area of the blood donors in Pakistan. Urban areas have less prevalence than semi-urban areas.

Keywords

blood donation, chemiluminescent immunoassay, co-infections, replacement blood donors, transfusion transmissible infections, voluntary non-remunerated blood donors

Highlights

- The Indus Hospital and Health Network in Pakistan has made the first large-scale attempt to transition from a fragmented, demand-driven blood supply to a coordinated, centralized blood system.

- This study is the first to compare the transfusion-transmitted infection (TTI) trends between voluntary, non-remunerated and replacement blood donors in an approximate sample size of 0.6 million from two large provinces of the country.
- Replacement donors are associated with a higher frequency of TTIs. Another important variable affecting the frequency of TTI is the catchment area in which the blood donor resides in Pakistan: urban areas have a lower prevalence than semi-urban areas.

INTRODUCTION

Transfusion of blood and its components is an essential therapeutic modality. Unlike most other therapeutics, the product has to be sourced from humans before being tested and processed in blood centres [1]. Meeting the demand for this therapeutic resource is hence reliant on proactive blood donor mobilization programmes. Countries that lack effective blood donor mobilization programmes thus not only suffer from chronic shortages of blood, but also place onus of blood procurement squarely on the patient and/or their families—promoting a mode of donations called 'replacement donations'. It essentially involves replacement of a unit of blood already in stock at a blood centre with blood donated by the replacement donor (RD), or as directed donations—whereby the patient is directly transfused the blood donated by RD following testing.

Pakistan is one of the countries where a national blood transfusion service is practically non-existent. In addition, most blood banks of Pakistan lack voluntary donor mobilization programmes—a reality that automatically translates into replacement donations being the primary source of blood for patients. According to current estimates, over 3.5 million units of blood are collected in Pakistan annually, of which 80%–85% of blood donations are from RDs [2, 3]. Furthermore, many studies have shown that the safest blood donations are those that are collected from voluntary non-remunerated blood donors (VNRBDs) [4, 5], and that RDs have higher rates of transfusion transmissible infections (TTIs) [6–8].

As even the most sensitive currently available screening methods for TTI testing can miss detection during the serologic window period. The reality of TTI testing is starkly different in low- and lower middle-income countries like Pakistan. In most centres across Pakistan, TTI testing is being performed by rapid devices with variable sensitivities [9–11]. Unsafe blood transfusions thus form a major risk factor for the spread of TTIs like hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV) and syphilis. Only few large-scale studies have been published from our region, which directly compare the TTI rates in replacement versus voluntary donations [12].

In the past decade, Indus Hospital and Health Network (IHHN) in Pakistan has made the first large-scale attempt towards transition from fragmented, demand-driven blood supply to a coordinated, centralized blood system. Emerging as the largest centralized blood service in Pakistan, IHHN initiated mobilizing voluntary donors through dedicated donor mobilization teams. Operating based on the WHO principles of safe blood as a universal human right, blood is provided through four regional blood centres (RBCs) and multiple hospital blood banks (HBBs) in two provinces of Pakistan (Sindh and Punjab) in urban, semi-urban and rural areas.

In the transition process, we have had the opportunity to directly compare the TTI trends in voluntary versus replacement donations in an approximate sample size of 0.6 million. The aim of the current study was to identify trends of voluntary donations and provide a detailed comparative analysis of TTIs in RD versus VNRBD across two large provinces of Pakistan. Considering the large sample size, the study is one of the few ones providing objective evidence for the need to eliminate RDs in favour of voluntary blood donor mobilization in low- and lower middle-income countries.

MATERIALS AND METHODS

Study design

The study was approved by the Institutional Review Board of IHHN. Blood donor data were collected from several IHHN sites, including Karachi (IHHNBC-KHI), Shahbaz Sharif Hospital, HBB Lahore (Bedian and Sabzazar), RBC Multan, RBC Bahawalpur, Recep Teyep Erdogan Hospital (RTEH) HBB Muzaffargarh (MZJ), RBC Jamshoro, Civil Hospital HBB Hyderabad and Civil Hospital HBB Thatta. All blood donors found fit according to pre-defined criteria [13]. Data were collected from all aforementioned sites from 1 October 2017 to 30 May 2021. A total of 591,820 healthy blood donors were thus included.

Study participants

Before donation, potential donors were required to answer a detailed universal donor health questionnaire (Annexure A), which included data regarding their general health, life style, current or past febrile illness, weight loss, chronic disease, unusual or excessive bleeding, drug history, dental procedure, previous blood donation or transfusion, sexual history and high-risk behaviours followed by a short general physical examination [11]. Vitals (temperature, blood pressure, pulse) and weight were also recorded. Haemoglobin (Hb) was measured by point of care testing on DiaSpect/Hemocue to exclude any donor with Hb < 12.5 g/dL. Moreover, inspection was made for any marks of injectable drug abuse or any skin lesion at the venipuncture site.

Donors were excluded if they were below 17 years or above 60 years, weighed <50 kg, had a history of jaundice, malaria, asthma,

engaged in high-risk behaviour (i.e., unsafe sexual practices, drug abuse), had a history of HBV, HCV, HIV or syphilis, or were apparently unhealthy or malnourished. In addition to the above-mentioned causes, donors were temporarily deferred in case of any history of invasive procedure/injections in the last 3 months [14].

Laboratory tests

All blood donors were screened using serological testing performed by chemiluminescent immunoassay (CLIA) method on Architect i2000 SR (Abbott Diagnostic, USA) for HBV, HCV, HIV and syphilis, following manufacturer's instructions. The tests detect HBV surface antigen (HBsAg), anti-HCV antibodies, p24 antigen and HIV 1/2 antibodies and antibodies to *Treponema pallidum*. Screening for malaria was conducted through immunochromatographic test (ICT) using ACU Check kits. All reactive results were repeated and re-checked on the same sample using the same method.

Data analysis

Data were analysed using SPSS version 24. Descriptive statistics are reported as mean ± SD for continuous data and frequency (percentage) for categorical variables. Multiple response chi-square/Fisher's exact test was applied to find the association of donation types with age groups of donors and regions with seroprevalence of TTIs. *p*-Value <0.05 was considered as significant.

RESULTS

A total of 591,820 healthy blood donors (RD = 477,938 [80.7%], VNRBD = 113,882 [19.3%]) were screened at eight sites of IHHN. The highest number of VNRBDs was observed from Karachi 66,178 (11.2%) and highest RDs from Multan 184,808 (31.2%). Among these donors, 579,748 (97.9%) were male, 12,070 (2.04%) were females, while 2 (0.06%) were transgender. Age distribution according to type of donors at each site is depicted in Figure 1. In screening assays, 53,590/591,820 (9.06%) donors were reactive for various TTIs (Table 1). Among donors positive for TTIs, 5018 (4.4%) were VNRBDs, while 48,572 (10.2%) RDs were positive for any TTI, which reflect many fold higher rate of infection in RDs (*p*-value <0.05).

Because the study comprises different sites of the two large provinces of the country, the prevalence of TTIs was also assessed at intra-provincial level where the main centres of the province, that is, Karachi (a metropolitan city) and Lahore, were compared with the other sites to see significant difference, if present. The TTI positivity

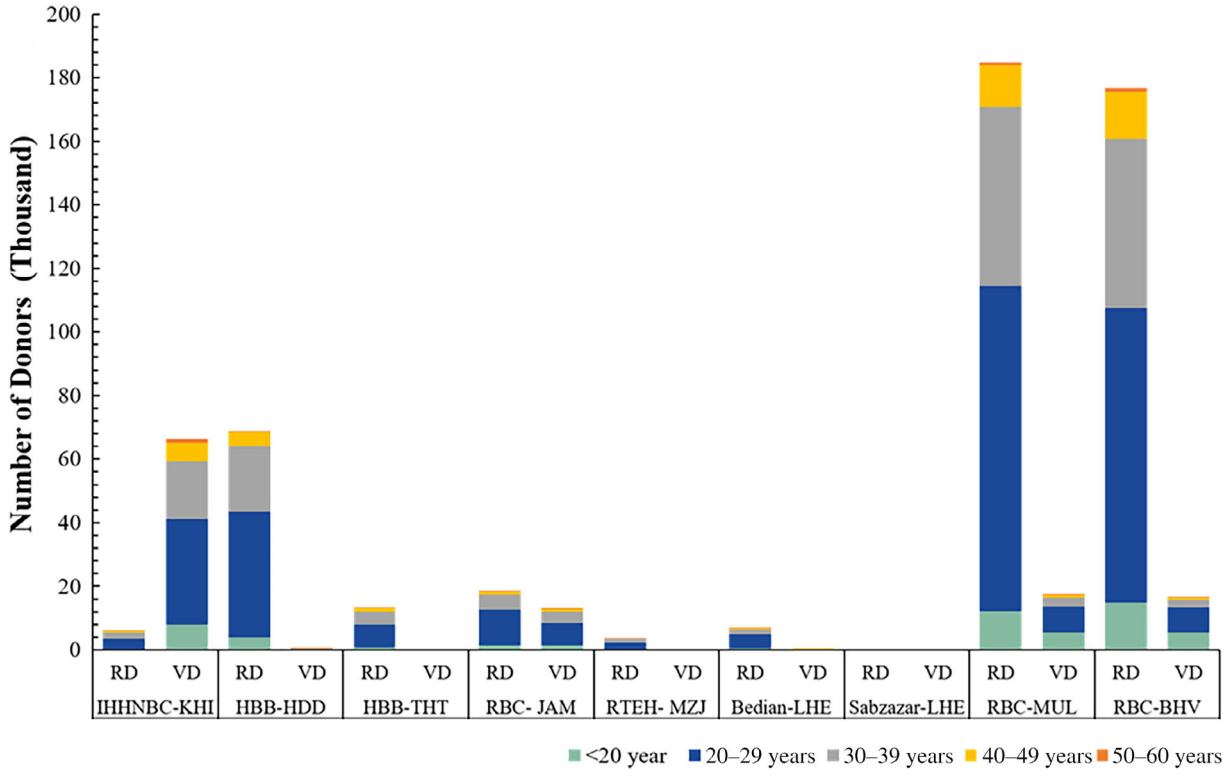

FIGURE 1 Distribution of donors at all sites according to age groups and the type of donations. HBB-HDD, Hospital Blood Bank Hyderabad; HBB-THT, Hospital Blood Bank Thatta; IHHNBC-KHI, Indus Hospital and Health Network sites, including Karachi; LHE, Lahore; RBC-BHV, regional blood centre Bahawalpur; RBC-JAM, regional blood centre Jamshoro; RBC-MUL, regional blood centre Multan; RD, replacement donor; RTEH-MZJ, Recep Teyep Erdogan Hospital Muzaffargarh; VD, voluntary donors.

TABLE 1 Total donors drawn and transfusion transmissible infections (TTIs) at each site.

	Total drawn = 591,820		Total TTIs = 53,590 (9.06%, 95% CI 8.98–9.13)				
			RD		VNRBD		
Site	RD	VNRBD	*n*	% (95% CI)	*n*	% (95% CI)	*p*-Value
IHHNBC-KHI	5873	66,178	317	5.40 (4.82–5.98)	2048	3.09 (2.96–3.23)	0.000[a,*]
RBC-MUL	184,808	17,567	18,697	10.12 (9.98–10.26)	1217	6.93 (6.56–7.31)	0.000[a,*]
RBC-BHV	176,735	16,525	17,412	9.85 (9.71–9.99)	875	5.30 (4.96–5.65)	0.000[a,*]
RTEH-MZJ	3531	32	169	4.79 (4.11–5.54)	0	0	0.402[b]
HBB-LHE	6702	139	126	1.88 (1.57–2.23)	0	0	0.186[b]
RBC-JAM	18,451	13,009	2385	12.93 (12.45–13.42)	846	6.50 (6.09–6.94)	0.000[a,*]
HBB-HDD	68,635	417	7369	10.74 (1.51–10.97)	31	7.43 (5.11–10.39)	0.000[a,*]
HBB-THT	13,203	15	2097	15.88 (15.26–16.52)	1	6.67 (0.17–31.95)	0.491[b]
Total	477,938 (80.7%)	113,882 (19.3%)	48,572	10.16 (10.08–10.25)	5018	4.41 (4.29–4.53)	0.000[a,*]

Abbreviations: CI, confidence interval; HBB-HDD, Hospital Blood Bank Hyderabad; HBB-THT, Hospital Blood Bank Thatta; HBB-LHE, Hospital Blood Bank Lahore; IHHNBC-KHI, Indus Hospital and Health Network sites, including Karachi; RBC-BHV, regional blood centre Bahawalpur; RBC-JAM, regional blood centre Jamshoro; RBC-MUL, regional blood centre Multan; RD, replacement donor; RTEH-MZJ, Recep Teyep Erdogan Hospital Muzaffargarh; VNRBD, voluntary non-remunerated blood donors.

[a]Chi-square test.

[b]Fisher's exact test.

*Significant value.

rates were compared between urban and semi-urban cities of Sindh and Punjab (Table 2). The prevalence of TTIs was highest in semi-urban Sindh, with Thatta showing the highest incidence. Further, as depicted in Table 2, the urban cities, Karachi and Lahore, showed lower seroprevalence for TTIs. In semi-urban cities, Thatta from Sindh and Multan from Punjab revealed the highest burden of TTIs. A detailed description of the prevalence of each TTI among RD and VNRBD at various sites of the country is displayed in Table 3. Among all TTIs, HCV and MP were found to be the most and the least frequent in both types of the donors, respectively. The highest rate of HCV, HBV and syphilis was observed in RDs of Thatta followed by Jamshoro, Multan and Bahawalpur. The frequency of co-infections was also analysed in both groups to get further insight into the infection patterns. In RDs, co-infection was observed in 2367 (0.5%), while in VNRBD, only 159 (0.1%) revealed co-infection for more than one TTI. Among these co-infections, co-existing hepatitis B and C was observed in highest frequency, that is, 990/2367 (42%) followed by HBV and syphilis co-infection in 436/2367 (18%) donors. The overall rate of co-infections according to the type of donors is shown in Figure 2.

DISCUSSION

Blood transfusion is a life-saving measure that supports millions of patients around the world. However, an ongoing challenge faced by many developing countries is to collect sufficient donations from voluntary donors [15]. In addition, despite the availability of stringent donor recruitment guidelines and highly sensitive laboratory testing in some countries, sub-optimal testing for TTIs still prevails in Pakistan and other developing countries. This makes the case for switching to VNRBD even stronger, as the risk of TTIs is likely to be low to begin with, obviating some detriment on account of escape of TTI detection through sub-optimal testing. In this study, a large cohort of VNRBD is compared with RD to identify the prevalence of TTIs and determine the geographic areas in Pakistan with a predilection for higher TTI prevalence among blood donors.

Most of the donors in our study were males, 579,748 (98%), with the highest proportion of donors (54%) between 20 and 29 years of age in both RD and VNRBD. Our results indicate that young males in the community were more inclined towards blood donations and are major contributors in meeting the demands of blood supply. On the other hand, this age group pattern in the study cohort is also reflective of the results of latest census, which shows that more than 50% population falls in 18 years and above age group, and the age group representing youth (15–24 years) constitutes 20% of the total population [16]. These large multi-centre data revealed only 2% contribution by female donors. Several cultural, social and nutritional factors contribute to fewer blood donations by female donors. In general, low weight and iron deficiency anaemia are quite common among females, resulting in high deferral. Other contributing factors include fear of needle prick, weakness and higher susceptibility to vasovagal reactions. Similar pattern of age and gender distribution among blood donors was reported from a recent study from our region, which clearly demonstrate male preponderance [10]. A more focused campaign to recruit female donors is required at the national level.

Of 591,820 healthy blood donors, the highest number of RDs was observed from Multan followed by Bahawalpur, while VNRBDs were from Karachi. To the best of our knowledge, this is the first study from Pakistan comprising a large cohort of VNRBD. The Indus

TABLE 2 Distribution of transfusion transmissible infections according to type of donations at all sites.

			Total	HBsAg			Anti-HCV			HIV			Syphilis			MP		
			RD															
Province	Type of sites	Sites	VNRBD	RD (%)	VD (%)	*p*-Value	RD (%)	VD (%)	*p*-Value	RD (%)	VD (%)	*p*-Value	RD (%)	VD (%)	*p*-Value	RD (%)	VD (%)	*p*-Value
Sindh	Urban	IHHNBC-KHI	5873	101 (1.7)	682 (1.0)	0.00[a,*]	117 (2.0)	795 (1.2)	0.00[a,*]	9 (0.2)	70 (0.1)	0.29[a]	87 (1.5)	493 (0.7)	0.00[a,*]	3 (0.1)	8 (0)	0.0[a,*]
			66,178															
	Semi-urban	HBB-HDD	68,635	1883 (2.7)	12 (2.9)	0.867[a]	3093 (4.5)	10 (2.4)	0.03[a,*]	122 (0.2)	3 (2.1)	0.00[b]	2128 (3.1)	5 (1.2)	0.02[a,*]	143 (0.2)	1 (0.2)	1.00[b]
			417															
		HBB-THT	13,203	483 (3.7)	0 (0)	1.00[b]	793 (6.0)	1 (6.7)	1.00[b]	30 (0.2)	0 (0)	1.00[b]	729 (5.5)	0 (0)	1.00[b]	62 (0.5)	0 (0)	1.00[b]
			15															
		RBC-JAM	18,451	585 (3.2)	282 (2.2)	0.00[a,*]	978 (5.3)	330 (2.5)	0.00[a,*]	31 (0.2)	17 (0.1)	0.40[a]	752 (4.1)	207 (1.6)	0.00[a,*]	39 (0.2)	10 (0.1)	0.0[a,*]
			13,009															
Punjab	Urban	HBB-LHE	6702	28 (0.4)	0 (0)	1.00[b]	79 (2.0)	0 (0)	0.411[b]	15 (0.2)	0 (0)	1.00[b]	4 (0.1)	0 (0)	1.00[b]	0	0	-
			139															
	Semi-urban	RBC-MUL	184,808	5039 (2.7)	461 (2.6)	0.425[a]	9115 (4.9)	566 (3.2)	0.00[a,*]	251 (0.1)	17 (0.1)	0.17[a]	4271 (2.3)	172 (1.0)	0.00[a,*]	21 (0)	1 (0)	1.00[b]
			17,567															
		RBC-BHV	176,735	4710 (2.7)	314 (1.9)	0.00[a,*]	8762 (5.0)	398 (2.4)	0.00[a,*]	288 (0.2)	20 (0.1)	0.19[a]	3618 (2.0)	140 (0.8)	0.00[a,*]	34 (0)	3 (0)	1.00[b]
			16,525															
		RTEH-MZJ	3531	60 (1.7)	0 (0)	1.00[b]	64 (1.8)	0 (0)	1.00[b]	8 (0.2)	0 (0)	1.00[b]	36 (0.1)	0 (0)	1.00[b]	1 (0)	0 (0)	1.00[b]
			32															

Abbreviations: HBsAg, hepatitis B virus surface antigen; HBB-HDD, Hospital Blood Bank Hyderabad; HBB-THT, Hospital Blood Bank Thatta; HBB-LHE, Hospital Blood Bank Lahore; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IHHNBC-KHI, Indus Hospital and Health Network sites, including Karachi; MP, malarial parasite; RBC-BHV, regional blood centre Bahawalpur; RBC-JAM, regional blood centre Jamshoro; RBC-MUL, regional blood centre Multan; RD, replacement donor; RTEH-MZJ, Recep Teyep Erdogan Hospital Muzaffargarh; VD, voluntary donors; VNRBD, voluntary non-remunerated blood donors.

[a]Chi-square test.

[b]Fisher exact test.

*Significant value.

TABLE 3 Intra-provincial distribution of various transfusion transmissible infections (TTIs) among blood donors.

Locations (*n*)	HBsAg% (95%CI)	HCV% (95% CI)	HIV% (95% CI)	Syphilis% (95%CI)	MP% (95% CI)	Total TTI% (95% CI)
Urban Sindh (Karachi) 72,501	1.09 (1.01–1.16)	1.27 (1.19–1.35)	0.11 (0.09–0.14)	0.80 (0.74–0.87)	0.02 (0.01–0.03)	3.28 (3.15–3.41)
Semi-urban Sindh 113,730	2.85 (2.76–2.95)	4.58 (4.46–4.70)	0.18 (0.16–0.20)	3.36 (3.26–3.47)	0.22 (0.20–0.25)	11.19 (11.01–11.38)
Urban Punjab (Lahore) 6841	0.41 (0.27–0.59)	1.15 (0.92–1.44)	0.22 (0.12–0.36)	0.06 (0.02–0.15)	0	1.84 (1.54–2.19)
Semi-urban Punjab 399,198	2.65 (2.60–2.70)	4.74 (4.67–4.80)	0.15 (0.13–0.16)	2.06 (2.02–2.11)	0.02 (0.01–0.02)	9.61 (9.52–9.70)

Note: Significant statistical difference (<0.05; chi-square test) was observed between urban Sindh and semi-urban parts of the province in regards to the TTIs. For urban and semi-urban Punjab, significant association was observed for all of the infections except HIV (chi-square test) and MP (Fisher exact test).

Abbreviations: HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MP, malarial parasite.

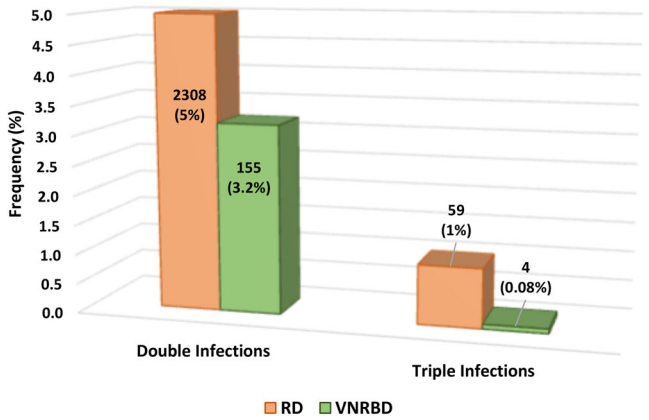

FIGURE 2 Distribution of co-infections between replacement (RD) and voluntary non-remunerated blood donors (VNRBDs).

Hospital Blood Centre, Karachi, constitutes the major proportion of VNRBD. A recently published study from Khyber Pakhtunkhwa showed more than 50% voluntary donations in the total cohort, however it was a single-centre study [17]. In comparison, our data were derived from multiple sites, hence more representative of the overall trend across the country. Published data from our neighbouring country, India, also showed a similar pattern of voluntary and replacement donations, as observed in our study [18, 19].

A big challenge in a culture of replacement donations is the promotion and retention of VNRBD. A continuous effort at the community level is required to change these practices. According to a report published by WHO, there is obvious progress in voluntary unpaid blood donations in high-income countries, while low-income countries like Pakistan are still struggling to sensitize their nation towards voluntary donations [15]. Dedicated professional donor mobilization teams are working in all the RBCs of IHHN-BTS to improve public awareness about voluntary blood donations that have initiated organized collection of VNRBDs at all sites, with the highest number in Karachi. Data from other sites showed that the trend in voluntary donations is still low, hence leading to an increased prevalence of TTIs. Lack of knowledge and misconceptions about blood donation in our community are the major factors behind the low number of VNRBDs [20].

A WHO fact sheet showed that the prevalence of TTIs is directly proportional to the economic status of countries. High-income countries with developed public health services, effective vaccination programmes and good literacy rates show lower frequencies of TTIs [15]. Pakistan is still facing these health- and education-related challenges, and consequently higher rate of TTIs is observed. The results of our study are significant in terms of detailed intra-provincial analysis being published for the first time from this region.

If we compare our results geographically, a significant difference for all TTIs was observed among the donors from Karachi in comparison with other sites of Sindh [21–23]. In general, there is a variation between the positivity rates in different studies, which might be due to difference in total sample size, strength of preliminary screening of donors and test kits, and algorithms used by different blood banks. Our results demonstrate that the rate of HIV is low but is rising with a similar pattern at all sites.

Like Sindh, the results from Punjab showed a significantly higher rate of TTIs from semi-urban Punjab in comparison with urban Punjab. However, data from urban Punjab are very small, but are suggestive of low positivity for all TTIs. Multan from semi-urban Punjab revealed the highest rate of TTIs, and these numbers are higher than the previously published study from the same region. Contrary to our findings, the seroprevalence of TTIs was found higher in other studies reported from Bahawalpur [24]. It is noteworthy to highlight that the results reported based on intra-provincial analysis are unique to this study and seek urgent attention from higher authorities.

In solitary infections, the highest positivity was observed for HCV from HBB Thatta followed by RBC Jamshoro. In a study from semi-urban Sindh, the highest frequency was reported for HCV, which is in agreement with our study [23]. Studies from Punjab showed relatively lower prevalence of HBV and HCV [25]. A recent study conducted by Abdullah and co-workers reported 1.65% HBV-positive cases among 76,530 blood donors in 2016–2017 [26]. In addition, Rauf and colleague reported 1.12% donors reactive for HBV in Faisalabad [27].

