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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.
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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.
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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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REVIEW

Vox Sanguinis ISBT International Society of Blood Transfusion

The efficacy and effectiveness of drinking interventions to reduce vasovagal reactions in blood donors: A systematic review and meta-analysis

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Abstract

Background and Objectives: Blood establishments strive to ensure the safety and comfort of blood donors while minimizing adverse events. This review aims to assess the efficacy and effectiveness of eating and/or drinking interventions before, during and/or after blood donation in reducing vasovagal reactions (VVRs).

Materials and Methods: We analysed randomized and non-randomized controlled trials comparing eating and/or drinking interventions to no intervention, placebo or usual practice on (pre-)syncopal VVRs and related symptoms. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used to assess the risk of bias and overall certainty of the evidence.

Results: Pre-donation water ingestion likely results in reduced on-site VVRs, compared to no water (2 fewer per 100 donors, moderate-certainty evidence). A pre-donation isotonic drink likely results in reduced VVRs, compared to usual practice (2 fewer per 100 donors, moderate-certainty evidence). Pre-donation salt-loaded sweetened lemon water may result in fewer off-site VVRs, compared to sweetened lemon water only (1 fewer per 100 donors, low-certainty evidence). Pre-donation water and a gel cap containing sucrose with 250 mg caffeine may result in fewer blood donor reaction ratings, compared to pre-donation water only (low-certainty evidence).

Conclusions: Pre-donation plain water ingestion or isotonic drink probably results in a large reduction in on-site and off-site VVRs. Pre-donation water ingestion with caffeine consumption or salt supplementation may result in a VVR reduction, compared to water ingestion only. Future large trials are required to increase the certainty of the effect of these and other interventions in the prevention of VVRs.

Keywords
blood donors, drink, prevention, systematic review, vasovagal reaction, water

Highlights

- Pre-donation plain water ingestion probably results in vasovagal reaction (VVR) reduction, compared to no intervention, but pre-donation caffeine- or salt-loaded water ingestion may result in a VVR reduction, compared to pre-donation water ingestion only.
- Pre-donation isotonic drink probably results in a VVR reduction, compared to the standard practice of advising to drink before donation and eating a snack immediately after donation.
- Future randomized controlled trials are required to further increase the certainty of the effect of these and other physiological interventions in the prevention of VVRs.

INTRODUCTION

Safe and sustainable blood supplies depend on the collection of blood from voluntary non-remunerated and low-risk donors. International data from the World Health Organization indicate that about 10–20 blood donors are needed per 1000 inhabitants to have an adequate blood supply [1]. It is therefore of great importance to recruit a sufficient number of donors and retain them after their first donation. In Europe, 90% of blood donations are performed by voluntary non-remunerated repeat blood donors [1]. However, the recruitment of first-time donors and retaining repeat donors is challenging and might be negatively influenced by deterrents such as deferrals, anxiety and adverse events [2].

To guarantee the safety of the donor, blood establishments make maximum efforts to provide a comfortable donation process and to minimize the risk of adverse events before, during and/or after the donation. A vasovagal reaction (VVR) is defined as 'a general feeling of discomfort and weakness with anxiety, dizziness and nausea, which may progress to loss of consciousness (faint)' [3]. On-site VVRs are the most common acute adverse reaction to blood donation, ranging from 1.4% to 7% for moderate VVRs (reactions with loss of consciousness for <60 s) to 0.1%–0.5% for severe VVRs (reactions with loss of consciousness for >60 s) [4]. The incidence of delayed off-site VVRs is lower (1.53 per 100,000 donors) but might have more severe implications, due to the possibility of inducing an accident or sustaining injuries due to falling [5]. This off-site VVR incidence is generally underreported in routine practice, because off-site VVRs in donor study populations who were systematically contacted in the first days after donation were much higher (15–37 per 1000 donors) [6, 7].

Donor protection practices are important to prevent VVRs. The underlying mechanisms of VVRs encompass an interplay between psychological and physiological elements. A psychological stress associated with the donation procedure (e.g., fear of needles or phlebotomy-related pain) can induce a VVR. Psychological prevention strategies such as donor education, counselling or social support might mitigate the on-site VVR incidence, particularly in first-time donors [8]. VVRs occurring because of physiologic factors, such as the loss of blood volume (±500 mL), tend to manifest at the end of the donation or in the post-donation period, particularly when compounded by an orthostatic posture. Strategies that could allay physiological changes that occur during or after the donation include interventions such as pre-donation water ingestion, applied muscle tension (AMT) during donation and/or providing salty snacks before and/or after the donation [8, 9]. A potential practice to prevent VVRs is the consumption of food and/or beverages before, during and/or after the blood donation. Different blood establishments provide specific food/drink recommendations including eating a light meal before donation, drinking approximately 500 mL water before and/or after donation or eating iron-rich food before and after a blood donation [10, 11]. The present systematic review aimed to identify, synthesize and critically appraise the best available evidence on the effectiveness of eating and drinking interventions to reduce VVRs in whole-blood donors.

MATERIALS AND METHODS

This systematic review, registered on the international prospective register of systematic reviews (PROSPERO, CRD42023421702), adhered to our methodological charter [12] and followed the Preferred Reporting Items for Systematic reviews and Meta-Aanlyses (PRISMA) guidelines [13].

Eligibility criteria

Studies addressing the following PICO question were included: 'In whole-blood donors (Population), is an eating or drinking intervention before, during, or after a donation (Intervention), compared to no intervention, placebo or usual practice (Comparator) effective to reduce vasovagal reactions (VVRs) (Outcome)?' Full texts were reviewed based on predefined criteria (Appendix S1).

Data sources and searches

The Cochrane Library, MEDLINE, PMC and Bookshelf (via the PubMed interface), Embase, CINAHL (via the Ebsco interface), Web of

Science core collection (Science Citation Index Expanded (SCI-Expanded) and Conference Proceedings Citation Index-Science (CPCI-S)) and clinicaltrails.gov were searched on 11 May 2023 using tailored search strings (Appendix S2).

Study selection

Search yields were exported to a citation program (Endnote software v20.5), duplicates were removed and the de-duplicated Endnote file was uploaded to the Rayyan software [14]. Three reviewers (D.V.d.S., D.M. and H.V.R.) independently performed the title and abstract screening followed by the full text assessment according to the eligibility criteria (see 'Eligibility criteria'). Disagreements were resolved by discussion.

Data extraction

Information concerning study design, population characteristics, intervention(s), comparator(s) and outcome(s) was extracted independently by three reviewers (D.V.d.S., D.M. and H.V.R.). Effect estimates were extracted directly from the study or calculated via Review Manager 5.4.1 software [15], for dichotomous outcome data as the risk ratio (RR) with 95% confidence interval (CI) and for continuous outcome data as the mean difference (MD) with 95% CI.

Data synthesis

Review manager 5.4.1 software was used to perform meta-analyses (where possible) [15]. Subgroup analyses were carried out for the type of study design (randomized vs. non-randomized controlled trials [RCT vs. non-RCTs]). (Pooled) effect estimates for relevant donor subpopulations were reported separately (e.g., male/female donors or first time/repeat donors), where possible. Results were considered statistically significant if $p < 0.05$. (Appendix S3).

Risk of bias and grading of the evidence

The risk of bias (RoB) was determined for each of the included studies by three reviewers independently (D.V.d.S., D.M. and H.V.R.) according to the Cochrane RoB Tool [16]. The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) determined the certainty of evidence [17]. The certainty of the evidence for each outcome was graded as high, moderate, low or very low. Experimental studies receive an initial grade of 'high' by default and could be downgraded as a result of RoB, inconsistency, indirectness, imprecision and/or publication bias. Summarized evidence conclusions were formulated according to the certainty of evidence and the magnitude of effect, which was reflected in the wording of the statements [18].

RESULTS

Study selection

Figure 1 depicts the study selection process. After deduplication, 1311 titles/abstracts were screened, followed by screening of 44 full texts.

We eventually included six experimental studies and one systematic review. This systematic review included RCTs assessing the effect of any interventions (including but not restricted to drinking interventions) to reduce VVRs [19]. Five studies in this review fitted our eligibility criteria and were additionally included. One included RCT was published as a conference paper but was not indexed in a database and therefore not retrieved via our database search [6].

This resulted in a total of 12 experimental studies, including 6 individual RCTs [6, 20–24], 2 cluster RCTs [7, 25] and 4 non-RCTs [26–30] with 2 references describing the results of 1 trial [29, 30].

Characteristics of included studies

Table 1 summarizes the characteristics of the 12 included trials. Eight studies compared pre-donation plain water ingestion (250–500 mL) to no intervention or a placebo group [20–22, 25–27, 30, 31]. In one RCT, participants received 500 mL of plain water before donation with/without AMT exercises during donation and were compared with a placebo/no intervention group [20]. One cluster RCT allocated participants to four different intervention arms: 500 mL of an isotonic drink or 500 mL of plain water, with and without AMT. In the two control groups, the usual practice was present (advice to drink before donation and eat a snack afterwards) [7]. Pre-donation fruit juice ingestion (350–450 mL) or the addition of caffeine to 280 mL of plain water was compared with no intervention [28] or pre-donation plain water ingestion only (280 mL) [23], respectively. One trial investigated the effect of sweetened lemon water (300 mL) before donation with salt supplementation (2.5 g) compared to sweetened lemon water alone [6]. No trials investigated the impact of eating interventions on the prevention or reduction in VVRs.

Seven trials were conducted in Western countries (United States, $n = 4$ [20, 21, 23, 27]; the Netherlands, $n = 1$ [29, 30]; Serbia, $n = 1$ [28]; and France, $n = 1$ [7]). Four studies were carried out in Asia (Japan, $n = 1$ [26] and India $n = 3$ [6, 22, 31]). One trial was conducted in South Africa [25].

On-site VVRs were assessed in 10 studies [6, 7, 20, 22, 25–28, 30, 31], and off-site VVRs (primary outcomes) were measured in 3 studies [6, 7, 30]. Five studies monitored signs and symptoms related to VVR or blood donation (secondary outcomes) [7, 20, 21, 23, 30]. A total of 32,926 study participants were included, with a mean age of 26 years (range: 19–38 years): 57% were male donors (range: 0%– 94%) and 57% were first-time donors (range: 2%–100%).

Risk of bias of included studies

Figure 2 provides an overview of the risk of bias across studies and domains, whereas Appendix S4 presents judgements per

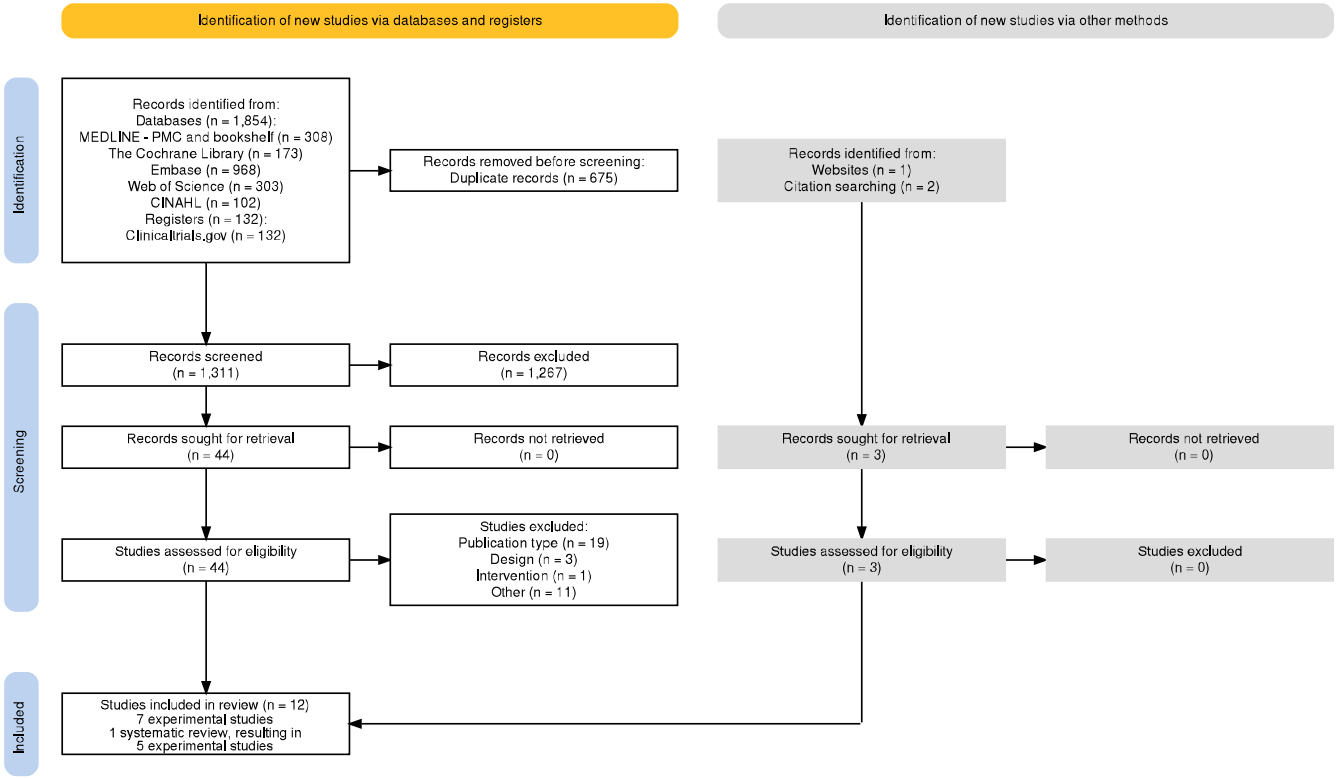

FIGURE 1 Study identification and selection process of the systematic review.

domain for each included study. High risk of selection bias was present in seven studies due to a lack of randomization and/or a failure of allocation concealment [7, 24–28, 30]. Two studies used a randomization procedure resulting in imbalanced demographics of the intervention versus the comparator group [25, 27]. Ten studies did not blind the participants and/or the involved staff to the intervention, which could have influenced the subjective (pre)-syncopal signs/symptoms and VVRs [7, 20–22, 24–28, 30]. Outcome assessors were blinded in only four studies [6, 7, 22, 23]. Seven studies were prone to attrition bias because no information was available on drop-out rates or whether a per-protocol or intention-to-treat analysis was performed [20, 21, 23, 24, 26–28]. Reporting bias was not present except for two studies [27, 28] where the available information was insufficient for a reliable judgement and one study that did not publish/register a study protocol and where no validated questionnaire was used [26]. Other limitations included no compliance to the allocated interventions or lacking information concerning compliance [22–24, 26, 28]. Memorization bias to off-site VVR reporting was mentioned in one study [7], whereas no standardized timing between the pre-donation drinking intervention and the blood donation was reported in another study [27]. One study mentioned inclusion bias because staff may not have consistently forwarded forms from unsuccessful collections to the administrative centre [30].

Effects of interventions

Detailed synthesis of findings tables can be found in Appendix S5.

Pre-donation plain water ingestion versus no intervention (eight studies, n = 21,791).

Primary outcomes

Pre-donation plain water ingestion (250–500 mL) resulted in fewer on-site staff-recorded VVRs compared to no intervention (RR 0.67, 95% CI: 0.55–0.81, $p < 0.0001$, seven studies, moderate-certainty evidence) [20, 22, 25–27, 30, 31] (Figure 3). One study also assessed self-reported on-site and off-site VVRs and found a significant reduction in on-site VVRs in the pre-donation plain water ingestion group (RR 0.86, 95% CI: 0.76–0.97, $p = 0.02$, low-certainty evidence) [30].

Reduced on-site VVRs were present in the following subpopulations: males [22, 27, 30, 31], females [22, 27, 30, 31], first-time donors [27, 30, 31], repeat donors [30], Caucasian donors [27], donors aged 20–29 years [22] and donors with a body mass index (BMI) of 18.5–25 kg/m^2 [22] (RR range 0.44–0.75, $p < 0.05$, low- to very-low-certainty evidence).

A significant difference in the severity of on-site VVRs could not be demonstrated (RR range 0.11–0.92, $p > 0.05$, low- to very-low-certainty evidence) [22, 25, 31], except for moderate VVRs

TABLE 1 Characteristics of included studies.

First author, year, country, study design	Intervention	Comparator	Volume of blood donation	Outcomes
Ando, 2009, Japan, non-RCT	300 mL bottled water pre-donation (n = 45, 34 ± 13 years, 53% males, 0% FT)	No water (n = 31, 34 ± 10 years, 55% males, 3% FT)	400 mL	Primary: on-site VVRs (pre-syncopal)
France, 2010, USA, RCT	500 mL bottled water pre-donation (n = 106, 20 ± 5 years, 48% males, 60% FT) 500 mL bottled water pre-donation + AMT during donation (n = 103, 20 ± 4 years, 47% males, 55% FT)	No water (n = 103, 20 ± 6 years, 49% males, 68% FT) Placebo (AMT pre-donation) (n = 102, 20 ± 3 years, 48% males, 60% FT)	Unclear	Primary: on-site VVRs (pre-syncopal) Secondary: signs and symptoms related to VVR/blood donation
Hanson, 2004, USA, RCT	500 mL bottled water pre-donation (n = 43, 44 ± 6 years (males) vs. 31 ± 6 years (females), 67% males, 100% FT)	No water (n = 40, 45 ± 6 years (males) vs. 30 ± 5 years (females), 35% males, 100% FT)	Unclear	Secondary: signs and symptoms related to VVR/blood donation
Kumar, 2020, India, RCT	300 mL salt-loaded (2.5 g) sweetened lemon water pre-donation (n = 1545, 20 ± 2 years, 85% males, 59% FT)	300 mL sweetened lemon water 30 minutes pre-donation (n = 1515, 20 ± 2 years, 85% males, 58% FT)	<9% of total blood volume or ≥9% (according to Nadler's formula)	Primary: on-site and off-site VVRs (pre-syncopal)
Kuttath, 2021, India, RCT	250 mL bottled water pre-donation (n = 457, 27 ± 7 years, 94% males, 100% FT)	No water (n = 443, 26 ± 7 years, 94% males, 100% FT)	350 mL	Primary: on-site VVRs + severity (mild, moderate, severe)
Morand, 2016, France, cluster RCT	500 mL slightly mineralized water pre-donation + post-donation snack (n = 762, 37 [IQR 26] years, 50% males, 12% FT) 500 mL slightly mineralized water pre-donation + AMT during donation + post-donation snack (n = 748, 38 [IQR 27] years, 49% males, 15% FT) 500 mL isotonic drink (0.68 g NaCl) pre-donation + post-donation snack (n = 775, 35 [IQR 27] years, 50% males, 12% FT) 500 mL isotonic drink (0.68 g NaCl) pre-donation + AMT during donation + post-donation snack (n = 737, 37 [IQR 26] years, 50% males, 9% FT)	Usual practice (advice to drink pre-donation) + post-donation snack (n = 774, 37 [IQR 28] years, 50% males, 15% FT) Usual practice (advice to drink pre-donation) + AMT during donation + post-donation snack (n = 780, 38 [IQR 27] years, 49% males, 15% FT)	<13% of total EBV with a maximum of 500 mL	Primary: on-site and off-site VVRs (pre-syncopal) Secondary: signs and symptoms related to blood donation (unusual tiredness)
Newman, 2007, USA, non-RCT	475 mL mineral water pre-donation (n = 1438, 52% males, 80% FT)	No water (n = 1457, 50% males, 77% FT)	525 mL	Primary: on-site VVRs (pre-syncopal)
Sauer, 1999, USA, RCT	280 mL water with gelcap containing sucrose 125 mg caffeine pre-donation (n = 21, 19 ± 1 years, 100% females, 100% FT) 280 mL water with gelcap containing sucrose 250 mg caffeine pre-donation (n = 20, 19 ± 1 years, 100% females, 100% FT)	280 mL water pre-donation (n = 21, 19 ± 1 years, 100% females, 100% FT)	Unclear	Secondary: signs and symptoms related to VVR/blood donation
Solanki, 2020, India, RCT	500 mL bottled water pre-donation (n = 3239, 36 ± 13 years, 86% males, 4% FT)	No water (n = 3239, 37 ± 13 years, 80% males, 4% FT)	350–450 mL	Primary: on-site VVRs (mild, moderate, severe)

(Continues)

TABLE 1 (Continued)

First author, year, country, study design	Intervention	Comparator	Volume of blood donation	Outcomes
Van den Berg, 2012, South Africa, cluster-RCT	500 mL water bottled water pre-donation (n = 1339, 18–19 years, 55% males, 24% FT)	No water (n = 1127, 18–19 years, 69% males, 25% FT)	475–575 mL	Primary: on-site VVRs (mild, moderate, severe)
Vavic, 2014, Serbia, non-RCT	350–450 mL fruit juice pre-donation (n = 1849, 18–19 years, 62% males, 100% FT)	No fruit juice (n = 1807, 18–19 years, 65% males, 100% FT)	350 or 450 mL	Primary: on-site VVRs (pre-syncopal)
Wiersum-Osselton, 2019, The Netherlands, non-RCT	500 mL water within pre-donation (n = 2006, 22 ± 3 years, 30% males, 42% FT) 330 mL water within pre-donation (n = 2291, 22 ± 3 years, 25% males, 44% FT)	Placebo – ball squeezing by hand before donation (n = 1838, 22 ± 3 years, 29% males, 34% FT) No water (n = 2165, 22 ± 3 years, 25% males, 42% FT)	500 mL	Primary: on-site and off-site VVRs (pre-syncopal) Secondary: signs and symptoms related to VVR/blood donation

Abbreviations: AMT, applied muscle tension; EBV, estimated blood volume; FT, first-time donors; IQR, interquartile range; RCT, randomized controlled trial; VVR, vasovagal reaction.

(i.e., loss of consciousness for <60 s) in male donors, which significantly occurred less in the pre-donation water ingestion group (RR 0.38, 95% CI: 0.15–0.97, $p = 0.04$, low-certainty evidence) [22].

Secondary outcomes

One study found significantly fewer symptoms related to a VVR or blood donation in the pre-donation plain water group (as calculated by the Blood Donor Reaction Inventory [BDRI] score: MD −0.36, 95% CI: −0.65 to −0.07, $p = 0.02$ for males and MD −0.46, 95% CI: −0.78 to −0.14, $p = 0.005$ for females, both very-low-certainty evidence) [21]. However, a statistically significant difference in the BDRI score could not be demonstrated in two other studies ($p > 0.05$, low- to very-low-certainty evidence) [20, 30].

One of these studies found that female and repeat donors experienced less tiredness post donation after drinking plain water (330 mL) (pre-donation: RR 0.87, 95% CI: 0.78–0.97, $p = 0.01$ for female donors; RR 0.78, 95% CI: 0.68–0.90, $p = 0.0004$ for repeat donors, both low-certainty evidence) [30].

Pre-donation plain water ingestion versus placebo (two studies, $n = 6773$).

Primary outcomes

Pre-donation plain water ingestion (250–500 mL) resulted in fewer on-site staff-recorded VVRs compared to a placebo group (RR 0.68, 95% CI: 0.54–0.86, $p = 0.001$, very-low-certainty evidence) [20, 30] (Figure 4). One study also assessed self-reported on-site and off-site VVRs and found a significant reduction in both VVRs in the pre-donation plain water ingestion group, compared to the placebo group (on-site VVRs: RR 0.79, 95% CI: 0.70–0.89, $p < 0.0001$, low-certainty evidence; off-site VVRs: RR 0.79, 95% CI: 0.64–0.99, $p = 0.04$, low-certainty evidence) [30]. This reduction in on-site VVRs was present in the female and repeat donors (RR range 0.60–0.81, $p < 0.05$, low-certainty evidence) [30].

Secondary outcomes

A statistically significant difference in signs/symptoms related to a VVR (e.g., fainting, anxiety) or blood donation (e.g., venipuncture pain, muscle soreness) between the pre-donation plain water ingestion group and the placebo group could not be demonstrated ($p > 0.05$, low- to very-low-certainty of evidence) [20, 30].

Pre-donation plain water ingestion (w/o AMT during donation) versus usual practice (w/o AMT during donation) (one study, $n = 4576$).

Primary outcomes

A statistically significant difference in on-site/off-site VVRs could not be demonstrated in donors who received pre-donation

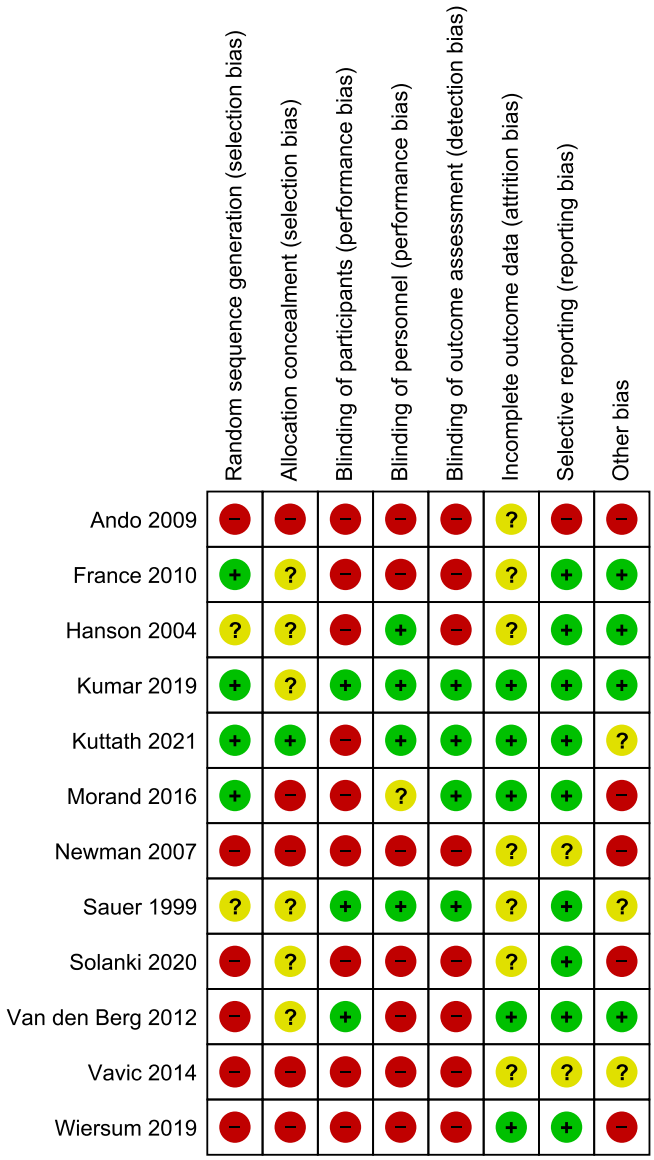

FIGURE 2 Risk of bias summary: Review authors' judgements about each risk of bias item for each included study investigating the effectiveness of drinking interventions. + Low risk of bias, − high risk of bias, ? unclear.

plain water ingestion (w/o AMT during donation), compared to the usual practice (i.e., advice to drink) ($p > 0.05$, low-certainty evidence) [7].

Secondary outcomes

A statistically significant difference in tiredness until 48 h post donation could not be demonstrated (odds ratio [OR] 0.90, 95% CI: 0.72–1.13, $p = 0.39$, low-certainty evidence) [7].

Pre-donation plain water ingestion + AMT during donation versus no intervention or placebo (one study, $n = 308$).

Primary outcomes

Fewer on-site VVRs were reported in donors who received pre-donation plain water and AMT during donation, compared to a placebo group (pre-donation AMT) (RR 0.38, 95% CI: 0.18–0.81, $p = 0.01$, very-low-certainty evidence) [20]. This statistically significant difference in on-site VVRs could not be demonstrated when comparing with donors who received no intervention (RR 0.53, 95% CI: 0.24–1.20, $p = 0.13$, very-low-certainty evidence) [20].

Secondary outcomes

Fewer signs/symptoms related to a VVR or blood donation were present in female donors receiving pre-donation plain water + AMT during donation, compared to female donors who received no intervention or placebo ($p < 0.05$, very-low-certainty evidence) [20].

Pre-donation isotonic drink (w/o AMT during donation) versus usual practice (w/o AMT during donation) (one study, $n = 4576$).

Primary outcomes

Fewer off-site VVRs were present in the group that received a pre-donation isotonic drink (0.68 g NaCl), compared to the usual practice group (RR 0.64, 95% CI: 0.42–0.96, $p = 0.03$, moderate-certainty evidence) [7] (Figure 5). A statistically significant difference in other primary outcomes (on-site + off-site VVRs, VVRs during blood donation and VVRs between the end of blood donation and leaving the unit) could not be demonstrated ($p > 0.05$, low-certainty evidence) [7].

Secondary outcomes

Occurrence of tiredness until 48 h post donation was less in the pre-donation isotonic drink group compared to the usual practice group (OR 0.75, 95% CI: 0.59–0.94, $p = 0.01$, moderate-certainty evidence) [7].

Pre-donation salt-loaded sweetened lemon water ingestion versus pre-donation sweetened lemon water ingestion only (one study, $n = 3060$).

Primary outcomes

A reduction of both on-site and off-site VVRs in donors after drinking 300 mL salt-loaded (2.5 g) lemon water before donation compared to donors receiving 300 mL lemon water only could not be demonstrated (RR: 0.68, 95% CI: 0.45–1.04, $p = 0.07$, low-certainty evidence) [32]. However, when looking at specific subpopulations, females and repeat donors experienced significantly fewer VVR (on- and off-site) after drinking salt-loaded lemon water (RR 0.41, 95% CI:

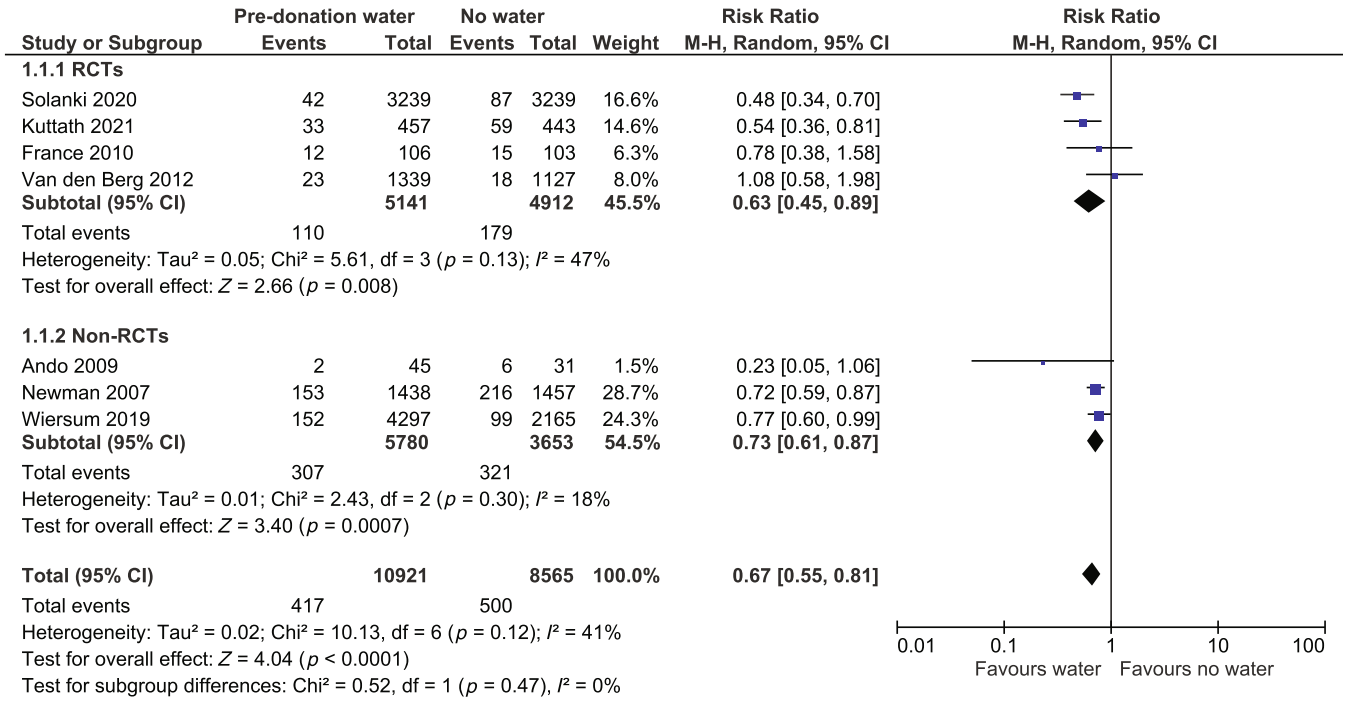

FIGURE 3 The number of on-site vasovagal reactions (VVRs): Study-specific risk ratios (RRs) representing the effectiveness of pre-donation plain water ingestion versus no intervention. Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two upper diamonds represent the pooled effect estimate (+95% CI) for the subgroups (randomized controlled trials [RCTs] and non-RCTs). The bottom diamond shows the pooled effect estimate (+95% CI) of the overall effect.

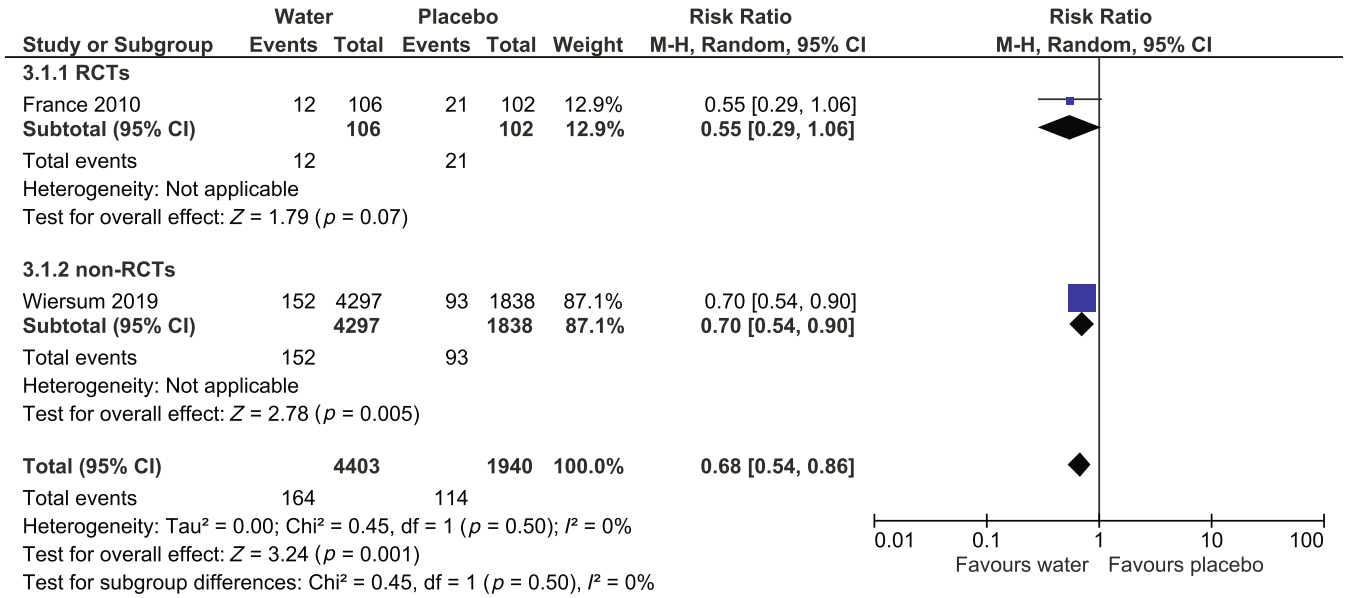

FIGURE 4 The number of on-site vasovagal reactions (VVRs): Study-specific risk ratios (RRs) representing the effectiveness of pre-donation plain water ingestion versus placebo. Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two upper diamonds represent the pooled effect estimate (+95% CI) for the subgroups (randomized controlled trials [RCTs] and non-RCTs). The bottom diamond shows the pooled effect estimate (+95% CI) of the overall effect.

0.17–0.99, $p = 0.045$ for females and RR 0.45, 95% CI: 0.22–0.90, $p = 0.02$ for repeat donors, both low-certainty evidence) [32].

Focusing on off-site VVRs only, a significant reduction was observed in favour of the salt-loaded lemon water group (RR: 0.43,

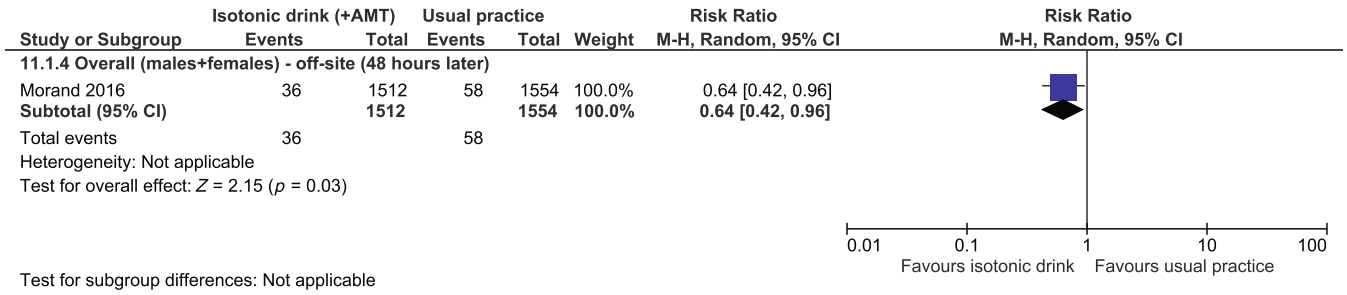

FIGURE 5 The number of off-site vasovagal reactions (VVRs): Study-specific risk ratios (RRs) representing the effectiveness of pre-donation isotonic drink versus usual practice. Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two upper diamonds represent the pooled effect estimate (+95% CI) for the subgroups (randomized controlled trials [RCTs] and non-RCTs). The bottom diamond shows the pooled effect estimate (+95% CI) of the overall effect.

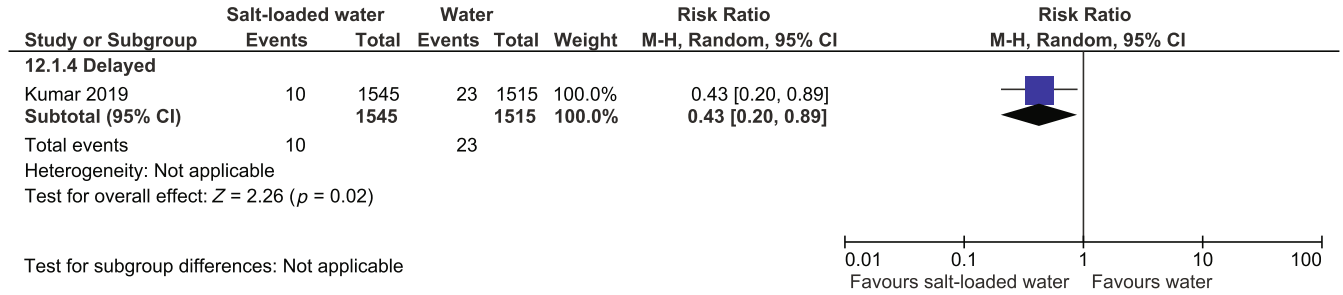

FIGURE 6 The number of off-site vasovagal reactions (VVRs): Study-specific risk ratios (RRs) representing the effectiveness of pre-donation salt-loaded sweetened lemon water ingestion versus pre-donation sweetened lemon water ingestion only. Each dot represents the RR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two upper diamonds represent the pooled effect estimate (+95% CI) for the subgroups (randomized controlled trials [RCTs] and non-RCTs). The bottom diamond shows the pooled effect estimate (+95% CI) of the overall effect.

95% CI: 0.20–0.89, $p = 0.02$, low-certainty evidence) [32] (Figure 6). This reduction was significant in the following subpopulations: donors aged 18–21 years (RR 0.43, 95% CI: 0.20–0.93, $p = 0.03$, low-certainty evidence) and repeat donors (RR 0.08, 95% CI: 0.01–0.65, $p = 0.02$, low-certainty evidence) [32].

Pre-donation water + caffeine ingestion versus pre-donation water ingestion only (one study, n = 62).

Secondary outcomes

Donors receiving 280 mL of water with a gelcap containing sucrose and 250 mg caffeine had fewer signs/symptoms related to a VVR or blood donation, compared to donors receiving 280 mL water only (MD −7.11, 95% CI: −13.91 to −0.31, $p = 0.04$, low-certainty evidence) [23]. This difference could not be demonstrated when donors received 280 mL water with a gelcap containing sucrose and 125 mg caffeine ($p > 0.05$, low-certainty evidence) [23] (Figure 7). A higher systolic blood pressure pre and post donation and a higher post-donation diastolic blood pressure were observed in the groups that received 125/250 mg caffeine and 250 mg caffeine, respectively. These changes were statistically significant but of no clinical relevance (MD range 6.60–8.20, $p < 0.05$, low-certainty evidence) [23]. No significant changes in heart rate pre and post donation could be demonstrated in both caffeine groups ($p > 0.05$, low-certainty evidence) [23].

Pre-donation fruit juice versus no intervention (one study, n = 3656).

Primary outcomes

Drinking 350–450 mL of fruit juice 30 min before donation resulted in fewer on-site VVRs, compared to no intervention (RR 0.57, 95% CI: 0.40–0.83, $p = 0.003$, very-low-certainty evidence) [28]. This reduction in on-site VVRs was present in the following donor subpopulations: male donors, female donors, donors with a body weight of 56–65 kg and donors with a blood pressure of 105/65–135/75 mmHg (RR range 0.42–0.60, $p < 0.05$, very-low-certainty evidence) [28].

DISCUSSION

The present systematic review identified eight RCTs and four non-RCTs comparing the absolute or relative efficacy and effectiveness of eating and drinking interventions to reduce VVRs in whole-blood donors. The following were demonstrated:

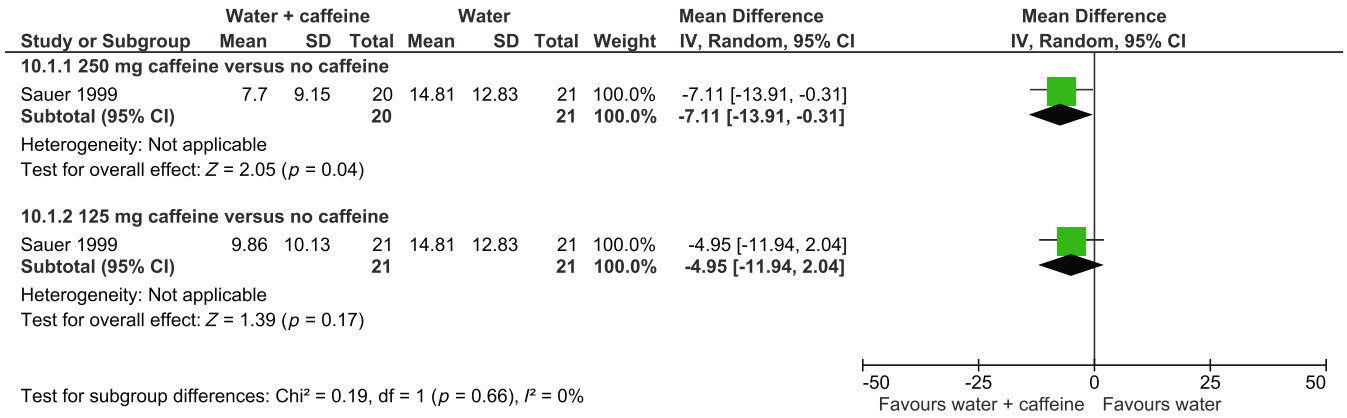

FIGURE 7 Signs and symptoms related to a blood donation/vasovagal reaction (VVR): Study-specific mean differences (MDs) representing the effectiveness of pre-donation salt-loaded sweetened lemon water ingestion versus pre-donation sweetened lemon water ingestion only. Each dot represents the MD of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The diamond represents the pooled effect estimate (+95% CI).

- Pre-donation water ingestion (250–500 mL) likely results in a large reduction in on-site VVRs (2 fewer on-site VVRs per 100 donations, moderate certainty evidence).
- Pre-donation isotonic drink (500 mL containing 0.68 g NaCl) w/o AMT during blood donation likely results in a large reduction of off-site VVRs (1 fewer off-site VVR per 100 donations, moderate-certainty evidence).
- Pre-donation salt-loaded sweetened lemon water consumption (300 mL containing 2.5 g NaCl) may result in a large reduction of off-site VVRs (1 fewer off-site VVR per 100 donations), especially in donors aged 18–21 years, repeat donors and female donors (low-certainty evidence).
- Pre-donation water ingestion 280 mL + 250 mg caffeine may result in a large reduction of donation chair recline rate (40 fewer reclines per 100 donations) and a moderate reduction of presyncopal reactions to blood donation (low-certainty evidence).
- The effect of drinking fruit juice before donation is uncertain (very-low-certainty evidence).
- No evidence is available that investigated the impact of eating interventions.

Absolute risk reductions of 1–2 fewer on-site/off-site VVRs per 100 donations with these preventive drinking interventions are clinically meaningful. For example, Belgian Red Cross-Flanders collected 240,000 whole-blood donations in 2022 [33]. Based on our evidence, preventive measures such as pre-donation (salt-loaded) water or isotonic drink consumption could prevent at least 2400 VVRs (per year). The impact of preventive measures on delayed off-site VVRs is especially important because no medical supervision is present, which could lead to potentially severe consequences in the first 24 hours after leaving the donation centre, such as a higher risk of being involved in traffic accidents or a higher falling risk with corresponding injuries. These preventive drinking interventions can also be considered cost effective (i.e., low cost) and are easily implementable.

To the best of our knowledge, only one other systematic review (published in 2016) identified 16 RCTs (search date: March 2015) of interventions (of which 5 were drinking interventions) designed to prevent or reduce VVRs in blood donors [19]. The authors concluded that the evidence was limited and did not provide strong support for administration of oral water prior to blood donation.

The body of evidence concerning drinking interventions was further increased by our systematic review with the inclusion of five additional trials, published between March 2015 and May 2023 [6, 7, 22, 24, 30]. The updated body of evidence provides moderate-certainty evidence in favour of pre-donation water ingestion or pre-donation isotonic drink consumption to reduce on-site/off-site VVRs.

Hence, our evidence serves as a direct scientific basis to underpin the current (or new) recommendations on pre-donation drinking interventions [11, 34, 35].

The major strength of this systematic review is the use of high-quality methodological standards to provide the best available and most up-to-date body of evidence concerning the impact of drinking interventions to reduce VVRs. Indeed, we conducted a systematic review (and meta-analyses) by using the Cochrane methodology that adheres to strict standards aiming to minimize bias, improve the accuracy of summarized data and maximize transparency and reproducibility [12]. In addition to the GRADE approach (to assess the certainty of evidence for each outcome), GRADE's informative statements (recommended by the GRADE working group [18] and added in the Cochrane Handbook [36]) to communicate the findings of systematic reviews of interventions provide a rigorous, transparent and applicable evidence-based information source for researchers, staff from blood establishments, guideline developers and/or decision makers.

A major limitation of the current review is that the included studies generally used a generic definition of a VVR, by including both pre-syncopal and syncopal reactions. This prevented us from conducting a subgroup analysis to assess the impact of drinking interventions on the (more severe) syncopal VVRs versus (less severe) pre-syncopal VVRs. Future research studies in this domain should make a distinction between pre-syncopal and syncopal VVRs.

A second limitation was that we restricted to searches in five different databases and one register (ClinicalTrials.gov) and did not

perform a search in other registers or relevant websites. Therefore, we did not identify one relevant RCT, which was published in the ISBT Science Series (not indexed anymore in our included databases), and was finally included by one of the co-authors (P.T.) [6]. Two relevant RCTs are currently ongoing: the first study is a cluster RCT in the United Kingdom (STRIDES trial) which will test the impact of four different (combinations of) preventive measures compared to the regular practice to prevent VVRs among >1 million whole-blood donors (500 mL isotonic drink before donation, 3 min rest on the donation chair after donation, new modified AMT and a psychosocial intervention). This trial was registered in the clinical trial registry recognized by WHO and ICMJE in October 2019 (ISRCTN 10412338) and the study protocol was published in August 2023 (after our search date, i.e., May 2023) [37]. The second ongoing trial is an RCT in France (PREDONPSY trial) that will test the impact of a combined psychological and physiological approach (ingesting a salty snack) in first-time whole-blood donors [38].

Today, moderate-certainty evidence is available on the preventive effect of pre-donation water or isotonic drink ingestion on VVRs. Evidence from future RCTs is needed to further demonstrate the (potential) impact of other preventive measures (such as the PREDONPSY trial or the STRIDES trial interventions).

In conclusion, pre-donation water ingestion (vs. no intervention) or an isotonic drink (vs. usual practice) probably results in a large reduction in on-site and off-site VVRs. Pre-donation water ingestion with caffeine consumption or salt supplementation may result in a VVR reduction compared to pre-donation water ingestion only. Future large trials are required to increase the certainty of the effect of these and other interventions in the prevention of VVRs.

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H.V.R., D.V.d.S. and D.M. conceptualized the study, H.V.R., D.V.d.S., D.M., J.K., V.T., P.T., E.D.B. and V.C. helped in writing original draft—review and editing the manuscript, H.V.R. helped in project coordination, H.V.R., E.D.B. and V.C. supervised the research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article and its Supporting Information.

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Repeated apheresis donations cause important iron deficiency in male Japanese donors

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Abstract

Background and Objectives: In Japan, apheresis donation of plasma is allowed to a maximum of 24 times a year, and plateletpheresis are counted as two plasmapheresis donations. Diversion of the initial blood flow is conducted for all donations, and additionally, blood remaining in apheresis machine circuit is lost. Here, we aimed to investigate on the health impact of frequent apheresis donations, as measured by the serum ferritin (sFer).

Materials and Methods: A total of 538 male apheresis donors and 538 age-matched whole blood (WB) donors, who gave informed consent to join the study, were enrolled. sFer were compared, according to age. Another group of 19 apheresis donors were followed during four consecutive donations.

Results: About half (48%) of repeat male apheresis donors had iron deficiency (sFer < 26 ng/mL), compared with lower rates (13.9%) among male WB donors. It was evident in all age groups, except for teenagers, possibly because of the lower number of donations. Follow-up of the 19 donors for 4 months revealed a progressive decrease in sFer.

Conclusion: Blood remaining in the apheresis machine circuit and diversion of the initial blood flow have been implicated in iron deficiency for many years. Taking the present results, the manufacturer of apheresis equipment was requested to improve it to allow rinseback of the remaining blood, which was achieved only for plateletpheresis. Until further improvement, plasmapheresis frequency was reduced to 12 times a year. Additional measures, such as oral supplementation of iron, need to be considered.

Keywords
frequent donation, iron deficiency, plasmapheresis, plateletpheresis, serum ferritin

Highlights

- Iron deficiency was observed at a higher rate among male apheresis donors compared with male repeat whole blood donors. This can be attributed to a higher frequency of donations allowed per year, the diversion of the initial blood flow and the blood remaining in the apheresis machine circuit.
- Apheresis machines not equipped with the rinseback system can contribute to iron deficiency in apheresis donors, and this needs improvement.
- Diversion of the initial blood flow is important for the prevention of bacterial contamination, and diverted blood is used for screening tests, but measures to replace iron needs to be implemented.

INTRODUCTION

Iron deficiency is reported to affect between 25% and 35% of regular blood donors worldwide [1, 2]. In Japan, more than 90% of donated blood comes from repeat or committed donors, at a voluntary non-remunerated (VNR) donation (VNRD) basis, with a male predominance (about 72%); however, the issue of iron deficiency has not yet been appropriately addressed among blood donors. According to the Annual Report published by the Japanese Red Cross Blood Services (JRCBS) 'Blood Services Statistical Data 2023 ～ Current Status of Blood Services ～', among the 5.5 million people who visited the blood donation centre in 2023, 536,084 (9.7%) were deferred, and among them, 251,369 (446.9%) were deferred due to low haemoglobin (Hb). Iron deficiency is not an issue only in whole blood (WB) donations. Repeat apheresis donors were also shown to have lower storage iron values compared with repeat WB donors and normal subjects, and a negative iron balance was found in 12.2% of males and 45.7% of females even before donation [3]. Others have also reported iron deficiency in apheresis donors [1, 4–9]. One study showed that 24% of plateletpheresis donors had iron deficiency, as defined as serum ferritin [sFer] <30 mg/L, and that frequent donors (donating every 2 weeks) were at a twice risk of iron deficiency [10]. Duggan et al. [11] reported that 9% of male plateletpheresis donors had iron deficiency, as defined as sFer <20 ng/mL. A more recent study from India demonstrated that male donors with ≥12 plateletpheresis donations per year had the highest prevalence of iron-deficient erythropoiesis (IDE) (41.3%) and absent iron stores (AIS) (26.7%) [5], giving almost 70% of their donors with iron deficiency. It was also confirmed in Japan as early as in 1998, when it was observed that 12.2% of male and 45.7% of female repeat apheresis donors were in a negative iron balance [3], and those with higher number of donations had lower levels of sFer in both genders [12]. It was attributed to the residual blood in the circuit of the apheresis equipment and the collection of blood for testing before every donation [5, 12]. Later on, with the aim to prevent bacterial contamination of blood products, in 2007, the diversion of the initial blood flow (25 mL) was implemented, further increasing blood loss. A previous study evaluating the erythrogram parameters (Hb, hematocrit and erythrocyte count) among plateletpheresis donors reported a negative effect of plateletpheresis on these parameters, explained by blood loss in the kits used for the procedure and cell lysis [13]. Others report no affection of sFer levels in plasma donors, but under different settings [14, 15].

In Japan, a more restrictive criteria of WB blood donation have been applied, allowing a maximum volume of 400 mL WB and annual twice donations for females and thrice for males. In a previous study [16], however, we demonstrated that approximately 31% of repeat female donors and 10% of male repeat donors had iron deficiency. Surprisingly, about 28% of female first-time/reactivated (FT/RA) donors, who should be quite similar to the general population, had iron deficiency, which was higher than that reported about 30 years ago (20.5%) [17]. Interestingly, however, in 1996, iron deficiency among female donors post-donation was reported to be as high as 37.7%, higher compared with about 31% in our recent data [16]. In the previous and the present studies, iron deficiency was defined as sFer < 26 ng/mL, AIS as sFer <12 ng/mL [18] and IDE as 12 ≤ sFer < 26 ng/mL.

In the present study, we aimed to investigate the iron status determined by sFer of our apheresis donors, who donate on a VNR basis and undergo diversion of the initial blood flow and screening tests at each donation, as an indicator of their health condition. This result will serve as the basis for discussions on the need to implement policies to mitigate iron deficiency in this donor population.

MATERIALS AND METHODS

Blood donation in Japan

Apheresis procedures are conducted for the preparation of platelet concentrates (PC), fresh-frozen plasma (FFP) and for the collection of plasma for fractionation. Apheresis donations include plateletpheresis and plasmapheresis, and one session of plateletpheresis is counted as 2 plasmapheresis sessions, allowing a maximum of 24 plasmapheresis sessions, with 2 weeks intervals, per year, for both males and females.

Males and females aged 18–69-year-old can donate plasma, but the age criterion for plateletpheresis is 18–54-year-old for females. Previously, the maximum volume of plateletpheresis collection was 400 mL, but in 2017, it was changed to allow a collection of a maximum of 600 mL, not exceeding 12% of the total blood volume (TBV) of the donor, for both platelets and plasma. The Hb criteria for apheresis donation is 12 g/dL for both genders, allowing females with Hb > 11.5 g/dL to donate plasma if the other blood count parameters are within normal ranges. These values are lower compared with the criteria applied for WB (Hb > 13.0 g/dL for males and >12.5 g/dL for females). In Japan, donors are allowed to donate by apheresis from the first donation.

For each apheresis session, the diversion of the initial flow (25 mL) is required for the prevention of bacterial contamination, and the diverted blood is used as samples for blood testing/screening. Both Trima Accel (Terumo BCT) and CCS (Haemonetics Japan) machines are used for the apheresis collection at the JRCBS, and it was known that more blood remained in the circuit of Trima Accel compared with CCS. This was dependent on the unavailability of the rinseback function in the Trima Accel. In the present study, apheresis donations include those intended for the preparation of PC, labile plasma and plasma for fractionation.

Donor inclusion

Blood donors who visited the Fukuoka Blood Centre (BC) for a plasma donation were given explanation about the study, and those who consented were enrolled. Repeat male apheresis donors, who donated more than 12 times in a 1-year period in the period 2 July 2018 to 30 March 2020 were included. Those who donated WB meanwhile were excluded. Informed consent was obtained from all donors enrolled in the study. As the control, age-matched male repeat donors, who donated WB (400 mL) in the same period, were included and evaluated. A total of 538 apheresis donors and 538 WB donors were enrolled.