In a previous study from Karachi, screening of 16,602 blood donors showed syphilis positivity in 2.1% of blood donors [21]. The

high prevalence of syphilis in the blood donor population is alarming as most of the blood donation centres in Pakistan do not routinely perform syphilis screening and donors are reluctant to declare the disease during pre-donation interviews due to the stigmatization. In a recent study, Sultan et al. reported *T. pallidum* in 0.91% of the blood donors [28]. In the succeeding year, Saeed et al. reported an overall frequency of syphilis in 284 of 18,274 (1.55%) healthy blood donors in Lahore [5]. While the incidence rate of 1.10% has been reported from Faisalabad [27]. In contrast to previously published studies, a rising trend is observed for syphilis in RDs at all sites of IHHN [21]. The positivity of syphilis from semi-urban areas of Sindh is much higher in our study compared with previous local studies. As cross reactivity is very common in treponemes, additional confirmatory testing is essential to evaluate the rate of false positivity. Although *T. pallidum* is sensitive to cold, transmission by blood products stored below 20°C is rare; however, the transfusion of platelets and level of organisms present in blood needs to be considered as potential source of transmission. HIV positivity shows similar pattern of prevalence at all sites and it is variably higher compared with previously published studies [21, 22]. Although malaria is common in this region, the prevalence in blood donors is still less than 1%. In a previous study, 0.89% of donors were found reactive for malarial parasite; however, our study revealed much lower rates of positivity for malaria from all sites of IHHN except Thatta [27].

Determination of co-infections among healthy blood donors has its own significance in terms of identifying the high 'risk behaviour' of those donors. All these infections share a common mode of transmission. Published literature suggests that the presence of co-infections points towards indulgence in high-risk behaviour like needle sharing by drug abusers and unsafe sexual practices. In the current study, the prevalence of co-infections was 0.42% in all blood donors. However, the results of a local study conducted in Karachi from 2013 to 2015 revealed reactivity for multiple TTIs (0.35%) among blood donors [2].

According to recently published studies, the cumulative frequency of TTIs among all blood donors in Pakistan varies between 4% and 9%, with an overall higher positivity in RDs as compared with VNRBDs [2, 5]. In contrast to all published studies from Pakistan, our study constitutes the highest number of VNRBDs. Both cohorts were compared for each TTI separately as well as for co-infections at all sites, and the results showed a consistently high rate of positivity in RDs. Our data showed lower rate of TTIs in Karachi that may be due to mainly urban site with higher literacy rate and higher voluntary donations. A recently published study from Karachi showed 8.07% incidence of TTIs; however, in contrast to our study, the cohort was mainly comprised of RDs [22]. Co-infections including double and triple infections were observed mainly in RD in which co-existing HBV and HCV combination was most frequent followed by HBV and syphilis. In relation with the present study, Ehsan and colleagues recently reported the frequency of co-infections among blood donors varying between 0.0099% and 0.35%. However, the highest number of co-infections was syphilis and HCV followed by HBV and HCV [2]. A study conducted on venereal infections in blood donors revealed significant difference in RD and VNRBDs [28]. Similarly, in comparison with RD, co-infection rate in our study was considerably low among VNRBDs, again providing evidence for the safest donations.

The limitations of the present study include the fact that the data for Lahore site are small, which may not be representative of the urban areas in Punjab. Another limitation of the study is the lack of supplemental testing to evaluate the possibility of false positivity.

In conclusion, the study showed higher prevalence of TTIs among RDs in comparison with VNRBDs. The highest prevalence was observed for HCV in both types of donors. The difference between urban and semi-urban areas is significant with higher rates of overall TTIs in semi-urban areas. Pakistan is in dire need of substantial increase in voluntary blood donations in order to maintain a safe and sustainable blood supply.

ACKNOWLEDGEMENTS

We thank Ms. Mamona Mushtaq, the former research associate, Indus Hospital and Research Center, Karachi, for her contribution in this work.

S.J. conceived and designed the manuscript and is also responsible and accountable for the accuracy and integrity of the work, N.M. drafted the initial manuscript, A.A. was involved in data collection and analysis, J.A. and A.N. were involved in critical review and editing of the manuscript and F.M. was involved in critical review and final approval. All authors have approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jamal S, Mansoor N, Ali A, Nadeem A, Aijaz J, Meraj F. Degree of blood safety of voluntary non-remunerated versus replacement blood donations: A multicentre study of the large cohort of blood donors from two provinces of Pakistan. Vox Sang. 2023;118:1078–85.

Received: 9 May 2023 | Revised: 11 September 2023 | Accepted: 18 September 2023

DOI: 10.1111/vox.13542

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Current state of technical transfusion medicine practice for out-of-hospital blood transfusion in Canada

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Canadian out-of-hospital blood transfusion programmes (OHBTPs) are emerging, to improve outcomes of trauma patients by providing pre-hospital transfusion from the scene of injury, given prolonged transport times. Literature is lacking to guide its implementation. Thus, we sought to gather technical transfusion medicine (TM)-specific practices across Canadian OHBTPs.

Materials and Methods: A survey was sent to TM representatives of Canadian OHBTPs from November 2021 to March 2022. Data regarding transport, packaging, blood components and inventory management were included and reported descriptively. Only practices involving Blood on Board programme components for emergency use were included.

Results: OHBTPs focus on helicopter emergency medical service programmes, with some supplying fixed-wing aircraft and ground ambulances. All provide 1–3 coolers with 2 units of O RhD/Kell-negative red blood cells (RBCs) per cooler, with British Columbia trialling coolers with 2 units of pre-thawed group A plasma. Inventory exchanges are scheduled and blood components are returned to TM inventory using visual inspection and internal temperature data logger readings. Coolers are validated to storage durations ranging from 72 to 124 h. All programmes audit to manage wastage, though there is no consensus on appropriate benchmarks. All programmes have a process for documenting units issued, reconciliation after transfusion and for transfusion reaction reporting; however, training programmes vary. Common considerations included storage during extreme temperature environments, O-negative RBC stewardship, recipient notification, traceability, clinical practice guidelines co-reviewed by TM and a common audit framework.

Conclusion: OHBTPs have many similarities throughout Canada, where harmonization may assist in further developing standards, leveraging best practice and national coordination.

Keywords

bleeding, haemorrhage, pre-hospital transfusion, transfusion medicine, trauma

Highlights

- In eight Canadian out-of-hospital blood transfusion programmes (OHBTPs), the majority focus on providing O RhD/Kell-negative red blood cells (RBCs) to rotor-wing transportation vehicles, with some also providing to fixed-wing and ground vehicles.
- All have routine inventory exchanged thrice or twice a week, with 1–3 coolers that are validated for storage durations ranging from 72 to 124 h.
- All programmes have methods of managing wastage, documenting units issued, reconciliation after transfusion and transfusion reaction reporting, and all incorporate training, although there is opportunity for harmonization.

INTRODUCTION

Trauma is one of the world's leading causes of mortality [1], with haemorrhage being one of the principal causes of death for this population [2, 3]. The survival of trauma patients suffering from haemorrhage is improved by transfusion therapy as well as by the speed of its initiation [4, 5]. Other causes of haemorrhagic shock include aneurysmal, gastrointestinal, peri- or post-operative and obstetric haemorrhage, resulting in an estimated 400,000 deaths per year worldwide [6–9]. Out-of-hospital blood transfusion (OHBT) has been associated with improved patient outcomes in major trauma patients when transport times are longer than 20 min [10]. OHBT programmes (OHBTPs) provide blood components and products to mitigate the mortality and morbidity related to major haemorrhage.

Canada is the second largest country in the world, spanning nearly 10 million square kilometres of access- and weather-challenged geography, with most of the population concentrated along the southern border. This, in combination with healthcare that is largely regionalized, makes access to blood products potentially limited, and the blood carried by critical care transport teams in OHBTPs in some circumstances is the first available to critically ill and injured patients. Reducing long transport times to centres providing definitive care, whether for transporting patients from the field or for inter-facility movement, has the potential to significantly improve clinical outcomes.

Though the literature is not conclusive in demonstrating consistent evidence for beneficial effects of OHBT [11–15], such programmes have been expanding in terms of implementation and breadth throughout Canada, as has been the case worldwide [16]. In Canada, the first OHBTPs started with the Shock Trauma Air Rescue Service (STARS) in Saskatchewan and the British Columbia Emergency Health Services (BCEHS) for inter-facility transport in 2013. Since then, other Canadian OHBTPs have emerged in different jurisdictions.

Despite the number of programmes already implemented, current literature and regulatory bodies have gaps in providing clear guidance for OHBTP practices in relation to laboratory technical policies and processes. Typically, hospital policies are applied and extrapolated for OHBT practice. To harmonize and coordinate best practices in Canada, stakeholders from the various OHBTPs and the transfusion medicine (TM) services are collaborating through the Canadian Prehospital and Transport Transfusion (CAN-PATT) Blood Programme Network [17]. We sought to conduct an environmental scan of technical TM-specific practices across Canadian OHBTPs. System similarities and differences across sites and programmes are presented to facilitate reflections on current practices and the development of future standards and potential optimal configurations that can be implemented.

METHODS

An online survey was developed and circulated through email to a technical and/or nursing representative at each of the Canadian OHBTPs regarding their technical TM-specific practice (T.R., S.F., A.B., C.C., M.F., Q.H., R.L., P.L., B.L., J.M. and L.S.). Given the technical focus of the survey, the survey content was developed and finalized by a nursing lead, medical laboratory technologist lead and medical lead from two programmes (S.F., T.R. and A.W.S.) and then sent out again to the CAN-PATT members for completion. CAN-PATT represents a multidisciplinary team including at least one physician OHBTP medical lead and the TM lead that supplies the OHBTP, and also includes other critical care paramedic and physician leaders. CAN-PATT members who were sent and contributed to the survey were included as collaborators in this paper.

Data collected and included are presented in Table 1.

Technical aspects from Canadian OHBTPs were compiled in the survey by technical practice leads and/or medical laboratory technologists involved in the individual provinces' OHBTPs. For the programme from Nova Scotia, the information was filled out by their utilization management coordinator. Approval and consent from the programmes managers and all participants were obtained to use the compiled data for descriptive analysis.

A descriptive comparison was made of the technical practices assessed in the survey. The differences and similarities were noted, which are discussed below. The Canadian OHBTPs technical practice specificity was also compared with those of other active international programmes. The stop date for data collection was set at March 2022, recognizing that the data needed to be finalized because of the constant evolution and expansion in Canadian OHBTPs. Only the practices of the programmes carrying emergency-use blood on board were assessed, rather than those solely for inter-facility and/or home transfusion programmes.

TABLE 1 Data abstracted from Canadian out-of-hospital blood transfusion programme (OHBTPs).

Data collected in the online survey	
OHBTP transportation type	Fixed-wing
	Rotor-wing
	Ground ambulance
Blood component and/or product information	Type of component and/or product provided
	Number of component and/or product provides
	Blood group
	Age of RBC units
Transport container information	Type of container
	Number of containers provided
	Packing special consideration
	Container size
	Validation for maximum storage time for blood component and/or product's temperature
	Restriction for thermal packing transport
Storage and temperature monitoring	Storage conditions of the carry bags
	Internal and external product's container temperature monitoring
	Usage of GPS tracking
Inventory exchange frequency	
Management of returned product considered for re-integration to TM inventories	
TM laboratories and clinical documentation	
Environment, Health, and Safety (EHS) training programme	

Abbreviations: GPS, global positioning satellites; RBC, red blood cell; TM, transfusion medicine.

RESULTS

During the study period (November 2021–March 2022), surveys were sent out to each of the leads from the various Canadian OHBTPs. All surveys were returned and included in the analysis. In total, all eight Canadian critical care transport organizations with an OHBTP were surveyed, which are shown geographically in Figure 1. The organizations included are listed from west to east: BCEHS which contains bases within Greater Vancouver and Nanaimo bases; STARS Alberta; STARS Saskatchewan, which is divided into Regina and Saskatoon regional programme; Saskatchewan Air Ambulance (SAA; where blood is supplied from Saskatoon); ORNGE (air ambulance service and OHBTP in Ontario) (Toronto Island), covering southern Ontario

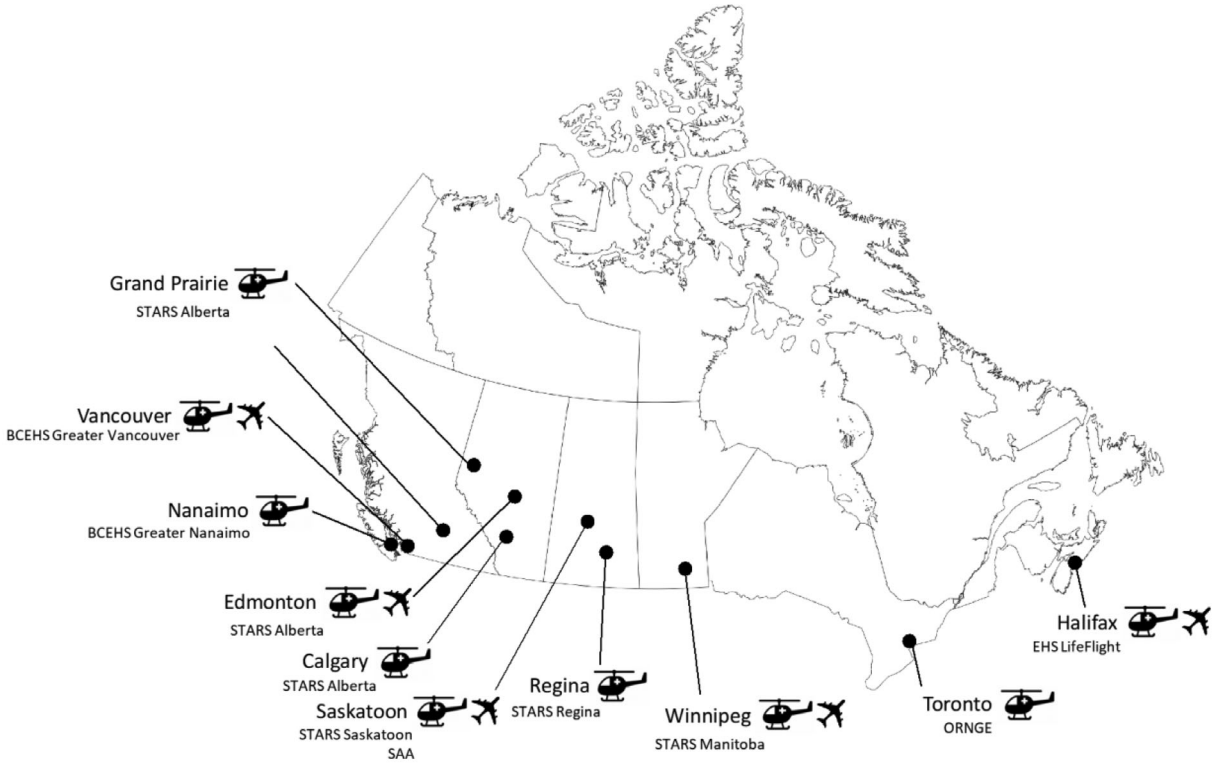

FIGURE 1 Helicopter icons signify the programme location supplies rotor-wing transportation; and airplane icons signify the programme location supplies fixed-wing transportation.

expanding to other sites across the province; and EHS LifeFlight (Nova Scotia). All OHBTPs participated in the survey. Data were collected from respondents from November 2021 to March 2022. A summary of the survey results is given in Table 2. A descriptive report previously published found the annual transfusion rates of these programmes as ranging from <1% to 7% [17].

OHBTP transportation type

All OHBTPs use various modes of transport. BCEHS Vancouver and EHS LifeFlight use ground ambulances and rotary and fixed aircraft, ORNGE utilizes rotary and fixed-wing aircraft, SAA utilizes fixed-wing aircraft and STARS Saskatchewan and Alberta use rotary-wing aircraft only. BCEHS Nanaimo uses rotary-wing aircraft in addition to ground ambulance. BCEHS and ORNGE are both exploring the feasibility of expanding across all service areas.

Blood component and product information

In terms of blood component availability in Canadian OHBTPs, all programmes provide 2 units of RBC of unmatched group O RhD negative per thermal packaging container. In addition, these units are K-negative with the aim of preventing alloimmunization against RhD and K antigens in persons of childbearing potential, which would potentially lead to haemolytic disease of the foetus and newborn.

The selection of RBCs based on age of RBC units varies across programmes. The age of RBC units selected is not due to concerns about the safety of the units but due to logistics for either return to hospitals as part of redistribution or minimizing impact of outdating as OHBTP stock. ORNGE and STARS Regina currently do not have documented criteria concerning the age of selected RBC units. In the BCEHS Vancouver programme, the RBC units selected are the freshest units available. Selected units in STARS Alberta, STARS Saskatoon and SAA programmes need to be between 14 and 21 days from expiry and more than 10 days from expiry, respectively. For BCEHS Nanaimo, fresher units are not specifically required. For EHS LifeFlight, the selected RBCs need to be >7 days old.

In addition, the BCEHS Vancouver programme also provides 2 units of group A thawed plasma that is not titred for anti-A and anti-B isohemagglutinins, as part of a pilot research programme. Each cooler includes 2 units of thawed plasma and 2 units of RBCs per cooler. Providing plasma units require cooling of thawed plasma for 3.5 h at 1–6°C to meet the validated storage requirements in the transport cooler.

Some Canadian OHBTPs are considering adding factor concentrates such as prothrombin complex concentrates (PCCs) and fibrinogen concentrate (FC) to their out-of-hospital transfusion inventory for

TABLE 2 Summary of technical practices in Canadian out-of-hospital blood transfusion programmes (OHBTPs).[a]

	ORNGE (Toronto)	STARS (Regina)	STARS (Saskatoon)	SAA (Saskatoon)	STARS (Alberta)	BCEHS (Greater Vancouver)	BCEHS (Nanaimo)	EHS LifeFlight (Nova Scotia)
Transport type	Rotor-wing	Rotor-wing	Rotor-wing	Fixed-wing	Rotor-wing	Rotor-wing Fixed-wing Ground Ambulance	Rotor-wing Ground Ambulance	Rotor-wing Fixed-wing Ground Ambulance
Inventory products	RBCs group O Neg, K neg	RBCs group O Neg, K neg	RBCs group O Neg, K neg	RBCs group O Neg, K neg	RBCs group O Neg, K neg	RBCs group O Neg, K neg Thawed plasma group A	RBCs group O Neg, K neg	RBCs group O Neg, K neg
Inventory exchange frequency	Thrice weekly (M/W/F)	Every 48 h except weekends	Thrice weekly (M/W/F)	Thrice weekly (M/W/F)	Twice weekly	Thrice weekly (M/W/F)	Twice weekly (T/F)	Thrice weekly (M/W/F)
Transport container	Crēdo ProMed Series 4 4 L transport cooler							
Validation for storage time (h)	96	80	96	96	124	100	104	72
Internal Temperature monitoring	Data logger	Data logger	None	None	Data logger with external display with probes in 33% glycerol solution	Data logger (Temptale4)		Data logger (ELPRO)
Training programme	Online—elements from Bloody Easy Lite and in-house developed operational training	In house demonstration in STARS site for their trainer	Online training modules, in-house demonstrations and review of the standard operating procedure and clinical practice guideline		In house (following Alberta Health Services transfusion policy and procedure)	Formal training with EHS Bootcamp, lab orientation, operational checklist, and online annual training		Not available

Abbreviations: BCEHS, British Columbia Emergency Health Services; EHS, Environment, Health, and Safety; RBCs, red blood cells; SAA, Saskatchewan Air Ambulance; STARS, Shock Trauma Air Rescue Service.
[a]Shading in the table highlights notable differences.

coagulation factor replacement in lieu of thawed plasma. This is largely considered an acceptable transfusion practice in Canada as a substitution in centres where thawed plasma is not available [18]. However, the use of factor concentrates in trauma patients in lieu of plasma has not been conclusively shown to improve survival, and there is no evidence available specifically for out-of-hospital patients [18]. As of survey completion, the STARS Saskatchewan OHBTP had been actively planning implementation of PCC and FC use in out-of-hospital settings. Common limitations for expanding OHBTP to PCC or FC use are principally space concern in the transportation vehicle and storage logistic planning at the transportation base. Other OHBTPs continue to have interest in implementing PCCs and FCs.

Inventory exchange frequency

Inventory is routinely renewed or exchanged every other weekday (Mondays, Wednesdays and Fridays) for all OHBTPs except STARS Alberta and BCEHS Nanaimo where RBCs are exchanged twice a week. For all OHBTPs, inventory re-stocking is done after transfusion events. When RBC units are returned to the hospital blood bank, they must meet standards at visual inspection similar to processes used for RBC units being returned from hospital settings, and the components must have been maintained at 1–6°C temperatures in keeping with Canadian Standards Association (CSA) standards for storing blood components [19]. All programmes audit to manage wastage, although there is no current consensus on appropriate benchmarks. The survey did not investigate the amount of wastage resulting from OHBTPs.

Transport container information

All programmes utilize the Credo ProMed Series 4 4 L transport cooler (Pelican BioThermal, Plymouth, MA), with occasional use of Canadian Blood Services-approved shipping boxes. ORNGE-Toronto delivers three coolers, and STARS Alberta three coolers, with one cooler stored at each of the three bases. BCEHS Vancouver, STARS Regina, STARS Saskatoon and SAA each use up to two coolers per aircraft, while EHS LifeFlight and BCEHS Nanaimo use one cooler.

Each programme performs local validation for determining the maximum storage time for their coolers used, with subsequent validations incorporating different temperature environments. The STARS Regina and EHS Lifeflight OHBTPs use the cut-off of 72 h recommended by the manufacturer and have also internally validated this storage duration. The STARS Regina OHBTP has validated the maximum storage time for >80 h. The ORNGE, STARS Saskatoon and SAA OHBTPs have validated their coolers internally for 96 h, with BCEHS Vancouver validating their coolers to 100 h and BCEHS Nanaimo up to 104 h. STARS Alberta has the longest validated storage duration, reaching 124 h. Even though the cooler is validated for up to 124 h, the maximum storage time in practice is 96 h.

External storage condition and temperature monitoring

The storage conditions and restrictions for the transport coolers vary between the different OHBTPs. Most coolers are kept at room temperature for external storage conditions. The ORNGE programme monitors storage at room temperature and humidity. They ensure that the ambient temperature is between 0 and 25°C. STARS Saskatoon, Regina and SAA OHBTPs record daily external storage temperatures and also have continuous temperature monitoring. Similarly, the STARS Alberta OHBTPs store the closed cooler in a temperature-controlled room and not in the helicopter during downtime due to the possibility of extreme temperatures outside in their area. The two BCEHS OHBTPs store the coolers in a pharmaceutical-grade fridge with manual temperature monitoring in place when not in the field. During any transport, the cooler must be accompanied by a trained critical care paramedic. The only programme that has introduced external cooler temperature monitoring is STARS Regina, with the room temperature recorded once a day by OHBTP personnel. No coolers have location-based tracking through global positioning satellites (GPS), based on the survey. In the ORNGE programme, the room temperature at the base is monitored.

Temperature data loggers are used to ensure internal temperature monitoring meets Health Canada standards, with the STARS Saskatoon and SAA programmes using internal validation data to denote that, if the cooler has not been opened, the product temperature is adequate up to the maximum storage duration and products can be accepted back into inventory upon receipt in the blood bank. STARS Alberta and STARS Regina recently moved forward to use data loggers with an indication of abnormal temperatures viewable externally. The external probes in 33% glycerol solution are used to confirm storage temperatures when the flight crew opens the cooler. The solution is in place to mitigate false positive temperature alerts due to fluctuation in the ambient temperature measured using other temperature monitors. For BCEHS programmes, internal validation data denotes, that if the cooler has not been opened, the product temperature is appropriate for the product to be accepted back into inventory. In addition, for quality control to inform the clinical team, data loggers have an alarm set for 1–10°C to guide the clinical team in transfusion decisions if there is potential compromise (using temperature ranges allowed by Canadian standards for transport compared to storage temperatures at 1–6°C). These data loggers are stored in refrigeration temperature and have a 15-min delay before start recording once packed, to minimize false alarms. ORNGE is also using data loggers to monitor storage temperature. A shared concern from the OHBTPs about this aspect is the lack of standardized policy related to blood administration in the event of a data logger alarm.

TM laboratories and clinical documentation

All programmes have processes for documenting any issues with blood products, for reconciliation after transfusions for the hospital

lab information system and for recording transfusion reactions. The clinical and TM laboratory documentation is broadly performed throughout all OHBTPs but using different methods. ORNGE issues a blood product shipment and transfusion form which is completed if units are transfused. STARS Regina issues a voucher with a colour-coded patient arm band and unique identifying number in addition to a transport log and checklist for staff picking up the box. They also include a request for the release of unmatched blood. In Saskatoon, a blood product issue voucher is also produced. STARS Alberta issues a provincial final disposition form that includes a transport log and checklist for the staff transfusing the units. For BCEHS, the cooler transport record needs to be signed in and out with the laboratory-cooler exchange and disposition log. Furthermore, the BCEHS activation checklist includes the medical order, patient's sample collection, patient's clinical record and transfusion reaction record, if applicable. Finally, the EHS LifeFlight programme issues a blood transport log sheet form.