The study was approved by the ethics committee of the JRCBS (2017-047).

In addition to the routine blood samples for blood group typing, infectious markers screening, haemogram and storage for the look-back survey, a serum sample for sFer measurement was collected from the blood diversion pouch and sent to the laboratory for testing.

Additionally, 19 apheresis donors, who had no history of donation in the previous 6 months, were followed-up for four consecutive donations for 4 months in terms of changes in sFer. The mean of sFer was calculated and transition confirmed among the four donations given by these donors.

sFer and haemogram measurement

sFer was measured using a biochemical test sample collected from the pouch of the diverted initial blood flow, along with other blood samples used for blood screening tests. sFer was measured in the automated biochemical analysis system LABOSPECT 008 (Hitachi, Tokyo, Japan), using the FER-Latex (X2) CN SEIKEN (Denka Seiken, Tokyo, Japan) kit, which includes the International Standard for Ferritin (National Institute for Biological Standards and Control; World Health Organization standard).

Haemogram (complete blood counts) was analysed in the Sysmex XE-2100 (Sysmex, Kobe, Japan).

Donor data and statistical analysis

Data of donors were extracted from the donor management system of the JRCBS. The following data were collected for all donors: gender, age, height, body weight (BW), body mass index (BMI), TBV, complete blood counts (red blood cell count [RBC], Hb, mean corpuscular volume [MCV], mean corpuscular Hb [MCH], MCH concentration [MCHC], white blood cell count [WBC], platelet count [PLT]) and sFer. The TBV (L) is calculated by the following formula: $TBV = 0.168H3 + 0.050W + 0.444$ for an adult male, where H is the height (in metres) and W is the BW (in kilograms), as previously reported [19].

In total, 538 male apheresis donors were analysed. For comparison, 538 WB donors matched for age and BW were included.

Using descriptive statistical analyses, age, sex, BMI, TBV, complete blood counts (RBC, Hb, MCV, MCH, MCHC, WBC, PLT) and sFer, were analysed as subgroups for evaluating the baseline characteristics of blood donors. Simultaneously, we also analysed sFer levels across age groups (10s, 20s, 30s, 40s, 50s and 60s). Additionally, sFer was compared using the Wilcoxon rank-sum test, whereas other items were compared using the unpaired *t*-test.

Donors were divided into four groups according to the sFer levels (<12.0, 12.0–25.9, 26.0–49.9 and ≥50.0 ng/mL). sFer levels of apheresis donors were compared with those of age-, BW- and height-matched WB donors.

We conducted univariable logistic regression analysis with the presence or absence of absolute iron deficiency (AIS; sFer < 12 ng/mL, ≥12 ng/mL) [2] or AIS and IDE (AIS + IDE; sFer < 26 ng/mL, ≥26 ng/mL) [20] as the dependent variable. Independent variables included age, TBV and complete blood counts (RBC, Hb, MCV, MCH, MCHC, WBC, PLT), which were categorized into two groups based on their median values. Then, multivariable logistic regression analysis, using the variables that showed significant results in the univariable analysis as confounding factors, was conducted. Logistic regression analysis was conducted to calculate odds ratio (OR) and 95% confidence interval (95% CI) with and without confounding factors. Additionally, sFer was compared using the Wilcoxon rank-sum test, whereas other items were compared using the unpaired *t*-test.

To confirm the changes of sFer levels after repeated apheresis donations, we followed 19 donors, who returned monthly for subsequent apheresis donations, for 4 months during the study period and conducted sFer and Hb measurements at each return donation. The mean (minimum, maximum) of the sFer of the 19 donors was calculated at each time point and compared.

TABLE 1 Demographics of apheresis and control (WB donor) groups.

	Apheresis group				Control group (WB donation)				Statistical
	Mean ± SD				Mean ± SD				
	$n = 538$	Min	Median	Max	$n = 538$	Min	Median	Max	p value[a]
Age (y.o.)	48.0 ± 11.5	19	49	69	47.8 ± 11.6	19	49	69	0.7026
Height (cm)	170.6 ± 6.2	130	171	185	170.6 ± 5.5	155	171	187	0.9170
Weight (kg)	67.7 ± 10.5	50	66	135	69.8 ± 9.2	52	69	108	**0.0004**
TBV (L)	4663.7 ± 573.7	3363	4587	8240	4770.7 ± 497.0	3719	4744	6669	**0.0011**
BMI	23.21 ± 3.09	17.5	22.8	39.9	23.97 ± 2.94	17.3	23.7	37.4	**<0.0001**
Hb (g/dL)	14.43 ± 1.07	11.8	14.5	17.4	15.03 ± 0.96	12.9	15.0	18.1	**<0.0001**
RBC ($\times 10^4/\mu L$)	478.6 ± 37.7	376	479	590	490.6 ± 38.2	384	490	628	**<0.0001**
MCV (fL)	89.8 ± 5.3	72	90	108	90.3 ± 4.3	76	90	104	0.1235
MCH (pg)	30.2 ± 2.2	22	31	37	30.7 ± 1.6	25	31	36	**<0.0001**
MCHC (%)	33.7 ± 0.9	30	34	37	34.0 ± 0.8	32	34	37	**<0.0001**
WBC ($\times 10^2/\mu L$)	55.4 ± 13.8	29	53	115	60.0 ± 14.5	25	58	127	**<0.0001**
PLT ($\times 10^4/\mu L$)	26.73 ± 5.74	11.3	26.4	49.4	25.56 ± 5.09	9.1	25.6	44.5	**0.0004**
Serum ferritin (ng/mL)	35.54 ± 35.03	0.0	26.7	332.3	112.30 ± 97.54	3.8	77.7	534.3	**<0.0001**

Note: Hb, RBC, MCV, MCH, MCHC, WBC, PLT are complete blood count variables. Statistically significant p values are shown bolded.
Abbreviations: BMI, body mass index; Hb, haemoglobin; MCH, mean corpuscular Hb; MCHC, MCH concentration; MCV, mean corpuscular volume; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; TBV, total blood volume; WB, whole blood; WBC, white blood cell count; y.o., years old.
[a]Statistical p values: Serum ferritin was analysed using the Wilcoxon rank-sum test, while all other parameters were analysed using unpaired t-tests.

Statistical analyses were conducted by SAS statistical analysis software (ver.9.4, SAS Institute Inc., Cary, NC).

RESULTS

Comparison of clinical and laboratory features and the sFer levels between male repeat apheresis donors and male repeat WB donors

Age-, BW- and height-matched WB donors were selected for comparison with the apheresis donors (reference group). TBV of the reference group was lower compared with WB donor group (4663.7 ± 573.7 L vs. 4770 ± 497.0, $p = 0.0011$), as well as BMI (23.2 ± 3.09 vs. 24.0 ± 2.94, $p < 0.0001$). In addition, the Hb level (14.4 ± 1.07 g/dL vs. 15.0 ± 0.96, $p < 0.0001$) and the other haemogram parameters were also significantly lower in the reference group compared with the WB group, except for PLT ($26.7 \pm 5.74 \times 10^9$/L vs. 25.6 ± 5.09, $p = 0.0004$), which was higher in the reference group, as shown in Table 1.

Comparison of the sFer levels according to age in both apheresis and WB donors and comparison of sFer levels between both groups

sFer level was significantly lower in the reference group compared with the WB group (median: 26.7 vs. 77.7 ng/mL, $p < 0.0001$), as shown in Table 1 and Figure 1.

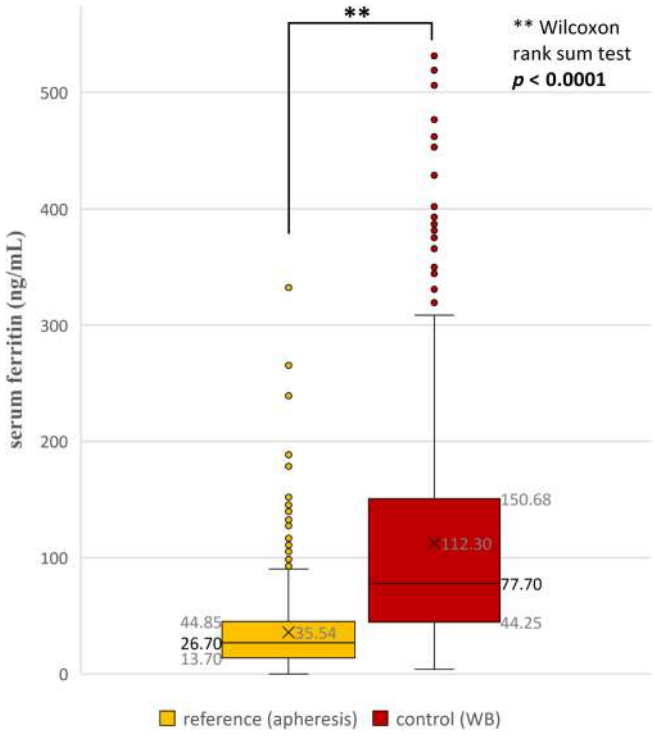

FIGURE 1 Comparison of the serum ferritin (sFer) levels (median with interquartile range [IQR]) of male apheresis donors and the age/body weight (BW)-matched whole blood (WB) (400 mL) male donors. The median serum ferritin level in the reference (apheresis) group was 26.7 ng/mL (Q1: 13.7, Q3: 44.8). In the control (WB) group, the median was 77.7 ng/mL (Q1: 44.4, Q3: 150.5). The difference was statistically significant (Wilcoxon rank-sum test: $p < 0.0001$).

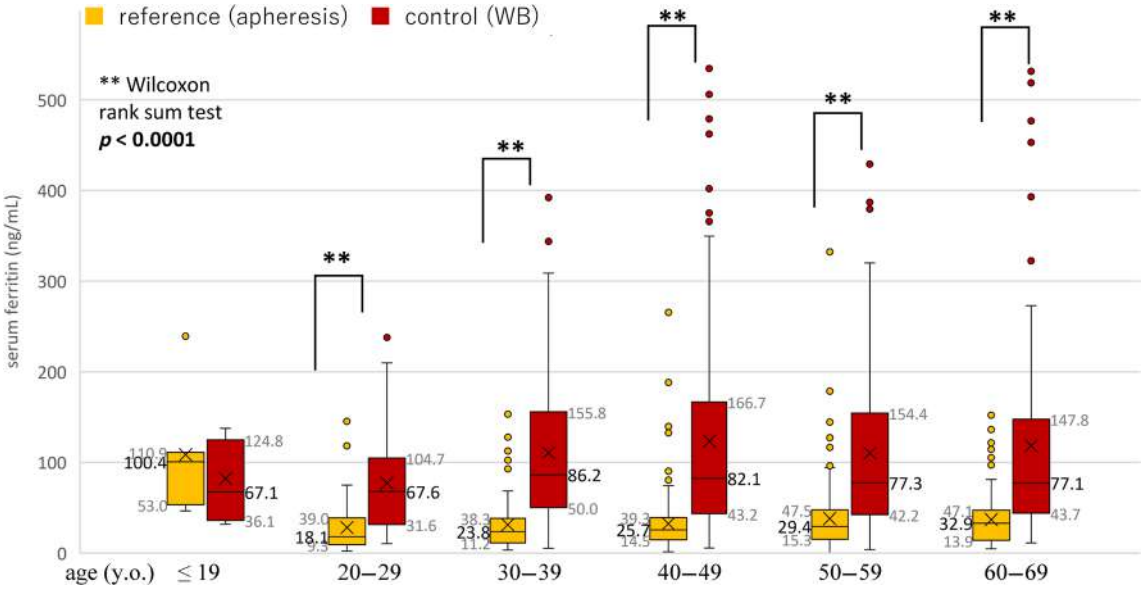

FIGURE 2 Comparison of serum ferritin (sFer) (median with interquartile range [IQR]) of male apheresis donors and whole blood (WB) (400 mL) donors, according to age. Age groups (10s: $N = 7$, 20s: $N = 42$, 30s: $N = 66$, 40s: $N = 159$, 50s: $N = 187$, 60s: $N = 77$): The median serum ferritin levels for the reference (apheresis) group versus the control (WB) group were as follows: 10s (100.4 vs. 67.1 ng/mL), 20s (18.1 vs. 67.6 ng/mL), 30s (23.8 vs. 86.2 ng/mL), 40s (25.7 vs. 82.1 ng/mL), 50s (29.4 vs. 77.3 ng/mL) and 60s (32.9 vs. 77.1 ng/mL). The Wilcoxon rank-sum test comparing the reference (apheresis) group to the control (WB) group showed no significant difference in the 10s age group, whereas for all other age groups, the difference was significant ($p < 0.0001$). y.o., years old.

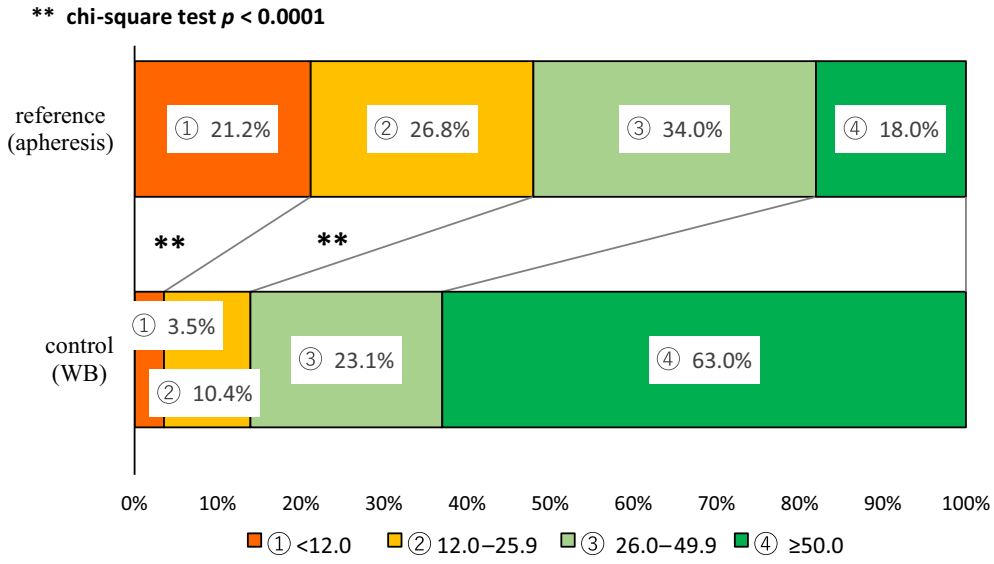

FIGURE 3 Rate of blood donors with different serum ferritin (sFer) levels. The 'reference' refers to the apheresis group, whereas the 'control' refers to the whole blood (WB) group. The categories are defined based on sFer levels as follows: (1) <12.0 ng/mL, (2) 12.0–25.9 ng/mL, (3) 26.0–49.9 ng/mL and (4) ≥50.0 ng/mL. The chi-square test comparing the 'reference' group to the 'control' group showed significant differences: For category 1 (21.2% vs. 3.5%, $p < 0.0001$) and for categories 1 + 2 combined (48.0% vs. 13.9%, $p < 0.0001$).

The reference group and the WB group included the same number of individuals, with the following distribution for each age groups: 10s ($n = 7$), 20s ($n = 42$), 30s ($n = 66$), 40s ($n = 159$), 50s ($n = 187$) and 60s ($n = 77$).

Among the reference group, the highest median sFer value was observed among the teenagers (100.4 mg/dL) and the lowest among the 20s (18.1 mg/dL), whereas the sFer values of 30s–60s were quite similar (range of median: 23.8 ng/mL). On the other hand, among WB

TABLE 2 Univariable and multivariable analyses of factors associated with absent iron stores (sFer < 12 ng/mL).

Demographic characteristic	sFer <12 (%)	sFer ≥12 (%)	Total (%)	χ^2		
Overall	***n* = 113**	***n* = 425**	***n* = 538**	***p* value**	**Unadjusted OR (95% CI)**	**Adjusted OR[a] (95% CI)**
Age group (y.o.)				0.0736		
<49	62 (54.9)	193 (45.4)	255 (47.4)		1.000	…
≥49	51 (45.1)	232 (54.6)	283 (52.6)		1.461 (0.963–2.217)	…
TBV (L)				**0.0010**		
<4587	72 (63.7)	197 (46.4)	269 (50.0)		1.000	1.000
≥4587	41 (36.3)	228 (53.6)	269 (50.0)		2.032 (1.324–3.119)	1.889 (1.083–3.296)
Hb (g/dL)				**<0.0001**		
<14.5	94 (83.2)	165 (38.8)	259 (48.1)		1.000	1.000
≥14.5	19 (16.8)	260 (61.2)	279 (51.9)		7.796 (4.588–13.247)	4.387 (2.371–8.116)
RBC ($\times 10^4$)				0.1049		
<479	48 (42.5)	217 (51.1)	265 (49.3)		1.000	…
≥479	65 (57.5)	208 (48.9)	273 (50.7)		0.708 (0.466–1.076)	…
MCV (fL)				**<0.0001**		
<89.9	98 (86.7)	168 (39.5)	266 (49.4)		1.000	1.000
≥89.9	15 (13.3)	257 (60.5)	272 (50.6)		9.994 (5.612–17.799)	4.686 (2.002–10.970)
MCH (pg)				**<0.0001**		
<30.5	103 (91.2)	164 (38.6)	267 (49.6)		1.000	1.000
≥30.5	10 (8.8)	261 (61.4)	271 (50.4)		16.385 (8.319–32.271)	2.684 (1.003–7.182)
MCHC (%)				**<0.0001**		
<33.8	98 (86.7)	157 (36.9)	255 (47.4)		1.000	1.000
≥33.8	15 (13.3)	268 (63.1)	283 (52.6)		11.152 (6.257–19.879)	5.219 (2.625–10.377)
WBC ($\times 10^2$)				0.7174		
<52.7	58 (51.3)	210 (49.4)	268 (49.8)		1.000	…
≥52.7	55 (48.7)	215 (50.6)	270 (50.2)		1.080 (0.713–1.635)	…
PLT ($\times 10^4$)				**<0.0001**		
<26.4	28 (24.8)	240 (56.5)	268 (49.8)		3.938 (2.466–6.289)	2.785 (1.567–4.950)
≥26.4	85 (75.2)	185 (43.5)	270 (50.2)		1.000	1.000

Note: Hb, RBC, MCV, MCH, MCHC, WBC and PLT are complete blood count variables. Statistically significant *p* values are shown bolded.
Abbreviations: CI, confidence interval; Hb, haemoglobin; MCH, mean corpuscular Hb; MCHC, MCH concentration; MCV, mean corpuscular volume; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; sFer, serum ferritin; TBV, total blood volume; WBC, white blood cell count.
[a]Adjusted OR was adjusted for TBV, Hb, MCV, MCH, MCHC and PLT.

(400 mL) donors, the lowest sFer was observed among the teenagers and 20s (67.1 and 67.6 ng/mL, respectively), whereas values were comparable from 30s to 60s (range of median: 77.1–86.2 ng/mL), as shown in Figure 2.

The median sFer values (reference vs. control WB) for each age group were as follows: 10s (100.4 vs. 67.1 ng/mL, $p = 0.7983$), 20s (18.1 vs. 67.6 ng/mL, $p < 0.0001$), 30s (23.8 vs. 86.2 ng/mL, $p < 0.0001$), 40s (25.7 vs. 82.1 ng/mL, $p < 0.0001$), 50s (29.4 vs. 77.3 ng/mL, $p < 0.0001$) and 60s (32.9 vs. 77.1 ng/mL, $p < 0.0001$). Among teenagers, no significant difference was observed, whereas in other age groups, the median of sFer in the reference group was significantly lower compared with the WB donor group ($p < 0.0001$). Excluding the non-significant difference observed in the teenager group, the range of the difference in median sFer values (400 mL WB—apheresis) ranged from 44.2 to 62.5 ng/mL. The difference rate of median sFer according to age was the highest among 20s, with a 73.2% difference, followed by the 30s, 40s and 50s, with the lowest proportion among the 60s.

Prevalence of AIS, sFer (<12 ng/mL) and IDE (sFer < 26 ng/mL) between reference and WB donor groups

The reference group showed significantly higher prevalence of AIS (21.2% vs. 3.5%, $p < 0.0001$) and AIS + IDE (48.0% vs. 13.9%, $p < 0.0001$) compared with the WB donor group (reference group vs. WB donor group, chi-square test *p* value), as shown in Figure 3. The prevalence of AIS and IDE among repeat WB donors was similar to those found in our previous report [16].

TABLE 3 Univariable and multivariable analyses of factors associated with iron deficiency (sFer < 26 ng/mL).

Demographic characteristic	sFer <26 (%)	sFer ≥26 (%)	Total (%)	χ^2		
Overall	***n* = 258**	***n* = 280**	***n* = 538**	***p* value**	**Unadjusted OR (95% CI)**	**Adjusted OR[a] (95% CI)**
Age group (y.o.)				0.2459		
<49	129 (50.0)	126 (45.0)	255 (47.4)		1.000	…
≥49	129 (50.0)	154 (55.0)	283 (52.6)		1.222 (0.871–1.716)	…
TBV (L)				**0.0157**		
<4587	143 (55.4)	126 (45.0)	269 (50.0)		1.000	1.000
≥4587	115 (44.6)	154 (55.0)	269 (50.0)		1.520 (1.082–2.136)	1.308 (0.888–1.926)
Hb (g/dL)				**<0.0001**		
<14.5	159 (61.6)	100 (35.7)	259 (48.1)		1.000	1.000
≥14.5	99 (38.4)	180 (64.3)	279 (51.9)		2.891 (2.036–4.103)	1.801 (1.210–2.682)
RBC ($\times 10^4$)				0.5948		
<479	124 (48.1)	141 (50.4)	265 (49.3)		1.000	…
≥479	134 (51.9)	139 (49.6)	273 (50.7)		0.912 (0.650–1.280)	…
MCV (fL)				**<0.0001**		
<89.9	160 (62.0)	106 (37.9)	266 (49.4)		1.000	1.000
≥89.9	98 (38.0)	174 (62.1)	272 (50.6)		2.680 (1.891–3.798)	1.721 (1.008–2.938)
MCH (pg)				**<0.0001**		
<30.5	171 (66.3)	96 (34.3)	267 (49.6)		1.000	1.000
≥30.5	87 (33.7)	184 (65.7)	271 (50.4)		3.766 (2.635–5.383)	1.438 (0.814–2.540)
MCHC (%)				**<0.0001**		
<33.8	171 (66.3)	84 (30.0)	255 (47.4)		1.000	1.000
≥33.8	87 (33.7)	196 (70.0)	283 (52.6)		4.586 (3.189–6.595)	3.084 (1.999–4.760)
WBC ($\times 10^2$)				0.1018		
<52.7	138 (53.5)	130 (46.4)	268 (49.8)		1.000	…
≥52.7	120 (46.5)	150 (53.6)	270 (50.2)		1.327 (0.945–1.863)	…
PLT ($\times 10^4$)				**<0.0001**		
<26.4	101 (39.1)	167 (59.6)	268 (49.8)		2.297 (1.626–3.246)	1.822 (1.242–2.672)
≥26.4	157 (60.9)	113 (40.4)	270 (50.2)		1.000	1.000

Note: Hb, RBC, MCV, MCH, MCHC, WBC and PLT are complete blood count variables. Statistically significant *p* values are shown bolded.
Abbreviations: CI, confidence interval; Hb, haemoglobin; MCH, mean corpuscular Hb; MCHC, MCH concentration; MCV, mean corpuscular volume; OR, odds ratio; PLT, platelet count; RBC, red blood cell count; sFer, serum ferritin; TBV, total blood volume; WBC, white blood cell count.
[a]Adjusted OR was adjusted for TBV, Hb, MCV, MCH, MCHC and PLT.

Univariable and multivariable analyses of the donors' features/haemogram data and the sFer

Univariable and multivariable analyses were conducted to identify factors associated with deficiency/depletion of iron stores among apheresis donors. In the univariable analysis, the factors significantly associated with AIS (sFer < 12 ng/mL) were TBV, Hb, MCV, MCH, MCHC and PLT were found as factors significantly associated (Table 2). As shown in Table 2, the adjusted OR and 95% CI for factors demonstrating significant differences were as follows: TBV OR, 1.889 (95% CI: 1.083–3.296), Hb 4.387 (2.371–8.116), MCV 4.686 (2.002–10.970), MCH 2.684 (1.003–7.182), MCHC 5.219 (2.625–10.377) and PLT 2.785 (1.567–4.950). In the univariable analysis of AIS + IDE (sFer < 26 ng/mL), the factors significantly associated were TBV, Hb, MCV, MCH, MCHC and PLT (Table 3). The adjusted OR and 95% CI were TBV 1.308 (0.888–1.926), Hb 1.801 (1.210–2.682), MCV 1.721 (1.008–2.938), MCH 1.438 (0.814–2.540), MCHC 3.084 (1.999–4.760) and PLT 1.822 (1.242–2.672), as shown in Table 3.

The changes in sFer levels with time in repeat apheresis donors

The changes in sFer levels were analysed in 19 apheresis donors, who were followed in four consecutive apheresis donations during 4 months period. Individual differences were observed in terms of sFer levels, but in general, there was a tendency of sFer decrease with increasing the number of donations, as confirmed by the mean values.

Compared with sFer, Hb levels were almost unchanged during the four donations as shown in Figure 4.

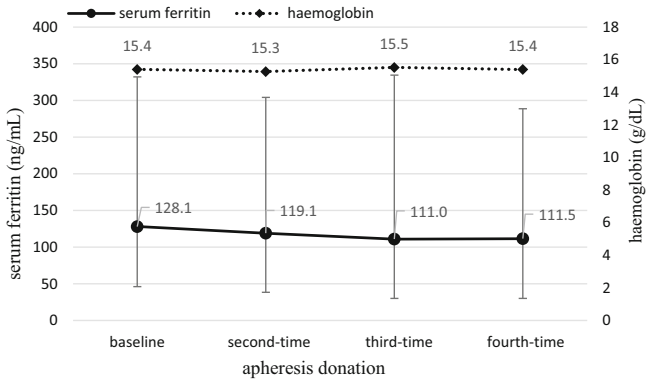

FIGURE 4 Changes in serum ferritin (sFer) levels and haemoglobin (Hb) levels among 19 male donors followed during four consecutive apheresis donations with 4 weeks intervals each. sFer levels include mean, minimum and maximum values, whereas Hb levels include only the mean ($n = 19$). The mean (min, max) sFer levels were as follows: at baseline, 128.1 ng/mL (46.2, 332.3 ng/mL); at the second time point, 119.1 ng/mL (38.3, 304.2 ng/mL); at the third time point, 111.0 ng/mL (30.0, 34.5 ng/mL) and at the fourth time point, 111.5 ng/mL (30.0, 288.8 ng/mL). The mean Hb levels were 15.4 g/dL at baseline, 15.3 g/dL at the second time point, 15.5 g/dL at the third time point and 15.4 g/dL at the fourth time point.

DISCUSSION

In the present study, the percentage of iron deficiency, as defined as sFer <26 ng/mL, was as high as 48% among male apheresis donors, whereas it was around 10% among male repeat WB donors.

A more recent study conducted after ours at the same blood establishment, the Fukuoka BC in Kyushu island, evaluated sFer of apheresis donors and found that 66.7% of male donors who donated more than 13 times a year were in an iron-deficient condition, whereas it was 24.1% among those who donated less than 13 times and 5.1% among those who did not donate. For female donors, they were even worse, with incidences of 88.9%, 60.7% and 52.6%, respectively [21]. It was attributed to the blood loss due to the diversion of the initial blood flow plus residual blood in the circuit of the apheresis equipment [21]. Similar results were reported from the United Kingdom, where the apheresis donation practice seems to be similar [10]. With different practices not based on VNRD, such as with source plasma donors in the United States, who seems to not be tested at every donation, and the residual blood in the machine is returned, the rate of iron deficiency was low [14].

In our series, we compared sFer levels of repeat apheresis donors with those of age-matched WB (400 mL) donors. WB donors had significantly higher BW, which also resulted in higher TBV and BMI, but similar age and height. Mean sFer levels were significantly lower among apheresis donors, compared with WB donors, for all age groups, except for teenagers. It cannot be attributed only to the higher BMI and the related indices.

In the multivariable analysis, the factors significantly associated with AIS were TBV, Hb, MCV, MCH, MCHC and PLT counts. Factors associated with iron deficiency (sFer < 26 ng/mL) were Hb, MCV, MCHC and PLT. Others have also demonstrated an association between low sFer and high PLT [4]. None of these factors, however, seem to be potential surrogate of sFer.

When we followed-up the sFer levels of 19 donors in four consecutive donations during a 4-month period, we observed that although of the individual variations in sFer fluctuation, the mean sFer progressively decreased, strongly suggesting that iron loss is dependent on the blood donation.

In the present study, we restricted our investigation to male repeat apheresis donors, but previous studies have investigated on female donors and showed that they behave similarly after repeat apheresis donations [12, 22]. We restricted our analysis to male donors because they constitute the majority of our blood donor population (approximately 70%). Additionally, premenopausal female donors have sFer levels affected by cyclic bleeding as well as by blood donation.

From our present results, it is evident that not only WB donors but also apheresis donors need to be appropriately managed to prevent and supplement iron loss. The diversion of the initial blood flow has been shown to be effective in preventing bacterial contamination of PC, and the diverted blood is effectively used as the sample for blood testing. On the other hand, residual blood in the circuit of apheresis equipment has been recognized as one of the reasons of iron deficiency among apheresis donors for many years. However, strategies to mitigate it have not been taken. Recently, based on our present data and the more recent report [21], the manufacturer of the apheresis equipment with the higher volume of residual blood was requested to improve the equipment to allow rinseback of the residual blood, and countermeasures were taken for plateletpheresis, but not for plasmapheresis. Thus, until the issue is completely solved, a maximum of 12, and not 24 times, plasmapheresis collection with this equipment is allowed. With this, we expect that the iron depletion of our apheresis donors will be at least partially improved. In addition, a study to measure sFer among WB donors receiving iron supplement is ongoing, and we expect this result will bring important information for the appropriate management of not only repeat WB donors but also apheresis donors.

A limitation of our study is that we restricted sFer measurements to male apheresis donors, excluding female donors from this investigation. Although we anticipate an improvement in the iron deficiency rate with the resolution of the rinseback issue, there will be no comparative data for the female donors. Additionally, only a small number of donors (19) were followed for four consecutive monthly donations. Further studies involving a larger number of donors are needed to better understand the changes in sFer levels among repeat donors.

Based on our current results, we concluded that apheresis donors need more effective management to prevent iron deficiency. While the diversion of the initial blood flow has proven effective in preventing bacterial contamination, and the diverted blood is effectively utilized as blood samples for screening tests, there may be room for discussions on the potential strategies to reduce blood loss during the apheresis sessions, once equipment issues are fully resolved.

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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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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Impact of recent criteria changes for the deferral criteria specific to men who have sex with men in France

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Abstract

Background and Objectives: In 2016, France allowed men who have sex with men (MSM) to donate blood if they had not had sex with men in the previous 12 months. In April 2020, this restriction was relaxed to 4 months due to the lack of negative impact observed on blood safety. This study assesses the impact of reducing this deferral period on epidemiological surveillance indicators.

Materials and Methods: This study compares infection surveillance indicators between two 30-month periods before (P1) and after (P2) this second deferral change.

Results: Overall, 79 donations tested positive for human immunodeficiency virus (HIV) (49 in P1 and 30 in P2), 322 for hepatitis C virus (HCV) (185 and 137), 622 for hepatitis B virus (HBV) (355 and 267) and 1684 for syphilis (799 and 885). Positive donation rates decreased between P1 and P2, except for syphilis: HIV (0.07/10,000 donations vs. 0.04; $p > 0.5$), HCV (0.25 vs. 0.20; $p < 0.05$), HBV (0.49 vs. 0.39; $p < 0.01$) and syphilis (1.10 vs. 1.29; $p < 0.001$). For all three viruses, residual risks of transmission by transfusion did not increase: HIV (1/7,800,000 donations vs. 1/10,500,000), HCV (1/25,200,000 vs. 1/47,300,000) and HBV (1/6,400,000 vs. 1/6,000,000).

Conclusion: Reducing the deferral period for MSM in April 2020 did not negatively impact residual risks, which remained very low, or the rate of positive donations, except for syphilis, which requires careful monitoring. To ensure equal access to blood donation, MSM have been allowed to donate blood under the same conditions as other donors since March 2022 (i.e., no more than one sexual partner in the last 4 months).

Keywords

blood donors, HBV, HCV, HIV, MSM, residual risk, syphilis

Highlights

- Reducing the deferral period for men who have sex with men from 12 to 4 months did not negatively impact the rates of positive donations for human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV).
- The rising rate of syphilis-positive donations needs to be monitored.
- The residual risks of HIV, HBV and HCV transfusion-based transmission have never been lower.

INTRODUCTION

To ensure the highest level of transfusion safety, all blood donor candidates are invited to fulfil a self-administered questionnaire, submitted to the physician or nurse responsible for pre-donation interview, to evaluate the donor eligibility. In France, to ascertain whether individuals may have been exposed to a transfusion-transmissible infection, all potential donors are required to disclose whether they have had multiple sexual partners in the preceding 4 months. Those who have had a single sexual partner are allowed to donate blood; those who have had more than one sexual partner are excluded from donation. In addition, donors are asked about other potential risks associated with sexual activity, including whether they have had a sexually transmitted infection in the previous 4 months, engaged in sexual activity in exchange for money or drugs or had an human immunodeficiency virus (HIV)-positive partner in the previous 12 months. Furthermore, in response to the HIV epidemic that emerged in the early 1980s, men who have sex with men (MSM) have been permanently excluded from donating blood.

As a result of enhancements in the selection of donors and the calibre of screening tests, coupled with a decline in the incidence of HIV among the general population, the residual risk (RR) of HIV transmission through transfusion has shown a gradual decline since the 1990s [1, 2]. Consequently, the policy of excluding MSM from blood donation began to be challenged in the 2000s [3–5]. Different strategies have been adopted in different countries. In 2011, the United Kingdom moved from a permanent deferral for MSM to a 12-month deferral since last sex between men [6]. This change was followed by both the United States [7] and the Netherlands in 2015 [8]. Canada chose to move from permanent exclusion to a 5-year deferral in 2013 [9].

In France, in 2016, following consultation with all stakeholders, the Ministry of Health changed the selection criteria for MSM from permanent exclusion to a 12-month deferral [10]. A compliance study conducted in 2017 to monitor this measure found that 0.73% of male blood donors had engaged in sexual activity with men in the 12 months preceding blood donation, meaning that they donated blood despite being ineligible [11]. Although the non-compliance rate is higher in France compared with Australia, Canada and the United Kingdom, where non-compliance was estimated at 0.23%, 0.26% and 0.34%, respectively [12–14], the opening of blood donation to MSM did not negatively impact epidemiological surveillance indicators [15]. Similar results were reported in Australia [16], where HIV-positive donation rates remained unchanged after the introduction of a 12-month exclusion period, and in Canada [17], where a 5-year followed by a 12-month delay was introduced. Furthermore, a risk analysis conducted in France showed that shortening the deferral period for MSM to 4 months, provided that they had not engaged in male-to-male sexual activity, would not affect the number of HIV-positive MSM donors or the RR of HIV transmission by transfusion [15].

In light of these results, the French Ministry of Health decided to reduce the deferral period for MSM. As of 2 April 2020, men who had not had sex with men in the last 4 months were allowed to donate blood. This article assesses the impact of this change in MSM selection criteria on epidemiological surveillance indicators. It should be noted that the specific deferral criterion for MSM was abolished in March 2022, thereby providing universal access to blood donation regardless of the sex of one's partners. Nevertheless, the hindsight is too short to enable an analysis of this change in this article.

MATERIALS AND METHODS

Epidemiological surveillance relies on data collected nationally by the National Blood Service (*Etablissement français du sang*) and the Army Blood Service (*Centre de Transfusion Sanguine des Armées*). This includes the number of donors and donations categorized by donor status (first-time or repeat). Additionally, for each donor testing positive for any of the markers included in blood screening, their sociodemographic and epidemiological characteristics such as sex, age, geographical origin and probable risk of acquisition are provided. The data used for epidemiological surveillance are either aggregated (number of donations, number of donors) or anonymous.

All blood donations are screened for HIV antibodies (Abs), HBs antigen (HBsAg), HBc Abs and HCV Abs as well as for HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV) viral genomes. A confirmatory and follow-up algorithm that includes HIV or HCV immunoblots and a neutralization procedure for HBsAg are used to classify reactive samples as positive.

A blood donation is considered positive for HIV or HCV if Abs and/or RNA are detected and for HBV if HBsAg or HBV DNA is present. A donation is classified as syphilis-positive if it is TPHA-positive, ELISA-positive and immunoblot-positive.

Santé publique France, the French National Public Health Agency, produces surveillance indicators based on these data, including

TABLE 1 Rate of human immunodeficiency virus (HIV)-positive donations with a comparison of the two 30-month periods before and after 2 April 2020.

	1 October 2017–1 April 2020	2 April 2020–30 September 2022	p[a]
First-time donors			
Number of donations	961,573	823,778	0.38
Number of HIV positive	28	18	
Rate per 10,000 donations	0.29	0.22	
Repeat donors			
Number of donations	6,325,890	6,019,152	0.17
Number of HIV positive	21	12	
Rate per 10,000 donations	0.03	0.02	
All donors			
Number of donations	7,287,463	6,842,930	0.07
Number of HIV positive	49	30	
Rate per 10,000 donations	0.07	0.04	

[a]Fisher's exact test.

positive donation rates, prevalence, incidence and RR estimates. To evaluate the impact of changing the MSM criteria in 2020, this study compared these indicators over two 30-month periods before and after the change: P1 (1 October 2017 to 1 April 2020) and P2 (2 April 2020 to 30 September 2022).

RR estimates were based on the following equation: $RR = I \times (WP/365)$, where I represents the incidence rate and WP the length of the window period. For HIV, HBV and HCV, the window periods were set at 9, 22 and 7 days, respectively [18, 19].

Incidence was calculated using the cohort method by dividing the number of donors who converted from negative to confirmed positive in each 30-month interval by the total person-years (PY), as previously described [20].

An additional method was used to estimate HIV RR based on HIV incidence calculated with an enzyme immunoassay (EIA-RI) to identify recent infections (≤180 days) [21]. This method, used on all anti-HIV-1-positive blood donations, takes into account all donors (first-time and repeat) [22].

To compare data between different analysed groups, Fisher's exact test was used. The Fleiss quadratic method [23] was used to obtain 95% confidence intervals (95% CIs) for incidence rates and RR estimates.

RESULTS

Rate of HIV-positive donations and risk of acquisition of HIV-positive blood donors

Between 1 October 2017 and 30 September 2022, 79 donations tested positive for HIV, with 49 occurring in P1 (1 October 2017–1 April 2020) and 30 in P2 (2 April 2020–30 September 2022).

A comparison of the two 30-month periods before (P1) and after (P2) the deferral change shows no significant modification in the rate of HIV-positive donations: 0.07 HIV-positive donations per 10,000 donations in P1 versus 0.04 in P2 ($p = 0.07$). The rate decreased from 0.29 to 0.22 among first-time donors ($p = 0.38$) and from 0.03 to 0.02 ($p = 0.17$) among repeat donors (Table 1).

Among men with an identified probable risk of acquisition, sex between men relations accounted for 61% (14/34) and 59% (13/24) in P1 and P2, respectively. No significant differences were observed with regard to the donor's status (Table 2).

Three donors (two MSM and one man who have sex with women) in P1 as well as one man who have sex with women in P2 donated during the very early phase of HIV infection (positive HIV-RNA and negative HIV Abs).

Rates of donations positive for HBV, HCV and syphilis

A comparison of the two 30-month periods reveals a significant decrease in the rate of HBV-positive donations (0.49 per 10,000 donations in P1 vs. 0.39 in P2; $p = 0.006$) and HCV-positive donations (0.25 vs. 0.20; $p = 0.04$) (Figure 1). Note that the rate of HBV-positive donations increased among first-time donors in 2022. However, as this analysis does not take into account the entire year, this does not affect the evaluation. A significant increase in the syphilis-positive rates occurred between P1 and P2 (1.10 vs. 1.29; $p = 0.000$). This trend was observed in both repeat and first-time donors, from 0.49 per 10,000 donations in P1 to 0.62 in P2 ($p = 0.002$) and from 5.09 to 6.22 ($p = 0.002$), respectively.

Between 1 October 2017 and 30 September 2022, syphilis-positive blood donors were more frequently men (74.0%) and first-time donors (59.4%). The proportion of first-time male donors significantly increased after 2 April 2020, from 66.3% in P1 to 73.4% in P2 ($p = 0.013$). Similarly, the proportion of syphilis-positive MSM donors significantly increased from 17.3% in P1 to 27.1% in P2 ($p = 0.000$). However, caution should be exercised when interpreting

TABLE 2 Probable risk of acquisition of human immunodeficiency virus (HIV)-positive donors with a comparison of the two 30-month periods before and after 2 April 2020.

	1 October 2017–1 April 2020		2 April 2020–30 September 2022		p^b
	N	%[a]	*N*	%[a]	
First-time donors					
Men	18		15		0.73
Sex with men	4	44%	9	64%	
Sex with women	3	33%	5	36%	
Other	2	22%	0	0%	
Unknown/not reviewed	9		1		
Women	10		3		
Sex with men	9	100%	3	100%	
Unknown	1		0		
Total	28		18		
Repeat donors					
Men	16		9		0.73
Sex with men	10	71%	4	50%	
Sex with women	4	29%	4	50%	
Other	0	0%	0	0%	
Unknown/not reviewed	2		1		
Women	5		3		
Sex with men	5	100%	3	100%	
Total	21		12		
All donors					
Men	34		24		1.00
Sex with men	14	61%	13	59%	
Sex with women	7	30%	9	41%	
Other	2	9%	0	0%	
Unknown/not reviewed	11		2		
Women	15		6		
Sex with men	14	100%	6	100%	
Unknown	1		0		
Total	49		30		

[a]Percentages calculated among known probable risk of acquisition.
[b]Fisher's exact test (sex with men vs. sex with women and other).

this result because of the high proportion of donors with unknown risk factors (50.7% in P1 and 41.7% in P2).

Estimation of incidence rate and RR of HBV, HCV and HIV using the cohort method

Between 1 October 2017 and 30 September 2022, 10 incident cases of HBV (5 in P1 and 5 in P2), 6 incident cases of HCV (4 in P1 and 2 in P2) and 17 incident cases of HIV (10 in P1 and 7 in P2) were observed among donors who gave blood at least twice in a 30-month period.

Incidence rates were estimated at 0.27 per 10,000 donations for HBV (0.26 in P1 and 0.28 in P2; $p > 0.5$), 0.16 for HCV (0.21 in P1 and 0.11 in P2; $p > 0.5$) and 0.45 for HIV (0.52 in P1 and 0.39 in P2; $p > 0.5$).

The RR for HBV was estimated at 1/6,400,000 donations in P1 and 1/6,000,000 in P2; for HVC, the RR was 1/25,200,000 in P1 and 1/47,300,000 in P2; and for HIV, the RR was 1/7,800,000 in P1 and 1/10,500,000 in P2. In P2, this corresponds to one potentially undetected HBV-positive donation every 2 years, one potentially undetected HCV-positive donation every 18 years and one potentially undetected HIV-positive donation every 4 years.

These RR estimates are the lowest observed since epidemiological surveillance began. Between 2002 and 2004 with the generalization of individual nucleic acid tests for HIV and HCV and 2020–2022, the RR for HIV and HBV decreased four-fold, while that for HVC decreased by a factor of seven (Figure 2).

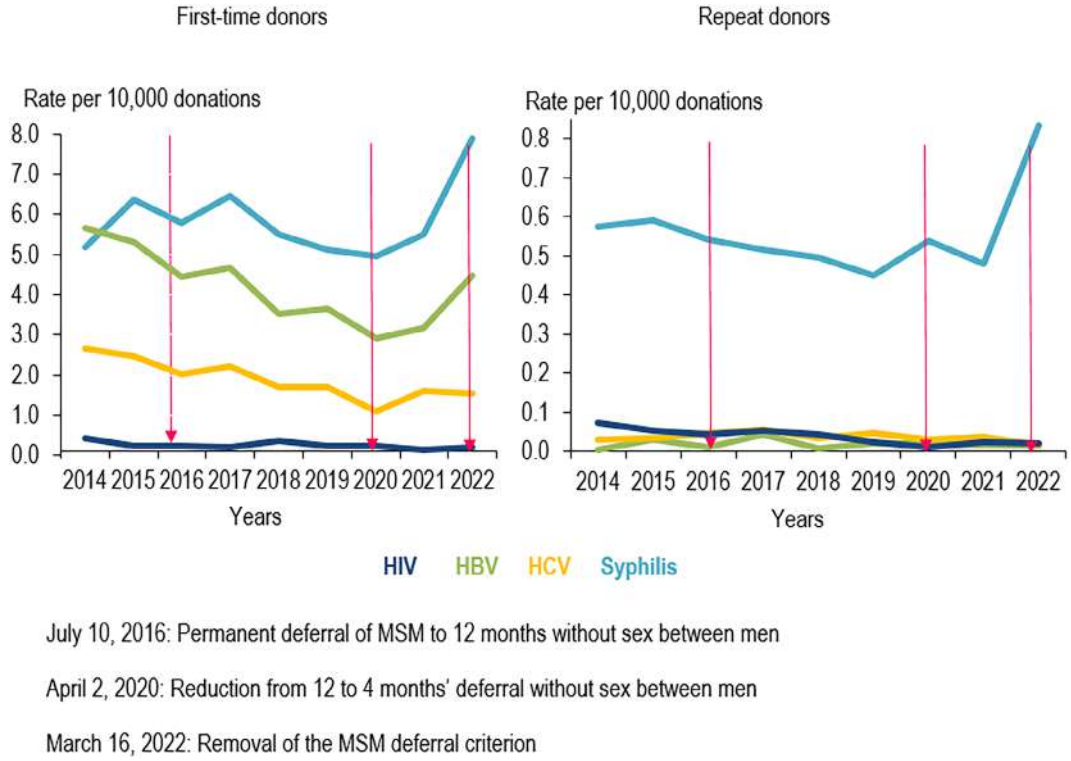

FIGURE 1 Rates of donations positive for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and syphilis by type of donor, 2014–2022.

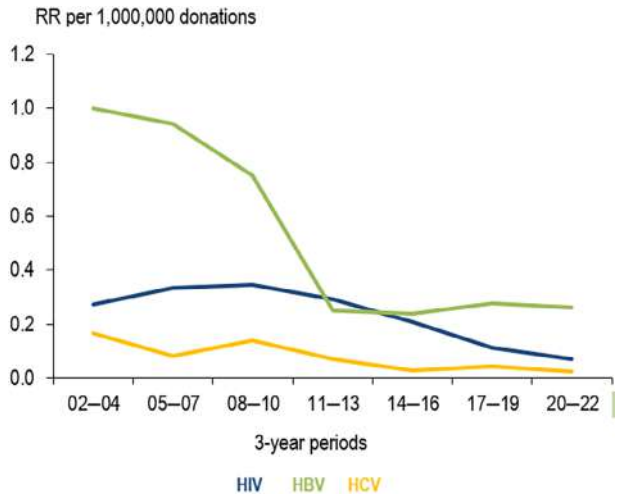

FIGURE 2 Residual risk (RR) of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), 2002–2022.

Estimation of the incidence and RR of HIV using the EIA-RI

Of the 74 HIV-1 donations that underwent testing with EIA-RI over the two 30-month periods, 22 (29.7%) were identified as recently infected (≤180 days). Of them, 15 were identified in P1 and 7 in P2, respectively, representing 32.6% and 25.0% of screened donations positive for HIV-1 during these two periods. These recently infected donors were mainly men (9/15 in P1 and 6/7 in P2) and first-time donors (11/15 and 5/7). After accounting for donors for whom the probable risk of acquisition could not be determined (one in P2), five male donors in both P1 and P2 declared having had sex with men.

The incidence rates estimated from these recent infections were 0.51 per 100,000 donor-years in P1 and 0.27 in P2, with no significant difference. These rates allow us to estimate the RR of HIV transmission through transfusion as 1 potentially undetected positive donation per 8 million donations in P1 and 1 per 15.1 million donations in P2 (Table 3).

DISCUSSION

The epidemiological surveillance of blood donors shows that the change implemented in April 2020 from 12- to 4-month deferral for men who have had sex with men did not affect transfusion safety. No significant increase was observed in terms of the rate of HIV-positive donations, number of MSM among HIV-positive donors, number of early infections (positive HIV-RNA and negative HIV Abs), HIV incidence or RR between the two 30-month periods. In P2, the estimated HIV RR was 1 per 10.5 million donations using the cohort method, which included only donors making at least two donations during the 30-month period. The HIV RR was 1 per 15.1 million donations using the EIA-RI. These estimates correspond to approximately one potentially HIV-infected and undetected donation every 4–6 years. However, no HIV infection following a blood transfusion has been

TABLE 3 Estimation of the incidence and residual risk (RR) of human immunodeficiency virus (HIV) in blood donors using the enzyme immunoassay with a comparison of the two 30-month periods before and after 2 April 2020.

Periods	Incident cases[a]	Donor-years (DY)	HIV incidence per 100,000 DY (95% CI)	HIV RR per 1,000,000 donations (95% CI)	HIV RR, 1/*n* donations
1 Oct 2017–1 Apr 2020	15	2,959,081	0.51 (0.29–0.86)	0.12 (0.00–0.59)	1/8,000,000
2 Apr 2020–30 Sep 2022	7	2,600,753	0.27 (0.12–0.58)	0.07 (0.00–0.40)	1/15,100,000
1 Oct 2017–30 Sep 2022	22	5,559,834	0.40 (0.25–0.61)	0.10 (0.00–0.42)	1/10,200,000

Abbreviation: CI, confidence interval.
[a]Incident cases are identified using the enzyme immune-assay (EIA-RI), which identifies infections of less than 6 months.

reported by the haemovigilance network for many years. The last documented HIV transmission via blood transfusion in France occurred in 2002 [24].

Similarly, HBV and HCV indicators did not increase between the two study periods. The rise in the rate of HBV-positive donations observed among first-time donors in 2022 (Figure 1) was not observed when evaluating the change in selection criteria in 2020, because the second 30-month period does not include the entire year of 2022, which had the highest rate of HBV-positive donations, while the first 30-month period, which includes part of 2020, had the lowest rate. Compared with the first 30-month period, the rate of HBV-positive donations among first-time donors remained stable. This increase in the rate of HBV-positive donations could be attributed to the use of nucleic acid test screening assays with higher sensitivity in 2022 [25]. However, this did not affect the overall results of opening blood donation to MSM.

In contrast to HIV, HBV and HCV, syphilis is the only marker for which the decline in the rate of positive donations has been less pronounced since the 2010s, with an increase observed since 2021 [26]. The increase is consistent with the epidemiology of syphilis in the general French [27] and European [28] population, which is mainly driven by MSM. Consequently, the observed increase in the number of syphilis-positive donations among both first-time and repeat donors following the switch to a 4-month deferral for MSM was not unexpected. Moreover, the tests used by the National Blood Service cannot distinguish between active syphilis and serological sequelae (i.e., syphilis present for a long time). While MSM are the population with the highest number of active syphilis cases, they are also, de facto, the population with the highest number of serological sequelae. However, it is difficult to determine the impact of this change in the donor selection criteria for MSM on syphilis rates because of the inability to identify the probable risk of acquisition for a significant number of positive donors (46% across the two periods) [26]. Another potential explanation for the observed increase in syphilis donation rates is technical in nature: the National Blood Service has used high-sensitivity assays for syphilis Abs screening since late 2021, which may have led to an increase in the number of detected cases. The higher rate of syphilis-positive donations observed following the opening of blood donation to MSM was also not unexpected, given the observation of a similar trend following the introduction of MSM donation of quarantined apheresis plasma in July 2016, under the same deferral conditions as other donors. In fact, by repeating the tests at a certain interval after the donation, this study made it possible to safely assess the epidemiology of sexually transmitted pathogens and showed that about 50% of syphilis-positive MSM donations corresponded to old cases of syphilis [29]. Thus, the observed increase in the rate of syphilis-positive donations may simply reflect an infection that occurred earlier in the donors' lives rather than a current lifestyle associated with an increased risk of sexually transmitted infections.

The decrease of HIV-positive donation rate and of the HIV RR observed in recent years, especially due to improvements in screening tests and in the quality of blood donor selection, has not been affected by the change in the deferral period for MSM from 12 months to 4 months. This result is consistent with other reports in the literature. Indeed, several countries also recently revised their deferral criteria for MSM, without any negative impact on transfusion safety. In Canada, the permanent exclusion of MSM, which had been in place since 1977, was gradually reduced to 5 years, 1 year and 3 months without altering the HIV RR [30]. Similar to our findings, an increase in the rate of positive syphilis was observed. However, the data did not confirm whether this increase was due to MSM blood donors [31]. Similarly, in Australia, the rate of syphilis among donors increased from 2015 to 2020 with the MSM deferral remaining unchanged at 12 months [32]. In the United Kingdom, the gradual reduction of the MSM deferral period from permanent to 12 months and then to 3 months had no impact on transfusion safety [33]. In 2020, that country implemented risk-based sexual criteria for blood donation based on sexual behaviour [34]. This approach, known as 'For the Assessment of Individualized Risk' (FAIR), is considered fairer than excluding all individuals with sexual partners in high-risk groups, including MSM, from donating blood for several months. Similar criteria have been implemented in other countries. Since 2021, donation candidates in Israel are no longer asked about their sexual orientation. Instead, they are asked if they have been engaged in high-risk sexual activity with one or more new partners in the last 3 months using gender-neutral language [35]. Similarly, in Canada since 2022 [36] and in the United States since 2023 [37], donors are asked whether they

have had a new sexual partner in the last 3 months and whether they have had more than one sexual partner in the last 3 months (only in Canada). If so, donors are additionally asked as to whether they have engaged in anal intercourse within the preceding 3-month period, leading to a 3 months deferral. A review of the experience of gender-neutral donor selection in several high-income countries reveals a largely positive and acceptable outcome for stakeholders, donors and staff [38]. In the Netherlands, where successive relaxations of the MSM exclusion criteria have had no significant impact on transfusion safety, the number of syphilis-positive donations increased following the transition to a 4-month deferral period for MSM. Nevertheless, this did not impede the implementation of an inclusive and non-discriminatory donor selection policy in January 2024 [39].

This analysis of the impact of changing the deferral period for MSM in France from 12 to 4 months suffers from two limitations. First, the second period after the deferral change (P2) included the years 2020 and 2021, which were characterized by lower exposure to sexual risk behaviours due to the social distancing measures implemented in response to the COVID-19 pandemic, particularly among MSM [40, 41]. Secondly, the P2 period also includes the 6 months following 16 March 2022 during which no MSM-specific criteria were applied to donations. As these two limitations, respectively, tend to reduce and increase the risk in P2, we may consider that their effects cancel each other out. It is important to note that despite successive measures leading to open access to blood donation for MSM, the RRs of HIV, HBV and HCV transfusion-based transmission have never been lower.

Since 16 March 2022, MSM in France have been allowed to donate blood under the same conditions as other donors, that is, on the condition that they have had no more than one sexual partner in the last 4 months. The French Ministry of Health made the decision to remove the deferral criteria specific to MSM with the aim of eliminating discrimination in blood donation. As a result, the new selection criteria are not based on the gender of the donor and his/her partner. The decision was made following consultation with all stakeholders and advice from the High Council of Public Health. This new measure is carefully monitored to detect any increase in the rate of positive donations for various markers, particularly for syphilis. As 30 months had not yet elapsed after this change, there was insufficient hindsight to analyse it in this article, but a review will be conducted to evaluate the impact of the full re-integration of MSM as blood donors using the same method as with the two previous changes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data were collected nationally by the National Blood Service (*Etablissement français du sang*) and the Army Blood Service (*Centre de Transfusion Sanguine des Armées*).

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

The association between attitude towards facemasks, quality of donation experience and relationship with healthcare providers: A cross-sectional exploratory study

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Abstract

Background and Objectives: Facemasks represent an essential measure of prevention against the spread of infectious diseases; however, they lessen the ability to convey and understand emotions through facial expressions. In blood donation settings, facemask wearing could interfere with professionals' tasks, reduce the satisfaction of blood donors and affect their future blood donation behaviour. This preliminary cross-sectional study explored the association of mandatory facemask wearing with the quality of the blood donation process at the end of the coronavirus 2019 (COVID-19) pandemic.