Training programme

Most programmes have specific TM education. BCEHS programmes use a combination online training modules adapted from the University of Toronto's Transfusion Camp for Non-Physician Prescribers [20], a laboratory orientation and a review of the standard operating procedure and clinical practice guideline. STARS Alberta/Saskatchewan sites and SAA utilize a combination of online training modules, in-house demonstrations and review of the standard operating procedure and clinical practice guideline as a part of their yearly competency training, while ORNGE uses a variety of online training modules adapted from the Bloody Easy Lite [21] and Blood on Board programme.

DISCUSSION

In this descriptive assessment of the technical aspects of the out-of-hospital transfusion practices in Canadian OHBTPs, the authors have identified similarities and differences across the various programmes. All programmes are using Credo cooler to provide RBC units that are RhD negative and Kell-negative. Inventory renewal, validation for maximum storage time for their coolers and methods to develop transfusing staff competency vary among Canadian OHBTPs. After collecting descriptive data on transfusion practice [17], we sought to compare Canadian practices, as there is limited information on the technical and operational aspects of practice in international OHBTPs when reviewing the current literature, which presents a challenge when applying it to Canadian practice and when seeking to implement best practice. Given that OHBTP practices are still emerging, even at the time of publishing this article, there will be updates in practice, including the inclusion of PCCs and FC in the STARS Saskatchewan and SAA programmes, expansion of the blood programmes to additional bases in the BCEHS and ORNGE programmes and the incorporation of Apple AirTags for cooler tracking in the BCEHS programme.

The literature available to date has focused on the clinical aspects of OHBTPs and the clinical impacts of OHBT with different types of blood products. Reviewing this literature shows similarities, although there are also some differences to our practice. A European Society of Anesthesiology survey reviewed the OHBTP practice [22] in 189 services from 14 European countries in 2016 and 2017. Although practice changes have been significant in the 5-year period since that survey, it demonstrated that rotor-wing aircraft were the most frequent transport vehicle used for blood products. In that report, 36% of the respondents reported the use of fresh plasma or lyophilized plasma. This is consistent with other OHBTPs providing blood components and products including group O low-titre whole blood in jurisdictions worldwide [16]. However, there is conflicting evidence on the utility of these additional components and products in the current OHBT literature, as well as limitations of availability and local regulations [12, 13, 23, 24].

Regarding the blood component use by OHBTPs around the world, London's Air Ambulance Charity in the United Kingdom, with the initiative 'Blood on Board', reported carrying group O negative RBC units [25] and demonstrated that the use of O negative RBC units in the out-of-hospital setting did not change the proportion of group O negative RBCs transfused overall. The Thames Valley Air Ambulance, a UK-based Air Ambulance organization, carries 2 units of O negative and K negative RBC units and 2 units of thawed blood group A plasma [26], similar to other UK OHBTPs and the BCEHS programme. The Norwegian helicopter emergency medical services (EMSs) implemented an OHBTP with freeze-dried plasma in 2013 and then transitioned to low-titre cold-stored whole blood in 2015, no longer carrying RBC units [27]. The use of whole blood is also emerging in programmes throughout the United States, with one of the first civilian ground EMS-reported programmes out of Texas in 2017 [28].

London's Air Ambulance previously reported using the Golden Hour Box TM (Pelican BioThermal, MN, USA), which contains 4 units of RBCs and a data-logging device [29]. The availability of 4 units of RBC units per box is typically more than that stored in coolers used in Canada. This cooler is validated to keep a steady-state temperature of 2–4°C for up to 72 h. The Thames Valley Air Ambulance is using an insulated Credo Cube cooler (Peli BioThermal, Maple Grove, Minnesota, USA) with a temperature logger contained in the box [26].

The European Society of Anesthesiology survey reassuringly showed no evidence of wastage [22] or loss of traceability when using blood products on board the emergency transport, but we need to be cautious using these results because the absence of official reports of wastage coming from a service does not mean there is no wastage. However, the importance of robust procedures for inventory exchange, documentation of transfusions and reconciliation after transfusions cannot be overstated. The Canadian OHBTPs have made this a significant focus of their respective programmes.

Recently, the Trauma, Hemostasis and Oxygenation Research-American Association of Blood Banks (THOR-AABB) Working Party [30] published recommendations for implementing OHBTPs

including some recommendations on the technical aspects of this practice covering the storage of blood products outside of the hospital blood bank and transportation in addition to the documentation of the out-of-hospital transfusion and communication with the hospital team. This Working Party based their recommendations on these aspects mainly on expert opinions, given the nature of OHBTPs being emerging practice. They recommend the validation of the coolers used to transport blood products, which is performed in all Canadian OHBTPs; however, they specify that it is not needed when continuous internal ambient air temperature monitoring is performed. They also provide a recommendation to specify periodically revalidating the coolers, although no particular details were suggested.

Health Canada standards for TM practice have traditionally focused on blood operators and hospital/regional transfusion services [19]. When applying these standards to the OHBTPs, hospital transfusion services interpret the standards and extrapolate as best as possible to ensure the safety and traceability of the transfusion processes.

As an example, there are differing interpretations around transportation and storage temperature requirements as applied to OHBTP. Storage temperatures are delineated to be at 1–6°C and transportation temperatures at 1–10°C, which are the same metrics found in Yazer and colleagues' [30] recommendations for RBC units based on AABB Standard. Some Canadian OHBTPs keep RBC units at storage temperature only, while other programmes allow coolers to be at transportation temperatures to be returned to inventory if in the aircraft for less than 24 h, as a temperature of 1–10°C is allowed if the transport duration is 24 h or less. The specific standard addressing transportation states that it is defined as between or within the healthcare establishment, in the same or between contiguous buildings. We believe standards providing guidance relating to OHBTPs could assist transfusion programmes and accreditation assessors.

Other aspects that we believe could be further harmonized and addressed in Canadian OHBTP practice include storage during extreme temperature environments, transfusion documentation practices onboard aircraft, stewardship, recipient notification, processes to maintain traceability, clinical practice guidelines co-reviewed by TM services and a common audit framework. Work has already begun in Canada in this regard through the CAN-PATT Blood Programme Network [17]. As an example, a modified RAND Delphi was used to develop consensus statements and audit frameworks to guide Canadian OHBTPs [31]. While geographical and jurisdictional differences can be respected, we believe principles and tenets can be shared.

The strength of this survey comes from the inclusion and collaboration of all current out-of-hospital and transport transfusion programmes in Canada, which allow an accurate representation of the current state. A limitation of this survey is that assessing current practice is not necessarily reflective of a 'gold standard', and given OHBT is a relatively nascent field, practice is under constant re-evaluation and change. Our article also does not describe tracking data and deviations for storage temperature, transport temperature and wastage, as well as actions from those deviations, which may be considered in the future and would provide guidance for other OHBTPs. There is still further work to be done to harmonize practices while accounting for different practice settings, where putative best practices have not been determined.

The results of this survey demonstrate that although OHBTPs across Canada employ similar technical practices, some variations remain. Further collaboration is needed to harmonize practice and coordinate national initiatives [17, 32].

ACKNOWLEDGEMENTS

We would like to thank the tireless work of critical care paramedics, transfusion medicine technologists and transfusion safety officers who support these programmes across Canada. We would also like to thank the Canadian Pre-hospital and Transport Transfusion (CAN-PATT) Blood Programme Working Group for facilitating the data-gathering for this project.

I.B.-N. performed the research and wrote the first draft of the manuscript. T.R., S.F. and A.W.S. collected and analysed the data. T.R., S.F., A.B., C.C., J.D., M.F., A.Gr, Q.H., R.La., P.L., Y.L., B.L., J.M., S.N., O.P., L.S. and J.T. provided the data and review for local practices used for the study. S.F., M.P., A.Gr., A.Gu., R.Le., Y.L., S.N., B.N., M.P., O.P. and J.T. provided critical review of the manuscript. I.B.-N. and A.W.S. designed the study and were responsible for the final version of the study.

CONFLICT OF INTEREST STATEMENT

Y.L. has research funding from Canadian Blood Services and Octapharma and is a consultant with Choosing Wisely Canada. A.W.S. has received consultancy fees from Octapharma Canada and honoraria from CSL Behring. The remaining authors do not have any conflicts of interest in relation to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Blais-Normandin I, Rymer T, Feenstra S, Burry A, Colavecchia C, Duncan J, et al. Current state of technical transfusion medicine practice for out-of-hospital blood transfusion in Canada. Vox Sang. 2023;118:1086–94.

Received: 16 April 2023 | Revised: 23 August 2023 | Accepted: 1 September 2023

DOI: 10.1111/vox.13536

SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

A case of haemolytic disease of the fetus and newborn attributed to a novel antigen in the RHAG blood group system

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: A newborn presented with jaundice in Thailand. The cord red cells tested positive by direct antiglobulin test (DAT) for an unknown maternal red cell antibody. Initial blood group sequencing suggested that the infant carried a novel variant *RHAG c.140T>C*, responsible for a low-prevalence antigen in the RHAG blood group system (ISBT 030). We report here on testing of samples from the infant's parents and older sibling to define a new antigen in the RHAG system.

Materials and Methods: Massive parallel sequencing (MPS) using a custom-designed panel was performed on all four family members. Extended serological testing was also performed to determine whether family members with the same variant as the infant showed reactivity with the antibody in the maternal plasma.

Results: We identified a novel single nucleotide variant (SNV) (*RHAG c.140T>C*, p.[Phe47Ser]) in samples from three of the four family members tested (the infant, the older sibling and the father). The variant was not detected in the mother's sample. Maternal plasma showed positive agglutination with all family members tested; however, when tested with routine panel cells, no reactivity was observed.

Conclusion: This case study showed that the presence of the novel variant (*RHAG c.140T>C*), encoding a p.(Phe47Ser) change in the RhAG glycoprotein, was the apparent cause of incompatibility between maternal plasma and that of red cells from the proband, father and older sibling of the proband. We propose this variant to be a new low-prevalence antigen in the RHAG blood group system.

Keywords

blood group, haemolytic disease of the fetus and newborn, massive parallel sequencing, RHAG, serological testing, Rh-associated glycoprotein

Highlights

- We report the resolution of a case of haemolytic disease of the fetus and newborn with serological and molecular family studies that showed inheritance of a novel paternally derived antigen by two of his children.

- Testing identified this antigen to be caused by a novel variant (*RHAG c.140T>C*), encoding a p.(Phe47Ser) change in RhAG.
- The resulting missense variant was predicted to cause a low-prevalence antigen with the RHAG:1 phenotype.

INTRODUCTION

The Rh blood group system comprises over 50 antigens, including the well-recognized D, C, c, E and e antigens [1]. Rh-associated glycoprotein (RhAG, CD241) [2] is essential to the structural integrity and stability of erythrocytes. RhAG carries five antigens: the high-prevalence Duclos (RHAG:1) and DSLK (RHAG:3) and the low-prevalence Ol^a (RHAG:2), Kg (RHAG:5), and SHER (RHAG:6) [1]. The Rh proteins RhD and RhCE, which share approximately 40% homology in amino acid sequence with RhAG, assemble with RhAG in a trimeric confirguration to form the core Rh complex, interacting with accessory chains glycophorin B (GPB), Landsteiner-Wiener (LW) protein and integrin-associated protein (IAP) [3].

The *RHAG* gene, consisting of 10 exons and located on chromosome 6, encodes the RhAG glycoprotein and modulates Rh antigen expression. Some variations in the *RHAG* gene are sufficient to disrupt Rh complex formation and induce spherocytosis [1]. Missense variants, altered splicing, small deletions and complete deletions of the *RHAG* gene have been reported in the literature [2,4]. When *RHAG* variations affect Rh antigen expression on the red cell membrane, these are phenotypically grouped into reduced (Rh_{mod}) or complete absence (Rh_{null}) of Rh antigen expression [5]. Mild anaemia and stomatocytes are associated with the Rh_{null} phenotype.

We report a novel *RHAG* blood group allele and show in a study of immediate family members that inheritance of this allele is consistent with a low-prevalence antigen responsible for haemolytic disease of the fetus and newborn (HDFN).

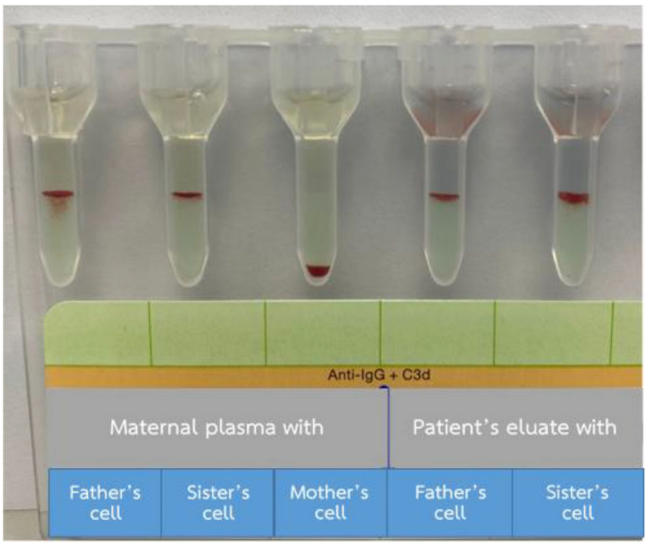

FIGURE 1 Antibody investigations performed by Ramathibodi Hospital Blood Bank, Thailand. Reactivity of maternal plasma/patient's eluate with father's, mother's and older sister's cells.

METHODS

A female newborn in Thailand was found to be jaundiced. She had a haemoglobin of 15.3 g/dL and hyperbilirubinaemia. Red blood cells (RBCs) from the cord blood sample reacted 4+ in the direct antiglobulin test (DAT). Her blood was referred for further investigation for suspected HDFN.

Serology

Phenotyping was performed using standard serological methods following manufacturer's instructions with Bio-Rad's ID-System RhD + Phenotype and DiaClon Line and Polyclonal Reagents (DiaMed GmbH, Cressier, Switzerland).

Antibody screening and identification was performed using column agglutination indirect antiglobulin test (CAT IAT) with Bio-Rad's

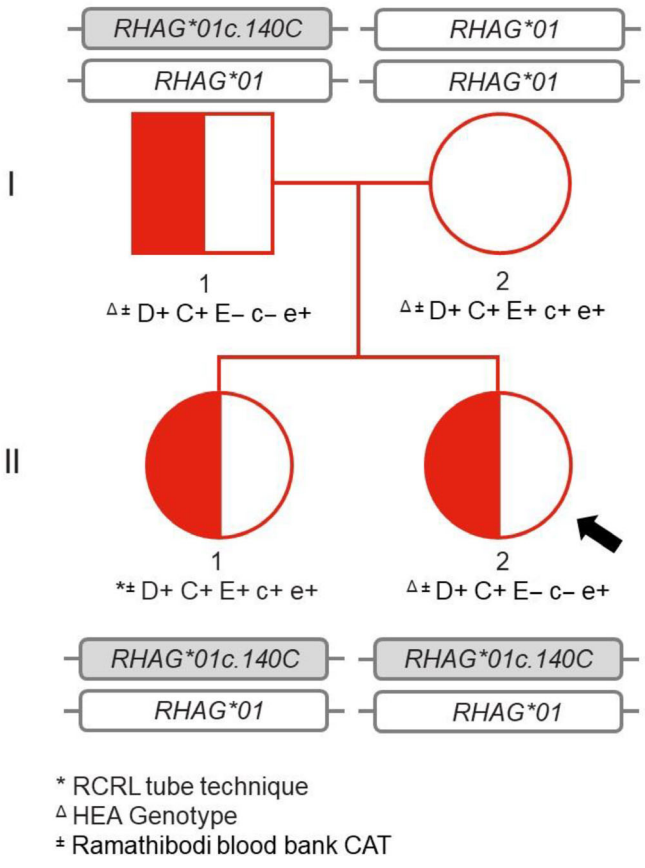

FIGURE 2 Pedigree chart of family (arrow indicates proband). *RCRL, red cell reference laboratory; ΔHEA, human erythrocyte assay; CAT, column agglutination.

ID-System LISS/Coombs (DiaMed GmbH, Cressier, Switzerland). The reactivity of the maternal antibody with chemical- (dithiothreitol) and enzyme- (papain, trypsin) treated RBCs of the proband, sibling, and father were tested both before and after treatment using CAT IAT.

Molecular testing

Genomic DNA was extracted from EDTA blood samples. Genotyping was performed using a single nucleotide poylmorphism (SNP) array (Immucor PreciseType™ HEA Molecular BeadChip Test [BioArray Solutions, Immucor, Warren, NJ]) and sequenced using a custom-targeted sequencing panel with the Illumina DNA Prep with Enrichment Kit for library preparation and sequenced using the Illumina MiSeqDx™ Instrument (Illumina, San Diego, CA). The custom-targeted sequencing panel enabled comprehensive genotyping for International Society of Blood Transfusion (ISBT) blood group systems 001-043 and transcription factors KLF1 and GATA1. DNA sequence reads were aligned against the human genome reference sequence (GRCh37) in order to identify variants relative to the reference sequence using QIAGEN CLC Main Workbench 20.0 (QIAGEN, Aarhus, Denmark).

RESULTS

The maternal antibody was reactive in CAT IAT with RBCs of the infant's father and older sibling (see Figure 1) but did not react with any other panel cells tested, including red cells positive for the antigen V, C^w, Lu^a, Kp^a, Co^b, s^D, St^a, Hop, Mi^a and cord cells. Extended antibody investigations found no apparent specificity. An eluate prepared from the infant proband's cells was reactive with the father's and older sibling's cells. Enzyme and chemical modification of the incompatible red cells had no effect on reactivity with the antibody.

The paternal RBC phenotype was B, D+, C+, c–, E–, e+, Le(a+b–), Jk(a+b+), P1+, M+, N+, S–, s+, Fy(a+b–). The maternal RBC phenotype was B, D+, C+, c+, E+, e+, Le(a–b+), Jk(a+b+), P1+, M+, N–, S–, s+, Fy(a+b–). The sibling's RBCs were typed as B, D+, C+, c+, E+, e+. Lastly, the RBCs of the proband were group B, D+. Serology testing using standard anti-sera reagents showed no significant reduction in the expression of RhD and RhCE antigens.

Blood samples collected from the infant, parents and sibling of the proband ($n = 4$), all of Thai ethnicity, were sent for further molecular analysis at the Red Cell Reference Laboratory (RCRL), Brisbane.

A novel variant *RHAG c.140T>C* (GenBank OL541903, rs2127360274) in exon 1 was found on custom-targeted sequencing

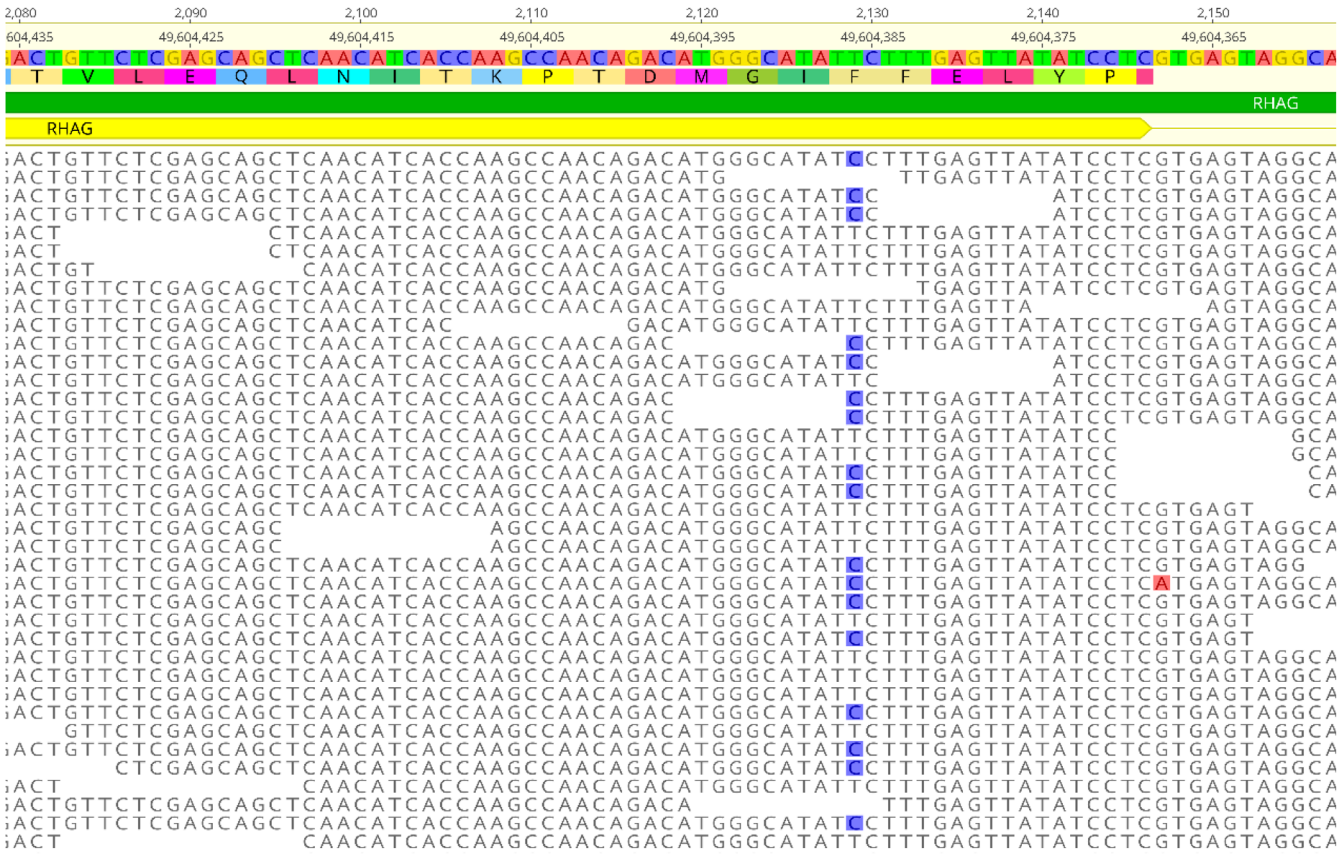

FIGURE 3 Custom-targeted panel sequencing showing the mismatch of proband sequence (highlighted in blue on the sequence reads) on alignment to reference human genome (GRCh37); (as shown in the first line of nucleotides).

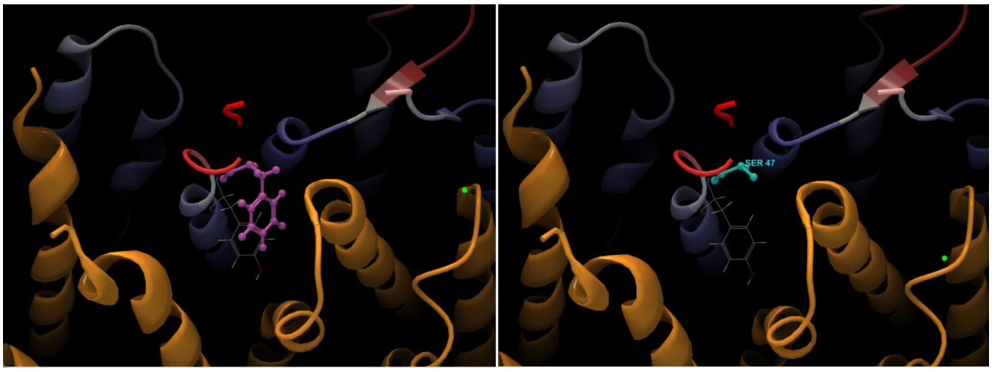

FIGURE 4 3D protein model prediction of reference p.(Phe47) (left) and of the variant p.(Phe47Ser) (right).

panel in the proband, older sibling and father (see Figures 2 and 3). This nucleotide substitution led to an amino acid change p.(Phe47Ser) in the RhAG blood group glycoprotein. The variant was found in 110 of 334 DNA sequence reads in the proband, 179 of 432 DNA sequence reads in the paternal sample and 292 of 815 DNA sequence reads in the older sibling, consistent with heterozygosity for the variant. As no other variants were detected in sequence encoding the RHAG blood group, the most probable genotype of the proband, sibling and father was *RHAG*01/*01c.140C* with a predicted phenotype of RHAG:1 and a possible low-prevalence antigen.

The maternal sample matched the reference sequence (GRCh37) encoding the *RHAG* blood group and did not carry the variant (*RHAG c.140T>C*) found in the infant and paternal samples. The maternal *RHAG* genotype was *RHAG*01/*01* with the corresponding RHAG:1 phenotype. Additionally, the low-prevalence *GYPB*23* allele, which expresses the s^D antigen, was also detected at the heterozygous level in the mother and both children. A recent study reported the genotype frequency for this allele as 2.2% (4/184) in Thai blood donors. For this case it was not possible to confirm the s^D antigen expression by serology as anti-s^D was unavailable for testing in the referring hospital [6].

The novel variant *RHAG c.140T>C* and the resulting amino acid change from phenylalanine to serine are predicted to reside in the second transmembrane domain of RhAG; however, we are currently performing transfection studies to show that it is in fact located external to the membrane and thus resulted in a novel epitope on the red cell surface. The software prediction tools PolyPhen-2 [7] and SIFT [8] (used to predict the effect of an amino acid substitution on protein structure and function) classified the change as benign (PolyPhen-2) and tolerated (SIFT). No other mutations were detected in the RhAG blood group glycoprotein.