Materials and Methods: A sample of 615 voluntary unpaid Italian blood and plasma donors completed an online survey assessing their attitude towards facemask wearing, the perceived distress due to facemasks in the different steps of the donation process, self-reported vasovagal reactions after donation and the intention to donate again.

Results: Nearly 24% of donors reported a worsened quality of the donation process due to facemask wearing, and 36% reported moderate to severe distress during the donation itself. Donors with a more negative attitude towards facemasks reported a worse donation experience, mainly related to the interactions and the communication with physicians and nurses, and a higher probability of experiencing vasovagal reactions at their last donation. No significant correlations were observed between negative facemask attitudes towards facemask wearing, distress or future intention to donate blood/plasma.

Conclusion: Facemasks have worsened the quality of blood and plasma donations for one fourth of donors, confirming the interference with the quality of communications and relationships with healthcare professionals.

Keywords

adverse reactions, blood donation, communication, distress, facemasks, intention to donate

Highlights

- Facemasks have worsened the quality of the donation experience, especially regarding communications with healthcare providers.
- Donors with negative attitudes towards facemasks are more likely to report vasovagal reactions after donation.
- Facemasks do not reduce the intention to donate in the following 6 months.

INTRODUCTION

Blood and blood products are essential resources for healthcare systems worldwide. During times of crisis and health emergencies, the demand for these products becomes much more compelling. During the coronavirus disease 2019 (COVID-19) pandemic, a serious shortage of blood products due to a reduction in active blood donors was registered [1] with up to a 38% decrease in blood donations [2]. Donors who adhered to COVID-19 preventive measures were less likely to donate blood [2]. Studies focusing on motivational factors demonstrated differences between COVID-19 convalescent and non-convalescent plasma donors, with higher donor-return rates among the latter [3]. Donor satisfaction remains a crucial factor influencing future donations during COVID-19 [4, 5], with donors who felt unsafe reporting lower intentions to return to donate [6]. It is well-established that critical factors related to donor satisfaction include the quality of healthcare interactions and the detection and prevention of adverse reactions. In particular, studies have indicated that the good interpersonal skills of nurses and the availability of social support can reduce the likelihood of adverse reactions and improve the likelihood to return for future donations, among blood donors [7, 8]. Furthermore, research suggests that adverse reactions experienced during initial donations can forecast donor dropout and reduce the likelihood of subsequent donations, especially among new donors [9, 10].

Until May 2023, several measures were implemented to reduce the risk of COVID-19 infections and to guarantee the health of both blood donors and recipients. These measures included scheduling donations and registration procedures, limiting the number of donors in waiting rooms, spacing out chairs and beds, regularly sanitizing donors' hands, disinfecting equipment and mobile units and minimizing close contact between donor and medical staff. However, the measure that mostly impacted the donation process was the mandatory use of facemasks for donors and healthcare professionals [11]. Although facemask mandates played an essential role in curbing the spread of the virus, they also profoundly impacted the quality of communication and relationships between healthcare providers and patients in many healthcare contexts [12–15] by limiting the ability to identify people and express and recognize emotions and interfering with communication processes. Specifically, facemasks have been proven to hinder the ability to recognize the identity of a known person [16, 17]. This aspect can be relevant in healthcare settings where personal acquaintance between providers and patients can facilitate trustful interactions; when considering the blood donation context, facial recognition can be considered fundamental, as regular donors are often known by healthcare staff. Furthermore, facemasks can disrupt emotion recognition [18, 19], which has a pivotal role in general human interactions, and more specifically in healthcare where the ability to properly recognize emotions can be important to recognize patients' discomfort, anxiety and distress and promptly address them. In blood donation settings, it is particularly relevant to correctly and promptly detect anxiety, often linked to fear of needles or blood, and early signs of side effects, such as vasovagal reactions.

Facemasks may also impact verbal and non-verbal communication. Specifically, facemasks interfere with acoustic vocal expression [20], leading individuals to raise their voices or repeat information to ensure clarity. Moreover, they hinder non-verbal cues [21], which are crucial during many stages of the blood donation procedure, including donor counselling and donation monitoring. Only two previous studies have assessed the impact of facemasks on the donation process. The first one [12] reported that facemasks impaired clinicians' ability to communicate with donors. The second one [22] reported higher vasovagal reaction rates among blood donors in 2020 and 2021 compared with previous years, linking these data to facemask wearing during the COVID-19 pandemic. Despite these worrying figures, data exploring the donors' perspective on the facemask mandates during the COVID-19 pandemic are missing.

This exploratory cross-sectional study aimed to evaluate the association of the mandatory facemasks policy on different aspects of the donation process from the donors' perspective. In particular, it sought to address the following questions:

1. Did the implementation of mandatory facemask wearing lead to a decline in the quality of the donation experience? Which stages of

the donation process were perceived as more affected by the introduction of mandatory facemask usage?
2. Did donors who hold negative attitudes towards facemasks show a decreased likelihood of donating within the next 6 months? Additionally, did they report experiencing more adverse post-donation reactions?
3. Did donors who hold negative attitudes towards facemasks are more likely to wear surgical facemasks compared to Filtering Face Piece (FFP2)?

METHODS

Participants and procedure

All the voluntary unpaid whole blood and plasma donors who donated whole blood or plasma between September 2022 and February 2023 at the blood donation centre of Associazione Volontari Italiani del Sangue - Italian Association of Blood donors (AVIS) Provinciale Bergamo ($n = 16{,}811$) were invited by email to participate in the study. AVIS Provinciale Bergamo sent the email invitation (as part of their monthly newsletter) only to donors that had donated whole blood or plasma within the previous 6 months. The invitation included a study description and the Google form link for participation. Before completing the survey, participants were asked to sign the informed consent form digitally. The average time to complete the survey was 15 min. This study was approved by the Ethical Committee of the University of Milano-Bicocca (protocol no. 624/2021).

Measures

The survey included the following assessments:

1. Subjective vasovagal symptoms after the most recent donation were assessed using the four-item version of the Blood Donation Reactions Inventory (BDRI) [23] that include four sensations (faintness, dizziness, weakness and light-headedness) rated on a 6-point Likert scale from 'not at all' to 'to an extreme degree' with higher scores indicating greater symptoms.
2. Attitude towards facemasks was assessed using a 12-item scale [24], rated on a 7-point Likert scale ranging from 1 = strongly disagree to 7 = strongly agree. The scale provides a global measure of negative attitudes towards facemasks. It includes six domains (ineffectiveness of facemasks, mask-wearing as an inconvenient habit, masks as aesthetically unappealing, masks as an interpersonal barrier and physical inconvenience—difficulty breathing and overheating).
3. The distress of wearing a facemask was measured through an ad-hoc developed item ('How much distress did you feel when wearing a facemask?') rated on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much). This question was asked for each of the four steps of the donation process (i.e., waiting room, welcoming procedure, medical visit, donation).
4. Attitudes towards maintaining facemasks in blood/plasma donation services in the future for donors, healthcare providers (physicians and nurses) and administrative staff were assessed on a 7-point Likert scale ranging from 1 (not at all) to 7 (very much).

A subset of questions focused on the impact of facemasks on different aspects of the donation experience was also completed by those participants who had made at least one donation before the introduction of mandatory facemasks:

1. 'How has your donation experience changed after the introduction of facemasks?' rated on a 7-point Likert scale ranging from 1 (strongly worsened), 4 (not changed), 7 (strongly improved).
2. 'How has the length of the welcoming procedure/medical visit/donation changed after the introduction of facemasks?' rated on a 7-point Likert scale ranging from 1 (strongly lengthy) to 7 (strongly shortened).
3. 'How has the quality of communication/relationship with doctor/nurse changed during the medical visit/donation procedure after the introduction of facemasks?' rated on a 7-point Likert scale ranging from 1 (strongly worsened), 4 (not changed), 7 (strongly improved).
4. Finally, participants indicated the type of facemask mainly used for the donations (surgical vs. FFP2) and indicated their intention to donate again answering the question 'How likely is it that you donate blood or plasma in the next six months?' on a 7-point Likert scale ranging from 1 (very unlikely) to 7 (very likely).

Analysis

The descriptive analysis determined the study variables' mean values and standard deviations. Pearson's zero-order and partial correlations were conducted to explore the associations between variables. *T*-tests were employed to compare donors who utilized a surgical facemask with those who used an FFP2 facemask. Cohen's *d* was computed to assess effect sizes for the *t*-tests. The significance level was set at $p < 0.05$. All statistical analyses were conducted using SPSS 26.

RESULTS

In total, 632 donors—out of the 16.811 donors who received the invitation email—filled in the survey. However, 18 did not provide informed consent, and therefore, 615 donors (64.1% males, whose most recent donation was of whole blood for 67.0% and plasma for 33.0%) were included in the analysis (response rate 3.66%).

The mean age of donors was 45.42 ± 11.80 years (range, 18–70 years).

All were Italian, 6.9% made 1–2 donations, 8.5% 3–5 donations, 9.3% 6–10 donations and 75.5% more than 10 donations.

Effects of facemasks wearing on donation experience

About 70% of donors reported no effect of the introduction of mandatory facemask wearing on the donation experience, whereas 23.9% reported negative effects. Interestingly, affected donors are younger ($F = 7.930$; df = 2; $p < 0.001$; $\eta^2 = 0.028$), reported higher BDRI scores ($F = 10.481$; df = 2; $p < 0.001$; $\eta^2 = 0.037$) and have a worsened attitude towards facemasks ($F = 68.161$; df = 2; $p < 0.001$; $\eta^2 = 0.20$). No gender difference emerged between affected and not-affected donors ($X^2 = 0.403$, df = 2, $p = 0.817$). Nevertheless, 41% of donors reported moderate to intense distress due to facemask wearing during the overall donation process. When considering the different steps of the donation process (waiting room, administrative procedure, medical visit, donation), the most impacted step was the donation itself, with 36% of donors reporting moderate to intense distress. When asked about the effect of facemask wearing on specific aspects of the donation process, nearly 20% of donors reported worsened communication and relationships with physicians and nurses. The effect of facemasks on the length of donation procedures was further reduced, and nearly 10% of donors reported an increase in the time needed for the donation processes (Table 1). Furthermore, about 55% of donors reported a moderate to strong agreement for maintaining facemasks for healthcare providers (physicians and nurses), while they were less willing to keep them for donors and administrative staff.

A correlation matrix was calculated to verify the relationship between facemask attitude and the quality of the donation experience (Table 2). Significant negative correlations were observed between facemask attitudes, facemask distress and donation experience change (with worse facemask attitudes and higher facemask distress correlated with a worsened donation experience).

The same pattern emerged regarding the quality of doctors' and nurses' relationships and communication with donors: poorer attitudes towards facemasks and higher facemask-related distress correlated with a decline in the quality of healthcare provider–donor communication and relationship.

Finally, a strong positive correlation emerges between age and change in donation experience ($r = 0.166$, $p < 0.001$), with older donors reporting better donation experience. Conversely, a negative correlation was found between age and attitude towards the facemask—physical inconvenience subscale ($r = -0.160$, $p < 0.001$), with older donors reporting a more positive attitude.

Effect of attitudes towards facemasks wearing on donation intention and adverse reactions

A partial correlation matrix was calculated to verify the relationship between facemask wearing, the intention to donate again in the following 6 months and subjective vasovagal reactions at the most recent donation, controlled by the age of donors. Although none of the variables considered correlated with the intention to donate, there was a strong correlation between BDRI total score, and the attitudes towards facemasks—physical inconvenience (Table 3).

TABLE 1 Descriptive statistics of the impact of facemasks on donation and willingness to maintain facemasks.

	Mean ± standard deviation	%
Change of donation experience after introduction of mandatory facemasks[a]	3.74 ± 0.930	23.9% (worsened, ≤3) 70.1% (the same, =4) 6.0% (improved, >4)
Distress facemask-related	**Mean ± standard deviation**	**% distress moderate/ intense (≥4)**
Total distress	3.16 ± 2.105	41.1%
Distress in the waiting room	2.66 ± 2.060	29.2%
Distress during welcoming procedure	2.65 ± 2.055	29.1%
Distress during medical visit	2.67 ± 2.053	29.3%
Distress during donation	3.06 ± 2.203	36.5%
Quality of relationship and communication	**Mean ± standard deviation**	**% worsened quality (≤3)**
Quality of doctor–donor relationship	3.82 ± 0.897	17.3%
Quality of nurse–donor relationship	3.82 ± 0.929	19.2%
Quality of doctor–donor communication	3.77 ± 0.918	19.3%
Quality of nurse–donor communication	3.80 ± 0.941	19.7%
Length of donation procedures	**Mean ± standard deviation**	**% increased length (≤3)**
Welcoming procedure	3.89 ± 0.763	12.0%
Medical visit	3.89 ± 0.634	10.0%
Donation	3.93 ± 0.586	8.0%
Maintenance of facemasks	**Mean ± standard deviation**	**% agreement moderate/ high (≥4)**
For blood donors	3.55 ± 2.204	47.0%
For physicians	3.93 ± 2.199	55.1%
For nurses	3.95 ± 2.213	55.6%
For administrative staff	3.44 ± 2.144	45.0%

Note: Higher values indicate higher levels of distress.
[a]Only participants who donated before and after the introduction of facemasks were included in the analysis.

Type of facemasks, attitudes towards them and changes in the donation experience

Donors using surgical facemasks reported higher distress in all the stages of the donation process, along with a more negative attitude towards facemasks and a worsened overall donation experience. No significant differences were observed in communication and relationships with healthcare providers or subjective post-donation vasovagal reactions (Table 4).

TABLE 2 Zero-order correlation matrix between attitude towards facemasks, facemask-related distress and impact on donation experience.

	Donation experience change ($N = 548$[a])	Doctor relationship change	Doctor communication change	Nurse relationship change	Nurse communication change
Attitude towards facemask—total	−0.392*	−0.262*	−0.230*	−0.219*	−0.219*
Attitude towards facemask—ineffective	−0.462*	−0.276*	−0.250*	−0.245*	−0.240*
Attitude towards facemask—inconvenient habit	−0.474*	−0.231*	−0.215*	−0.219*	−0.204*
Attitude towards facemask—unappealing	−0.341*	−0.186*	−0.161*	−0.157*	−0.161*
Attitude towards facemask—interpersonal effect	−0.295*	−0.284*	−0.262*	−0.251*	−0.248*
Attitude towards facemask—physical inconvenience	−0.496*	−0.275*	−0.275*	−0.250*	−0.247*
Facemask distress	−0.550*	−0.313*	−0.287*	−0.284*	−0.282*

[a]Only participants who donated before and after the introduction of facemasks were included in the analysis.
*$p < 0.001$.

TABLE 3 Partial correlation matrix controlled by age between attitude towards facemask, facemask distress, future donation intention and BDRI.

	Likelihood to donate again in the next 6 months	BDRI
Donation experience change	−0.038	−0.077
Attitude towards facemask—total	0.012	−0.003
Attitude towards facemask—ineffective	0.023	0.001
Attitude towards facemask—inconvenient habit	0.013	0.050
Attitude towards facemask—unappealing	−0.007	−0.036
Attitude towards facemask—interpersonal effect	−0.004	−0.022
Attitude towards facemask—physical inconvenience	0.039	0.155*
Facemask distress	0.039	0.052

Note: $N = 615$.
Abbreviation: BDRI, Blood Donation Reactions Inventory.
*$p < 0.001$.

DISCUSSION

To the best of our knowledge, this study represents the first exploration of the association between the attitudes towards facemask wearing with the quality of blood donation process from the donors' perspective. It provides important insights into donors' experiences and attitudes towards facemasks, showing distress, more vasovagal reactions and a worsened quality of the donation experience (mainly in the relationship with healthcare providers) due to facemask wearing.

Although strongly recommended by the Centro Nazionale Sangue [25], currently, the use of facemasks in blood collection sites is no longer mandatory in Italy. However, in hospital settings, facemask mandates may be enforced during certain periods of the year, such as the seasonal flu peak. For these reasons, the data provided by this study could prove invaluable in formulating strategies to enhance blood donors' retention when facemasks must be used, independently of the COVID-19 infection.

While wearing facemasks has not significantly changed the overall quality of the donation experience for the majority of blood and plasma donors, they have been found to have a detrimental effect on nearly one fourth of donors, particularly among younger individuals, with higher BDRI score, and less favourable to maintaining facemasks for themselves, and healthcare professionals. This effect is most pronounced during some specific steps of the donation process. Areas related to communication and relationships with physicians and nurses appear to be the most affected, confirming the results of a qualitative study on healthcare providers in blood donation settings [12].

The positive correlations between BDRI scores and negative attitude towards facemasks (in particular due to the physical inconvenience caused by facemasks such as difficulty to breathe or overheat) suggest that individuals experiencing greater difficulties with facemasks may be at a heightened risk of vasovagal symptoms. A similar pattern was reported in a wide retrospective study on vasovagal reactions [22], which found an increase in vasovagal reactions during 2020 and 2021 compared with previous years, probably due to COVID-19 restrictions such as facemask mandates. Bani et al. [12] reported that nurses perceived a reduction in their ability to detect early signs of vasovagal prodromal symptoms (such as lips and face paleness) in blood donors wearing facemasks. The majority of donors expressed support for the continued use of facemasks by healthcare professionals, beyond the pandemic emergency. However, they were less inclined to endorse the maintenance of facemasks for themselves and administrative staff. These results underscore the recognition among donors of the utility of facemasks in terms of protection and perceived safety, aligning with perspectives previously reported by professionals [12].

TABLE 4 Comparison between facemask types.

	Surgical ($N = 363$) M (SD)	FFP2 ($N = 241$) M (SD)	*t*	*p* value	*d*
BDRI	1.61 (2.81)	1.39 (2.70)	0.950	0.342	-
Facemask distress	15.18 (10.34)	12.32 (8.73)	3.537	<0.001	0.29
Facemask distress—waiting room	2.85 (2.15)	2.29 (1.78)	3.363	0.001	0.28
Facemask distress—welcoming procedure	2.85 (2.15)	2.28 (1.76)	3.424	0.001	0.29
Facemask distress—medical visit	2.87 (2.15)	2.29 (1.75)	3.431	0.001	0.29
Facemask distress—donation	3.27 (2.26)	2.67 (2.01)	3.341	0.001	0.28
Donation experience change	3.60 (0.86)	3.99 (0.94)	−4.971	<0.001	0.43
Doctor relationship change	3.78 (0.92)	3.92 (0.79)	−1.777	0.076	-
Doctor communication change	3.77 (0.92)	3.82 (0.85)	−0.704	0.482	-
Nurse relationship change	3.80 (0.98)	3.90 (0.79)	−1.332	0.183	-
Nurse communication change	3.77 (0.98)	3.88 (0.83)	−1.348	0.178	-
Attitude towards facemask—total	2.32 (1.59)	1.62 (1.13)	5.878	<0.001	0.51
Attitude towards facemask—ineffective	2.69 (1.79)	1.85 (1.27)	6.340	<0.001	0.54
Attitude towards facemask—inconvenient habit	3.35 (1.93)	2.73 (1.67)	4.093	<0.001	0.34
Attitude towards facemask—unappealing	1.79 (1.33)	1.43 (1.01)	3.537	<0.001	0.31
Attitude towards facemask—interpersonal effect	1.84 (1.31)	1.55 (1.06)	2.857	0.004	0.24
Attitude towards facemask—physical inconvenience	3.51 (1.90)	2.99 (1.69)	3.383	0.001	0.29

Note. $N = 612$ (only three subjects reported to use 'reusable facemasks' and were excluded by this analysis).
Abbreviation: BDRI, Blood Donation Reactions Inventory; FFP2, Filtering Face Piece 2; M, mean; SD, standard deviation.

Regarding the effect of facemask mandates on the perceived duration of the donation process, only a minority of donors noticed an increase in the length of the procedures; most reported that the duration remained unchanged. This perception contrasts with that of physicians and nurses, who reported an increase in the duration of the donation process [12].

Facemask wearing can significantly affect the communication process including giving information, listening to and understanding blood donors, especially when both professionals and donors wear facemasks. Yet, if only professionals wear facemasks, the effect is confined to one member of the interaction, thereby reducing the overall impact on communication.

Physicians and nurses reported that wearing facemasks negatively affected their ability to relate and communicate with blood donors, describing these interactions as less empathic, more impersonal and experiencing overall relational impoverishment [12]. These results are corroborated by the donors' perspective, regardless of the type of facemask used (surgical vs. FFP2). However, it is interesting to note that donors using surgical facemasks reported worse attitudes and higher discomfort towards facemasks compared to those wearing FFP2 masks. This result seems counterintuitive considering the higher distress associated with FFP2 masks [26, 27]. Furthermore, previous studies comparing the impact of different facemasks on acoustic voice measures suggest that surgical masks may be the better choice to minimize the impact on verbal communication [20]. Similar results were reported in other studies [28, 29] that demonstrate that different types of masks generally yield similar accuracy in environments with low levels of background noise, but differences between masks become more apparent in environments characterized by high levels of noise mainly for homemade cloth masks and N95 respirator.

However, it is possible that donors with a worse general attitude towards facemasks, if forced to use them, may prefer to use the surgical ones, therefore explaining the higher aversion towards FFP2 masks reported by our donors. If this hypothesis proves to be true, it would suggest that surgical facemask wearing could serve as an indirect indicator of donors with more negative attitudes towards facemasks. Consequently, more attention should be directed towards donors wearing surgical facemasks.

Overall, the present work underscores the need to strengthen the relationship between healthcare staff and donors both before and after blood donation to mitigate the detrimental effect of facemask wearing on relational aspects. Although no significant relationship emerges between facemask attitudes and intention to donate in the near future (6 months), the potential long-term impact of facemasks on future donations and donor retention. Our study warns that younger donors are at higher risk of experiencing the detrimental effects of facemask mandates on the donation process.

Some limitations must be considered. First, the sample size is limited to one blood collection centre, and this limits the generalizability of the results. Another limitation is the low response rate, which can be due to the inability to send reminders to participants and the inclusion of the invitation in a general newsletter email from the association involved in the recruitment. These factors can limit the visibility of the research proposal. A further limitation lies in the cross-sectional design of the study that limited the reliability of the donors perception of the use of facemasks on donation experience, and a longitudinal

study is warranted to detect a reliable impact. However, the abolition of the mandatory facemask use makes it impossible for a longitudinal study as well as a replication of a cross-sectional study until the eventual replication of similar conditions.

It is important to note that this survey was done at the end of the COVID-19 pandemic, and the familiarity of participants with the facemasks wearing could have reduced the contrast of the perceived quality of the donation experience.

Another limitation relies on a possible recall bias, as donors were asked to answer to the survey thinking about their most recent donation in a 6 months period.

Finally, the exclusive use of self-reported measures represents another limitation; this is particularly important for the intention to donate in the future, and an objective measure (donation attempts recorded by the donation centre) should be considered in future longitudinal studies. Furthermore, future studies should include objective measures of blood donation side effects (such as registered side effects).

Considering the pivotal role that donor satisfaction has in influencing future donations, particularly among new donors [4, 6, 30, 31], it is extremely important to intensify efforts aimed at balancing the effects of facemasks. This may involve enhancing the level of care provided to donors cultivating the communication and relational aspects of the process, such as dedicating more time to interactions, asking more frequently about their well-being and implementing closer post-donation monitoring.

In conclusion, wearing facemasks worsened the blood donation experience for one fourth of donors, mainly due to difficulties in communication and relationships with physicians and nurses. The long-term effect of facemasks on donor retention requires further exploration. Meanwhile, more efforts are needed to monitor the quality of the donation experience when facemasks are worn.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The study data are not publicly available. Reasonable, Institutional Review Board-approved requests may be addressed to the corresponding author.

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

The prevalence of hepatitis B virus, human T-lymphotropic virus and human immunodeficiency virus in patients receiving blood transfusions in South Africa

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Abstract

Background and Objectives: South Africa has a high prevalence of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) and to a lesser extent human T-lymphotropic virus (HTLV). Each of these agents is transfusion-transmissible (TT) but deciding whether to implement preventive screening depends upon knowledge of background prevalence in transfused patients. We determined the prevalence of HIV, HBV and HTLV I/II among blood transfusion recipients in South African hospitals.

Materials and Methods: We obtained identity-unlinked samples used for blood cross-matching at 634 South African hospitals served by the South African National Blood Service (SANBS). The ABBOTT Alinity S® Immunochemiluminescent system measured HIV, HBV and HTLV I/II antibodies. Repeatedly reactive samples were confirmed using the Roche Cobas® 8000. Logistic regression was performed to investigate the determinants of associations for HIV, HBV and HTLV infections.

Results: The overall prevalences of HIV, HBV and HTLV were 37.8%, 7.4% and 0.6%, respectively. The HIV prevalence in blood recipients was twice as high as general population estimates. Public hospital patients had a significantly higher prevalence compared with private hospital patients for HIV and HBV. HIV prevalence was significantly higher in females, and HBV prevalence was significantly higher in males, excluding the unknown gender results.

Conclusion: Patients receiving blood transfusions in South Africa have high rates of HIV and HBV infection that should be taken into consideration when determining

donor screening strategies for other viral infections. Measurable prevalence of HTLV indicates endemicity of this infection in South Africa.

Keywords
HBV, HIV, HTLV, patient, prevalence

Highlights

- The prevalence of human immunodeficiency virus (HIV) in blood recipients was twice as high as general population estimates.
- HIV prevalence was significantly higher in females, and hepatitis B virus (HBV) prevalence was substantially higher in males.
- Patients receiving blood transfusions from the South African National Blood Service have high rates of HIV and HBV infection that should be taken into consideration when determining donor screening strategies for other viral infections.

INTRODUCTION

South Africa is the country most affected by the ongoing human immunodeficiency virus (HIV) epidemic in the world, with 18% of adults living with HIV, accounting for 15% of new global infections and 11% of global Acquired Immunodeficiency syndrome-related deaths [1].

For hepatitis B virus (HBV) infection, Spearman and Sonderup [2] suggested that an estimated 65 million people in Africa are chronically infected and 2.5 million of them are in South Africa. According to Schweitzer et al. [3], the hepatitis B surface antigen (HBsAg) seroprevalence was estimated at 6.7%, pointing to high intermediate endemicity with an estimated 3.5 million individuals chronically HBV infected in South Africa.

There is a paucity of data on human T-lymphotropic virus (HTLV) prevalence in the South African general population. One study done by Bhigjee et al. [4], showed a seroprevalence of HTLV among patients in KwaZulu-Natal to be 2.6%.

In this environment, the South African National Blood Service (SANBS) collects and tests blood donations. The prevalence of HIV in first-time blood donors was 1.13% [5], and the incidence in repeat donors was estimated at between 1.56 and 1.94 per 1000 person-years between 2012 and 2016 [6]. The hepatitis B virus prevalence in the first-time donor population was found to be 0.66%, which is significantly lower compared with other studies in the general population [5], A 2013 cross-sectional study of HTLV prevalence among 46,752 South African blood donors confirmed that HTLV prevalence was 0.16% in Black donors, 0.02% in both White and Coloured donors, and 0% in South African Asian donors, for an overall prevalence of 0.062% extrapolated to the 2013 blood donor population [7]. The South African healthcare system consists of two sectors: public and private. Transfusion events across both sectors are predominantly distributed in the following clinical disciplines: Medical (30.4%), Gynaecology/Obstetrics (18.1%), Intensive Care Unit (ICU) (13.8%), General Surgery (11.6%), Paediatrics (7.7%) and Haematology/Oncology (5.5%) [8].

The problem of HIV/HTLV co-infection and its potential pathologic effects have been debated for the past 20 years [9]. It is estimated that rates of HTLV or HTLV-2 co-infections in HIV-infected hospital patients are at least 100 to 500 times greater than in the general population [10]. HTLV may be detrimental to the HIV-infected individual with increased risk for the development of neurologic complications including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), leukaemia and lymphoma [10].

Currently, there is little data available on the HIV, HBV and HTLV prevalence in transfused hospital patients in South Africa. This information is essential for understanding the disease burden in the transfusion recipient population. Receipt of an infectious unit may have lower consequences in a patient already infected with the virus [11]. On the other hand, co-infection with a different virus may be deleterious. Currently the SANBS have implemented screening strategies for HIV, HCV and HBV which reduces the possibility of Transfusion Transmissible Infections (TTI) from these viruses, whereas SANBS does not test for HTLV and HTLV screening is not mandated by the World Health Organization (WHO) or regulatory bodies within South Africa. Vermeulen et al. [12], estimate that without implementing HTLV screening, 3.55 symptomatic cases of TT-HTLV would occur annually.