SNP-array based testing with the PreciseType™ HEA Molecular BeadChip and custom-targeted sequence panel predicted the proband's RBC phenotype to be D+, C+, E−, c−, e+, K−, Fy(a+b−), Jk(a+b+), M+, N−, S−, s+, s^D+.

DISCUSSION

The presence of a novel *RHAG c.140T>C* variant at the heterozygous level resulted in the expression of a low-prevalence antigen, which was most likely responsible for this case of HDFN in the infant. It was found in samples of the infant, sibling and father, but absent in the mother's sample. The first sibling had no signs of HDFN post-delivery and her red cell DAT was negative. Further testing to delineate intergenerational inheritance through the paternal line was attempted, however, permission was denied for further testing from the father.

Three-dimensional protein model prediction comparing the reference and variant demonstrated alteration of the amino acid structure (see Figure 4) [9]. Although predictive tools classified the variant as benign and tolerable, the antigen expressed as a result of this change was sufficiently immunogenic to produce an antibody capable of provoking HDFN, as reported in this case. The variant's interference on the assembly of Rh complex was insignificant, with unaffected RhD and RhCE expression.

A review of the ISBT-published RHAG blood group alleles revealed varied presentations and clinical sequelae of variants [2]. To date only two other variants have been described in exon 1 of the *RHAG* gene. A 54-year-old Turkish male presenting with DAT negative haemolytic anaemia was found to be homozygous for a c.12delA (p.Phe5fs) deletion in exon 1 of the *RHAG* gene, causing a Rh_{null} blood group phenotype [10]. The other case identified a single nucleotide transversion in the ATG codon, causing a missense change (ATG[Met]→ATT[Ile]) for translation initiation of RhAG glycoprotein (formerly Rh50 at time of study), resulting in a Rh_{mod} phenotype [11].

Genetic and genomic studies are important tools to resolve low-prevalence antigen/antibody cases of clinical significance. While the novel *RHAG c.140 T>C* variant did not affect Rh blood group antigen expression, the immunogenicity of the resulting RhAG antigen led to HDFN. The novel variant from this case was presented to the ISBT Working Party for Red Cell Immunogenetics and Blood Group Terminology at the 33rd Regional ISBT Congress (Gothenburg, Sweden, June 2023) and has been provisionally accepted as a new antigen in the RHAG system — designated the allele name *RHAG*01.07* and antigen name RHAG:7 or THIN. Transfection studies to confirm novel epitope expression due to *RHAG c.140T>C* will lead to its conferral.

ACKNOWLEDGEMENTS

All authors devised the manuscript. S. Chatterjee collected and analysed data and wrote and reviewed the manuscript. G.M. performed molecular testing, analysed data and wrote and reviewed the

manuscript. S. Chiawchan, S. Chanthet and P.K. collected samples, performed serological testing and reviewed the manuscript. C.H., T.P. and J.D. reviewed the manuscript. Y.L. collected and analysed data and wrote and reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Chatterjee S, Millard G, Chiawchan S, Chanthet S, Daly J, Hyland C, et al. A case of haemolytic disease of the fetus and newborn attributed to a novel antigen in the RHAG blood group system. Vox Sang. 2023;118:1095–9.

Received: 20 March 2023 | Revised: 28 August 2023 | Accepted: 8 September 2023

DOI: 10.1111/vox.13537

SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Prevalence of red blood cell alloantibodies among blood donors in the French Military Blood Institute: A 10-year retrospective study

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Screening for red blood cell alloantibodies (RBC-Ab) is a critical step in ensuring blood transfusion safety performed by blood donation screening laboratories. We aim to evaluate the prevalence of the RBC-Ab among healthy blood donors.

Materials and Methods: Antibody screening of serum of all voluntary blood donors was performed as a routine immune-haematological procedure by a solid-phase method on a fully automated immunohaematology analyser. Positive sera were further investigated to identify the specificity of RBC-Ab by a commercially available red cell panel.

Results: Between January 2012 and December 2021, a total of 212,218 donations were screened for the presence of RBC-Ab, 74% from male donors ($n = 157,898$) and 26% from female donors ($n = 54,320$). Mean age at donation time was 32 ± 12 years. A total of 1007 donations were screened positive (0.47%), and 131 were confirmed positive for alloantibodies in their serum, yielding a prevalence of 0.06% (95% confidence interval: 0.05–0.07). Most frequent alloantibodies identified were of RH blood group system (64%), followed by anti-MNS (19%), anti-Kidd and Lewis (6% each) and anti-KEL (4%). The results showed a statistically higher prevalence of alloantibodies in women than men. Our results showed a lower prevalence as compared to the available data, which might be related to our study population.

Conclusion: The prevalence of positive antibody screening in healthy donors in this study was found to be 0.47%, while the prevalence of alloantibodies was 0.06%. The most common alloantibodies were anti-RH1 (25%) and anti-RH3 (24%).

Keywords

alloantibodies, antibody screening, blood donation

Highlights

- The prevalence of red blood cell alloantibodies (RBC-Ab) was low in our predominantly male population (0.06%).
- Female donors (0.15%) were more likely to have anti-RBC antibodies than male donors (0.03%).
- The most common RBC antibodies were anti-RH1 (D) and anti-RH3 (E).

INTRODUCTION

Alloantibodies may be detected in blood donors who have either been transfused previously or in female donors with previous obstetric events. Rarely, alloantibodies can develop in the absence of erythrocyte antigenic stimulation, for example, through cross-reaction with viral, parasitic or bacterial antigens. In France, up to now, a history of blood transfusion means a permanent deferral of blood donors, decreasing the prevalence of anti-red blood cell antibodies (anti-RBC-Ab) in blood donors. However, considering that these antibodies can occasionally cause severe transfused-related issues, guidelines and regulatory authorities require a systematic screening for anti-red cell antibodies at every donation [1, 2]. Depending on the platform used for screening, the frequency of anti-RBC-Ab may vary. Some blood donation screening laboratories identify these antibodies after a positive screening, which allows for specific management of blood donors; indeed, such information could be useful if a blood donor becomes a blood recipient or during pregnancy for female donors. Because, according to national regulations, blood products with anti-red cell antibodies, which can lead to adverse events if transfused to a patient, are to be discarded and blood donors permanently deferred [2], knowledge about the prevalence of antibody screening is of special interest to anticipate the workflow and evaluate the cost of this loss. From a donor's point of view, this description will help them to understand their natural course and prevalence before any transfusion. During the past 10 years, our institute has performed antibody screening on the same platform with the same assay. The aim of our study was to evaluate the prevalence of anti-red cell antibody among blood donors and to describe their specificity.

MATERIALS AND METHODS

This study was conducted at the French Military Blood Institute (FMBI), which is responsible for the blood supply chain, from collection to delivery, for French Military Medical Centres ($n = 4$) and overseas operations. As for the French Blood Establishment, FMBI follows the same French national regulation on every field of transfusion. We retrospectively reviewed antibodies against red blood cells detected among blood donations (whole blood, apheresis platelets or plasma and combined apheresis) from 1 January 2012 to 31 December 2021. Indeed, during that 10-year period, no significant changes were made in our blood donation screening laboratory techniques.

All blood donors coming to FMBI (mobile drives or collection centres) were screened according to criteria established by the French regulation [3]. Especially, donors who have ever been transfused are permanently deferred. Pre-donation interview of donors collects details regarding their basic profile (age, sex), any history of previous transfusion and any clinically significant disease, among others. A history of anti-RBC-Ab leads to a permanent deferral if the alloantibody is of transfusion interest (see the list below). If no dangerous alloantibody is identified, the first donation is discarded but the donor is eligible for subsequent donations. The donor will, however, undergo the same blood donation screening during a new donation. All female donors were screened for detailed obstetric and gynaecological history, especially childbirth and abortion. Hence, data regarding sex, age, medical history, transfusion history and pregnancy history were collected from the medical-technical software used for medical interview.

Our transfusion establishment performs screening for antibodies on each donation with an automated coated-microplate technology, Neo plateform (Immucor, France), based on the use of an indirect antiglobulin test. Red blood cells used included the following antigens (which represent the target of alloantibodies of interest in transfusion): RH1 (D), RH2 (C), RH3 (E), RH4 (c), RH5 (e), KEL1 (Kell), KEL2 (cellano), FY1 (Fya), FY2 (Fyb), JK1 (Jka), JK2 (Jkb), MNS1 (M), MNS2 (N), MNS3 (S), MNS4 (s), LE1 (Lea), LE2 (Leb) and LU2 (Lub) (Immucor, France). The sensitivity of the method allows at least the detection of an anti-RH1 national standard titrating at a maximum of 50 ng/mL. The analytical system was controlled by using, at the beginning and end of the series, control samples containing anti-KEL1 whose titre was guaranteed to be one-fourth dilution in the technique used and on a red cell containing the corresponding 'heterozygous' expression antigen.

When positive, samples were tested by an automated gel-card-based technique (Bio-Rad, France) with three O-type red cells that detect antibodies to the RH1 antigens RH2, RH3, RH4, RH5, KEL1, KEL2, KEL4, FY1, FY2, JK1, JK2, MNS1, MNS2, MNS, MNS4, LE1, LE2, P1 and LU2. The following RH phenotypes were mandatorily represented: (i) RH:1,2,−3,−4,5 (D+C+E−c−e+), (ii) RH:1,−2,3,4,−5 (D+C−E+c+e−), (iii) RH:−1,−2,−3,4,5 (D−C−E−c+e). In addition, a 'homozygous' phenotypic expression is used for FY1, JK1, JK2 and MNS3 antigens. Positive samples with the latter technique were then manually analysed on 20 red cells without and with a papaïne pretreatment to identify the antibody's specificity. All these red blood cells of phenotype O contain the following antigens: RH1, RH2, RH3, RH4, RH5, RH8, KEL1, KEL2, KEL3, KEL4, FY1, FY2, JK1, JK2, MNS1, MNS2, MNS3, MNS4, LE1, LE2, P1, LU1 and LU2. A direct anti-globulin test (DAT) was performed in all the cases with positive auto control. Following the French regulation, identification of an alloantibody was ascertained after testing the absence of the antigen on donor red blood cells; especially for anti-RH1, the presence of a partial RH1 or a weak RH1 was assessed [4].

Statistical analysis

The data were retrieved and entered into a Microsoft Excel sheet, and analysis was performed with GraphPad Software (Prism version 9).

RESULTS

A total of 212,218 donations were analysed: 91% whole blood ($n = 193,188$), 5% apheresis plasma ($n = 9978$), 4% apheresis platelets ($n = 8616$) and 1% combined apheresis ($n = 436$). A majority of the donation came from male donors (74%, $n = 157,898$) and 26%

TABLE 1 Prevalence of positive screen results and alloantibodies identification among blood donors.

	Women	Men	M:W ratio	Total
Total donation	54,320	157,898	3:1	212,218
New donors	19,182	104,801	5:1	123,983
Recurrent donors	35,138	53,097	1:1.5	88,235
Positive antibody screen result	407	600	1.5:1	1007
New donors	152	189	1:1.2	341
Recurrent donors	255	411	1:1.6	666
Positive antibody confirmatory result	79	52	0.7:1	131
New donors	38	29	0.8:1	67
Recurrent donors	41	23	0.6:1	64
Alloantibodies positive donation	58	36	0.6:1	94
New donors	31	19	0.6:1	50
Recurrent donors	27	17	0.6:1	44
Autoantibodies positive donation	10	10	1:1	20
New donors	2	5	2.5:1	7
Recurrent donors	8	5	0.6:1	13
Inconclusive panel	11	6	0.5:1	17
New donors	5	5	1:1	10
Recurrent donors	6	1	0.2:1	7

from female donors ($n = 54,320$). The mean age at donation was 32 ± 12 years. Most donors were military personnel ($n = 142,431$, 67.2%), while 17.7% were civilians ($n = 37,606$); this information was missing for 15.1% ($n = 32,676$). Among the 212,218 donations, 123,983 (58%) came from new donors (15% from women, 85% from men) and 88,232 (42%) from recurrent donors (40% from women, 60% from men). This re-partition was significantly different ($p < 0.001$). Blood type re-partition was as follows: 44% O group ($n = 93,291$), 42% A group ($n = 89, 303$), 10% B group ($n = 20,737$) and 4% AB group ($n = 8883$). Four donations were non-typeable because of the irregular antibody. A total of 1007 (0.47%) donations were screened positive (90% whole blood [$n = 915$], 6% apheresis plasma [$n = 65$] and 4% apheresis platelets [$n = 27$]) and subsequently processed for further analysis. Prevalence of positive screening was significantly higher among recurrent donations as compared to new donations (0.75% vs. 0.28%, respectively, p <0.001). Among them, a majority (87%, $n = 976$) did not reveal any specific alloantibody. Only 13% ($n = 131$) were positive and exhibited at least one confirmed positive reaction, accounting for a global prevalence of 0.06% (95% confidence interval [CI]: 0.05–0.07). Among them, 72% ($n = 94$) were typable, 15% ($n = 20$) were autoantibodies and 13% ($n = 17$) were inconclusive (Table 1). Comparing new donors and recurrent donors, 51% of confirmed positive reaction (67/131) was found among new donors and 59% among recurrent donors (64/131). Finally, among the 94 typable alloantibodies, only one recurrent donor had a new donation after the identification of an anti-MNS1 without haemolytic activity at 37°C. Calculation of the number of donations before the occurrence of the first confirmed positive reaction was not performed. Statistical analysis showed a significant higher prevalence in women than men (0.15% vs. 0.03%, $p = 0.001$) and no blood type effect was revealed, except regarding RH1 type; indeed, RH:–1 donors were significantly more likely to exhibit alloantibodies (0.12% vs. 0.05%, $p < 0.001$) (Table 2). Age of donors with or without alloantibody was not significantly different (33 ± 12 vs. 32 ± 12, respectively, $p = 0.46$), even among women ($p = 0.28$).

TABLE 2 Alloantibodies in blood donations according to gender, ABO and RH type.

	Positive	Negative	Frequency (%)
Gender			
Male	52	157,846	0.03
Female	79	54,241	0.15
ABO blood type			
A	50	89,253	0.06
B	14	20,723	0.07
O	55	93,236	0.06
AB	8	8875	0.09
Inconclusive	4	0	
RH1 type			
Negative	44	36,261	0.12
Positive	85	175,824	0.05
Inconclusive	2	2	

Analysis of the 131 alloantibodies revealed 13 different specificities. Among them, alloantibodies against antigen of the RH system were the most frequent (64%): anti-RH1 and anti-RH3 representing 25% and 24% of the total, respectively, followed by anti-RH8 (11%)

TABLE 3 Specificity of alloantibodies among blood donors according to gender of donors.

Specificity	*n*	Frequency (%)	Women	Men
RH1	24	25	17	7
RH3	23	24	14	9
RH4	4	4	4	0
RH8	10	11	7	3
KEL1	3	3	2	1
KEL3	1	1	0	1
JK1	4	4	3	1
JK2	2	2	1	1
LE1	5	5	2	3
LE2	1	1	0	1
MNS1	14	15	6	8
MNS2	1	1	1	0
MNS3	2	2	1	1
Total	94	100	58	36

and anti-RH4 (4%). Focusing on anti-RH1, among the 24 donors with anti-RH1 antibodies, 17 were women and 7 were men, all were RH:−1, 14 were group O, 9 were group A and 1 was group B. The investigation of these cases revealed passive immunization in three women due to anti-RH1 treatment for early miscarriage, and in three other women due to a recent pregnancy with a prophylactic infusion of anti-RH1 immunoglobulin. Unfortunately, data were missing for the 11 remaining women, and we cannot hypothesize the origin of these alloantibodies. All the seven men with anti-RH1 were all questioned a second time regarding a medical history of transfusion, but none of them acknowledged having such a treatment. Other specificities in KEL, JK, LE and MNS systems are presented in Table 3. Of note, anti-MNS1 represents the third most frequent alloantibody, accounting for 15% of the total. Results are presented in Table 3.

DISCUSSION

We report here data on both non-specific and specific screening of anti-RBC-Ab among blood donors. Indeed, the data available in the literature did not provide this prevalence of non-specific reactions, although they are of specific interest for blood donation laboratories, both for assessing the impact on workflow and for allowing performance comparison with other techniques. However, the notably high rate of non-specific reactions is concerning and needs to be investigated in order to differentiate between excessive sensitivity of screening and high specificity of the confirmation test.

Based on a literature review, the reported incidence of anti-RBC-Ab in the donor population varies from 0.05% to 2.4% [5–10]. The highest frequency of alloantibodies is seen among young women (aged between 26 and 30 years), where it can be three times higher than among male donors [7]. In a recent study, age, female sex, RH1 status and medical history (transfusion or pregnancy) were found to be significant risk factors for anti-RBC-Ab in blood donors [10]. In our study, the overall frequency of alloimmunization among healthy donors was 0.06% (95% CI: 0.05–0.07). This incidence of anti-RBC-Ab might be lower than some others. This can be explained by the fact that males constituted 74% of our donor population. Previous data, reported in a U.S. military blood centre, were in the same range as ours, with a rate of 0.02% of clinically significant antibodies [11]. Indeed, given the 'high' frequency of anti-RH1 among RH:−1 female donors, due to pregnancies, our result could underestimate the overall prevalence of alloantibodies, as previously shown [6, 7, 12]. However, our sex ratio among blood donors is close to that reported by Pahuja et al. or Garg et al. [5, 8], where the prevalence was 0.05% and 0.09%, respectively. The discrepancy of alloimmunization rates can also be related to blood donor selection criteria, which may differ between countries, and to different serological techniques. Of note, in France, a history of transfusion leads to a permanent deferral for any blood donation type. Adding the low proportion of women among blood donors and considering that pregnancy and transfusion are the main drivers of positive anti-RBC-Ab, these two factors may explain the relative low rate of antibodies in our population, compared to that in the study by Karafin and Winters, reporting a prevalence of 0.51% and 0.89%, respectively [10, 13].

The Rh blood group system is one of the most complex blood group systems known. The RH1 antigen is considered to be the most immunogenic of all antigens after A and B and has the potential to cause clinically significant haemolytic disease of the fetus and newborn. In our study population, the incidence of anti-RH1 among alloantibodies was 25% (24/94). Interestingly, some anti-RH1 were discovered among men who were never transfused. A possible reason for these anti-RH1 could be related to an RH1 variant, allowing natural alloimmunization against the missing part. As reagents used to type RH1 in blood donors must identify partial RH1 antigens, this explanation is possible as long as these antibodies could appear without a transfusion or pregnancy history. To decipher this unusual invent, we implemented a systematic request for genotyping among donors identified as RH1 type with an allo anti-RH1 antibody, after obtaining their consent. This should be further investigated. In our study, the most frequent antibodies against RH minor antigens were anti-RH3, consistent with previous reports [4, 5]. Less frequent were the anti-Lewis antibodies. The second most frequent alloantibodies identified in our study were from the MNS blood group system. The frequency of anti-M was found to be 15%. Anti-M is generally a naturally occurring alloantibody that does not react at 37°C and is not clinically significant for transfusion but can cause a problem in pre-transfusion testing. It is clinically significant when detected at 37°C, and in that case, cross-match-compatible antigen-negative blood should be given to prevent any haemolytic transfusion reaction. The Lewis blood group system is different from other blood group systems in that the antigens (Lea and Leb) are formed in the plasma and absorbed onto the red cell membrane. Transfused red cells absorb Lewis antigens from the plasma of the recipient, and within several days of the transfusion the phenotype of the circulating transfused red cells becomes the same as the patient's red cell phenotype. Antibodies specific for Lewis antigens are naturally

occurring and usually IgM, complement-activating and reactive at or below room temperature. Lewis antibodies may be clinically relevant if the antibody causes in vitro haemolysis during serological laboratory testing, and antigen-negative blood should be selected for transfusion.

There is a paucity of literature on the clinical significance of anti-RBC-Ab in transfusion recipients, with some speculating that low levels of immune antibodies may have no clinical relevance [8]. However, high levels can cause destruction of the recipient's red blood cells. These reactions can be further reduced by using red blood cells suspended in an additive solution. However, in paediatric patients and when large volumes of plasma are transfused (such as fresh frozen plasma and apheresis platelets), these antibodies should be given higher consideration. Screening of the donor's plasma is a relatively simple test and can detect potent antibodies to clinically significant antigens. Future studies should aim to clarify the clinical significance of anti-RBC-Ab and their role in transfusion reactions. Finally, our study contributes to a better understanding of the immuno-haematological characteristics of blood donors and can also be useful for blood donation screening laboratories to evaluate the need for confirmation reagents, as well as for blood product preparation services to determine the impact of these antibodies on the quantity of blood products available.

ACKNOWLEDGEMENTS

S.P., E.F. and C.M. designed the research study; L.P. and C.M. acquired and analysed the data; C.M. supervised the research; L.P. and C.P. wrote the first draft. All authors reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Pons S, Poirrier L, Fleuriot E, Martinaud C. Prevalence of red blood cell alloantibodies among blood donors in the French Military Blood Institute: A 10-year retrospective study. Vox Sang. 2023;118:1100–4.

Received: 11 July 2023 | Revised: 8 September 2023 | Accepted: 8 September 2023

DOI: 10.1111/vox.13538

SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

An optimized procedure for Luminex-based human platelet antigen-specific antibody screening and identification (PakLx assay) with a cost-effective approach and improved sensitivity

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: Detection of anti-platelet antibodies is required for the diagnosis of foetal/neonatal alloimmune thrombocytopaenia. The most commonly used methods for anti-platelet antibody detection are the monoclonal antibody-specific immobilization of platelet antigens (MAIPA) and the Luminex bead assay (PakLx). However, for economic reasons, the use of the PakLx assay is limited.

Materials and Methods: In the present study, we evaluated the performance of an optimized protocol based on a half-volume of PakLx reagents. We compared two alternative procedures: one with a half-volume of all components including patient samples, and another based on a half-volume of reagents but a standard volume of patient sample.

Results: Our results obtained with a panel of 67 samples demonstrate improved sensitivity when using a standard sample volume.

Conclusion: In the event of an inconclusive result with this optimized protocol (e.g., incomplete panel of positive Luminex beads), we recommend testing the sample with an alternative protocol (e.g., MAIPA or the original PakLx protocol).

Keywords

CD36, foetal/neonatal alloimmune thrombocytopenia, human platelet antigen, Luminex

Highlights

- A multiplex assay based on Luminex (Lmx) technology is available, allowing rapid screening of anti-human platelet antigen (HPA) alloantibodies.
- Two procedures were compared with the original Lmx-based protocol for the detection of anti-HPA: one with a half-volume of all components including patient samples, and another based on a half-volume of reagents but a standard volume of patient sample.
- We observed an improved sensitivity when using a standard sample volume with a half-volume of reagents.

INTRODUCTION

Platelet immunology investigations are essential for the diagnosis and therapy of alloimmune disorders such as foetal/neonatal alloimmune thrombocytopenia (FNAIT [1]), platelet refractoriness and post-transfusion purpura. The diagnosis of alloimmunization relies on (1) the detection of the antibodies and (2) the identification of the cognate antigen. To date, monoclonal antibody-specific immobilization of platelet antigens (MAIPA [2]) is considered the gold-standard reference method in platelet immunology. This assay has good sensitivity

and specificity but is time-consuming (it takes at least 5 h). Each glycoprotein (GP) target is tested individually, thus requiring a large volume of plasma or serum. Moreover, it is known that MAIPA sometimes fails to detect anti-CD36 (GPIV) iso-antibodies, probably because of the competition between human antibodies and currently available mouse-anti-CD36 monoclonal antibodies [3].

To overcome these issues, a multiplex assay based on Luminex (Lmx) technology has been designed, allowing rapid screening of anti-human platelet antigen (HPA) alloantibodies in about 2 h, starting from a very small volume of biological sample (10 µL) (PakLx, Immucor). Assay performance has been documented [4], showing good sensitivity to detect the most frequent allo-antigens (e.g., anti-HPA-1a and HPA-5a/b) as well as iso-antibodies against CD36. In our practice, the use of Lmx method is restricted to emergency situations because it is faster than MAIPA. The method could also be applied in non-urgent situations, but this is not usually the case for economic reasons (it is at least four times more expensive than MAIPA). In this study, we evaluated the performance of an optimized protocol based on a half-volume of PakLx reagents.

STUDY DESIGN AND METHODS

Samples

Sixty-seven samples were tested. Fifty-two samples were collected from FNAIT cases referred to the HLA-HPA Reference Laboratory at the Brittany Blood Centre (Rennes, France) for platelet antibody testing. Written informed consent was obtained for all cases in accordance with the Declaration of Helsinki. Nine samples corresponded to external quality controls. Three samples were international antibody standards against HPA-1a, HPA-3a and HPA-5b, purchased from the National Institute for Biological Standards and Control (NIBSC).

TABLE 1 Detailed PakLx assays evaluated in the study.

	Original PakLx protocol	Half-volume PakLx protocol	Improved half-volume PakLx protocol
PakLx beads	40 µL	20 µL	20 µL
Plasma/serum	10 µL	5 µL	10 µL
Incubation 1 h at room temperature; three washes with 200 µL of wash buffer			
Goat anti-human IgG phycoerythrine	50 µL	25 µL	25 µL
Incubation 30 min at room temperature			
Add 150 µL of wash buffer and read on the Luminex flow cytometer			

Abbreviations: IgG, immunoglobulin G; PakLx, Luminex bead assay.

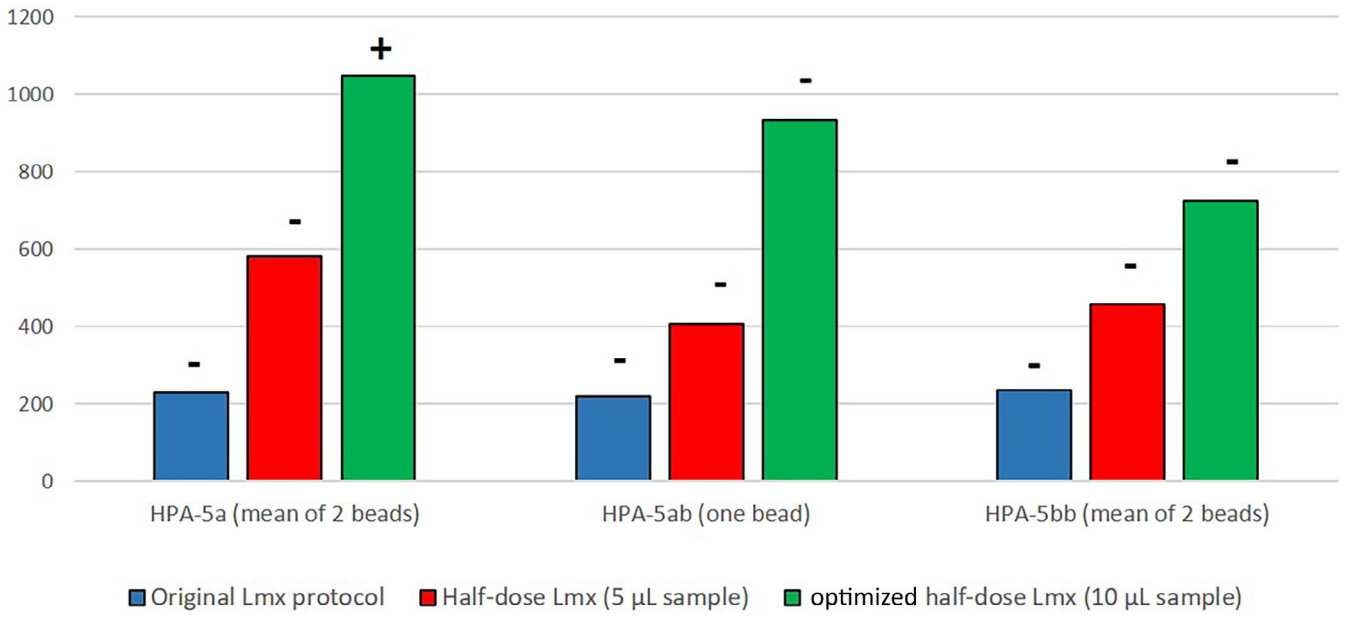

FIGURE 1 Mean fluorescence intensities measured in Luminex (Lmx) for a weak anti-HPA-5a-positive sample detectable only in the monoclonal antibody-specific immobilization of platelet antigens (MAIPA) cross-match with father's platelets. Three PakLx protocols were tested: the manufacturer's original protocol (blue bars), the half-volume protocol with 5 µL of sample (red bars) and the improved half-volume protocol with 10 µL of sample (green bars). The interpretation of the Match'It software ('Bead Reactivity') was given for each bar (−: negative; +: positive). HPA, human platelet antigen.

Reagents and methods

All samples (except three, containing anti-CD36 iso-antibodies) were screened with the MAIPA procedure (ApDia, Belgium), with monoclonal antibodies (MoAb) P2 to GPIIb-IIIa, Gi9 to GPIa-IIa and SZ1 to GPIb-IX. Samples as well as positive and negative controls were retested with PakLx (Immucor) as per the three protocols, as described in Table 1.

Mean fluorescence intensities (MFIs) were analysed using Match'It software supplied by the manufacturer.

RESULTS AND DISCUSSION

A total of 64 samples were tested in MAIPA and PakLx. Seventeen samples were positive in MAIPA in the presence of anti-HPA alloantibodies. They were all positive with the original as well as the half-volume protocols regardless of the sample volume tested (5 or 10 µL). Antibodies were specific to HPA-1a ($n = 7$), HPA-1b and 2b ($n = 1$), HPA-1b, 3b and 5b ($n = 1$), HPA-3a ($n = 1$), HPA-4a ($n = 1$), HPA-5a ($n = 2$) and HPA-5b ($n = 4$).

Among the 47 negative samples in MAIPA, 45 were negative with the original as well as the half-volume PakLx protocol, with either 5 or 10 µL of serum (no false-positive result). Two samples were of particular interest because they had tested negative with the original PakLx protocol and positive with the half-volume PakLx protocol:

1. One sample was distributed during the 2019 International Society of Blood Transfusion (ISBT) Workshop (sample #6, kindly supplied by Dr Nuria Nogues, Banc de Sang I Teixits, Barcelona, Spain). It corresponded to a mother's plasma in a context of foeto-maternal HPA-1b and HPA-3a incompatibility. Following the original PakLx protocol, Match'It software generated a negative result despite significant differences in the MFIs of the HPA-1/HPA-3 beads. Interestingly, the same sample with the half-volume PakLx protocol was interpreted as positive by the Match'It software regardless of the volume of sample tested (5 µL: half-volume or 10 µL: improved protocol),

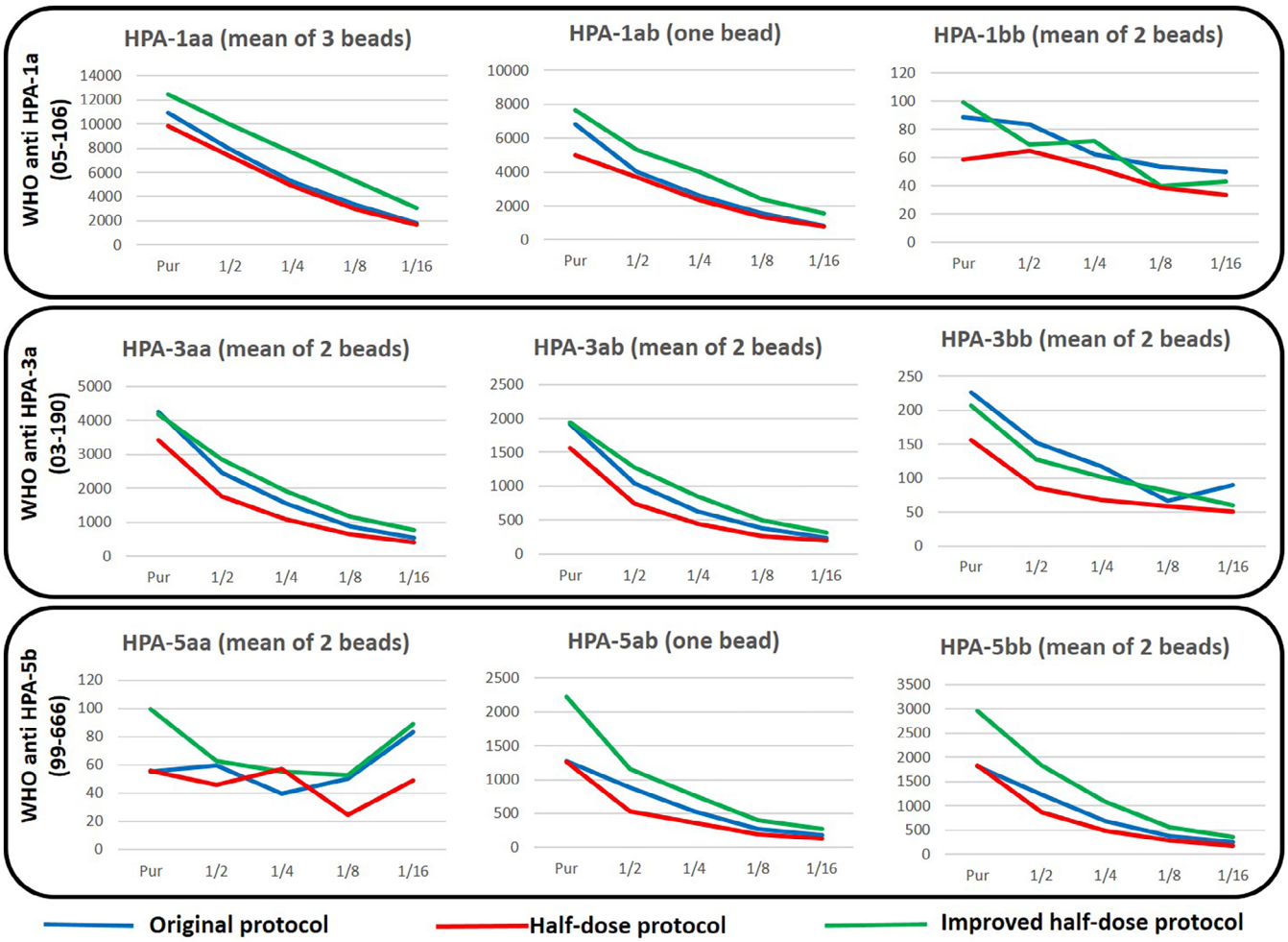

FIGURE 2 Mean fluorescence intensities observed in Luminex with the original (blue line), half-volume (red line) and optimized half-volume (green line) PakLx protocols. Serial dilutions of the NIBSC reference samples 05-106 (anti-HPA-1a), 03-190 (anti-HPA-3a) and 99-666 (anti-HPA-5b) were tested. HPA, human platelet antigen.

confirming the presence of weak anti-HPA-1b and anti-HPA-3a alloantibodies, as expected.

2. A second sample was of particular interest: it was collected from a mother in a clinical context of in utero death and foeto-maternal HPA-5a incompatibility and referred to our laboratory. The sample was MAIPA-negative in screening/identification with a panel of donor platelets, but the cross-match on father's fresh platelets was positive against GPIaIIa. There were no HLA antibodies in the maternal serum; hence we ruled out a potential false-positive reaction in MAIPA. The original PakLx protocol was negative, as well as the half-volume PakLx protocol with 5 µL of serum. Interestingly, the improved half-volume PakLx assay (10 µL of serum) was positive for the two homozygous HPA-5a PakLx beads (Figure 1). This suggests that the sensitivity of the improved half-volume PakLx protocol was better than that of the half-volume protocol.

To confirm this observation, we compared the sensitivity of the three PakLx protocols on serial dilutions of the NIBSC reference samples 05-106 (anti-HPA-1a, minimum dilution detectable: 1/2), 03-190 (anti-HPA-3a, minimum dilution detectable: 1/8) and 99-666 (anti-HPA-5b, minimum dilution detectable: 1/2) (Figure 2). The samples were still positive at the dilution 1/16, whatever the protocol (further dilutions not tested). In terms of MFIs, background noises were similar for all protocols on negative beads (HPA-1bb, 3bb and 5aa). The original and half-volume protocols produced similar MFIs for HPA-1a and 5b antibodies. For HPA-3a, MFIs were slightly lower with the half-volume protocol. With the improved half-volume protocol, we confirmed improved sensitivity with increased MFIs on positive beads for all three reference samples (HPA-1aa/1ab, 3aa/3ab and 5ab/5bb).

Finally, we tested three samples containing anti-CD36 isoantibodies (not tested in MAIPA). They were all positive with both half-volume protocols. MFIs on CD36 beads were higher with the improved half-volume protocol (data not shown).

Our study shows that the half-volume PakLx protocol performs similar to the original protocol, thus confirming the results of Bhandari and colleagues [5]. For two weakly positive samples, increased sensitivity was observed when using 10 µL of sample (optimized protocol described in detail in Table 1). Consequently, since January 2023, we have decided to follow the optimized protocol (half-volume reagents but standard volume of patient sample) for patient diagnosis and for external quality controls. In the event of an inconclusive result with the optimized protocol (e.g., incomplete panel of positive beads), we control the sample with MAIPA. For laboratories that do not offer an alternative method, we recommend confirming the result with the manufacturer's original protocol.

ACKNOWLEDGEMENTS

We are extremely grateful to Dr Nuria Nogues (Banc de Sang I Teixits, Barcelona, Spain) for supplying additional volumes of Sample #6 from the 2019 ISBT Platelet Immunology Workshop.

G.B. designed the study; J.G. performed the research; G.B. wrote the first draft; G.B. and V.R. reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Bertrand G, Griffon J, Renac V. An optimized procedure for Luminex-based human platelet antigen-specific antibody screening and identification (PakLx assay) with a cost-effective approach and improved sensitivity. Vox Sang. 2023;118:1105–8.

Received: 4 August 2023 | Revised: 5 September 2023 | Accepted: 17 September 2023

DOI: 10.1111/vox.13543

SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

A novel reagent for the screening of haptoglobin-deficient blood donors

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Funding information
The authors received no specific funding for this work.

Abstract

Background and Objectives: In Japan, the prevalence of haptoglobin deficiency is approximately 1 in 4000. Haptoglobin-deficient individuals may produce anti-haptoglobin from allo-immunization, leading to serious transfusion reactions. Therefore, implementation of a consistent supply of haptoglobin-deficient fresh frozen plasma is crucial. We developed a novel reagent to facilitate large-scale identification of haptoglobin-deficient individuals as potential donors of plasma products.

Materials and Methods: We established mouse monoclonal anti-haptoglobin-producing cell lines (three clones) using the hybridoma method by immunizing mice with the haptoglobin protein. Purified antibodies were conjugated with carboxylate-modified polystyrene latex beads and used for haptoglobin measurements by the latex agglutination method using an automatic analyser (LABOSPECT008). Samples with low protein concentrations were re-examined by enzyme-linked immunosorbent assay to confirm the results. Additionally, the *haptoglobin* gene was amplified by polymerase chain reaction to confirm the *haptoglobin* deletion allele (Hp^{del}).

Results: From February to October 2022, 7476 blood donor samples were screened. Two haptoglobin-deficient and 21 low-haptoglobin-expressing individuals were identified. Two haptoglobin-deficient donors were found homozygous for Hp^{del}, and 19 (90%) of the 21 low-haptoglobin-expressing individuals were heterozygous for Hp^{del}, which includes the first reported case of heterozygous $Hp^{del}/Hp^{Johnson}$.

Conclusion: We developed a new reagent for the detection of haptoglobin deficiency, which is automatable and inexpensive and appears useful for large-scale screening of blood donors.

Keywords

haptoglobin-deficient donor, reagent for screening

Highlights

- In the Japanese population, the prevalence of haptoglobin (Hp) deficiency is approximately 1 in 4000. Hp-deficient individuals produce anti-Hp, which can cause serious transfusion reactions.
- We developed a novel reagent for the screening of Hp-deficient blood donors.

- Of 21 donors with low Hp expression, 19 (90%) were confirmed to be heterozygous for the *Hp* deletion allele (Hp^{del}), which includes the first reported case of heterozygous $Hp^{del}/Hp^{Johnson}$.

INTRODUCTION

Haptoglobin (Hp) is a plasma glycoprotein that binds free haemoglobin, thus preventing oxidative damage [1]. The complex is rapidly removed from the circulation by a specific receptor (CD163) found on macrophages. Three common phenotypes, namely Hp1-1, Hp2-1 and Hp2-2, are the products of two closely related genes Hp^1 and Hp^2, which are located on chromosome 16 [2]. The frequency of the Hp^1 and Hp^2 genes varies worldwide depending on the population [1]. In addition to common polymorphisms, an approximately 28-kb deletion in the *Hp* gene, that is, the *Hp* deletion allele (Hp^{del}), has been described [3, 4]. The distribution of Hp^{del} is limited in East Asian populations [5]. Homozygous individuals (Hp^{del}/Hp^{del}) do not produce any Hp, and heterozygous individuals (Hp^2/Hp^{del}) produce lower levels of Hp in their serum than those without Hp^{del} [4]. Hp^{del}/Hp^{del} individuals have a risk of undergoing anaphylactic transfusion reactions if they produce anti-Hp [6]. The reported prevalence of Hp deficiency is approximately 1 in 4000 (0.025%) in the Japanese population [3, 7]. In Japan, 6 (1.6%) cases have been reported to be Hp-deficient with anti-Hp among 367 anaphylaxis cases between May 1993 and December 2000 [6]. Since 1 in 4000 Japanese individuals (0.025%) is Hp-deficient, the prevalence of Hp deficiency among anaphylaxis cases was approximately 64-fold higher. Indeed, there have been several reports of reactions due to Hp deficiency in Japan [8]. A study conducted by the Japanese Red Cross Society (JRCS) over a 20-year period (from 1997 to 2016) revealed that the frequency of Hp deficiency was 0.14% (35 cases) among the 24,337 patients with adverse events including cases other than non-haemolytic transfusion reactions [9]. It was 4.6 times higher than among healthy blood donors, suggesting a relationship between Hp deficiency and adverse events. In addition, all the individuals with anti-Hp possessed not only immunoglobulin (Ig) G-type antibodies but also concomitant IgE-type antibodies. It has been pointed out that the IgE type of anti-Hp may be the cause of anaphylaxis.

Although it is possible to remove plasma components from red blood cells and platelet concentrates by washing, removal of plasma proteins from fresh frozen plasma (FFP) is not feasible. Therefore, it is still necessary to produce FFP derived from Hp-deficient donors. Previously, the JRCS established a registry of Hp-deficient donors. In 2010, samples from 272,068 individuals who donated blood to the JRCS were screened at the Kanto-Koshinetsu Block Blood Center, and 78 Hp-deficient donors were found [7]. Thirteen years have passed since then, so approximately half of them are over 50 years of age, and those over 70 years are no longer eligible to donate (Figure 1, as of 2023). The screening of 2010 was based on the turbidimetric immunoassay (LABOSPECT 008, Hitachi High-Tech, Tokyo, Japan) using commercially available reagents (N-assay TIA Hp, Fukushima, Japan), with an estimated cost of ¥200 ($1.37) per sample. Thus, to allow a more cost-effective, large-scale screening of Hp-deficient blood donors, we attempted to produce a novel reagent based on the latex agglutination method using an automatic analyser (LABOSPECT008).

MATERIALS AND METHODS

Production of mouse monoclonal antibodies reactive with Hp

First, mouse monoclonal antibody-producing cell lines were produced by the hybridoma method through immunization of mice with the Hp protein (Haptoglobin, Catalogue No. 16-16-080116, Athens Research & Technology, Athens, GA, USA). Three clones of anti-Hp-producing cell lines (CBC-441, CBC-443 and CBC-447) were established. Mouse monoclonal anti-Hp, from the ascitic fluid of mice injected with each hybridoma cell line, was purified using protein-A Sepharose (GE Healthcare UK Ltd., Buckinghamshire, England).

Latex agglutination method for Hp detection

Each antibody (CBC-441, CBC-443 and CBC-447) was conjugated with carboxylate-modified polystyrene latex beads (Fujikura Kasei Co., Ltd., Tokyo, Japan). Four millilitres of latex beads solution (0.5% in 10 mM boric acid, pH 7.3) was combined with 100 µL of water-soluble carbodiimide (10 mg/mL in 10 mM boric acid, pH 7.3; Dojindo Molecular Technologies, Inc., Kumamoto, Japan) and incubated for 20 min at room temperature. Each antibody (0.8 mg) was added to the latex bead solution and incubated for 1 h at room temperature.

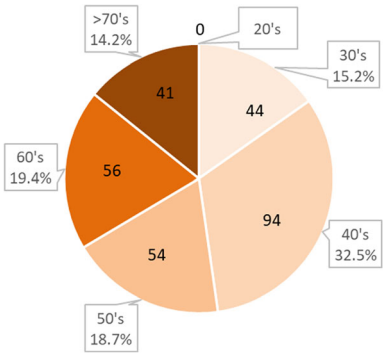

FIGURE 1 Age distribution of the registered haptoglobin-deficient blood donors in April 2023.

Latex beads were blocked with 1.05 mL of 10% bovine serum albumin (BSA) solution for 1.5 h at 52°C and then centrifuged, and the supernatant was discarded. The latex beads were re-suspended in reaction buffer (0.5% BSA, 100 mM MES-NaOH, pH 6.0) and incubated for 24 h at 37°C. Antibody-conjugated latex beads were mixed with an equal volume of another type of antibody-conjugated latex beads for combinations of two clones (Reagent 2).

Hp was measured by the latex agglutination method using an automatic analyser (LABOSPECT008, Hitachi High-Tech Corporation). Quantitation was performed based on the reaction rate of the test serum compared to that of the standard Hp (#16-16-080116, Athens Research & Technology).

Samples

Five Hp-deficient samples were used as negative controls. Random blood samples were obtained from 7476 donors from February to August 2022, and the Hp concentrations were measured using LABOSPECT008 at the Kanto-Koshinetsu Block Blood Center. Written informed consent was obtained from all blood donors before blood sampling. This study was approved by the ethics committee of the JRCS (#2019-030-2) and adhered to the principles laid out in the Declaration of Helsinki.

Enzyme-linked immunosorbent assay for Hp detection

A 96-well microplate (#469078, Maxsorp, Nalge Nunc, Radnor, PA, USA) was coated with diluted anti-human Hp rabbit polyclonal antibody (#A0030, DAKO, Santa Clara, CA, USA). After washing the plate three times with phosphate-buffered saline (PBS) containing 0.05% Tween 20 (PBS-T), 25 μL of the test sample was added and incubated at room temperature for 10 min. After washing with PBS-T three times, 50 μL of horseradish peroxidase-labelled anti-human Hp goat antibody (#PA-2121-1, EY Laboratories, Inc., San Mateo, CA, USA) diluted 10,000 times with PBS-T containing 1% BSA was added to each well and incubated for 20 min at room temperature. After washing with PBS-T, 50 μL of 3,3′,5,5′-tetramethylbenzidine substrate solution (#5120-0053, KPL, Milford, MA, USA) was added to each well and allowed to react for 5 min. Human plasma as standard (IMMAGE Immunochemistry Systems Cal 1 #449560, Beckman Coulter, Brea, CA, USA) was serially diluted to the concentrations of 0.003, 0.03, and 0.3 mg/dL, then the differential absorbance was measured from which a standard curve was created, and the measurement sensitivity was confirmed. The absorbance of the test serum and of the standard Hp were compared to determine the concentration of Hp.

PCR for detecting Hp^{del} and Hp^1/Hp^2 typing

Genomic DNA was extracted from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Tokyo, Japan). To detect the Hp^{del}, we performed PCR using specific primers (H-del-U, H-del-L, H-Ex1-U and H-Ex1-L) for the *Hp* gene [3]. Briefly, genomic DNA (20–40 ng) was amplified by 35 cycles of PCR in a 10 μL reaction volume containing PCR buffer with 0.4 units of LA-Taq (TaKaRa, Kyoto, Japan), 0.2 μL of 10 mM dNTPs, 0.5 μL of 99.5% dimethyl sulfoxide (Wako, Osaka, Japan), 0.2 μL of 20 μM H-del-U, 0.2 μL of 20 μM H-del-L, 0.2 μL of 20 μM H-Ex1-U and 0.2 μL of 20 μM H-Ex1-L under the following conditions: 1 cycle of 1 min at 94°C, and 35 cycles of 10 s at 98°C, 30 s at 61°C and 30 s at 72°C (Veriti, Applied Biosystems, Waltham, MA, USA). We also performed PCR using specific primers (H-Ex1-U and H-Ex7-L2) for Hp^1/Hp^2 typing [10]. Briefly, genomic DNA (20–40 ng) was amplified by 25 cycles of PCR in a 20-μL reaction volume containing 2 μL of 10× PCR buffer with 0. 2 μL (1.0 units) of LA-Taq (TaKaRa), 2 μL of 25 mM $MgCl_2$, 3.2 μL of 2.5 mM dNTPs, 0.4 μL of 10 μM H-Ex1-U and 0.4 μL of 10 μM H-Ex7-L2 under the following conditions: 1 cycle of 2 min at 94°C and 35 cycles of 10 s at 98°C, 30 s at 60°C and 8 min at 72°C (GeneAmp PCR System 9700, Applied Biosystems).

RESULTS

Selection of monoclonal antibodies for the latex agglutination method

By using three clones of the anti-Hp-producing cell lines (CBC-441, CBC-443 and CBC-447), we developed a reagent for the latex agglutination method. For preparing antibody-coated latex beads, instead of using one monoclonal antibody, we selected a combination of the two monoclonal antibodies, which showed the highest detection sensitivity and specificity; the combination of CBC-441/CBC-443 gave the best results for detecting Hp.

Setting of the cut-off values

The absorbance of 10 positive control samples (Hp concentration: 0.15 mg/dL) and 10 blank samples was measured (Figure 2a). There was a significant difference in the absorbance values between the +2 standard deviation (SD) of the blank samples and −2SD of the tentative cut-off controls. Therefore, the cut-off value was set at 0.15 mg/dL. Next, we measured 20 random samples and 5 samples from the Hp-deficient donors (Figure 2b). The absorbance values of the Hp-negative and Hp-positive samples could be clearly distinguished.