This study investigated the prevalence of HIV, HBV, HTLV and co-infections thereof in patients requiring blood transfusion.

METHODS

An unlinked cross-sectional study was conducted on 6983 transfused patients in hospitals across South Africa except for the area served by the Western Cape Blood Service.

SANBS has 85 blood transfusion cross-match laboratories in 8 of the 9 provinces serving 90% of the country's hospitals. These provinces have been divided into 7 operational zones, namely, Eastern Cape, Egoli, KwaZulu Natal, Mpumalanga, Northern, Vaal, Free State and Northern Cape. Two thirds of the transfused patients within these zones are from provincial hospitals, and the remaining patients are from private hospitals [8]. To represent the overall transfused population, the collection of samples was stratified by hospital based on

the percentage of blood transfusion requisitions received annually per hospital.

Residual cross-match plasma samples were collected from all blood transfusion laboratories proportionally based on historical blood and blood product usage data. After demographic and geographic data were retained, identifying codes were removed. Specimens were centrifuged at 3000 rpm, and the plasma was separated from the red cells. The plasma was stored frozen (−18°C and below) until all sampling for the hospital was complete. The samples were sent to the central donation testing laboratory where they were stored frozen for 2 months before analysis.

The specimens collected were tested for antibodies and/or antigens for HIV, HBV and HTLV on the Alinity S® (Abbott Diagnostics, Delkenheim, Germany) immunochemiluminescent autoanalyser using the Alinity S® HIV Ag/Ab Combo (antigen–antibody–antigen), HBsAg and HTLV I/II assays. All samples that tested initially reactive were repeated in duplicate on the Alinity. Confirmation of repeat-reactive samples was performed on the cobas® E801 (Roche Diagnostics, Rotkreuz, Switzerland) electrochemiluminescent autoanalyser using the cobas® Elecsys HIV Duo (antigen–antibody–antigen), HBsAg II for HIV and HBV, respectively. HTLV confirmation was performed on the cobas® E411 (Roche Diagnostics, Rotkreuz, Switzerland) electrochemiluminescent autoanalyser using the HTLV I/II assays.

We calculated frequencies and descriptive statistics and performed bivariate analyses using the chi-square test and separate multivariable logistic regression models to assess the association of patient demographics characteristics with HIV, HBV and HTLV infection. Due to sample quality and sample volume, 894 repeat-reactive patient samples tested with the Abbott Alinity S® assay could not be confirmed using the Roche Cobas® E801 To address the missing results for HIV, HBV and HTLV, we imputed the data using the survey impute function in SAS University Edition (SAS Institute, North Carolina, USA) with the Hot-deck method [13]. This method employs a set of cells and randomly selects one as the donor to impute the recipient cell [13]. Prevalence was calculated both as an unadjusted proportion and after standardization by age and sex to the South African general population using the direct method. Statistical analyses were conducted with SPSS® version 25 (IBM, Chicago, Illinois) software and SAS university edition (SAS Institute, North Carolina, USA).

Research ethics approvals were obtained from the Medical Research Council/VUT and the SANBS human research ethics committee (2017/13).

RESULTS

Study population

We analysed results from 6983 specimens collected from 634 hospitals distributed across 8 out of the 9 South African provinces. All age groups were represented with fewer sample numbers in the 0–10-year-old and 81 years and older (Table 1) excluding the unknown age group. Patients below the ages of 20 made up 5.8% of the sample,

TABLE 1 Blood transfusion patient characteristics from May 2017 to May 2018 ($N = 6983$).

	N (%)
Gender	
Female	4379 (62.7)
Male	2591 (37.1)
Unknown	13 (0.2)
Age group	
0–10	107 (1.5)
11–20	303 (4.3)
21–30	849 (12.2)
31–40	984 (14.1)
41–50	769 (11.0)
51–60	702 (10.1)
61–70	726 (10.4)
71–80	489 (7.0)
80+	231 (3.3)
Unknown	1823 (26.1)
Blood group	
A	1881 (26.9)
B	1191 (17.1)
AB	294 (4.2)
O	2962 (42.4)
Unknown	655 (9.4)
Zone	
Egoli	1761 (25.2)
Northern	1693 (24.2)
KwaZulu Natal	1235 (17.7)
Vaal	927 (13.3)
Eastern Cape	516 (7.4)
Free State/North Cape	428 (6.1)
Mpumalanga	423 (6.1)
Hospital class	
Provincial Hospital	4441 (63.6)
Private Hospital	2542 (36.4)

10.3% of the patients were above the age of 70 years, and 26.1% of the patients' age group was unknown. Females made up two thirds of the transfused patient population excluding the unknown gender. Most blood transfusion recipients were from the Egoli zone (25.2%) followed by the Northern zone (24.2%) and KwaZulu-Natal zone (17.7%); Mpumalanga and Free State and Northern Cape zones comprised the fewest (6.1%). Provincial hospital patients were the biggest contributors to the sample (63.6%). (Table 1).

Prevalence

Out of the 2763 Abbott Alinity S repeat-reactive patient samples for HIV, 708 could not be confirmed using the Roche Cobas® E801 and

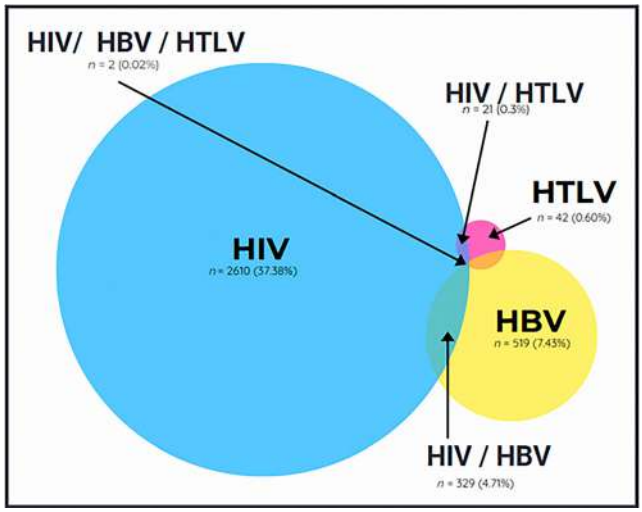

FIGURE 1 Concurrent infections of blood transfusion patient from May 2017 to May 2018. HBV, hepatitis B virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

thus were imputed. Among these, 675 samples were inputted as positive and 33 as negative. Similarly, for HBV, of the 531 Abbott Alinity S repeat-reactive patient samples, 455 could not be confirmed using the Roche Cobas® E801 and were imputed, with 444 imputed as positive and 11 as negative. For HTLV, of the 49 Abbott Alinity S repeat-reactive patient samples, 17 could not be confirmed with the Roche Cobas® E801. Among these, 13 samples were imputed as positive and 4 as negative. Including the imputed results, the overall pre-transfusion prevalence of HIV, HBV and HTLV in transfused recipients was 37.40%, 7.40% and 0.60%, respectively. After standardizing to the age- and sex-distribution of the South African population, HIV, HBV and HTLV prevalence were 33.04%, 7.14% and 0.56%, respectively, excluding the unknown gender and age results. Figure 1 shows the breakdown of co-infections, with the majority being co-infected with HIV and HBV (329), followed by co-infections with HIV and HTLV (21). There were only two (0.02%) concurrent infections between all three viruses (HIV, HTLV and HBV). Prevalence by demographic for each marker can be seen in Tables 2–4. All associations seen in the bivariate analysis remained significant in the multivariable analyses described below, excluding all unknown variables (age, blood group and gender).

Multivariable logistic regression

In the multivariable analyses, females had an adjusted odds ratio (aOR) of 1.3 (confidence interval [CI], 1.17–1.44) for having an HIV infection and in contrast an aOR of 0.73 (CI, 0.61–0.88) having an HBV infection, both compared with males this result excluded the unknown gender. When compared with the Free State/Northern Cape zone, transfused patients in the Mpumalanga zone had an aOR of 2.4 (CI, 1.82–3.24) and 2.0 (CI, 1.13–3.5) for HIV and HBV infection, respectively, followed by the KwaZulu-Natal zone (aOR, 1.5 [CI, 1.22–1.97] and 1.9 [1.19–3.20]), respectively. The Vaal zone had an odds of HIV infection of 1.4 (CI, 1.17–1.92) and the Eastern Cape zone had double the odds of HBV infection (aOR, 1.78 [CI, 1.04–3.15]), both compared with the Free State/Northern Cape zone. Provincial hospital transfusion recipients were more likely to be HIV and HBV positive with odds of 1.5 (CI, 1.17–1.92) and 1.35 (CI, 1.11–1.64), respectively, compared with private hospital patients. There was no significant difference in HIV and HBV prevalence across the patients' blood groups, results excluded the unknown blood.

In the multivariable analysis for HTLV-positive patients, female patients had an odds of 2.05 (CI, 1.02–2.59) for HTLV infection compared with male patients; these results excluded the unknown gender. There was no significant difference in HTLV infection between zones, age groups, blood groups or hospital class in either the bivariate or multivariable analysis with the exclusion of unknown gender, age and blood group results.

Discussion

In this study of blood transfusion recipients, we found a very high HIV, intermediate HBV and detectable but low HTLV infection among transfused patients in SA. Demographic and geographic associations with these viral infections were similar to those previously reported in SA general population [2, 4, 6, 7, 9, 10]. Co-infections were mostly observed for HIV and HBV.

Because we were surprised by the high HIV prevalence in our patients, we wanted to compare them to the general South African population after accounting for differences in age and sex by statistical standardization. According to Stats SA [14], the 2018 estimated HIV prevalence in the general South African population is approximately 13.1%. The total number of people living with HIV is estimated at approximately 7.52 million in 2018. After standardizing our results by age and sex to the South African general population, we found an HIV prevalence in pre-transfused patients of 33.04%, almost three times higher than population estimates when excluding the unknown gender and age results. Age- and sex-specific prevalence in transfused patients was also at least twice as high as the general population in most age/sex categories, excluding the unknown gender and age results [15].

Differences in prevalence between subgroups observed in this study align with findings documented in other research publications [16]. The regions of Mpumalanga, KwaZulu-Natal and Vaal geographical regions in South Africa are the most affected by HIV compared with the general population [17]. Both this study and our own found that similar results were observed in this study for gender HIV infection, showing that females had a higher HIV prevalence than males [17]. Women are disproportionately affected by HIV in South Africa due to a combination of biological, social and economic factors [17].

According to Parikh and Veenstra [17], an HIV prevalence of 25.7% was found among patients visiting primary health care facilities across four South African provinces which is slightly below what was

TABLE 2 Prevalence and demographic associations of HIV seropositivity in transfused hospital patients, May 2017 to May 2018.

Demographic data	Total *N*	HIV-reactive *N* (%)		
Total	**6983**	**2610 (37.4)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Gender				
Female	4379	1773 (40.5)	1.44 (1.30–1.60)	1.30 (1.17–1.44)
Male	2591	833 (32.2)	—	1.00
Unknown	13	4 (30.8)	0.94 (0.29–3.06)	0.68 (0.18–2.11)
Age				
0–10	107	15 (14.0)	0.40 (0.22–0.70)	0.73 (0.46–1.14)
11–20	303	73 (24.1)	0.77 (0.57–1.05)	0.98 (0.78–1.19)
21–30	849	370 (43.6)	1.87 (1.52–2.32)	0.96 (0.78–1.19)
31–40	984	589 (59.9)	3.62 (2.94–4.45)	0.99 (0.80–1.21)
41–50	769	406 (52.8)	2.71 (2.19–3.36)	0.92 (0.74–1.14)
51–60	702	205 (29.2)	1.00	1.00
61+	1446	123 (8.5)	0.23 (0.18–0.29)	0.86 (0.71–1.05)
Unknown	1823	829 (45.5)	2.02 (1.68–2.44)	1.28 (1.07–1.54)
Blood group				
A	1881	660 (35.1)	0.93 (0.82–1.05)	0.98 (0.86–1.11)
B	1191	473 (39.7)	1.14 (0.99–1.31)	1.13 (0.98–1.30)
AB	294	104 (35.4)	0.94 (0.74–1.21)	0.97 (0.75–1.25)
O	2962	1087 (36.7)	—	1.00
Unknown	655	286 (43.7)	1.34 (1.13–1.59)	1.41 (1.18–1.69)
Zone/region				
Egoli	1761	605 (34.4)	1.16 (0.93–1.46)	1.13 (0.90–1.43)
Northern	1693	580 (34.3)	1.16 (0.92–1.452)	1.12 (0.89–1.42)
KwaZulu Natal	1235	511 (41.4)	1.57 (1.24–1.98)	1.55 (1.22–1.97)
Vaal	927	357 (38.5)	1.39 (1.09–1.77)	1.50 (1.17–1.93)
Eastern Cape	516	205 (39.7)	1.46 (1.12–1.92)	1.30 (0.99–1.72)
Free State/North Cape	428	133 (31.1)	—	1.00
Mpumalanga	423	219 (51.8)	2.38 (1.80–3.15)	2.43 (1.82–3.25)
Hospital class				
Provincial	4441	2053 (46.3)	2.22 (2.00–2.46)	1.50 (1.17–1.93)
Private	2542	710 (27.9)	—	1.00

Note: Crude and adjusted odds ratios (OR) were derived from logistic regression models.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

found in the hospitalized patients included in this study. Finding is likely due to Berksonian bias, also called admission rate bias which was first described in 1946 [18]. This bias results from the fact that patients with the disease or condition are more likely to be hospitalized than patients without the disease or condition. This certainly applies to HIV which causes several conditions which might results in medical care or hospitalization [18]. HIV infection poses complex challenges, especially in managing haematologic complications like anaemia, thrombocytopenia and coagulopathies, which significantly affect patient well-being and prognosis [16]. Blood transfusions are crucial to addressing these issues, requiring careful attention and specialized care [16]. Parikh and Veenstra reported HIV prevalences of 34% and 36% in two primary health care facilities clinics, in line with the findings within this study [17].

According to Schweitzer et al. [3], the HBsAg seroprevalence was estimated at 6.7% in South Africa, pointing to high intermediate endemicity with an estimated 3.5 million individuals chronically HBV infected. After standardizing for age and sex we found an HBV prevalence of 7.17% which is similar to the estimated population prevalence of 6.7%, suggesting little bias related to hospitalization for HBV, once again this standardization excluded the unknown age and gender results. With the introduction of the universal HBV vaccination in 1995 [19], it was expected that there would be a noticeable decrease in HBV prevalence in the younger age groups (20 years and below) compared with older age groups (31 years and above) which was not the case within this study. Interesting to note is that there seems to be less admission rate bias for HBV, perhaps because most HBV infection remain asymptomatic for much longer periods [19].

TABLE 3 Prevalence and demographic associations of HBV seropositivity in transfused hospital patients, May 2017 to May 2018.

Demographic data	Total *N*	HBV reactive *N* (%)		
Total	**6983**	**519 (7.4)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Gender				
Female	4379	295 (6.5)	0.77 (0.64–0.92)	0.73 (0.61–0.88)
Male	2591	223 (8.8)	—	1.00
Unknown	13	1 (7.7)	0.89 (0.12–6.84)	0.75 (0.04–3.89)
Age				
0–10	108	4 (3.7)	0.55 (0.20–1.57)	1.14 (0.51–2.28)
11–20	304	26 (8.9)	1.34 (0.81–2.21)	0.88 (0.50–1.47)
21–30	852	59 (7.2)	1.07 (0.72–1.59)	0.95 (0.65–1.39)
31–40	993	90 (9.4)	1.43 (0.99–2.07)	0.98 (0.68–1.42)
41–50	772	58 (7.6)	1.17 (0.78–1.74)	0.71 (0.46–1.07)
51–60	706	46 (6.5)	—	1.00
61+	1448	72 (5.0)	0.75 (0.51–1.10)	0.90 (0.64–1.28)
Unknown	1832	164 (9.1)	1.41 (1.01–1.98)	1.20 (0.87–1.67)
Blood group				
A	1881	134 (7.1)	1.01 (0.80–1.26)	1.01 (0.81–1.27)
B	1191	94 (7.9)	1.12 (0.87–1.45)	1.11 (0.85–1.42)
AB	655	25 (3.8)	0.52 (0.34–0.79)	1.21 (0.77–1.84)
O	2962	210 (7.1)	—	1.00
Unknown	655	56 (8.6)	1.23 (0.90–1.67)	1.21 (0.88–1.64)
Zone/region				
Egoli	1761	122 (6.9)	1.52 (0.94–2.47)	1.43 (0.89–2.40)
Northern	1693	120 (7.1)	1.56 (0.96–2.53)	1.52 (0.95–2.54)
KwaZulu Natal	1235	109 (8.8)	1.98 (1.21–3.22)	1.91 (1.19–3.20)
Vaal	927	67 (7.2)	1.59 (0.95–2.66)	1.58 (0.96–2.71)
Eastern Cape	516	43 (8.3)	1.86 (1.07–3.20)	1.78 (1.04–3.15)
Free State/North Cape	428	20 (4.7)	—	1.00
Mpumalanga	423	38 (9.0)	2.01 (1.15–3.52)	1.96 (1.13–3.50)
Hospital class				
Provincial	4463	357 (8.0)	1.28 (1.0–1.56)	1.35 (1.11–1.64)
Private	2552	162 (6.3)	—	1.00

Note: Crude and adjusted odds ratios (OR) were derived from logistic regression models.
Abbreviations: CI, confidence interval; HBV, hepatitis B virus.

The patient population trends in this study align with findings well-documented in Moonsamy et al. research publications [20]. The regions of Mpumalanga, KwaZulu-Natal and Vaal geographical regions in South Africa are the most affected by HBV comparing the general population [20]. The higher prevalence of HBV among males in South Africa can be attributed to several factors. Men are more likely to engage in high-risk behaviours such as unprotected sex and intravenous drug use, which increase the likelihood of HBV transmission. Additionally, cultural practices and societal norms might lead to lower healthcare-seeking behaviour among men, resulting in reduced vaccination rates and lower access to preventative measures [20].

Anyanwu et al. [21] estimated the HTLV prevalence in South Africa to be 1%, which is slightly higher than the observed (0.60%) or age- and sex-standardized (0.56%) prevalence found in this study. According to Vermeulen et al. [22], the prevalence of HTLV in South African blood donors was 0.062% with 0.16% in Black donors, both of which are lower than previously reported prevalence in the general population and the results of this recipient study. In contrast to Berksonian bias, this could be due to the healthy donor effect whereby blood donors are selected for better health compared to the general population [11]. The prevalence of HTLV was highest in the Mpumalanga and KwaZulu-Natal regions and among female patients, which aligns with previously published results [22].

Currently, HTLV screening of blood donors is not mandated by the WHO or by regulatory standards in South Africa and SANBS does not test for HTLV. However, SANBS uses both buffy coat and filter

TABLE 4 Prevalence and demographic associations of HTLV seropositivity in transfused hospital patients, May 2017 to May 2018.

Demographic data	Total *N*	HTLV reactive *N* (%)		
Total	**6983**	**42 (0.6)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Gender				
Female	4379	33 (0.8)	2.18 (1.04–4.56)	2.05 (1.02–4.59)
Male	2591	9 (0.4)	—	1.00
Unknown	13	0 (0)	0 0	0.00 0
Age				
0–30	1252	7 (0.6)	0.91 (0.37–2.24)	0.87 (0.36–1.94)
31–60	2440	15 (0.6)	—	1.00
61+	1439	7 (0.5)	0.79 (0.32–1.94)	0.66 (0.26–1.53)
Unknown	1810	13 (0.7)	1.17 (0.56–2.46)	0.67 (0.29–1.46)
Blood group				
A	1881	13 (0.7)	1.21 (0.58–2.49)	1.25 (0.59–2.57)
B	1191	7 (0.6)	1.02 (0.42–2.48)	1.01 (0.39–2.36)
AB	294	0 (0)	0 (0)	0.00 (0)
O	2962	17 (0.6)	—	1.00
Unknown	655	5 (0.8)	1.33 (0.49–3.63)	1.42 (0.46–3.63)
Zone/region				
Egoli, Vaal and Northern	4360	21 (0.5)	0.64 (0.27–1.52)	0.81 (0.35–2.23)
Mpumalanga and KwaZulu Natal	1644	14 (0.9)	1.14 (0.46–2.84)	1.24 (0.50–3.53)
Eastern, North Cape and Free state	937	7 (0.8)	—	1.00
Hospital class				
Provincial	4441	31 (0.7)	1.62 (0.81–3.22)	1.41 (0.72–2.98)
Private	2542	11 (0.4)	—	1.00

Note: Crude and adjusted odds ratios (OR) were derived from logistic regression models.
Abbreviations: CI, confidence interval; HTLV, human T-lymphotropic virus.

based leukoreduced red blood cell products which has been shown to reduce transfusion transmission to 1% [23]. In the Vermeulen et al. publication, SANBS assumed an HTLV transfusion-transmitted efficiency of 10% and a clinical manifestation of 6%, estimating that unscreened blood would result in 3.55 clinical cases of transfusion-transmitted HTLV disease annually. There could therefore be a very small risk of transfusion transmission of HTLV to HIV-infected transfusion recipients occurring within South Africa [12]. Assessments of whether or not to test for a specific TTI are complex and nuanced, especially in a resource-constrained setting such as South Africa. The underlying and not insignificant HTLV prevalence from non-transfusion routes found in this study and no reported cases of TT-HTLV in the independent-haemovigilance programme in the past 10 years provides corroboration in the decision not to test donors for HTLV in South Africa at this time [24].

There are some limitations to this study. Patient race was not recorded on the request forms for blood transfusion recipients and could not be used in data analysis. Due to sample quality and sample volume 708 samples for HIV, 455 samples for HBV and 17 samples for HTLV could not be confirmed using the Roche assays, although we did impute these data. The lack of statistical significance for the association of HTLV with demographic variables is probably due to the small number of HTLV-positive samples in this study. Finally, we only included three TTI in the study and specifically did not study the hepatitis C virus, which comparatively has a low prevalence in South African donors [25].

In conclusion, this study provides estimates of HIV, HBV and HTLV prevalence in hospitalized transfusion recipients and offers useful public health information for understanding the burden on the health and/or social care system. It also provides data for determining blood donor screening strategies for other viral infections and for patient blood management. Finally, it confirms that HTLV is endemic at a low prevalence in South Africa.

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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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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Use of preoperative erythropoietin-stimulating agents is associated with decreased thrombotic adverse events compared to red blood cell transfusion in surgical patients with anaemia

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Abstract

Background and Objectives: Preoperative red blood cell (RBC) transfusions increase post-operative venous thromboembolic (VTE) events. Erythropoietin-stimulating agents (ESAs) increase VTE risk in cancer patients; we aimed to assess ESA versus RBC-associated VTE risks in a broad population of surgical patients.

Materials and Methods: We queried TriNetX Diamond Network from 2006 to 2023, comparing patients with anaemia within 3 months preoperatively who received preoperative ESAs with or without intravenous (IV) iron to patients who received preoperative RBCs. Sub-analyses included (1) all surgeries and (2) cardiovascular surgeries. We propensity score matched for demographics, comorbidities, medical services, post-treatment haemoglobin (g/dL) and, for all-surgery comparisons, surgery type. Outcomes included 30-day post-operative mortality, VTE, pulmonary embolism (PE), disseminated intravascular coagulation (DIC) and haemoglobin.

Results: In our 19,548-patient cohorts, compared with preoperative RBC transfusion, ESAs without IV iron were associated with lower mortality (relative risk [RR] = 0.51 [95% confidence interval (CI), 0.45–0.59]), VTE (RR = 0.57 [0.50–0.65]) and PE (RR = 0.67 [0.54–0.84]). Post-operative haemoglobin was higher in the ESA without IV iron cohort compared with the transfusion cohort (10.0 ± 1.4 vs. 9.4 ± 1.8 g/dL, $p = 0.002$). Cardiac surgical patients receiving ESAs with or without IV iron had lower risk for post-operative mortality, VTE and PE ($p < 0.001$) than those receiving RBCs. Post-operative haemoglobin differed between patients receiving ESAs with IV iron versus RBCs (10.1 ± 1.5 vs. 9.4 ± 1.9 g/dL, $p = 0.0009$).

Conclusion: Compared with surgical patients who were transfused RBCs, ESA recipients had reduced 30-day post-operative risk of mortality, VTE, PE and DIC and increased haemoglobin levels. IV iron given with ESAs improved mortality.

Keywords

blood transfusion, cardiac surgery, perioperative transfusion, plasma, thromboembolism

Highlights

- In the preoperative period, erythropoietin-stimulating agents (ESAs) given without iron supplementation reduced the risks of post-operative mortality, venous thromboembolism, pulmonary embolism and disseminated intravascular coagulation as compared with red blood cell transfusions.
- Adding intravenous iron supplementation to ESAs has a significantly lower risk of mortality as compared with giving these agents without iron.
- There is a need for larger randomized studies investigating the safety and efficacy of ESAs, with and without iron, for managing preoperative anaemia.

INTRODUCTION

Hospitalized and surgical patients are at increased risk for venous thromboembolic (VTE) events, one of the most common and impactful causes of preventable healthcare costs, morbidity and mortality [1–3]. Risk factors for VTE events include malignancy, immobility, changes to blood flow and endothelial injury, which is summarized with the classic Virchow's triad model [4]. Increasing evidence has demonstrated that perioperative red blood cell (RBC) transfusions increase the risk for VTE events [5–9]. Consequently, patients undergoing surgical procedures may require special management to reduce morbidity and mortality from VTE events.

Given the increased VTE risk with perioperative RBC transfusions, previous studies have investigated methods to increase patient haemoglobin using alternative treatments such as iron supplementation and erythropoietin-stimulating agents (ESAs) [10]; however, both treatment modalities have risks and benefits that should be weighed carefully. Prior studies in patients with cancer and chronic kidney disease (CKD) indicated that ESAs, while able to increase haemoglobin concentrations, subjected patients with cancer to increased risk of VTEs among other morbid events [11–15].

Although ESA use for patients with cancer and CKD has shown evidence of increased risk for VTE events [16, 17], there is less evidence specific to the broader surgical patient population. A 2020 meta-analysis examining the use of ESAs plus iron supplementation versus controls of placebo or only iron in patients undergoing non-cardiac surgery indicated positive outcomes for patients given ESAs [18]. They demonstrated reduction in the need for transfusions and non-inferiority in terms of combined adverse patient outcomes, which included VTE. While this is encouraging, VTE-specific data were not analysed. Furthermore, this study did not examine the full breadth of surgical patients, instead focusing on orthopaedic, gastrointestinal and gynaecological procedures. Thus, the true effect of ESAs on VTE-specific risk in this patient population and in those undergoing other procedures, especially cardiac, is unknown.

The purpose of this study was to investigate the risk of VTE events in surgical patients treated with ESAs with or without additional intravenous (IV) iron supplementation compared to surgical patients receiving RBC transfusions. By investigating these populations and potential adverse outcomes, it may be possible to reduce healthcare costs and the substantial morbidity and mortality associated with VTE as a preventable perioperative adverse outcome.

MATERIALS AND METHODS

We conducted a retrospective cohort analysis utilizing the TriNetX Diamond Network (Cambridge, MA, USA), a cloud-based platform which includes electronic medical records as well as medical and pharmaceutical claims for over 213 million patients. The database includes regular and extensive data quality assessments, rejecting records that do not meet TriNetX's quality standards. We queried the network from January 1, 2019, to December 31, 2023, and study data were collected and analysed as of May 2024. Data regarding demographics, diagnoses from *International Classification of Diseases* (ICD-9, ICD-10) codes, medications from RxNorm codes and procedures from Current Procedural Terminology (CPT) codes were used for analysis.