Quantitative measurement of low concentrations of Hp

In the plotted reaction curve with the Hp reagent, 30 mg/dL produced the maximum absorbance value, but higher concentrations decreased it (Figure 2c). The normal Hp range is 19–170 mg/dL, meaning that the absorbance value obtained with this reagent does not correlate

with the Hp concentration in most donors. However, a linear curve was obtained in the low Hp concentration range. Thus, we considered this reagent would be useful for measuring Hp in the low-concentration and Hp-deficient ranges, which is ideal for the identification of Hp-deficient individuals. We confirmed that the limit of detection was 0.075 mg/dL.

Screening 7476 samples revealed 2 Hp-deficient and 21 low-Hp expression donors

From February to August 2022, 7476 blood donor samples were screened at the Kanto-Koshinetsu Block Blood Center. Samples were selected randomly and measured qualitatively to detect Hp-deficient and low-Hp samples. Samples with low absorbance values below 400 were selected. These samples were diluted twofold with a normal saline solution and re-tested to confirm that the absorbance of the retested sample was half that of the initial value to distinguish samples with a low concentration from those with prozone interference.

From the screening of 7476 samples, two Hp-deficient individuals and 21 individuals with a low expression of Hp were detected. All 23 samples were confirmed to have an Hp concentration of <0.3 mg/dL or zero by enzyme-linked immunosorbent assay (ELISA) (Table S1). The two Hp-deficient donors were confirmed to have no antibodies against Hp.

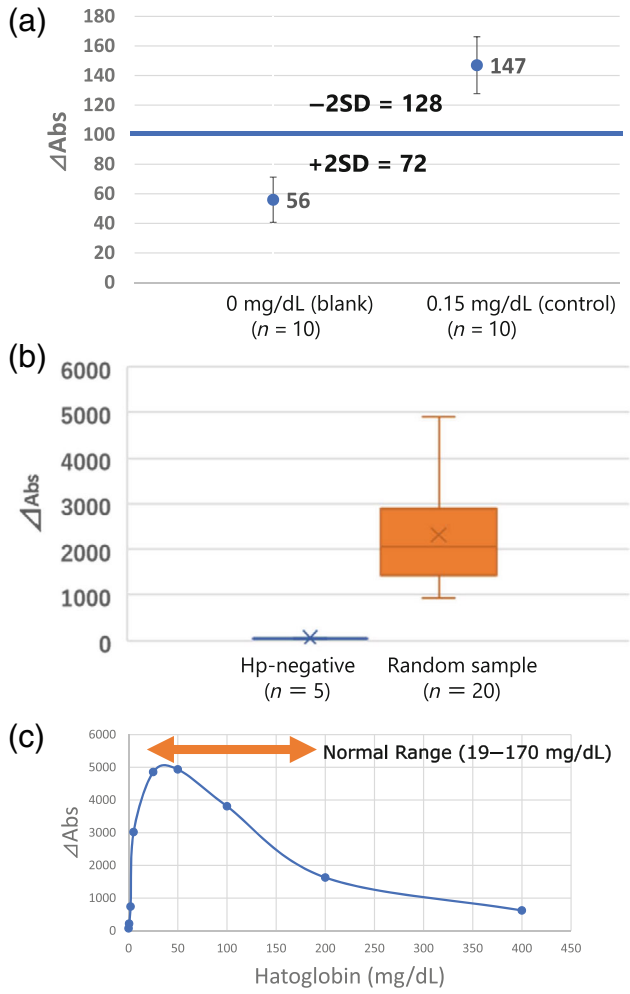

FIGURE 2 (a) The absorbance values of the 10 blank samples and 10 control samples with the haptoglobin (Hp) concentrations of the tentative cut-off values. (b) The absorbance values of the negative and positive samples by the latex agglutination method using an automatic analyser (LABOSPECT008, Hitachi High-Tech Corporation, Tokyo, Japan). (c) The plotted reaction curve with the novel reagent. Abs, absorbance; SD, standard deviation.

Majority (90%) of the 21 donors with low-Hp expression were heterozygous for the *Hp*^{del}

The two Hp-deficient individuals were confirmed to be homozygous for *Hp*^{del} by PCR (Figure 3a, Table S1). Of the 21 donors with low-Hp expression, 19 donors (90%) were confirmed to be heterozygous for *Hp*^{del}. Among these heterozygous donors, the non-*Hp*^{del} allele was the *Hp*^{2} type in 18 individuals and the *Hp*^{Johnson} type in 1 individual (Figure 3b). Heterozygous *Hp*^{del}/*Hp*^{Johnson} was also identified in our previous research and was included as a control in the present study (last lane in Figure 3b); however, no actual heterozygous *Hp*^{del}/*Hp*^{Johnson} case has been reported until now. Therefore, this is the first reported case of heterozygous *Hp*^{del}/*Hp*^{Johnson}. Homozygous *Hp*^{2}/*Hp*^{2} and heterozygous *Hp*^{1}/*Hp*^{2} were also confirmed in two donors with low-Hp expression without *Hp*^{del}.

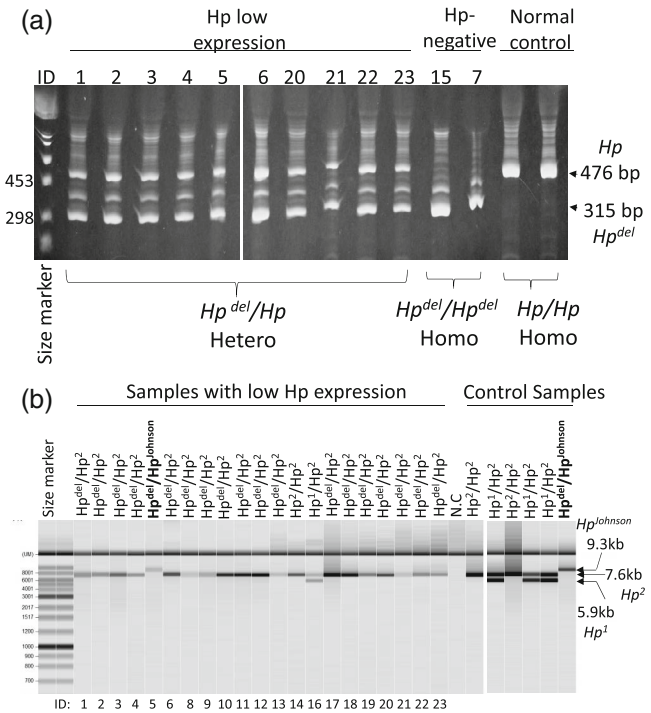

FIGURE 3 (a) Polymerase chain reaction (PCR) for detecting *Hp*^{del}. (b) PCR for *Hp*^{1}/*Hp*^{2} typing. Hp, haptoglobin.

DISCUSSION

Previously, 272,068 Japanese blood donors had been screened [7] and 78 Hp-deficient donors (0.029%) identified; in addition, 72 IgA-deficient donors (0.0057%) had been identified among 1.26 million donors [10]. Interestingly, 31.6% of the IgA-deficient donors had anti-IgA, while only one of the Hp-deficient donors had anti-Hp. It was inferred that most of the anti-IgA were naturally occurring, while the anti-Hp were produced through acquired immunity. As such, it is strongly suspected that anti-Hp may be the cause of severe transfusion reactions. Outside of Japan, it has been reported that 1 in 1500 Koreans and 1 in 1000 Chinese are Hp-deficient [3], and a case of transfusion reaction due to anti-Hp was reported [11]. In addition, the reported prevalence of anhaptoglobinaemia has been reported to be 1 in 1000 among European Caucasians [12], 1.7% among Australians [13], 4% among African Americans [14] and >30% among West Africans [15]. However, the high frequency of anhaptoglobinaemia in malaria-endemic areas is attributed to haemolytic diseases. Careful re-analysis of 10 serum samples from anhaptoglobinaemia cases revealed that 6 of the 10 cases were of the Hp2-2 type and had a low Hp concentration, 1 case was of the Hp2-1 type and only 3 cases had true Hp deficiency [16]. Therefore, it is important to distinguish between true Hp deficiency and secondary Hp deficiency or low-Hp expression. With our novel reagent, we were able to clearly distinguish between cases with true Hp deficiency and cases with low Hp concentrations. Therefore, our novel reagent is expected to be useful for reaching a definitive diagnosis when Hp deficiency is suspected in clinical practice.

In this study, we detected 21 (0.28%) individuals with low Hp expression among the 7476 screened cases; of these, 90% (19/21) were heterozygous for the Hp^{del} gene. We confirmed that 18 of these 19 individuals were heterozygous with Hp^{del}/Hp^{2}, and the remaining individual is the first reported case to be heterozygous with $Hp^{del}/Hp^{Johnson}$. Functional differences in the clearance of haemoglobin from plasma and the modulation of immune responses between Hp1-1, Hp2-1 and Hp2-2 have been reported, but the association between the subtypes and specific diseases remains unclear [1]. It should also be noted that Hp-deficient individuals did not show any specific health problems, although Hp-knockout mice tended to suffer greater oxidative damage and failed to repair or regenerate damaged renal tissues after sever haemolysis [17].

In summary, we successfully produced a novel screening reagent that enables the measurement of low concentrations of Hp with a turbidimetric immunoassay. Using this reagent, two Hp-deficient donors were detected among 7476 screened donors. Our reagent has a limit of detection of 0.075 mg/dL, which is lower than that of the commercially available reagents (limit of detection: 1 mg/dL or more). This reagent will be useful to cost-effectively screen blood donors to identify new Hp-deficient individuals, allowing the establishment of a new Hp-deficient registry, which will contribute for the safety of blood transfusion therapy. Hp deficiency is also observed at a relatively high frequency in other regions of Asia, and therefore this reagent may also be useful for them to establish their Hp-deficient donor registry.

ACKNOWLEDGEMENTS

N.W.-O. designed the research study, performed the research and wrote the first draft of the manuscript. A.S., A.O., G.T., Y.S., M.A. and T.S. contributed essential reagents and acquired and analysed the data. Y.W., K.K., D.T., T.O. and K.M. supported the research as managers or directors. N.-H.T. edited the manuscript. M.U. supervised the research and reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Watanabe-Okochi N, Sato A, Okuyama A, Tomiyoshi G, Suzuki Y, Watanabe Y, et al. A novel reagent for the screening of haptoglobin-deficient blood donors. Vox Sang. 2023;118:1109–14.

Received: 5 October 2023 | Accepted: 6 October 2023

DOI: 10.1111/vox.13549

INTERNATIONAL FORUM

Vox Sanguinis ISBT International Society of Blood Transfusion

International Forum on Blood Donation in Individuals with Current, Past or Germline Predisposition to Malignancy: Summary

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INTRODUCTION

Global cancer rates are on the rise, driven by population growth and ageing, epidemiologic risk factors such as obesity, as well as the success of coordinated early-detection programs, particularly in high-income countries [1]. Additionally, with increasing accessibility and sensitivity of molecular testing, pre-malignant conditions, including familial cancer predisposition syndromes, are increasingly recognized.

Historically, active or past malignancy resulted in permanent deferral from blood donation. In view of increasing demand and challenges maintaining supply, as well as recognizing a negligible risk of cancer transmissibility via allogeneic blood products [2–4], many blood services now accept donations from individuals with certain current or past cancer diagnoses [5–8]. However, practices vary depending on tumour type, as well as between blood services. Additionally, guidelines may not encompass donors with pre-malignant conditions or hereditary cancer predisposition syndromes, in part due to lack of data to inform decision making.

Genetic variants that predispose to haematological malignancy have been recently recognized in the 2016 World Health Organization (WHO) Classification of Haematopoietic Neoplasms [9]. Variants in *DDX41* are the most common, display an autosomal dominant inheritance pattern, affect up to 6.2% of adult patients with myelodysplasia and acute myeloid leukaemia and were recently reported in approximately 1 in 430 healthy biobank participants in the United Kingdom [10, 11].

Recognizing a heightened risk of leukaemogenesis in the transplant setting, screening for genetic predisposition to haematological malignancy in potential stem cell donors deemed at high risk is now recommended by international society guidelines [12]. Conversely, no current publications exist regarding blood donation eligibility. However, a recent survey of North American blood services reported 21 of 37 services (56.8%) would permanently defer potential donors with clonal haematopoiesis of indeterminate potential (CHIP), an acquired disorder with pre-malignant potential [8].

Individuals with a personal or family history of cancer may be particularly motivated to give blood, having benefitted from the altruistic donations of others. Blood services must balance the risks of donation by these individuals with demand for sufficient national blood supplies, as well as providing adequate counselling to potential, actual and deferred donors. This survey aims to capture current patterns of donor selection and deferral for individuals with current, past or germline predisposition to malignancy, to inform evidence-based policy and development of guidelines for these individuals.

SUMMARY

Of 25 invited respondents, we received 12 responses from 12 countries: Australia, Canada, France, Germany, Japan, Hong Kong, Indonesia, Italy, Netherlands, South Africa, United Arab Emirates and the United Kingdom.

An overview of the 12 responses is presented in Table 1 and summarized in detail in the following sections.

TABLE 1 Summary of survey responses from 12 participating countries.

	Section 1: Potential donors with current solid organ malignancy			Section 2: Potential donors with current haematological malignancy			Section 3: Potential donors with past solid organ malignancy			Section 4: Potential donors with past haematological malignancy			Section 5: Potential donors with genetic/familial predisposition to solid organ malignancy			Section 6: Potential donors with genetic/familial predisposition to haematological malignancy		
	Existing guidelines	Accept donations	Recall products	Existing guidelines	Accept donations	Recall products	Existing guidelines	Accept donations	Recall products	Existing guidelines	Accept donations	Recall products	Existing guidelines	Accept donations	Recall products	Existing guidelines	Accept donations	Recall products
Australia	Yes	Yes[a]	No	Yes	No	Yes	Yes	Yes[a]	No	Yes	No	Yes	No	Yes	No	No	Yes	No
Canada	Yes	Yes[a]	No	Yes	No	Yes	Yes	Yes[a]	No	Yes	No	Yes	No	Yes	No	No	Yes	No
France	Yes	No	No	Yes	No	No	Yes	Yes[a]	No	Yes	No	No	No	Yes	No	No	Yes	No
Germany	Yes	Yes[a]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
Hong Kong	Yes	Yes[a]	Yes	Yes	No	Yes	Yes	Yes[a]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
Indonesia	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No
Italy	Yes	Yes[a]	No	Yes	No	No	Yes	Yes[a]	No	Yes	No	No	No	Yes	No	No	Yes	No
Japan	Yes	No	Yes	Yes	No	Yes	Yes	Yes[a]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
Netherlands	Yes	Yes[a]	No	Yes	No	Yes	Yes	Yes[a]	No	Yes	No	Yes	No	Yes	No	No	Yes	No
South Africa	Yes	Yes[a]	Yes	Yes	No	Yes	Yes	Yes[a]	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
United Arab Emirates	Yes	Yes[a]	No	Yes	No	No	Yes	Yes[a]	No	Yes	No	No	Yes	Yes	No	No	Yes	No
United Kingdom	Yes	Yes[a]	Yes	Yes	No	Yes	Yes	Yes[a]	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No
Total answered 'Yes'	11	9	5	11	0	8	11	10	5	11	0	8	2	12	0	0	12	0

[a]Conditional acceptance (e.g., based on tumour type, receipt of curative treatment and/or time elapsed since curative treatment).

For sections 1-6, the following questions were asked for each scenario presented:

1-6a. Are there guidelines for selection of these blood donors?
1-6b. Under what conditions are these people able to donate?
1-6c. If a donor had previously donated and was later identified to have a current history of solid organ malignancy at time of prior donation, would you attempt to recall products already donated?

Section 1: Blood donors with a current history of solid organ malignancy

Eleven of 12 participating countries had existing donor guidelines for patients with current solid organ malignancy. The exception was Indonesia, where, despite the lack of formal guidelines, these individuals are deferred from donation because of a current or past history of either solid organ or haematological malignancy.

With regard to donor eligibility, policy differed between malignancies considered minimally invasive and other malignancies. Examples of minimally invasive malignancies include basal cell carcinoma of the skin, squamous cell carcinoma of the skin and cervical intraepithelial neoplasia. Nine of 12 respondents (75%; Australia, Canada, Germany, Hong Kong, Italy, Netherlands, South Africa, United Kingdom, United Arab Emirates) allowed donations from individuals with minimally invasive malignancies, typically without a period of deferral, provided that curative treatment had been administered and wounds had healed. Some respondents required a physician's letter or histopathology report documenting complete excision. In comparison, three respondents imposed deferrals on these individuals; in France, there is a deferral period of 12 months following excision of carcinoma in situ; in Japan, the deferral period is 5 years; in Indonesia deferral is permanent. Furthermore, all 12 respondents imposed deferral periods on all other solid organ tumour types. Precise wording of the respective guidelines is summarized in Table 2.

Five of 12 respondents (42%; Germany, Hong Kong, Japan, South Africa and the United Kingdom) stated they would recall or discard blood products if the donor was subsequently identified to have developed active solid organ malignancy at or after the time of donation. In Germany, only products currently in stock would be discarded, and no recalls would be made. Additionally, in Germany, plasma manufacturers would be notified for cancer diagnoses made up to 10 years after donation. In Hong Kong, only cancer diagnoses made within 3 months of donation would warrant product recall. In South Africa, this would depend on the time between diagnosis and donation, as well as on the tumour type, with recalls generally performed only for melanoma. In the United Kingdom, in addition to recall of in-date components, the clinician in charge would also be notified if products had already been transfused.

Of interest, in Canada, recall of products from donors with active solid organ malignancies is no longer performed, because of the large number of retrievals resulting from this policy and negligible concerns of cancer transmissibility in this setting.

Section 2: Blood donors with a current history of haematological malignancy

In contrast to active solid organ malignancy, no respondents allowed donation of blood components from individuals with active haematological malignancy, under any circumstances.

Eight of 12 respondents (67%; Australia, Canada, Germany, Hong Kong, Japan, Netherlands, South Africa, United Kingdom) would attempt to recall products if active haematological malignancy was identified following a donation. This number was higher than the number of services attempting recall for active solid organ malignancies; respondents from Australia, Canada and the Netherlands indicated they performed recalls only in the setting of active haematological but not solid organ malignancies. In contrast, recall procedures were identical in the other five countries for both active solid and haematological malignancies. The specific guidance for recalls is summarized in Table S1.

Section 3: Blood donors with a past history of solid organ malignancy

None of 12 respondents allowed unconditional donations from individuals with past solid organ malignancy. However, most (11/12, 92%) allowed donation from some donors with past malignancy depending on tumour type, documentation of cure and/or a minimum amount of time elapsed since cancer treatment. These results are summarized in Table 2. In the case of seven countries (58%, France, Germany, Hong Kong, Italy, Netherlands, United Arab Emirates and the United Kingdom), donation was permissible only for non-melanoma skin cancer and carcinoma in situ, with other more invasive tumour types being permanently deferred.

Four countries (Australia, Canada, Japan and South Africa) allowed donation for solid organ malignancies with any tumour histology, contingent on >5 years having elapsed since curative treatment. Additionally, in Italy, exceptions can be extended for donors with cured solid organ malignancy who have rare red cell phenotypes, provided they are more than 5 years from completion of curative treatment without expectation of recurrence. Of interest, the Canadian donor guidelines are currently under discussion, with a view to shorten the deferral period to 12 months for most solid tumours and for melanoma, considering negligible transmissibility from allogeneic donations in these patients and in line with current American Red Cross recommendations [13]. The policy for donors with a past history of solid organ malignancy is also currently under review in the Netherlands.

Five of 12 respondents (42%) stated they would recall products from donors with past history of solid organ malignancy; these were the same respondents that would perform recall for donors with active solid organ malignancy (Germany, Hong Kong, Japan, South Africa and the United Kingdom).

TABLE 2 Deferrals for current or past solid organ malignancy.

	Minimally invasive cancers (e.g., non-metastasized BCC and SCC of skin, CIN of cervix)	Other solid organ malignancy
Australia	BCC and SCC of skin: accept after curative treatment and all wounds are healed CIN: accept after curative treatment and all wounds are healed; defer for 2 months from the date of cone biopsy Melanoma in situ: accept after curative treatment, after review by a designated medical officer of the blood service	Defer until 5 years following the end of curative treatment
Canada	Accept after curative treatment	Defer until 5 years following the end of curative treatment (under discussion to change the deferral period to 12 months)
France	Defer until 12 months following the end of curative treatment	Defer permanently
Germany	Accept if a medical certificate is available of a successfully completed curative therapy, complete surgery or histopathology	Defer permanently
Hong Kong	BCC of skin: accept after curative treatment CIN: accept after curative treatment, and a follow-up smear did not show abnormal cells	Defer permanently
Indonesia	Defer permanently	Defer permanently
Italy	Accept after curative treatment	Defer permanently (exceptions are established in particular situations, e.g., donors with rare blood groups fully recovered without expectation of recurrence 5 years after completion of treatment in active follow-up)
Japan	Defer until 5 years following the end of curative treatment	Defer until 5 years following the end of curative treatment
Netherlands	BCC of skin: accept after curative treatment Carcinoma in situ: accept after curative treatment	Defer permanently
South Africa	BCC and SCC of skin: defer until 2 weeks following excision, if completely excised and healed CIN: lesions treated by laser, cautery or cone biopsy may be acceptable if the donor is fit and the 6 month follow-up Pap smear is negative	Defer until 5 years following the end of curative treatment If prostate cancer localized to the prostate only, defer until 4 months after prostatectomy/ brachytherapy, provided the PSA is within acceptable ranges
United Arab Emirates	BCC of skin: accept after curative treatment and all wounds are healed. If any systemic medical treatment was required, defer until 2 years following completion of systemic treatment Carcinoma in situ: accept after curative treatment and discharge from follow-up. Donors who have been returned to screening following treatment can be accepted	Defer permanently
United Kingdom	BCC of skin: accept after curative treatment and all wounds are healed. If any systemic medical treatment was required, defer until 2 years following completion of systemic treatment CIN, vulval, ductal carcinoma in situ of breast, prostatic intraepithelial neoplasia: accept after curative treatment and discharge from follow-up Melanoma in situ: accept after curative treatment, after review by a designated medical officer of the blood service	Defer permanently

Abbreviations: BCC, basal cell carcinoma; CIN, cervical intraepithelial neoplasia; PSA, prostate-specific antigen; SCC, squamous cell carcinoma.

Section 4: Blood donors with a past history of haematological malignancy

No respondents allowed donation of blood components from individuals with a past history of haematological malignancy, under any circumstances. Additionally, the same eight respondents (67%) that would attempt to recall products from a donor with active haematological malignancy would also do so if a past history of haematological malignancy was declared. Of note, this would be subject to medical enquiry in Canada, where there is no specific policy for recall of products in this situation.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

In contrast to active and/or past history of solid and haematological malignancy, where guidelines were well established in the majority of surveyed blood services, only 2 respondents of 12 (United Kingdom, United Arab Emirates) reported existing donor guidelines for individuals with germline predisposition to solid organ malignancy. Within these guidelines, individuals with a high risk of cancer due to family history or following genetic tests, including recipients of prophylactic surgery or on prophylactic medication such as tamoxifen, are accepted as donors.

Despite a lack of formal guidelines, all 12 respondents stated they would accept donations from individuals with genetic predisposition to solid organ malignancy, and no recalls would be initiated if this information was disclosed following a donation.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

As with genetic/familial predisposition to solid organ malignancy, none of the surveyed blood services had existing donor guidelines for individuals with germline predisposition to haematological malignancy. Despite this, all 12 respondents stated they would accept donations from individuals with genetic predisposition to haematological malignancy, and none would recall blood products donated from these individuals.

One respondent (Hong Kong) indicated that potential donors with identified genetic/familial predisposition had not previously been encountered at their blood service. Similarly, the respondent from South Africa noted that with limited access to genetic screening, the proportion of donors with access to this kind of information is currently extremely limited. Furthermore, deferral based on theoretical risks in South Africa is balanced against other pressures on sufficiency of the blood supply, such as human immunodeficiency virus prevalence, poverty and food security.

Finally, the adjacent issue of monoclonal gammopathy of uncertain significance (MGUS) was raised by one respondent (Italy). This is considered a pre-malignant condition with an average risk incidence of transformation to overt plasma cell myeloma of approximately 1% per annum. Despite no evidence to suggest that blood or plasma donation increases the risk of transformation to overt malignancy in these individuals, or is transmissible to transfusion recipients, MGUS is considered a reason for permanent deferral in Italy and by other blood services [14].

Section 7: Theoretical concerns surrounding donations

7a. Which donors raise concern for the risk of exacerbation of underlying cytopenias, if present?

7b. Which donors raise concern for the potential for increased risk of adverse donor reactions?

7c. Which donors raise concern for the risk to the recipient receiving cellular products with potential acquired red cell or platelet dysfunction?

7d. Which donors raise concern for transmission of malignancy to the recipient?

Potential donors with active haematological malignancy were perceived by respondents to carry the highest risk from donating blood, with regard to both donor and recipient safety, as summarized in Table 3. Regarding specific risks, the majority of respondents reported concerns regarding exacerbation of donor cytopenias (9 respondents, 75%), adverse donor reactions such as injection site bruising or infection (11 respondents, 92%), risk to the recipient of acquired red cell and platelet dysfunction (9 respondents, 75%) and theoretical risk of cancer transmission (8 respondents, 67%). The high perceived risk from active haematological malignancy is reflected in respective donor eligibility guidelines, which are particularly stringent regarding deferral of these donors.

Individuals with current or past solid organ malignancy, or past haematological malignancy, were also perceived as high-risk potential donors. However, the risk of cancer transmission was notably perceived as lower in individuals with past solid organ malignancy, reported as a concern by just two respondents (17%), compared with current haematological malignancy (reported as a concern by eight respondents, 67%), as well as past haematological malignancy (seven respondents, 58%).

In contrast, individuals with genetic/familial predisposition to solid organ or haematological malignancy were considered very low to negligible risk. However, one respondent (United Arab Emirates) reported concerns regarding increased adverse donor reactions and risk to the recipient of acquired red cell and platelet dysfunction.

DISCUSSION AND SURVEY CONCLUSIONS

Overall, there was moderate variation across blood services internationally in the approach to donor selection and product recall for individuals with current, past or germline predisposition to cancer.

Broadly, donors with current/past haematological malignancies were perceived as highest risk with regard to adverse events for both donors and recipients. This was followed by donors with current solid organ malignancies and then by donors with past solid organ malignancies. Increasing risk appetite for accepting donors with past solid organ malignancies was noted, with abolishment of product recalls and ongoing discussion regarding a shorter deferral period for these individuals in Canada, and a review of guidelines currently in progress in the Netherlands.

Reflecting the high degree of concern surrounding potential donors with current/past haematological malignancy, a consistent finding across all 12 blood services was permanent deferral for donors with these medical conditions. Donors affected by current/past haematological malignancy also triggered more recalls than other risk categories. However, this may reflect the historical policy based on the

TABLE 3 Theoretical concerns surrounding donation.

	Exacerbation of donor cytopenias	Increased adverse donor reactions	Risk to recipient of acquired red cell and platelet dysfunction	Risk to recipient of cancer transmission
Current solid organ malignancy	8 (67%)	9 (75%)	5 (42%)	5 (42%)
Current haematological malignancy	9 (75%)	11 (92%)	9 (75%)	8 (67%)
Past solid organ malignancy	5 (42%)	3 (25%)	2 (17%)	2 (17%)
Past haematological malignancy	5 (42%)	6 (50%)	6 (50%)	7 (58%)
Genetic/familial predisposition to solid organ malignancy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Genetic/familial predisposition to haematological malignancy	0 (0%)	1 (8%)	1 (8%)	0 (0%)

precautionary principle rather than evidence-based practice, with contemporary publications recognizing a lack of evidence that leukaemias and lymphomas are transmissible by blood donation [4, 15, 16]. Furthermore, this contrasts with recent Council of Europe guidelines, which no longer recommend permanent deferral for all individuals with a history of leukaemia/lymphoma as of the 2023 update [6]. An increasing trend of acceptance of donations from individuals with current/past haematological malignancy was also noted in a recent North American survey of blood services, where 32/37 (87%) respondents would permanently defer individuals with active myelodysplastic or myeloproliferative malignancies but 1 (3%) would accept these donors and 4 (11%) would accept donations after deferral periods ranging from 1 to 5 years from remission [8].

Another consistent finding across all 12 blood services was a lack of guidelines for donors with genetic predisposition to solid/haematological malignancy. The exceptions were the United Kingdom and the United Arab Emirates, which were notable for formally accepting donors with familial solid organ cancer predisposition syndromes, even if treated with prophylactic medications or surgeries. Despite the absence of guidelines, individuals with genetic predisposition to solid/haematological malignancy were also assessed to be acceptable donors in all 10 other surveyed blood services. One respondent flagged concerns for potential defective red cell/platelet products and increased donor adverse reactions in individuals with germline predisposition to haematological malignancy. The risk of platelet dysfunction with pathogenetic variants of *RUNX1*, *ANKRD26* and *ETV6* and immunodeficiency with pathogenic *GATA2* variants is well described [17]. Individuals with cellular dysfunction resultant from these syndromes typically present with cytopenias [17], and this may be an effective way of identifying and excluding donors at high risk of these complications.

Variable access to genetic testing should be highlighted as a potential reason for lack of guidelines for familial predisposition syndromes in many countries. Limited access to, and/or experience with, familial genetic testing was demonstrated in responses from Hong Kong and South Africa. In view of the relatively high background population frequency of these variants [17, 18], this suggests that many current blood donors may have undiagnosed germline predisposition syndromes, and may in fact have successfully donated for years. In contrast, a recent North American survey reported that 21 of 37 services (56.8%) would permanently defer patients with CHIP, an acquired pre-malignant condition affecting up to 10% of individuals age >60 with risk of progression to haematological malignancy of approximately 0.5%–0.1% per year [19, 20]. As wider uptake of genetic testing becomes available, the codification of donor eligibility within policy and guidelines, to ensure a consistent approach, will become increasingly important.

Finally, the challenge of balancing theoretical donor and recipient risk with demands on providing sufficient national blood supply should be underscored. The permanent deferral policy for adequately treated solid organ malignancies in Italy is notably modifiable at the discretion of a transfusion physician in situations of inventory shortage, such as in the case of donors with rare red cell phenotypes. The transfusion literature provides support for this and other inclusive donor policies, with negligible documented risk of cancer transmission via blood donation, and demonstration of reduced deferral rates following implementation of expanded eligibility criteria for donors with a history of cancer [7]. The continued review and adaptation of existing donor guidelines therefore comprises an important aspect of maintaining adequate blood inventory.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Baggio D, Fox LC, Wood EM, Aditya RN, Goldman M, van den Berg K, et al. International Forum on Blood Donation in Individuals with Current, Past or Germline Predisposition to Malignancy: Summary. Vox Sang. 2023;118:1115–21.

Received: 5 October 2023 | Accepted: 6 October 2023

DOI: 10.1111/vox.13550

INTERNATIONAL FORUM

Vox Sanguinis ISBT International Society of Blood Transfusion

International Forum on Blood Donation in Individuals with Current, Past or Germline Predisposition to Malignancy: Responses

Diva Baggio | Lucy C. Fox | Erica M. Wood | Robby Nur Aditya | Mindy Goldman | Karin van den Berg | Sabine Kayser | Patrick Wuchter | Noriko Namba | Nelson H. Tsuno | Shigeyoshi Makino | Cheuk Kwong Lee | Naim Akhtar | Farrukh Shah | Gail Miflin | Daniele Prati | Massimo La Raja | Ursula La Rocca | Pascale Richard | Pierre Tiberghien | Robert J. Harley | May Y. Raouf | Ranjita Sharma | Suminder Kaur | Sanne Bruijns | Henriette Prakke-Weekamp | Nancy Dunbar

INDONESIA

Robby Nur Aditya

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
No.

1b Under what conditions are these people able to donate?
NEVER able to donate.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
No.

2b Under what conditions are these people able to donate?
NEVER able to donate.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
No.

3b Under what conditions are these people able to donate?
NEVER able to donate.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?
No.

4b Under what conditions are these people able to donate?
NEVER able to donate.

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the

prior donation, would you attempt to recall components already donated?

No.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?

No.

5b Under what conditions are these people able to donate?

ALWAYS able to donate.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?

No.

6b Under what conditions are these people able to donate?

ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of SOLID ORGAN malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of SOLID ORGAN malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

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CANADA

Mindy Goldman

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?

Yes.

1b Under what conditions are these people able to donate?

NEVER able to donate.

Regulatory guidance:

Canadian Standards Association (CSA) Standards for blood and blood components, CAN/CSA-Z902-20.

Precise wording from relevant guidance document:

5.3.7 Cancer

Donors previously diagnosed with a haematological malignancy (e.g., leukaemia or lymphoma) or with melanoma shall be permanently deferred. Donors previously diagnosed with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ of the cervix may be accepted after curative treatment. Donors previously diagnosed with other types of cancer shall be deferred for 5 years, unless they have been evaluated and deemed suitable to donate by a blood centre physician, in accordance with operating procedures.

Reference:

Canadian Standards Association Standard Z902-20, Blood and Blood Components.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Comments:

We used to do this, causing many retrievals, but stopped several years ago, since there is no evidence of cancer transmission by blood or blood components.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
Yes.

2b Under what conditions are these people able to donate?
NEVER able to donate.

Regulatory guidance: Canadian Standards Association (CSA) Standards for Blood and Blood Components, CAN/CSA-Z902-20.

Precise wording from relevant guidance document:
See 1b, CSAZ902-20, section 5.3.7.

Reference:
Canadian Standards Association standard Z902-20, Blood and Blood Components.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:
We would recall in date transfusible components donated in the 12 months prior to the report of the malignancy. For example, if the donor informed us 6 months after their whole blood donation that they have developed leukaemia, we would recall the plasma for transfusion or cryoprecipitate. The red cells and platelets from the donation have either been transfused or expired (so are no longer in date). We would not recall source plasma.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
Yes.

3b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

For most solid tumours, people can donate 5 years after the end of curative treatment (as per standard above). We are now trying to change this to 12 months. We do not require letters or blood test results, but rely on the history obtained from the donor.

Regulatory guidance:
Canadian Standards Association (CSA) Standards for Blood and Blood Components, CAN/CSA-Z902-20.

Precise wording from relevant guidance document:
See 1b, CSAZ902-20, section 5.3.7.

Reference:
Canadian Standards Association Standard Z902-20, Blood and Blood Components.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?
Yes.

4b Under what conditions are these people able to donate?
NEVER able to donate.

Regulatory guidance:
Canadian Standards Association (CSA) Standards for blood and blood components, CAN/CSA-Z902-20.

Precise wording from relevant guidance document:
See 1b, CSAZ902-20, section 5.3.7.

Reference:
Canadian Standards Association standard Z902-20, Blood and Blood Components.

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:
This might generate a medical enquiry, since not exactly covered in our retrieval manual. It would likely result in a recall of in date, transfusible components (similar to when a donor calls and says that they developed the haematological malignancy post-donation), because the donor did not actually meet our criteria.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.

5b Under what conditions are these people able to donate?
ALWAYS able to donate.

Regulatory guidance:
Not applicable.
Specific citation:
Not applicable.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the

time of the prior donation, would you attempt to recall components already donated?

No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?

No.

6b Under what conditions are these people able to donate?

ALWAYS able to donate.

Regulatory guidance:

Not applicable.

Specific citation:

Not applicable.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:

None of the above.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:

None of the above.

Section 8: Additional comments

We periodically reassess our criteria, based on available evidence, and have moved from a permanent to a 5-year deferral for most solid tumours. This decreased donor deferrals substantially [1]. We are now hoping to move to a 1-year deferral post-curative treatment for most solid tumours and for melanoma. Most US blood operators have a 1-year post-curative treatment deferral policy [2]. As donors undergo screening to detect early cancers, cancer treatment has improved, and donors are older, very precautionary policies put in place decades ago should be reassessed. There is ample data on the lack of transmissibility of cancers [3].

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SOUTH AFRICA

Karin van den Berg

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?

Yes.

1b Under what conditions are these people able to donate?

SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results).

Please specify:

Persons with certain carcinomas in situ may donate, but any malignancy that is more advanced than in situ has an automatic deferral.

Precise wording from relevant guidance document:

All solid organ tumours, e.g., sarcoma (Sa005) – defer 5 years. If after 5 years there is no evidence of recurrence and the donor is well, he or she may be reinstated. For donors undergoing radiotherapy: * If donor has had brachytherapy for prostate cancer, defer 4 months from the time of radiation implants (see Prostatic cancer). (Ra003) * Defer for 5 years if radiation was used to treat other malignant conditions. Donors may be acceptable after 5 years, but only after consultation with the Donor Medical Manager and a letter from the treating doctor (Ra004). (See specific cancer.) For donors undergoing chemotherapy: * Defer according to type of cancer and treatment. Long-term therapy such as Tamoxifen is regarded as chemotherapy. * A donor who has successfully completed chemotherapy and remains in remission for at least 5 years may donate.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

It would depend on the type of solid organ tumour and the time since the last donation and the diagnosis of the malignancy. We have, to my recollection, only ever done this for melanoma and were only able to recall the plasma as the red cells had been issued already.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?

Yes.

2b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

Leukaemia, lymphoma and any other haematological malignancy – defer indefinitely (Ca034).

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

It would depend on how long before the diagnosis the last donation was made.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?

Yes.

3b Under what conditions are these people able to donate?

SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

As a general rule, donors with a history of solid organ malignancy may donate if they have been disease free and off treatment for 5 years. Melanoma has an indefinite deferral and certain non-invasive cancers may have shorter deferral periods.

Precise wording from relevant guidance document:

Breast cancer (simple lumpectomy; Br009): even if completely excised, and on no other therapy – defer for 5 years. Cancer of the cervix: • Carcinoma in situ (CIS) lesions treated by either laser, cautery (Ce007) or cone biopsy may be acceptable if donor is fit and the 6-month follow-up PAP smear is negative (Ca005). NB: No letter is required if the cone biopsy was done more than 5 years ago. • All other cancers of the cervix, defer 5 years (Ca004). See Radiation therapy and chemotherapy. Skin cancers: • Basal cell and squamous carcinoma – deferral for minor procedure: acceptable after 2 weeks if completely excised and healed. • Melanoma in situ acceptable after 5 years of being disease free. Histology report is required (Ca007). • Melanoma – defer indefinitely (Ca008). Prostate cancer (Pr004) a. If the cancer is localized to prostate only: The donor is acceptable 4 months after prostatectomy (Pr007)/brachytherapy (Pr005), provided the PSA is within acceptable ranges (Pr007) b. Defer for 5 years if cancer extends beyond the prostate gland (Pr006). All solid organ tumours, e.g., sarcoma (Sa005) – defer 5 years. If after 5 years there is no evidence of recurrence and the donor is well, he or she may be reinstated. A letter from treating doctor is required, unless the donor has been disease free for more than 10 years (Ca009). For all cancers, see Chemotherapy, Radiation therapy and Hormone inhibitors.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

It depends on the type of malignancy (generally only for melanoma) and the time between the last donation and the diagnosis.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?

Yes.

4b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

Leukaemia, lymphoma and any other haematological malignancy – defer indefinitely (Ca034).

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

It would depend on the time since the last donation.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.

5b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results).

Please specify:
We do not ask about genetic/familial predisposition to solid organ malignancy, but if a donor were to offer this information, we would accept the donor.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?
No.

6b Under what conditions are these people able to donate?
ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Comments:
We do not ask about genetic/familial predisposition to solid organ malignancy, but if a donor were to offer this information, we would not attempt to recall previously donated components.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

Section 8: Additional comments

Within the South African context, we need to carefully balance the safety and the sufficiency of the blood supply (we have ~15% HIV prevalence among the target blood donor population with an even high prevalence of poverty and food insecurity). We therefore must be very circumspect about deferring on theoretical risks. In addition, with limited access to genetic screening, the proportion of donors with access to this kind of information is extremely limited.

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GERMANY

Sabine Kayser and Patrick Wuchter

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:
People who have or have had a malignancy are to be excluded from blood donation permanently. Exemptions are carcinoma in situ, if a medical certificate is available of a successfully completed curative therapy, complete surgery or pathohistology.

Reference:
https://www.bundesaerztekammer.de/themen/medizin-und-ethik/wissenschaftlicher-beirat/stellungnahmen-richtlinien-jahresberichte/haemotherapie-transfusionsmedizin/richtlinie-zur-gewinnung-von-blut-und-blutbestandteilen-und-zur-anwendung-von-blutprodukten-richtlinie-haemotherapie: Richtlinie zur Gewinnung von Blut und

Blutbestandteilen und zur Anwendung von Blutprodukten (Richtlinie Hämotherapie) Chapter 2.2.4.3.1.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Products on stock will be discarded. No recalls of products. Plasma manufacturer will be informed (up to 10 years after donation), based on individual contracts.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?

Yes.

2b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

Persons with haematological or lymphatic diseases are to be excluded from blood donation.

Reference:

https://www.bundesaerztekammer.de/themen/medizin-und-ethik/wissenschaftlicher-beirat/stellungnahmen-richtlinien-jahresberichte/haemotherapie-transfusionsmedizin/richtlinie-zur-gewinnung-von-blut-und-blutbestandteilen-und-zur-anwendung-von-blutprodukten-richtlinie-haemotherapie: Richtlinie zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Richtlinie Hämotherapie) Chapter 2.2.4.3.1.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Products on stock will be discarded. No recalls of products. Plasma manufacturer will be informed (up to 10 years after donation), based on individual contracts.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?

Yes.

3b Under what conditions are these people able to donate?

NEVER able to donate.

Regulatory guidance:

Precise wording from relevant guidance document:

People who have or have had a malignancy are to be excluded from blood donation permanently. Exemptions are carcinoma in situ, if a medical certificate is available of a successfully completed curative therapy, complete surgery or pathohistology.

Reference:

https://www.bundesaerztekammer.de/themen/medizin-und-ethik/wissenschaftlicher-beirat/stellungnahmen-richtlinien-jahresberichte/haemotherapie-transfusionsmedizin/richtlinie-zur-gewinnung-von-blut-und-blutbestandteilen-und-zur-anwendung-von-blutprodukten-richtlinie-haemotherapie: Richtlinie zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Richtlinie Hämotherapie) Chapter 2.2.4.3.1.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Products on stock will be discarded. No recalls of products. Plasma manufacturer will be informed (up to 10 years after donation), based on individual contracts.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?

Yes.

4b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

People who have or have had a malignancy are to be excluded from blood donation permanently. Exemptions are carcinoma in situ, if a medical certificate is available of a successfully completed curative therapy, complete surgery or pathohistology.

Reference:

https://www.bundesaerztekammer.de/themen/medizin-und-ethik/wissenschaftlicher-beirat/stellungnahmen-richtlinien-jahresberichte/haemotherapie-transfusionsmedizin/richtlinie-zur-gewinnung-von-blut-und-blutbestandteilen-und-zur-anwendung-von-blutprodukten-richtlinie-haemotherapie: Richtlinie zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Richtlinie Hämotherapie) Chapter 2.2.4.3.1.

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Products on stock will be discarded. No recalls of products. Plasma manufacturer will be informed (up to 10 years after donation), based on individual contracts.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.

5b Under what conditions are these people able to donate?
ALWAYS able to donate.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?
No.

6b Under what conditions are these people able to donate?
ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

Section 8: Additional comments

People who have or have had a malignancy (including haematological disorders) are never allowed to donate (including if they are cured).

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JAPAN

Noriko Namba, Nelson H. Tsuno and Shigeyoshi Makino

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:

In case of a history of malignancy (except for haematological malignancy), at least 5 years must have passed after complete response was achieved.

Reference:
https://www.mhlw.go.jp/content/001007127.pdf

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
Yes.
2b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:
Eligible donors should not have a history of cancer (limited to haematological malignancy) or Creutzfeldt–Jakob disease.
Reference:
https://www.mhlw.go.jp/content/001007127.pdf

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
Yes.
3b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

At least 5 years have passed after complete response was achieved.
Precise wording from relevant guidance document:
In case of a history of malignancy (except for haematological malignancy), at least 5 years must have passed after complete response was achieved.
Reference:
https://www.mhlw.go.jp/content/001007127.pdf

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:
Components are to be recalled if the donors have history of solid organ malignancy, and the donations are done within 5 years after complete response was achieved.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?
Yes.
4b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:
Eligible donors should not have a history of cancer (limited to haematological malignancy) or Creutzfeldt–Jakob disease.
Reference:
https://www.mhlw.go.jp/content/001007127.pdf

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.
5b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Unless they have history of genetic/familial solid organ malignancy.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?
No.
6b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Unless they have history of genetic/familial haematological malignancy.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Comments:

If a donor reports history of genetic/familial malignancy at the time of donation, the component is to be recalled.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
None of the above.

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HONG KONG

Cheuk Kwong Lee

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

At present, we allow those with history of carcinoma of cervix and basal cell carcinoma of skin who are declared fully recovered to donate blood.

Precise wording from relevant guidance document:

Accept if: after successful treatment for basal cell carcinoma of skin or cervical carcinoma in situ and a follow-up smear did not show abnormal cells.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:

Normally recall if the diagnosis was made within a short time from donation. Normally will not recall if onset >3 months.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
No.

2b Under what conditions are these people able to donate?
NEVER able to donate.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:

Normally recall if the diagnosis was made within a short time from donation. Normally will not recall if onset >3 months.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
Yes.

3b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Accept if: after successful treatment for basal cell carcinoma of skin or cervical carcinoma in situ and a follow-up smear did not show abnormal cells.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:
Normally recall if the diagnosis was made within a short time from donation. Normally will not recall if onset >3 months.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?
Yes.
4b Under what conditions are these people able to donate?
NEVER able to donate.
4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Comments:
Normally recall if the diagnosis was made within a short time from donation. Normally will not recall if onset >3 months.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.
5b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results).

Please specify:
We do not have such policy and have never encounter this before.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?
No.

6b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

We do not have such policy and have never encounter this before.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
None of the above.
7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
None of the above.
7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
None of the above.
7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
None of the above.

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UNITED KINGDOM

Naim Akhtar, Farrukh Shah and Gail Miflin

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.
1b Under what conditions are these people able to donate?
NEVER able to donate.

Regulatory guidance:
Precise wording from relevant guidance document:
Malignancy Obligatory: Must not donate. Discretionary (a) If this was a non-metastasized basal cell carcinoma (rodent ulcer) and local

treatment is completed and all wounds are healed, accept. If any systemic medical treatment was required and has been completed at least 24 months previously, accept. (b) If the potential donor has a non-haematological (non-clonal) pre-malignant condition (e.g., polyposis coli or Barrett's oesophagus) that is being regularly monitored, or has had a similar condition cured and has been discharged from follow-up, accept. (c) If the potential donor has been cured of a carcinoma in situ (CIS) and discharged from follow-up, accept. Donors who have been returned to screening following treatment for CIS can be accepted. Examples of CIS include cervical or vulval CIS, ductal CIS of the breast (DCIS), prostatic intraepithelial neoplasia (PIN) and squamous cell CIS of the skin (also known as intraepithelial squamous cell carcinoma or Bowen's disease). (d) If the potential donor has had a diagnosis of melanoma in situ (including lentigo maligna), refer to DCSO to confirm they have not had an invasive melanoma (e.g., lentigo maligna melanoma). Donors who have already been cleared by a DCSO can be accepted.

Reference:

This entry was last updated in: DSG-WB Edition 203, Release 61. JPAC website

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Recall and discard if still in date. Inform clinician in charge if transfused to patient.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?

Yes.

2b Under what conditions are these people able to donate?

NEVER able to donate.

Regulatory guidance:

Precise wording from relevant guidance document:

Haematological Disease Obligatory: Must not donate if (a) Malignant. (b) A clonal disorder, e.g., primary polycythaemia (rubra vera), essential thrombocythaemia or monoclonal gammopathy of unknown significance (MGUS). Discretionary (a) If following specialist investigation a polycythaemia is not diagnosed as *polycythaemia rubra vera*, or another myeloproliferative neoplasm, and no treatment or further investigation is planned, accept. (b) If following specialist investigation a thrombocythaemia, or another myeloproliferative neoplasm, is not diagnosed as *essential thrombocythaemia* and no treatment or further investigation is planned, accept.

Reference:

This entry was last updated in: DSG-WB Edition 203, Release 58 JPAC website

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Recall and discard if in date. Inform clinician in charge if product transfused to patient.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?

Yes.

3b Under what conditions are these people able to donate?

SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Malignancy: If this was a non-metastasized basal cell carcinoma (rodent ulcer) and local treatment is completed and all wounds are healed, accept. If any systemic medical treatment was required and has been completed at least 24 months previously, accept.

Precise wording from relevant guidance document:

Malignancy Obligatory: Must not donate. Discretionary (a) If this was a non-metastasized basal cell carcinoma (rodent ulcer) and local treatment is completed and all wounds are healed, accept. If any systemic medical treatment was required and has been completed at least 24 months previously, accept. (b) If the potential donor has a non-haematological (non-clonal) pre-malignant condition (e.g., polyposis coli or Barrett's oesophagus) that is being regularly monitored, or has had a similar condition cured and has been discharged from follow-up, accept. (c) If the potential donor has been cured of a carcinoma in situ (CIS) and discharged from follow-up, accept. Donors who have been returned to screening following treatment for CIS can be accepted. Examples of CIS include cervical or vulval CIS, ductal CIS of the breast (DCIS), prostatic intraepithelial neoplasia (PIN) and squamous cell CIS of the skin (also known as intraepithelial squamous cell carcinoma or Bowen's disease). (d) If the potential donor has had a diagnosis of melanoma in situ (including lentigo maligna), refer to DCSO to confirm they have not had an invasive melanoma (e.g., lentigo maligna melanoma). Donors who have already been cleared by a DCSO can be accepted. (e) Potential donors with a high risk of cancer due to family history or following genetic tests, even if had or having prophylactic surgery, or on prophylactic medication (e.g., Tamoxifen), or on routine follow-up, accept.

Reference:

This entry was last updated in: DSG-WB Edition 203, Release 61. JPAC website

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Recall and discard.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?

Yes.

4b Under what conditions are these people able to donate?

NEVER able to donate.