TriNetX adheres to the Health Insurance Portability and Accountability Act (HIPAA), and the data de-identification process is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. Only aggregate patient counts are provided to protect patient health information. Because this study did not use individually identifiable data, it was exempt from the Institutional Review Board. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Cohorts and outcome measures

We compared surgical patients aged ≥18 years diagnosed with anaemia (ICD-10-CM D50-53, D55-59, D60, D61, D63 and D64) within 3 months to 1 day preoperatively who received preoperative ESA (RxNorm 105694, 283838) with or without IV iron (VA TN410) but not RBC transfusion (ICD-10-PCS 30233P0-1, 30233N0-1, HCPCS P9057, P9021-2, P9038-40, P9016) with patients who received preoperative RBC transfusion but not ESAs (Figure 1). We conducted sub-analyses by surgical type: (1) all surgeries (CPT 1003143) and (2) cardiovascular surgeries (CPT 1006056). We conducted subgroup analyses for all surgical and cardiovascular surgical patients who

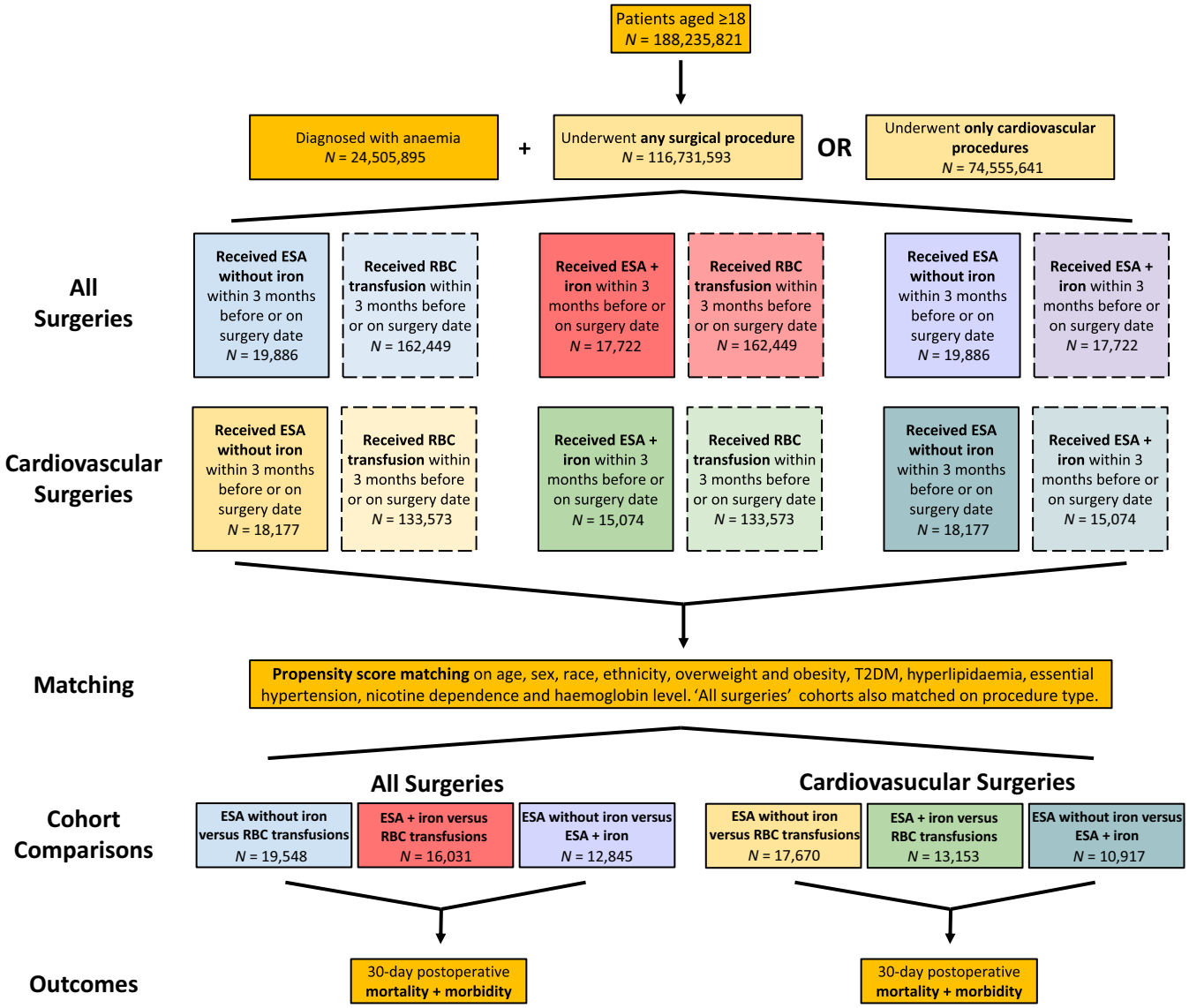

FIGURE 1 Cohort construction. ESA, erythropoietin-stimulating agents; RBC, red blood cells; T2DM, type-2 diabetes mellitus.

received ESAs without IV iron versus RBC transfusion within 1 month of surgery.

Outcomes included 30-day post-operative mortality, VTE (ICD-10-CM I80, I81, I82.0, I82.1, I82.2, I82.3, I82.4, I82.6, I82.8, I82.9, I82.A, I82.B, I82.C, O08.2, O22.3, O22.5, O87.1 and O88.2), pulmonary embolism (PE) (I26), disseminated intravascular coagulation (DIC) (D65) and haemoglobin measured within 30 days post-operatively (Table S1).

Statistical analysis

A 1:1 propensity score matching was performed using greedy nearest-neighbour matching algorithms with a calliper width of 0.1 pooled standard deviations to account for confounding variables. All row orders were randomized to eliminate bias from nearest neighbour algorithms. Standardized mean differences were used to assess balance. We propensity score matched for patient characteristics at surgery, overweight and obesity (ICD E66), type 2 diabetes (E11), hyperlipidaemia (E78), essential hypertension (I10), ischaemic heart diseases (I20–I25), neoplasms (C00–D49), nicotine dependence (F17), outpatient (CPT 1013626) and inpatient (1013659) services, CKD (N18), history of coagulation disorders (Z86.2, D68), hypothyroidism (E03), prior PE (I26) or VTE (I82), pregnancy and obstetrics (1, O00–O9A), inflammatory polyarthropathies (M05–M14), non-infective enteritis and colitis (K50-K52) and post-treatment haemoglobin (9014, g/dL) levels <7, 7–12 and >12 to account for anaemia severity. Additionally, we matched on medication use including anticoagulants (VA BL110), long-term use of anticoagulants (ICD Z79.0), platelet aggregation inhibitors including aspirin (VA BL117) and antihaemorrhagics (BL116). We propensity score matched for surgery type for comparisons of all surgical patients and for cardiovascular surgery type in our comparisons of cardiovascular cohorts. Please refer to Table S2 for all codes used in propensity score matching. Cohorts were compared using relative risks (RR) and 95% confidence intervals (CI). For continuous data, we conducted analyses using independent *t*-

TABLE 1 Post-matching demographics of all cohorts.

	Surgical patients (ESA without IV iron vs. RBC)			Surgical patients (ESA + IV iron vs. RBC)			Surgical patients (ESA without IV iron vs. ESA + IV iron)		
Demographics	**ESA**	**RBC**	**SMD**	**ESA + IV iron**	**RBC**	**SMD**	**ESA**	**ESA + IV iron**	**SMD**
Patients (*n*)	19,548	19,548	—	16,031	16,031	—	12,845	12,845	—
Age (years ± SD)	68.7 ± 12.4	69.0 ± 12.5	0.02	66.5 ± 12.9	67.3 ± 13.0	0.06	67.3 ± 13.0	67.3 ± 12.5	0.001
Female	55.33%	54.01%	0.03	47.40%	46.35%	0.02	50.73%	50.32%	0.008
Black or African American	7.99%	7.90%	0.003	8.52%	8.65%	0.004	8.55%	8.66%	0.004
American Indian or Alaska Native	0.00%	0.00%	—	0.00%	0.00%	—	0.00%	0.00%	—
Asian	0.65%	0.60%	0.005	0.55%	0.53%	0.003	0.61%	0.62%	0.001
Native Hawaiian or other Pacific Islander	0.00%	0.00%	—	0.00%	0.00%	—	0.00%	0.00%	—
White	20.38%	20.86%	0.01	19.43%	19.40%	0.0006	20.39%	19.94%	0.01
Unknown race	0.00%	0.00%	—	0.00%	0.00%	—	0.00%	0.00%	—
Hispanic or Latino	3.51%	3.37%	0.008	3.97%	3.79%	0.009	3.99%	3.81%	0.009
Not Hispanic or Latino	29.10%	29.23%	0.003	28.56%	28.74%	0.004	29.67%	29.10%	0.01
Unknown ethnicity	67.38%	67.40%	0.0004	67.48%	67.46%	0.0003	66.35%	67.09%	0.02
	Cardiovascular surgical patients (ESA without IV iron vs. RBC)			**Cardiovascular surgical patients (ESA + IV iron vs. RBC)**			**Cardiovascular surgical patients (ESA + IV iron vs. ESA)**		
	ESA	**RBC**	**SMD**	**ESA + IV iron**	**RBC**	**SMD**	**ESA**	**ESA + IV iron**	**SMD**
Patients (*n*)	17,670	17,670	—	13,153	13,153	—	10,917	10,917	—
Age (years ± SD)	68.7 ± 12.5	69.0 ± 12.3	0.03	66.6 ± 12.9	67.5 ± 12.7	0.08	67.2 ± 13.2	67.2 ± 12.7	0.006
Female	55.56%	53.98%	0.03	48.09%	46.34%	0.04	50.95%	50.55%	0.008
Black or African American	8.00%	8.28%	0.01	8.49%	8.67%	0.006	8.69%	8.85%	0.006
American Indian or Alaska Native	0.00%	0.00%	—	0.00%	0.00%	—	0.00%	0.00%	—
Asian	0.64%	0.62%	0.002	0.62%	0.64%	0.002	0.70%	0.65%	0.006
Native Hawaiian or other Pacific Islander	0.00%	0.00%	—	0.00%	0.00%	—	0.00%	0.00%	—
White	20.41%	20.80%	0.01	19.67%	19.59%	0.002	20.13%	19.72%	0.01
Unknown race	0.00%	0.00%	—	0.00%	0.00%	—	0.00%	0.00%	—
Hispanic or Latino	3.51%	3.55%	0.002	4.05%	3.75%	0.02	4.07%	4.07%	<0.0001
Not Hispanic or Latino	28.92%	29.81%	0.02	28.67%	29.18%	0.01	29.49%	29.16%	0.007
Unknown ethnicity	67.57%	66.63%	0.02	67.29%	67.07%	0.005	66.45%	66.78%	0.007

Note: Em dash denotes places where a SMD was not or could not be calculated, such as for sample size or between two patient counts of 0.
Abbreviations: ESA, erythropoietin-stimulating agents; IV, intravenous; RBC, red blood cell; SD, standard deviation; SMD, standardized mean difference.

tests. Statistical significance was defined as a two-sided alpha of less than 0.05.

RESULTS

All surgical patients: ESA without IV iron versus RBC

Before matching, there were 19,886 surgical patients with preoperative anaemia who were treated with preoperative ESAs without IV iron but not RBC transfusion and 162,449 surgical patients with preoperative anaemia who were treated with preoperative RBC transfusion but not ESAs; please see Table S3 for pre-matching demographics. After matching, the 19,548-patient cohorts were similar in characteristics; please see Table 1 for post-matching demographics. Pre- and post-matching comorbidities are illustrated in Table S4 and procedure distributions are illustrated in Table S5. When compared with preoperative RBC transfusion, preoperative ESAs without IV iron were associated with lower 30-day post-operative risk of mortality (1.59% vs. 3.11%, RR = 0.51 [95% CI, 0.45–0.59]), VTE (1.67% vs. 2.94%, RR = 0.57 [0.50–0.65]) and PE (0.66% vs. 0.97%, RR = 0.67 [0.54–0.84]) (Table 2 and Figure 2). There was no

TABLE 2 Effect of ESA with or without IV iron versus RBC given within 3 months before surgery on 30-day post-operative outcomes after matching.

Event or haemoglobin level	Surgical patients (ESA without IV iron vs. RBC)				Surgical patients (ESA + IV iron vs. RBC)				Surgical patients (ESA without IV iron vs. ESA + IV iron)			
	ESA	RBC	RR [95% CI]	*p*-Value	ESA + IV iron	RBC	RR [95% CI]	*p*-Value	ESA	ESA + IV iron	RR [95% CI]	*p*-Value
Mortality (%)	1.59%	3.11%	0.51 [0.45–0.59]	<0.0001	1.44%	2.86%	0.50 [0.43–0.59]	<0.0001	1.52%	1.39%	1.09 [0.89–1.33]	0.40
VTE (%)	1.67%	2.94%	0.57 [0.50–0.65]	<0.0001	1.97%	3.06%	0.65 [0.56–0.74]	<0.0001	1.74%	1.85%	0.94 [0.79–1.13]	0.51
PE (%)	0.66%	0.97%	0.67 [0.54–0.84]	<0.0001	0.57%	0.97%	0.59 [0.45–0.76]	<0.0001	0.59%	0.56%	1.06 [0.77–1.46]	0.74
DIC (%)	0.05%	0.07%	0.71 [0.32–1.61]	0.41	0.06%	0.07%	0.91 [0.39–2.14]	0.83	0.08%	0.08%	1.00 [0.42–2.40]	1.00
Haemoglobin level[a]	10.0 ± 1.4	9.4 ± 1.8	—	0.002	10.5 ± 1.3	9.6 ± 1.7	—	0.001	10.0 ± 1.5	10.4 ± 1.4	—	0.12
	Cardiovascular surgical patients (ESA without IV iron vs. RBC)				**Cardiovascular surgical patients (ESA + IV iron vs. RBC)**				**Cardiovascular surgical patients (ESA without IV iron vs. ESA + IV iron)**			
	ESA	RBC	RR [95% CI]	*p*-Value	ESA + IV iron	RBC	RR [95% CI]	*p*-Value	ESA	ESA + IV iron	RR [95% CI]	*p*-Value
Mortality (%)	1.61%	3.28%	0.49 [0.43–0.57]	<0.0001	1.51%	3.06%	0.49 [0.42–0.58]	<0.0001	1.54%	1.46%	1.06 [0.85–1.31]	0.62
VTE (%)	1.62%	3.13%	0.52 [0.45–0.60]	<0.0001	1.99%	3.02%	0.66 [0.57–0.77]	<0.0001	1.58%	1.90%	0.83 [0.68–1.02]	0.07
PE (%)	0.67%	1.01%	0.66 [0.52–0.83]	0.0004	0.55%	0.95%	0.58 [0.43–0.77]	0.0002	0.68%	0.56%	1.21 [0.87–1.70]	0.26
DIC (%)	0.06%	0.10%	0.59 [0.27–1.28]	0.18	0.08%	0.08%	0.91 [0.39–2.14]	0.83	0.09%	0.09%	1.00 [0.42–2.40]	1.00
Haemoglobin level	10.1 ± 1.5	9.4 ± 1.9	—	0.0009	10.4 ± 1.4	9.5 ± 1.7	—	0.004	10.2 ± 1.5	10.4 ± 1.4	—	0.37

Abbreviations: CI, confidence interval; DIC, disseminated intravascular coagulation; ESA, erythropoietin-stimulating agents; IV, intravenous; PE, pulmonary embolism; RBC, red blood cells; RR, relative risk; VTE, venous thromboembolism.

[a]*T*-test of mean post-operative haemoglobin level (g/dL), values outputted as mean haemoglobin (g/dL) ± standard deviation.

difference in the rate of DIC (0.05% vs. 0.07%, RR = 0.71 [0.32–1.61]). Mean post-operative haemoglobin level was similar between those who received ESAs and those who received RBCs (10.1 ± 1.4 vs. 9.4 ± 1.8 g/dL, $p = 0.002$).

After matching, there were 16,731 patients in the subgroup treated within 1 month of surgery (Table S7). There were similar risks for mortality, VTE and PE to the 3-month treatment group (Table 3). The 1-month ESA without iron subgroup had a lower risk for DIC (0.06% vs. 0.14%, RR = 0.44 [0.21–0.91]) and no difference in haemoglobin level (10.0 ± 1.5 vs. 9.6 ± 1.8 g/dL, $p = 0.81$) compared with RBC transfusions.

All surgical patients: ESA with IV iron versus RBC

These trends persisted when comparing preoperative ESAs with IV iron administration against preoperative RBC transfusion. After matching, 16,031 patients were in each cohort (Table 1). Compared with those receiving RBC transfusions, patients receiving ESAs with IV iron had lower risk of 30-day post-operative mortality (1.44% vs. 2.86%, RR = 0.50 [0.43–0.59]), VTE (1.97% vs. 3.06%, RR = 0.65 [0.56–0.74]), PE (0.57% vs. 0.97%, RR = 0.59 [0.45–0.76]) and had a higher post-operative haemoglobin (10.5 ± 1.6 vs. 9.9 ± 1.7 g/dL, $p < 0.0001$) (Table 2, Figure 2). Those treated with ESAs with IV iron

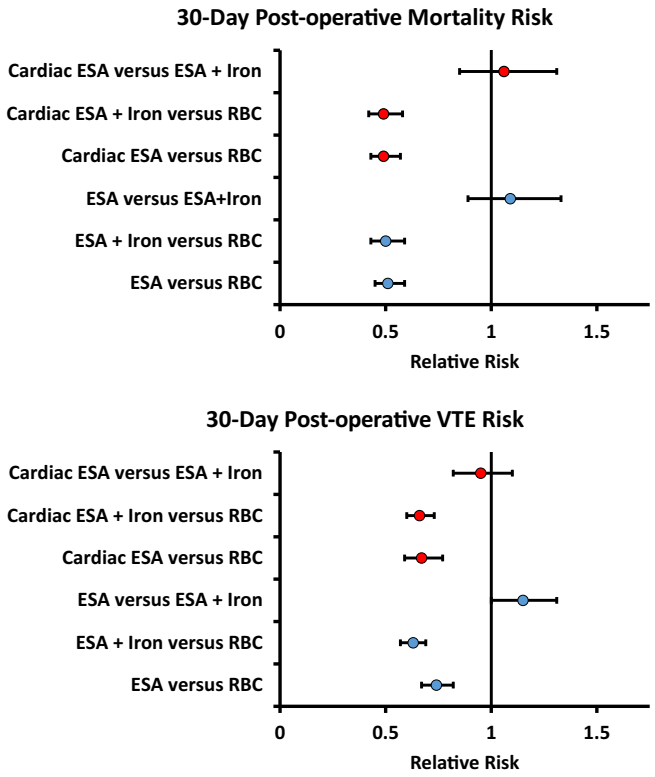

FIGURE 2 Forest plots of 30-day post-operative (a) mortality and (b) venous thromboembolic (VTE) risks associated with erythropoietin-stimulating agents (ESA), ESA with intravenous (IV) iron and red blood cell (RBC) transfusion treatments for all-combined surgery and cardiovascular surgery cohorts.

had no difference in risk of DIC (0.06% vs. 0.07%, RR = 0.91 [0.39–2.14]).

All surgical patients: ESA without IV iron versus ESA with IV iron

After matching, there were 12,845 patients in both treatment groups (Table 1). When comparing ESAs without IV iron to ESAs with IV iron, there was no significant difference in mortality (1.52% vs. 1.39%, RR = 1.09 [0.89–1.33]), VTE (1.74% vs. 1.85%, RR = 0.94 [0.79–1.13]), PE (0.59% vs. 0.56%, RR = 1.06 [0.77–1.46]), DIC (0.08% vs. 0.08%, RR = 1.00 [0.42–2.40]) or post-operative haemoglobin (10.0 ± 1.5 vs. 10.4 ± 1.4 g/dL, $p = 0.12$); (Table 2 and Figure 2).

Cardiovascular surgical patients: ESA Without IV iron versus RBC

We next examined cardiovascular surgical patients. After matching, 17,670 cardiovascular surgical patients received preoperative ESAs but not RBC transfusions and 17,670 patients received RBC transfusions but not ESAs (Table S3 for pre-matching demographics, Table 1 for post-matching demographics, Table S4 for pre- and post-matching comorbidities and Table S6 for pre- and post-matching procedures). Cardiovascular surgical patients receiving ESAs were at lower 30-day post-operative risk of mortality (1.61% vs. 3.28%, RR = 0.49 [0.43–0.57]), VTE (1.62% vs. 3.13%, RR = 0.52 [0.45–0.60]), PE (0.67% vs. 1.01%, RR = 0.66 [0.52–0.83]) and had a higher haemoglobin level (10.1 ± 1.5 vs. 9.4 ± 1.9 g/dL, $p = 0.0009$) (Table 2 and Figure 2). There was no significant difference in post-operative DIC (0.06% vs. 0.10%, RR = 0.59 [0.27–1.28]).

After matching, there were 17,670 patients in the subgroup treated within 1 month of surgery (Table S7). The subgroup of patients treated within 1 month of surgery had similar risks as the 3-month group for all outcomes (Table 3).

Cardiovascular surgical patients: ESA with IV iron versus RBC

After matching, 13,153 cardiovascular surgical patients received ESAs and IV iron administration but not RBC transfusion, and 13,153 cardiovascular surgical patients received RBCs but not ESAs (Table 1). Compared with preoperative RBC transfusions, ESAs and IV iron were associated with decreased risk of 30-day post-operative mortality (1.51% vs. 3.06%, RR = 0.49 [0.42–0.58]), VTE (1.99% vs. 3.02%, RR = 0.66 [0.57–0.77]), PE (0.55% vs. 0.95%, RR = 0.58 [0.43–0.77]), DIC (0.08% vs. 0.08%, RR = 0.91 [0.39–2.14]) and increased post-operative haemoglobin (10.4 ± 1.4 vs. 9.5 ± 1.7 g/dL, $p = 0.004$) (Table 2 and Figure 2).

Cardiovascular surgical patients: ESA without IV iron versus ESA with IV iron

There were 10,917 cardiovascular surgical patients who received ESAs and 10,917 cardiovascular surgical patients who received ESAs with IV iron after matching. There was no difference in 30-day mortality (1.54% vs. 1.46%, RR = 1.06 [0.85–1.31]), VTE (1.58% vs. 1.90%, RR = 0.83 [0.68–1.02]), PE (0.68% vs. 0.56%, RR = 1.21 [0.87–1.70]), DIC (0.09% vs. 0.09%, RR = 1.00 [0.42–2.40]) or haemoglobin level (10.2 ± 1.5 vs. 10.4 ± 1.4 g/dL, $p = 0.37$) between groups (Table 2 and Figure 2).

DISCUSSION

From a large retrospective database, patients with a diagnosis of anaemia within 3 months before surgery that were propensity matched and showed treatment with preoperative ESAs, with or without IV iron, was associated with lower 30-day mortality, VTE and PE, compared with patients transfused with RBCs. This finding was consistent among all surgical patient cohort and cardiovascular surgical cohorts as well.

Anaemia is prevalent with observational study estimates varying between 16% and 52% of cardiac surgical patients cohort meeting the World Health Organization (WHO) definition of anaemia [19–21].

TABLE 3 Subgroup analysis on the effect of ESA without IV iron versus RBC given within 1 month before surgery on 30-day post-operative outcomes after matching.

	All surgical patients				Cardiovascular surgical patients			
Event or haemoglobin level	ESA	RBC	RR [95% CI]	*p*-Value	ESA + IV iron	RBC	RR [95% CI]	*p*-Value
Mortality (%)	1.66%	3.60%	0.46 [0.40–0.53]	<0.0001	1.61%	3.35%	0.48 [0.42–0.55]	<0.0001
VTE (%)	1.74%	3.19%	0.55 [0.47–0.63]	<0.0001	1.62%	3.19%	0.51 [0.44–0.59]	<0.0001
PE (%)	0.70%	1.00%	0.70 [0.55–0.88]	0.002	0.67%	1.04%	0.64 [0.51–0.81]	<0.0001
DIC (%)	0.06%	0.14%	0.44 [0.21–0.91]	0.02	0.06%	0.10%	0.59 [0.27–1.28]	0.18
Haemoglobin level[a]	10.0 ± 1.5	9.6 ± 1.8	—	0.06	10.1 ± 1.5	9.6 ± 1.8	—	0.01

Abbreviations: CI, confidence interval; DIC, disseminated intravascular coagulation; ESA, erythropoietin-stimulating agents; IV, intravenous; PE, pulmonary embolism; RBC, red blood cells; RR, relative risk; VTE, venous thromboembolism.

[a]*T*-test of mean post-operative haemoglobin level (g/dL), values outputted as mean haemoglobin (g/dL) ± standard deviation.

Preoperative anaemia is a modifiable risk factor that is associated with worse outcomes in non-cardiac and cardiac surgeries [22–25]. This elevated risk in those with preoperative anaemia is still present even when adjusting for transfusions [22]. Anaemic patients are indeed more likely to be transfused which is associated with significantly worse mortality, morbidity and overall healthcare costs [22].

ESAs have been used successfully to treat patients with preoperative anaemia before surgery. Since the institution of the Food and Drug Administration's black box warning on ESAs for potential association with VTEs [26], they have not been used as often for preoperative anaemia management, except for bloodless medicine patients or those with haematological disorders. However, a recent meta-analysis in 28 trials in non-cardiac and cardiac surgeries found ESAs were not associated with an increased incidence of thromboembolic events (RR = 1.02 [95% CI, 0.78–1.33], $p = 0.68$) [27].

RBC transfusions have been shown to be associated with VTEs in large studies. The proposed mechanism could be due to decreased cell membrane deformability and increased endothelial adherence that occurs with the storage of red cells [28]. In this large, multi-centre study, we found patients treated with ESAs had lower rates of VTE compared with those treated with RBC transfusions. Additionally, there were higher 30-day post-operative mortality rates in those treated with RBC transfusions compared to those treated with ESAs.

In several studies, patients with cancer-induced anaemia were shown to have a higher risk of experiencing a VTE while being treated with ESAs [29]. In a meta-analysis of 44 randomized controlled trials and 13,196 patients with chemotherapy-induced anaemia, the risk of VTE was greater in those treated with ESAs (odds ratio [OR] = 1.48 [95% CI, 1.28–1.72]; $I^2 = 0.00\%$) [30]. In the subgroup analysis of 18 chemotherapy studies with long-term follow-up, there continued to be an elevated risk for VTE in patients treated with ESAs compared with controls ($n = 6498$; OR = 1.47 [95% CI, 1.24–1.74]; $I^2 = 0.00\%$). However, there was no effect of ESAs on mortality or disease advancement.

A proposed mechanism behind VTEs in chemotherapy-induced anaemia patients treated with ESAs may be due to iron-restricted erythropoiesis and could be alleviated by IV iron administration. In one study, the authors hypothesized that VTEs associated with those managed with ESAs could be affected by thrombocytosis resulting from ESA-induced iron-restricted erythropoiesis [31]. ESAs rely on iron stores in the bone marrow for erythropoiesis; however, if there is relative iron deficiency, iron-restricted erythropoiesis occurs reducing effectiveness. Absolute iron deficiency is also associated with thrombocytosis. Henry et al. examined 187 chemotherapy-induced anaemia patients that were treated with erythropoietin and IV ferric gluconate, oral ferrous sulphate or no iron. Patients with thrombocytosis >350,000 cells/μL were three times more likely to develop a VTE (OR = 2.90, $p = 0.036$) and had a four times greater incidence of VTE (RR = 4.40, $p = 0.13$, Poisson regression). Patients treated with iron had much less relative risk of thrombocytosis (RR = 0.70, $p = 0.013$) and decreased incidence of VTE.

Our study also found anaemic surgical patients treated with ESAs with iron had a lower risk of 30-day mortality compared with those who had a transfusion. The risk of post-operative mortality associated with intraoperative transfusions has been well established. LaPar et al. analysed 33,411 cardiac surgical patients from 9 centres who had primary, isolated coronary artery bypass graft (CABG) surgery [22]. They found that patients exposed to a transfusion had a much greater associated risk of mortality (OR = 4.3, $p < 0.001$), even after risk-adjustment, compared with haematocrit level alone. Similarly, Glance et al. examined 10,100 patients undergoing general, vascular or orthopaedic surgery in a retrospective cohort study and showed intraoperative blood transfusion was associated with increased risk of death (OR = 1.29 [95% CI, 1.03–1.62]) [32].

In our current much larger study of 16,031 patients in the surgical cohort and 13,153 patients in the cardiac surgical cohort, we found that there was no difference in terms of mortality, VTEs, PEs or DIC between those treated with ESAs with iron and ESAs without iron. Further study is needed to understand how iron treatment with ESAs impacts post-operative outcomes and whether some categories of anaemia, such as iron deficiency anaemia, have greater benefit.