Regulatory guidance:

Precise wording from relevant guidance document:

Haematological Disease Obligatory: Must not donate if: (a) Malignant. (b) A clonal disorder, e.g., primary polycythaemia (rubra vera), essential thrombocythaemia or monoclonal gammopathy of unknown significance (MGUS). Discretionary: (a) If following specialist investigation a polycythaemia is not diagnosed as *polycythaemia rubra vera*, or another myeloproliferative neoplasm, and no treatment or further investigation is planned, accept (b) If following specialist investigation a thrombocythaemia, or another myeloproliferative neoplasm, is not diagnosed as *essential thrombocythaemia* and no treatment or further investigation is planned, accept. See if relevant anaemia haemochromatosis haemoglobin disorders haemolytic anaemia immune thrombocytopenia malignancy polycythaemia and raised haemoglobin. Additional Information: Clonal disorders result from the proliferation of a single cell. Because they have the potential to become malignant, they are treated in the same way as malignancy. Information: This is a requirement of the Blood Safety and Quality Regulations 2005. Reason for change: The discretionary and see if relevant sections have been updated to include the revised Polycythaemia and Raised Haemoglobin entry. Donor Information: If you wish to obtain more information regarding a personal medical issue please contact your National Help Line. Please do not contact this website for personal medical queries, as we are not in a position to provide individual answers.

Reference:

This entry was last updated in: DSG-WB Edition 203, Release 58 JPAC website

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

Recall and discard.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?

Yes.

5b Under what conditions are these people able to donate?

ALWAYS able to donate.

Precise wording from relevant guidance document:

Potential donors with a high risk of cancer due to family history or following genetic tests, even if had or having prophylactic surgery, or on prophylactic medication (e.g., Tamoxifen), or on routine follow-up, accept.

Reference:

This entry was last updated in: DSG-WB Edition 203, Release 61. JPAC website

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?

No.

6b Under what conditions are these people able to donate?

ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of SOLID ORGAN malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

Section 8: Additional comments

Currently not formally risk assessed.

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ITALY

Daniele Prati, Massimo La Raja and Ursula La Rocca

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Only in case of specific conditions (basalioma and in situ cancer of the cervix after surgical removal)

Regulatory guidance:

Precise wording from relevant guidance document:

All individuals with a history of malignant neoplasms, haematological neoplasms or neoplasms associated with viral conditions are excluded. Donors with a history of basal cell carcinoma or in situ carcinoma of the cervix after neoplasm removal may be accepted.

Specific citation:

Reference:

Health Minister Decree, 2 Nov 2015. https://www.centronazionalesangue.it/wp-content/uploads/2017/07/GU-SG-n.300-del-28-12-2015_SO_069.pdf

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
Yes.

2b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:

All individuals with a history of malignant neoplasms, haematological neoplasms or neoplasms associated with viral conditions are excluded. Donors with a history of basal cell carcinoma or in situ carcinoma of the cervix after neoplasm removal may be accepted.

Reference:

Health Minister Decree, 2 Nov 2015. https://www.centronazionalesangue.it/wp-content/uploads/2017/07/GU-SG-n.300-del-28-12-2015_SO_069.pdf

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
Yes.

3b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Only in case of specific conditions (basalioma and in situ cancer of the cervix after surgical removal) Exceptions are established in particular conditions, that is, donors with rare blood groups fully recovered without expectation of recurrence 5 years after the completion of treatment in active follow-up.

Regulatory guidance:

Precise wording from relevant guidance document:

All individuals with a history of malignant neoplasms, haematological neoplasms or neoplasms associated with viral conditions are excluded. Donors with a history of basal cell carcinoma or in situ carcinoma of the cervix after neoplasm removal may be accepted.

Reference:

Health Minister Decree, 2 November 2015. https://www.centronazionalesangue.it/wp-content/uploads/2017/07/GU-SG-n.300-del-28-12-2015_SO_069.pdf

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?

Yes.

4b Under what conditions are these people able to donate?

NEVER able to donate.

Regulatory guidance:

Precise wording from relevant guidance document:

All individuals with a history of malignant neoplasms, haematological neoplasms or neoplasms associated with viral conditions are excluded. Donors with a history of basal cell carcinoma or in situ carcinoma of the cervix after neoplasm removal may be accepted.

Reference:

Health Minister Decree, 2 Nov 2015. https://www.centronazionalesangue.it/wp-content/uploads/2017/07/GU-SG-n.300-del-28-12-2015_SO_069.pdf

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?

No.

5b Under what conditions are these people able to donate?

ALWAYS able to donate.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?

No.

6b Under what conditions are these people able to donate?

ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of SOLID ORGAN malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:

Donors with a CURRENT history of SOLID ORGAN malignancy.

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of SOLID ORGAN malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:

None of the above.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:

Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

Donors with a PAST history of HAEMATOLOGICAL malignancy.

Section 8: Additional comments

Risks for donors and recipients, if any, are minimal. The medical literature does not support the transmission of cancer from donors to recipients [1–3]. A temporary deferral for all kinds of cancer after complete recovery (5 years) is reasonable and based on the precautionary principle only. Longer or shorter duration of deferral may be decided at the discretion of the blood bank physician, based on individual risk assessment. However, we would like to mention MGUS,

characterized by progression to malignant conditions at a rate of approximately 1% per year [4]. MGUS is considered a pre-malignant condition, resulting in people being excluded from donating blood and components (in the majority of blood establishments). Monoclonal gammopathy is de facto considered a pre-malignant condition that precludes blood and component donation [5].

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FRANCE

Pascale Richard and Pierre Tiberghien

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:
Malignancy: permanent deferral except in situ cancer after treatment and recovery
Reference:
https://www.legifrance.gouv.fr/loda/id/JORFTEXT000039667225/?isSuggest=true

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
Yes.

2b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:
Malignancy: permanent deferral except in situ cancer after treatment and recovery
Reference:
https://www.legifrance.gouv.fr/loda/id/JORFTEXT000039667225/?isSuggest=true

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
Yes.

3b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

After recovery for in situ cancer (>12 months).
Precise wording from relevant guidance document:
Malignancy: permanent deferral except in situ cancer after treatment and recovery
Reference:
https://www.legifrance.gouv.fr/loda/id/JORFTEXT000039667225/?isSuggest=true

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?
Yes.

4b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:
Malignancy: permanent deferral except in situ cancer after treatment and recovery
Reference:
https://www.legifrance.gouv.fr/loda/id/JORFTEXT000039667225/?isSuggest=true

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.

5b Under what conditions are these people able to donate?
ALWAYS able to donate.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?
No.

6b Under what conditions are these people able to donate?
ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
None of the above.

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AUSTRALIA

Robert J. Harley

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

If a donor has any history of invasive cancer an allogeneic donation is not possible if, in the last 5 years: • the diagnosis was made or

• treatment was required or recommended for the disease or • they relapsed or had a recurrence of the disease.

Precise wording from relevant guidance document:

If a donor has any history of invasive cancer an allogeneic donation is not possible if, in the last 5 years: • the diagnosis was made or • treatment was required or recommended for the disease or • they relapsed or had a recurrence of the disease.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?

Yes.

2b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

Apply a permanent deferral.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

For fresh components – Yes, if diagnosis/symptoms within 2 months of last donation. For plasma for fractionation – No.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?

Yes.

3b Under what conditions are these people able to donate?

SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

If a donor has any history of invasive cancer an allogeneic donation is not possible if, in the last 5 years: • the diagnosis was made or • treatment was required or recommended for the disease or • they relapsed or had a recurrence of the disease.

Precise wording from relevant guidance document:

If a donor has any history of invasive cancer an allogeneic donation is not possible if, in the last 5 years: • the diagnosis was made or • treatment was required or recommended for the disease or • they relapsed or had a recurrence of the disease.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?

Yes.

4b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

Apply a permanent deferral.

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

Yes.

Comments:

For fresh components – Yes, if diagnosis/symptoms within 2 months of last donation. For plasma for fractionation – No.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?

No.

5b Under what conditions are these people able to donate?

SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

If well.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?

No.

6b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

If well at time of donation.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
None of the above.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

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UNITED ARAB EMIRATES

May Y. Raouf, Ranjita Sharma and Suminder Kaur

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Donors are permanently deferred except individuals with a history of in situ malignant disease such as basal cell carcinoma or cervical carcinoma in situ, if regularly monitored and considered successfully treated and in good health.

Precise wording from relevant guidance document:

Obligatory: Must not donate. Discretionary (a) If this was a non-metastasized basal cell carcinoma (rodent ulcer) and local treatment is completed and all wounds are healed, accept. If any systemic medical treatment was required and has been completed at least 24 months previously, accept. (b) If the potential donor has been cured of a carcinoma in situ (CIS) and discharged from follow-up, accept. Donors who have been returned to screening following treatment for CIS can be accepted. The prospective donor shall appear to be in good health and shall be free of major organ disease (e.g., heart, liver, cancer or abnormal bleeding tendency, unless determined suitable by the medical director).

Reference:

1. United Kingdom Blood Transfusion Services (UKBTS) Whole Blood and Component Donor Selection Guidelines (WB&CDSG) Edition 203 - 01 June 2007 Release 61 - 22 February 2022. 2. Standards for Blood Banks and Transfusion Services, 33rd Edition, effective April 1, 2022 3/3/2022 33rd ed.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
Yes.

2b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

Donors with current history of haematological malignancy are permanently deferred.

Precise wording from relevant guidance document:

Haematological Disease Obligatory: Must not donate if: (a) Malignant. (b) A clonal disorder, e.g., primary polycythaemia (rubra vera) essential thrombocythaemia or monoclonal gammopathy of unknown significance (MGUS).

Reference:

United Kingdom Blood Transfusion Services (UKBTS) Whole Blood and Component Donor Selection Guidelines (WB&CDSG) Edition 203 - 01 June 2007 Release 61 - 22 February 2022.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the

prior donation, would you attempt to recall components already donated?

No.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?

Yes.

3b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

Many malignancies spread through the blood stream and by invading surrounding tissues. Viruses that can be spread by blood and tissue donation can also cause some malignancies. For these reasons it is considered safer not to accept blood from people who have had a malignancy.

Reference:

United Kingdom Blood Transfusion Services (UKBTS) Whole Blood and Component Donor Selection Guidelines (WB&CDSG) Edition 203 - 01 June 2007 Release 61 - 22 February 2022.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?

Yes.

4b Under what conditions are these people able to donate?

NEVER able to donate.

Precise wording from relevant guidance document:

(1) Many malignancies spread through the blood stream and by invading surrounding tissues. Viruses that can be spread by blood and tissue donation can also cause some malignancies. For these reasons it is considered safer not to accept blood from people who have had a malignancy. (2) Defer permanently. Individuals with a history of malignant melanoma. Individuals with current or past haematological malignancy, including leukaemia (i.e. lymphoproliferative and myeloproliferative disorders), lymphomas, clonal haematological disorders (such as polycythaemia rubra vera and essential thrombocythaemia, paroxysmal nocturnal haemoglobinuria), myelodysplastic syndromes.

Reference:

1. United Kingdom Blood Transfusion Services (UKBTS) Whole Blood and Component Donor Selection Guidelines (WB&CDSG) Edition 203 - 01 June 2007 Release 61 - 22 February 2022. 2. WHO guidelines on assessing donor eligibility for blood donation.

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?

No.

5b Under what conditions are these people able to donate?

ALWAYS able to donate.

Precise wording from relevant guidance document:

Potential donors with a high risk of cancer due to family history or following genetic tests, even if had or having prophylactic surgery, or on prophylactic medication (e.g., Tamoxifen), or on routine follow-up, accept.

Reference:

United Kingdom Blood Transfusion Services (UKBTS). Whole Blood and Component Donor Selection Guidelines (WB&CDSG) Edition 203 - 01 June 2007 Release 61 - 22 February 2022.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?

No.

6b Under what conditions are these people able to donate?

ALWAYS able to donate.

Regulatory guidance:

Not applicable.

Specific citation:

Not applicable.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?

No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
None of the above.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.
Donors with a GENETIC/FAMILIAL PREDISPOSITION to HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a GENETIC/FAMILIAL PREDISPOSITION to HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

REFERENCES

United Kingdom Blood Transfusion Services (UKBTS) Whole Blood and Component Donor Selection Guidelines (WB&CDSG) Edition 203 - 01 June 2007 Release 61 - 22 February 2022.
WHO guidelines on assessing donor eligibility for blood donation.
Standards for Blood Banks and Transfusion Services, 33rd Edition, effective April 1, 2022 3/3/2022 33rd ed.

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THE NETHERLANDS

Sanne Bruijns and Henriette Prakke-Weekamp

Section 1: Blood donors with a current history of solid organ malignancy

1a Are there guidelines for selection of these blood donors?
Yes.

1b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results). Please specify:

All solid organ malignancies are forbidden, except: Carcinoma in situ is allowed after successful treatment; basalioma is allowed after successful treatment.

Precise wording from relevant guidance document:

Malignant disorders (see also pre-malignant disorders). Definitely reject, with the exception of the cases below. Approve after adequate treatment in basalioma. To be approved after adequate treatment in carcinoma in situ. Approve after adequate treatment in Queyrat erythroplasia, Van Bowen disease and Bowenoid papulosis.

1c If a donor had previously donated and was later identified to have a current history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 2: Blood donors with a current history of haematological malignancy

2a Are there guidelines for selection of these blood donors?
Yes.

2b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:

Same as solid malignancy: Malignant disorders (see also pre-malignant disorders) – Definitely reject.

2c If a donor had previously donated and was later identified to have a current history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Section 3: Blood donors with a past history of solid organ malignancy

3a Are there guidelines for selection of these blood donors?
Yes.

3b Under what conditions are these people able to donate?
SOMETIMES able to donate under specific conditions (e.g., with specialist letters or blood test results).

Precise wording from relevant guidance document:

The same policy as a recent malignancy: Malignant disorders (see also pre-malignant disorders). Definitely reject, with the exception of the cases below (7608). Approve after adequate treatment in basalioma. To be approved after adequate treatment in carcinoma in situ. Approve after adequate treatment in Queyrat erythroplasia, Van Bowen disease and Bowenoid papulosis.

3c If a donor had previously donated and was later identified to have a past history of solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 4: Blood donors with a past history of haematological malignancy

4a Are there guidelines for selection of these blood donors?
Yes.

4b Under what conditions are these people able to donate?
NEVER able to donate.

Precise wording from relevant guidance document:

The same policy as a recent haematological malignancy: Malignant disorders (see also pre-malignant disorders): Definitely rejected.

4c If a donor had previously donated and was later identified to have a past history of haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
Yes.

Section 5: Blood donors with a genetic/familial predisposition to solid organ malignancy

5a Are there guidelines for selection of these blood donors?
No.

5b Under what conditions are these people able to donate?
ALWAYS able to donate.

5c If a donor had previously donated and was later identified to have a genetic/familial predisposition to solid organ malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 6: Blood donors with a genetic/familial predisposition to haematological malignancy

6a Are there guidelines for selection of these blood donors?
No.

6b Under what conditions are these people able to donate?
ALWAYS able to donate.

6c If a donor had previously donated and was later identified to have a genetic/familial predisposition to haematological malignancy at the time of the prior donation, would you attempt to recall components already donated?
No.

Section 7: Theoretical concerns surrounding donations

7a Donors who raise concern for the risk of exacerbation of underlying cytopenias, if present, in the DONOR as a result of donation:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of SOLID ORGAN malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7b Donors who raise concern for the potential for increased risk of adverse DONOR reactions:
Donors with a CURRENT history of SOLID ORGAN malignancy.
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.

7c Donors who raise concern for the risk to the RECIPIENT receiving cellular products with potential acquired red cell or platelet dysfunction:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

7d Donors who raise concern for risk of transmission of malignancy to the RECIPIENT:
Donors with a CURRENT history of HAEMATOLOGICAL malignancy.
Donors with a PAST history of HAEMATOLOGICAL malignancy.

Section 8: Additional comments

The policy of donors with a past history of solid organ malignancy is currently under review and may change in the near future.

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How to cite this article: Baggio D, Fox LC, Wood EM, Aditya RN, Goldman M, van den Berg K, et al. International Forum on Blood Donation in Individuals with Current, Past or Germline Predisposition to Malignancy: Responses. Vox Sang. 2023;118:1122–44.

Received: 16 August 2023 | Revised: 7 September 2023 | Accepted: 12 September 2023

DOI: 10.1111/vox.13539

LETTER TO THE EDITOR

Vox Sanguinis ISBT International Society of Blood Transfusion

Neutralization capacity of convalescent plasma against SARS-CoV-2 omicron sublineages: Implications for donor selection

The distribution and dominance of omicron sublineages of SARS-CoV-2 is complex and varies greatly between settings. This poses a challenge to blood services wanting to provide COVID-19 convalescent plasma (CCP) to recently infected, immunocompromised patients. There is continued interest in CCP therapy, including evaluation in clinical trials, due to the poor therapeutic efficacy of monoclonal antibodies against omicron sublineages [1, 2]. Aotearoa New Zealand (NZ) followed a COVID-19 elimination strategy throughout 2020–2021, which included strong border entry restrictions and managed isolation and quarantine facilities [3]. These restrictions were not lifted until March 2022 such that the initial omicron sublineage BA.1 associated with wide-spread infection in many countries in late 2021 and early 2022 [4] had little penetrance in NZ. Rather, BA.2 dominated after the borders re-opened in March 2022, followed by BA.5 in the second half of the year [5]. These infection patterns may influence the neutralization capacity of stored CCP. The year 2023 has seen an increasingly complex picture in NZ and elsewhere, with multiple omicron sublineages co-circulating at varying levels of dominance [6], further complicating donor plasma selection. The aim of this study was to characterize stored CCP with respect to omicron sublineage neutralization to generate guidance for donor selection.

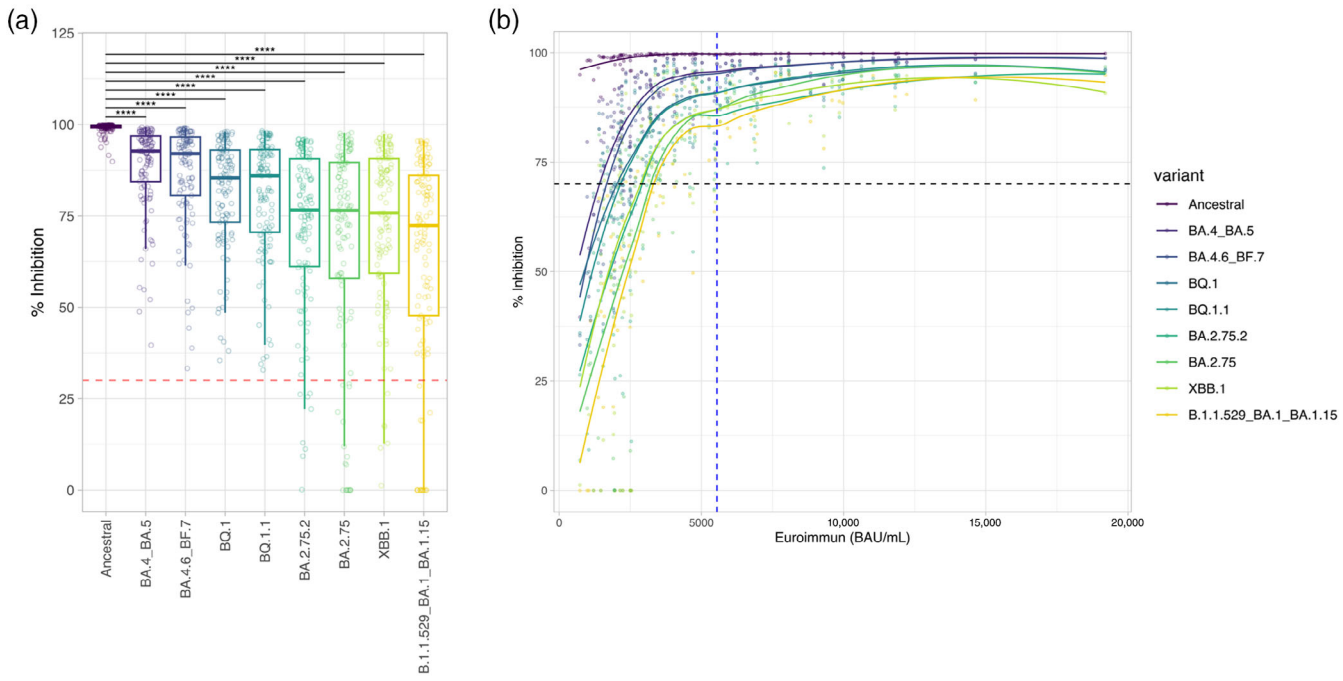

FIGURE 1 Surrogate neutralization assays with omicron sublineages determine total anti-S1 antibody cut-off. (a) Surrogate neutralization assays showed significantly reduced percentage (%) inhibition to all omicron sublineages compared with the ancestral strain (****$p < 0.0001$, two-sample Wilcoxon test with Bonferroni correction). The cut-off for positivity (30% inhibition) is shown as a red dashed line. (b) Comparison of % inhibition in the surrogate neutralization assay and total anti-S1 antibody concentration in BAU/mL shows a non-linear relationship with increased total antibodies leading to increased inhibition (locally estimated scatterplot smoothing used for line fitting with span of 0.7). Receiver operating characteristic curve analysis identified a cut-off of 5547 BAU/mL (blue dashed line) that identified all samples with >70% inhibition against all omicron sublineages (black dashed line) and 100% specificity.

Between 17 January 2022 and 21 October 2022, 113 samples were collected from NZ plasma donors who were vaccinated (at least two doses of the Pfizer/BioNTech mRNA vaccine) and had at least one SARS-CoV-2 infection. Vaccination and infection status were self-reported. Samples were assayed as part of a medicines regulator (MedSafe) approved program for CCP preparation. This study was assessed by the Health and Disability Ethics Committee, and additional consent was not required. Samples were tested for SARS-CoV-1 anti-S1 IgG (Euroimmun Quantivac) as described [7]. The neutralization capacity was assessed using a surrogate viral neutralization assay, which quantifies antibodies that block binding of the human ACE-2 receptor to the receptor binding domain (RBD) of SARS-CoV-2. Surrogate neutralization assays are highly correlative with live and pseudo viral neutralization assays [8, 9] and enable rapid screening of multiple variants in parallel. A multiplex assay incorporating ancestral RBD and RBD proteins derived from eight omicron sublineages (B.1.1.529/BA.1/BA.1.15, BQ.1.1, BA.2.75.2, BA.4.6/BF.7, XBB.1, BA.4/BA.5, BA.2.75, BQ.1) was performed at a sample dilution of 1:25 following the manufacturer's instructions (Meso Scale Discovery V-Plex SARS-CoV-2 Panel 33 [ACE-2]). Specificity was determined with 33 antenatal samples obtained prior to the COVID-19 pandemic as described [10]. All pre-pandemic samples were below the pre-determined cut-off of 30% inhibition (100% specificity).

The mean anti-S1 IgG was high at 4495.6 BAU/mL, with 99/113 (88%) donations above the 1800 BAU/mL cut-off required to qualify as a CCP donor in NZ. The highest level of blocking/neutralizing antibodies was detected to ancestral RBD (median inhibition 99.3%) reflecting responses to the vaccine strain, of which all donors had received at least two doses. The neutralization capacity against all omicron variants was significantly reduced compared with the ancestral RBD ($p < 0.001$, Figure 1a), with the lowest neutralization observed for BA.1 sublineages (median 55.8%) and the highest for BA.4/5 sublineages (median 86.9%). This neutralization pattern is reflective of omicron sublineage distribution in 2022 in NZ, with infection waves dominated by BA.2, followed by BA.4/5 and limited BA.1 transmission [5]. This suggests that variant dominance directly impacts the level of sublineage-specific neutralization in CCP and is supported by a recent observation in France where CCP had higher neutralization capacity for BA.1 following a wave of BA.1 infections in early 2022 [4].

A comparison of total anti-S1 antibody levels and neutralization antibodies revealed a relationship between total antibody and variant neutralization (Figure 1b). Similarly, neutralization antibodies were highly correlative between omicron sublineages such that samples with highest neutralization to one sublineage also tended to be high against other sublineages ($r > 0.79$ and $p < 0.001$ using Pearson correlation for all sublineage comparisons). A receiver operating characteristic (ROC) curve analysis comparing total antibody levels against all neutralizing antibodies/sublineages was performed to determine an antibody cut-off (BAU/mL) that identifies CCP with high neutralization activity for all sublineages (>70%). Maximizing for specificity, with this set at 100% (to minimize false positives and the risk of selecting CCP with lower neutralizing activity), yielded a cut-off of 5547 BAU/mL with an area under the curve (AUC) of 0.885 (0.864–0.907, 96% confidence interval [CI]). Some 30/113 (26.6%) of donations were above this level.

This newly defined cut-off, although excluding a larger proportion of donations, provides a simple means of identifying appropriate CCP when ongoing testing to newly emerging sublineages is not always feasible. This is especially relevant for NZ and other settings where multiple omicron sublineages are currently co-circulating, including the recently emerged XBB sublineages [2, 6]. Despite the CCP donors in this study being unlikely to have been infected with XBB strains, the elevated cut-off would ensure that CCP is selected with high neutralizing activity to this and other sublineages.

ACKNOWLEDGEMENTS

We thank New Zealand (NZ) blood donors for their contribution to convalescent plasma as well as staff in the NZ Blood Service Auckland Donation Accreditation Laboratory.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DOI: 10.1111/vox.13325

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