As with many observational studies, we describe associations in those with preoperative anaemia treated with ESAs with and without iron and VTE risk compared with preoperative RBC transfusions. This does not imply causation. A significant limitation of this study is the inability to account for number of RBC units transfused, which may

impact the risk for VTE and other outcomes. We lacked information on transfusion decision making, for example, haemoglobin transfusion thresholds; patients receiving RBC transfusions may be in more critical condition. However, we tried to adjust for patient status through matching by haemoglobin levels and relevant comorbidities. It is also limited by its dependence on ICD-10 coding and the accuracy of coding. We matched on multiple criteria, however, there may be confounding variables that were unaccounted for.

In conclusion, this large database study of surgical patients with anaemia treated with ESAs with and without iron preoperatively compared with those treated with RBC transfusions showed that when compared with RBC transfusions, ESAs were associated with a lower relative risk of 30-day post-operative mortality and VTEs. Larger randomized studies should be conducted to investigate the safety and efficacy of ESAs for preoperative anaemia management and for which population they are best suited.

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U.E.C. conducted data analysis; U.E.C., R.C.N. and N.B.H. drafted the manuscript; U.E.C., R.C.N., S.M.F., S.C., B.C.C., J.S.L., L.C.L. and N.B.H. provided significant edits to the manuscript.

CONFLICT OF INTEREST STATEMENT

S.M.F. is on the scientific advisory board for Haemonetics. N.B.H. has been on the scientific advisory board of Octapharma, USA and receives author royalties from Wolters Kluwer for contributions to uptodate.com. B.C.C. is a speaker for Haemonetics.

DATA AVAILABILITY STATEMENT

All data are publicly available on the TriNetX website (https://trinetx.com/).

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SUPPORTING INFORMATION

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

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ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

A comprehensive approach to continuous quality improvement of massive transfusion by developing key performance indicators

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Abstract

Background and Objectives: To develop key performance indicators (KPI) for use in quality assessment of our institutional goal-directed massive transfusion (GDMT).

Materials and Methods: A team comprising our transfusion and emergency medicine departments carried out a cross-sectional data analysis of GDMT in adult patients from January 2021 to December 2022. The study was rooted in the Define, Measure, Analyse, Improve, Control (DMAIC) approach. Features of KPIs were (a) importance, (b) scientific soundness and (c) feasibility. Study parameters were defined and analysed using measures of central tendencies and benchmark comparison.

Results: Ninety-two massive transfusion events occurred and 1405 blood components were used. Trauma was the leading cause, followed by postpartum haemorrhage and upper gastrointestinal bleeding. Appropriate GDMT activation was observed only in 43.47% of events. The turnaround time (TAT) was within the benchmark in 85.8% of events with an average of 16 ± 10 min. The average utilization of blood components was 20.5 (interquartile range [IQR] = 11.3) in the appropriate group and 5.5 (IQR = 4.25) in the inappropriate group with a wastage rate of 3.5%. Duration of activation was 6.19 ± 4.59 h, and the adherence to thromboelastography was 66.3%. Overall mortality was 45.65%, and the average duration of hospital stay was 6.1 ± 5.9 days.

Conclusion: The KPIs developed were easy to capture, and the analysis provided a comprehensive approach to the quality improvement of the GDMT protocol.

Keywords

blood transfusion, key performance indicators, major haemorrhage protocol, massive transfusion protocol, process improvement, quality indicators

Highlights

- This study was an honest attempt to develop key performance indicators (KPIs) for goal-directed massive transfusion in real-world scenarios.
- The KPIs developed were easy to capture while providing a comprehensive overview of massive transfusion.
- The need to improve the appropriate utilization of massive transfusion should be addressed in consultation with all the stakeholders and this study helped us to come up with innovative ideas, such as an 'Emergency Blood Request Form' and developing a massive transfusion audit team led by a transfusion safety officer.

INTRODUCTION

Major haemorrhage protocol (MHP) and/or massive transfusion protocols (MT) are designed for the efficient management of major bleeding resulting from conditions like trauma, major obstetric haemorrhage (MOH), upper gastrointestinal bleeding (UGIB) and aneurysm rupture [1–6]. Multiple definitions of massive transfusion in adults are available in literature: (a) more than 10 packed red blood cell (PRBC) units in 24 h, (b) more than 6 PRBC units in 6 h, (c) more than 5 PRBC units in 4 h and (d) more than4 blood products (PRBC and Plasma) in 30 min [7–10]. Institute-specific MHPs are implemented to manage patients with haemorrhagic shock, and they can either be a fixed ratio protocol (1:1:1 ratio of PRBC, plasma, and platelets or cryoprecipitate) or a goal-directed massive transfusion (GDMT). GDMTs tend to address the individual needs of the patients rather than following a 'one size fits all' approach in a fixed ratio MHP [11–17]. MHPs facilitate good communication and coordination between the departments, standard of practice, involvement of all stakeholders, ease of use, and improvement in patient care [18].

Our institute in southern India, with an average of 80,000–90,000 patient admissions annually, also has an academic Emergency Department and Transfusion medicine department, a dedicated quality management team, making this study unique, relevant and novel. The indications for MHP in our centre vary from trauma to gastrointestinal bleeding, from coagulopathy with complicated haemorrhage in snakebite to sepsis and from bleeding dyscrasias with haemorrhagic shock to obstetrical situations. We had switched from a formula-based MHP to GDMT in 2020. GDMT was implemented with the help of thromboelastography (TEG 5000, Haemonetics, USA) in Transfusion Medicine and a Stat laboratory in Emergency Medicine. Data from our centre showed that GDMT achieved a 17% reduction in blood component utilization, reduction in coagulopathies and improvement in patient survival [19]. Our institute pursues quality standards and is accredited by the National Accreditation Board for Hospitals and Healthcare Providers (NABH), the Quality Council of India (QCI) (https://nabh.co/nabh-standards/). Both the transfusion medicine and the emergency medicine departments have been accredited by NABH with the respective departmental accreditation standards as laid down by NABH, QCI. We have developed 13 quality indicators (QI) and benchmarks in our blood centre as per NABH standards. Universally acceptable QI and benchmarks in MHP might be difficult to develop because of the diverse nature of MHP practice [20, 21]. However, process excellence is an integral part of transfusion medicine, which directly and indirectly improves the quality of patient care [22]. Data pertaining to such parameters in a level-1 trauma centre in India are sporadic and sparse. This study was done to develop key performance indicators (KPI) and identify the areas in our institutional GDMT that need continuous process improvement.

METHODS

This was a cross-sectional data analysis from January 2021 to December 2022. The study was carried out after obtaining clearance from the Institute Ethics Committee (IEC number: 484/2023). Our institute practices a GDMT protocol (Table 1) implemented in 2020. The TEG-based management was adopted from the manufacturer's instructions, a normal reference range developed in our centre and from published literature [12, 17, 23, 24].

The study included all events of MHP activations in adult patients, and data were captured from the massive transfusion register in the Department of Transfusion Medicine. The data were entered into MS Excel; analysis used SPSS. Categorical variables were expressed as percentages and continuous variables as mean and standard deviation (SD). A chi-square test was done to find out the association between categorical variables, and an independent '*t*-test' for continuous variables.

Key performance indicators

KPIs were developed based on three principles: (1) contextual importance, (2) scientific soundness and (3) feasibility [25]. A multidisciplinary team of transfusion medicine specialists, emergency medicine specialists, and a quality management team was formed to identify the KPIs that can be utilized in our practice. The conceptualisation as well as creation of process improvement tools were adopted from the DMAIC (Define, Measure, Analyse, Improve and Control) (Six Sigma) approach by this team (Table 2). These KPIs were developed to capture the critical elements of the MHP and improve the areas that were not up to the standards. The areas were categorized into three

TABLE 1 Goal-directed bleeding management (GDMT) protocol.

GDMT				Investigation 1-ABG, CBC, PT, aPTT, rapid TEG, blood grouping, crossmatching
Pack 1-immediate spin crossmatch compatible				
2 O-neg. PRBC and 2 AB FFP or ABO compatible PRBC/FFP				
Based on Investigation 1				
Hb-low	Hb-low	Hb-low	Hb-low	
Platelet-N	Platelet-low	Platelet-N	Platelet-low	
Coagulation screen-N	Coagulation screen-N	Coagulopathy-present	Coagulopathy-present	
Pack 2A	Pack 2B	Pack 2C	Pack 2D	
2 PRBCs and 2 FFPS	2 PRBCs, 2 FFPs, 4 RDPs/1 SDP	2 PRBC, 2FFPs, 10 cryoprecipitate	2 PRBCs, 2FFPs, 4 RDPs and 10 cryoprecipitate	Investigation 2-ABG, CBC, PT, aPTT, rapid TEG
Based on investigation 2				
Hb-low	Hb-low	Hb-low	Hb-low	
Platelet-N	Platelet-low	Platelet-N	Platelet-low	
Coagulation screen-N	Coagulation screen-N	Coagulopathy-present	Coagulopathy-present	
Pack 3A	Pack 3B	Pack 3C	Pack 3D	
2 PRBCs and 2 FFPs	2 PRBCs, 2 FFPs, 4 RDPs/1 SDP	2 PRBC, 2 FFPs, 10 cryoprecipitate	2 PRBCs, 2 FFPs, 4 RDPs and 10 cryoprecipitate	

Abbreviations: ABG, arterial blood gas; aPTT, activated partial thromboplastin time; CBC, complete blood count; FFP, fresh-frozen plasma; neg., negative; PRBC, packed red blood cell; PT, prothrombin time; RDP, random donor platelets; SDP, Single donor platelets (apheresis); TEG, thromboelastography.

TABLE 2 DMAIC approach involved in this process improvement.

Define	Defining/developing KPIs
Measurement	Capturing data on various KPIs identified
Analyse	Analysing the data captured and comparing it to the institutional benchmarks.
Improve	From the data analysed, identifying gap areas in MT and developing preventive strategies.
Control	Developing/updating benchmarks, periodical audits, real-time audits, transfusion safety officer

Abbreviations: DMAIC, Define, Measure, Analyse, Improve, Control; KPI, key performance indicators; MT, massive transfusion protocols.

integral parts of the GDMT: (a) documentation, (b) process and (c) output (Figure 1) [25].

Definitions of study parameters

According to departmental policy, the first set of blood components will be released after immediate-spin crossmatching at room temperature with patient serum and donor red blood cells in the column agglutination method. Once the immediate spin compatibility was established, two units of PRBC and fresh-frozen plasma (FFP) were released in a cool box. Subsequently, components would be released after a type and screen, followed by an immediate spin cross-match.

Appropriateness of MHP

1. Appropriateness A: Transfusion of four or more units of PRBCs within 4 h.
2. Appropriateness B: Transfusion of ten or more units of PRBCs within 24 h.
3. If any of the above criteria is fulfilled, it was considered an appropriate transfusion.

Turnaround time

1. Turnaround time (TAT) 1–time to issue: Time from activation to the issue of blood components.
2. TAT 2–Lab TAT: The time from the samples were received until the components were ready to be issued.
3. The benchmark TAT for emergency issue is 30 min.

Wastage rate

The number of unused and discarded blood components in relation to the number of components issued during massive transfusion. This excludes returned components that were accepted back to inventory (within 30 min of issue with appropriate cold temperature maintenance).

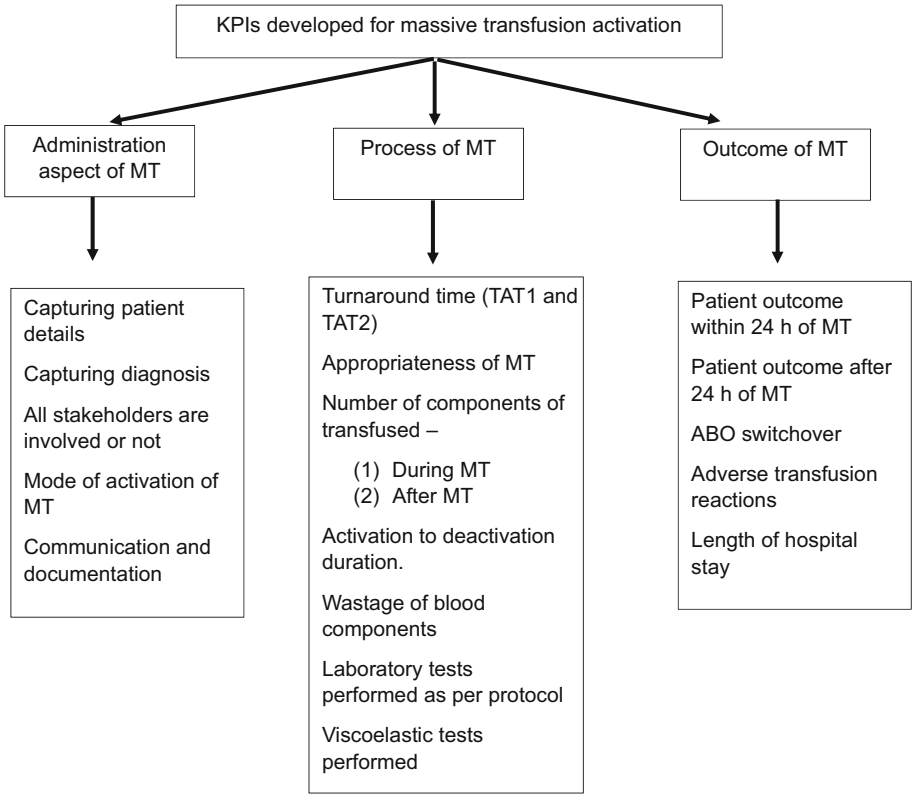

FIGURE 1 Developing the key performance indicators (KPIs) from the Massive transfusion process. MT, massive transfusion protocols; TAT, turnaround time.

ABO switchover

Defined as transfusing a patient with components of a different but compatible ABO group, usually due to a patient's particular need in the face of a lack of specific ABO group in the inventory.

Survival outcome

In-hospital death within 24 h of massive transfusion was captured as an early outcome. We assessed overall mortality as deaths from haemorrhagic shock and/or associated complications occurring during the current admission, irrespective of the time duration.

RESULTS

There were 92 events of GDMT activation in adult patients during the study period, and all of them were included for analysis. The median age among the study participants was 37 years, ranging from 25 to 53 years. The sex distribution was 70% men and 30% women, a ratio of approximately 2.3:1. The commonest causes were trauma ($n = 52$), obstetrical, UGIB with decompensated chronic liver disease (DCLD) followed by various other causes (Figure 2). The appropriateness of activation among various clinical conditions has been provided in

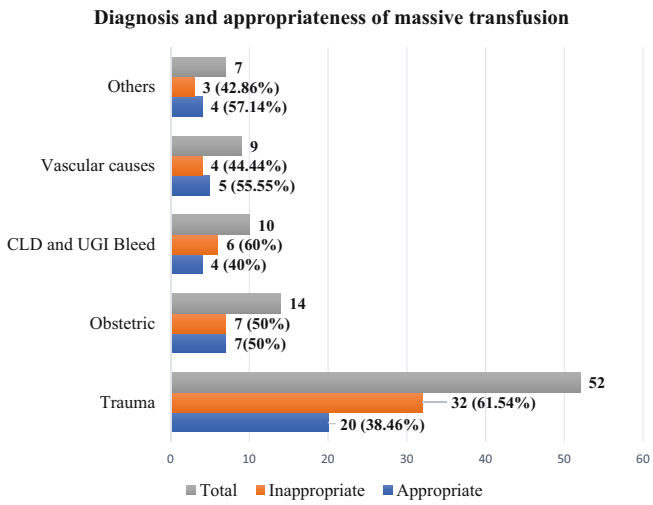

FIGURE 2 Diagnosis of patients who received a massive transfusion and the appropriateness of the activation. CLD, chronic liver disease, UGI, upper gastrointestinal.

Figure 2. All GDMT activations were by telephone. Patient details were captured in all the events, and all stakeholders were aware of the GDMT activation. The average TAT-1 was 16 ± 10 min, and TAT-2 was 13 ± 10 min. The TAT was outside the benchmark in

TABLE 3 Blood transfusion requirement comparison between appropriate and inappropriate massive transfusion activation.

Blood components		Appropriate activation ($n = 40$, 43.47%)	Inappropriate activation ($n = 52$, 56.52%)	p value
PRBC	Median (IQR)	6 (4.5)	3 (2.25)	<0.001
	Total	291	178	
FFP	Median (IQR)	4.5 (3.25)	2 (0)	<0.001
	Total	252	121	
RDP	Median (IQR)	5 (1.5)	3 (2)	0.002
	Total	226	33	
Cryoprecipitate	Median (IQR)	10 (2.5)	7 (8.25)	0.23
	Total	269	35	
Total components transfused	Median (IQR)	20.5 (11.3)	5 (4.25)	<0.001
	Total	1038	367	

Note: Data expressed in median (interquartile range [IQR]).
Abbreviations: FFP, fresh-frozen plasma; PRB, packed red blood cell concentrate; RDP, random donor platelets.

TABLE 4 Clinical outcome comparison based on the appropriateness of MT.

	Appropriate ($n = 40$)	Inappropriate ($n = 52$)	Overall ($n = 92$)
24-h mortality*	11 (27.5%)	24 (46.15%)	35 (38.04%)
Overall mortality*	14 (35%)	28 (53.84%)	42 (45.65%)
LOHS**	4.44 ± 3.90	6.83 ± 6.39	6.1 ± 5.9

Abbreviation: LOHS, Length of hospital stay; MT, massive transfusion protocols.
*$p > 0.05$ (Chi-square test).
**$p > 0.05$ (comparison of means).

14.2% of the events, and the reasons for the delays were captured in the massive transfusion register.

The data showed that 56.5% of GDMT activation (52/92) was inappropriate based on the study definitions. Detailed analysis of the amount of blood components transfused based on the appropriateness revealed a significant difference between the two groups (Table 3). The patients in the inappropriate group received three (IQR = 2.25) units of PRBC on average, whereas the appropriate group received six (IQR = 4.5) (Table 3). The total components transfused to the 'appropriate' group were 1038 (median = 20.5, IQR = 11.3) compared with 367 (median = 5, IQR = 4.25) to the inappropriate ones. The average duration of a massive transfusion was 6.19 ± 4.59 h from the time of activation to that of deactivation. The wastage rate of blood components in the study was 1.63% (23/1405), all which happened in inappropriate activations. Although the adherence to laboratory testing within 30 min of activation was 100%, TEG was done only in 66.3% of the MHP activations, higher in the appropriate group (85%, $n = 34$) compared with 50% ($n = 26$) in the inappropriate group.

The most common blood group among the patients was O, Rh(D)-positive (38%). ABO switchover took place in 5.4% of the events with non-O patients receiving type O PRBCs. No adverse transfusion events were reported during any MHP. The average hospital stay was 6.1 ± 5.9 days. Overall mortality was 45.65% (42/92); among these, 35% (14/40) were in the appropriate group, and 53.8% (28/52) in the inappropriate (Table 4). The pre- and post-massive transfusion laboratory values in Table 5 show the inappropriate category patients to have relatively better results than those in the appropriate group.

DISCUSSION

Designing and implementing MHP present unique challenges. It requires meticulous planning, estimating the need, managing logistical difficulties and making it easy for all to use [1]. Its implementation should be accompanied by a programme for continuous improvement [27, 28]. Our multidisciplinary team developed KPIs through the DMAIC approach to identify weak spots (Table 2). Such KPIs are scientifically sound, easy to capture and provide holistic information about MHP. They were validated with published literature on quality improvement of MHP [25, 29, 30]. Administrative aspects such as capturing patient data, diagnosis, involvement of stakeholders, mode of activation and deactivation of MHP showed a compliance rate of 100% and involvement of all the stakeholders.

The appropriateness of activation was a major concern, as 56.52% of the activations were inappropriate. A protocol alone is not adequate when it permits inappropriate usage over half the times it is applied. The blood ordering system did not meet the patient's needs, for justifiable as well as non-justifiable causes [26, 28, 31]. A justifiable cause would be the patient's death in the initial hours of resuscitation, especially in trauma. Another would be discharge against medical advice (DAMA). Activating massive transfusion as a method of

TABLE 5 Laboratory parameters and clinical outcomes of the patients compared categorically based on the appropriateness of massive transfusion activation.

	Pre MHP			Post MHP		
	Appropriate	Inappropriate	*p* value	Appropriate	Inappropriate	*p* value
Hb	8.74 ± 2.6	10.01 ± 3.37	0.05	9.53 ± 2.61	10.53 ± 2.46	0.15
HCT	26.18 ± 8.06	29.99 ± 9.63	0.05	28.15 ± 7.88	31.59 ± 6.6	0.06
Platelet count	193.33 ± 121.33	240.09 ± 96.93	0.05	134.41 ± 80.59	137.1 ± 53.45	0.87
PT	18.59 ± 8.79	13.1 ± 3.9	<0.001	16.86 ± 6.37	12.81 ± 2.35	0.02
aPTT	51.78 ± 33.89	30.68 ± 16.15	<0.001	53.21 ± 38.57	31.98 ± 9.01	0.04
pH	7.24 ± 0.21	7.28 ± 0.16	0.41	7.38 ± 0.12	7.34 ± 0.18	0.21

Abbreviation: aPTT, activated partial thromboplastin time; Hb, Haemoglobinm; HCT, Haematocrit; MHP, major haemorrhage protocol; PT, Prothrombin time.

procuring blood components would not be justifiable. Inappropriate requests affect patient care, lead to wastage of blood components, place an unwanted burden on inventory management [30, 32, 33] and impose extra costs on the patient. These can be resolved with specialized tools like the 'A3/Lean approach' and having a transfusion safety officer auditing the MHPs [21, 30, 34]. This can be addressed by physician education and the development of a massive transfusion predictive score. In view of this, we introduced a distinct 'Emergency Blood Request Form (EBRF)' with a different colour from routine requisition forms in order to reduce some of the inappropriate requests for MHP activation.

We had a compliance rate of 85% in meeting our benchmark emergency TAT of less than 30 min. Noncompliant cases could have been due to patients who were refusing medical advice, thereby losing precious time, and could affect the time between activation and receipt of a blood sample in the blood centre. Improvement in this area can result from (1) reducing the TAT 1 and TAT 2 in all cases and (2) reducing the benchmark for both [35]. Capturing the many factors affecting TAT will help us determine whether the delay is in sample transportation, blood component preparation, issue of component or transportation to bedside.

Despite a 100% compliance rate with the laboratory investigations, only 66.3% of the MHP events did a TEG assay during GDMT. Individualizing GDMT and other resuscitation measures might lead to greater use of TEG-guidance [14, 15]. Frequent stakeholder engagements, discussions with clinicians, an active hospital transfusion committee and organized medical education (CME) may all improve the adherence rate [4, 26, 36]. The clinical outcome was comparable between the appropriate and inappropriate groups (Table 4).

The following strategies can be adopted to improve quality. (1) Appropriateness: Implementing massive transfusion predictive scores and injury severity scores throughout the hospital will help to improve the appropriate activation of massive transfusion. Introducing a new 'Emergency issue request' instead of activating MHP if the requirement is only one or two PRBC units will lead to more judicious use of MHP. (2) TAT: Real-time capturing and evaluation of the time of massive transfusion activation, time of collecting the sample time of receiving the sample in the blood centre and time of issuing the blood components will lead to a proper understanding of any delay in delivering blood components. (3) Clinical audits of massive transfusion, as practiced by ANZBT (https://blood.gov.au/massive-transfusion-protocol-mtp-clinical-audit-tool). These will help to improve the quality and complications of massive transfusion. Audit analysis and discussion must take place in the hospital transfusion committee. (4) Formulating an audit team with a 'transfusion safety officer' preferably with a transfusion medicine background, whose duty will be conducting/supervising such audits [36]. (5) Improving compliance rates through conducting CMEs, inter-departmental discussions and demonstrations to improve awareness. (6) Creating 'institutional specific MHP benchmarks' will help to re-evaluate the quality standards.

The study was limited by the fact that there was a paucity of national reference standards for a comparison, and hence, the only option was to make a comparison with the institutional benchmark. Another limiting factor was the lack of real-time data capturing and analysis. The study did not include parameters like door-to-bed time, adjuncts to transfusion support, calcium replacement, hypothermia preventive methods, pre-hospital transfusions, other haemostatic agents and complications related to massive transfusion. As with any quality improvement approach, developing a set of parameters is insufficient for process improvement. Our goal is to take it to the next level by developing more specific KPIs, continuous periodic auditing and Hospital Transfusion Committee (HTC) discussions.

In summary, this was a sincere attempt to develop process excellence in MHP in our centre. The current study indicates that parameters like TAT, appropriateness, clinical outcome, documentation of the process, laboratory and VET tests and wastage rates are essential tools to assess the quality of a massive transfusion protocol. This study also shows that implementing QIs of massive transfusion is not difficult, and these data drive us to establish benchmarks. Once the gap areas are identified through an audit, it is imperative to investigate the possible corrective and preventive action approach for improvement. The implemented changes can be monitored through frequent audits for continuous quality improvement.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data will not be available as a public repository as per our institutional policy.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Biological impact of manual blood exchange in malignant *Bordetella pertussis* infection in infants

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Abstract

Background and Objectives: Manual blood exchange (MBE) is a leukoreduction therapy for hyperleukocytosis in *Bordetella* spp. infection. We describe the impact of BE on clinical and biological parameters in critically ill children with malignant pertussis.

Materials and Methods: This is a monocentric retrospective review of patients with malignant pertussis infection treated with MBE. It describes the evolution of haemodynamic, ventilatory, haematologic and metabolic characteristics before and after MBE.

Results: Between January 2006 and December 2021, nine patients (median age 43 days, range: 13–80 days) had 16 MBE for malignant pertussis. All patients were mechanically ventilated, and 7/9 patients developed pulmonary hypertension during their paediatric intensive care unit (PICU) stay. Overall, 3/9 patients survived, and the mean PICU length of stay was 8.5 days (range: 1–52 days). We found a significant reduction of the leukocyte count (pre-MBE: 61.8 G/L [interquartile range (IQR): 55.8–74.8] vs. post-MBE: 19.4 G/L [IQR: 17.7–24.1]; $p \leq 0.001$) and significant oxygenation improvement (pre-MBE SpO_2/FiO_2: 190 [IQR: 106–200] vs. post-MBE SpO_2/FiO_2: 242 [IQR: 149–250]; $p = 0.03$). The main side effects were a significant reduction of thrombocytes (pre-MBE: 411 G/L [IQR: 166.5–563.5] vs. post-MBE: 66 G/L [IQR: 46–82.5]; $p =$ <0.001) and of ionized calcium (iCa) (pre-MBE iCa: 1.3 [IQR: 1.22–1.37] vs. post-MBE iCa: 1.25 [IQR: 1.85–2.24]; $p = 0.03$).

Conclusion: MBE efficiently reduces leukocytes and improves oxygenation in severe *Bordetella pertussis* infection in infants. Careful monitoring of calcium and thrombocytes seems mandatory.

Keywords

blood exchange, *Bordetella pertussis*, hyperleukocytosis, PICU

Vladimir L. Cousin and Caroline Caulle contributed equally to this work and share first authorship.

Highlights

- In critically ill children, *Bordetella pertussis*-induced hyperleukocytosis could be effectively reduced by manual blood exchange.
- Manual blood exchange in *B. pertussis* improved oxygenation and decarboxylation.
- Thrombocytes and ionized calcium should be closely monitored during and after manual blood exchange as they may be significantly diminished and supplementation may be needed.

INTRODUCTION

Pertussis is a respiratory infection caused by *Bordetella* spp., which can lead to severe disease, especially in infants younger than 6 months, especially in case of insufficient immunization, with a high rate of paediatric intensive care unit (PICU) admission and a significant mortality rate [1–3]. Clinical presentation ranges from the recurrent spell of apnoea and bradycardia to severe bronchopneumonia and refractory hypoxemia with the development of pulmonary hypertension and shock [4, 5].

Hyperleukocytosis is pathognomonic of malignant pertussis and is associated with patients' admission in intensive care, requirement of mechanical ventilation, haemodynamic support and mortality [6, 7]. Its aetiology is not fully understood, but the role of pertussis toxin seems crucial [8, 9]. It is thought that the very high leukocyte count may induce hyperviscosity, leading to pulmonary hypertension and cardiovascular failure [10]. It has been proposed that a leukocyte count reduction using leukoreduction therapies could prevent the evolution of severe pertussis infection [5, 11]. Currently, those therapies include leukapheresis and manual blood exchange (MBE), with variable descriptions in malignant pertussis [2, 11]. MBE is more accessible in PICU settings and effective in reducing the number of leukocytes; a description of the impact on a patient's homeostasis and tolerance of such therapy is lacking in the literature.

In the following report, we discuss the impact of MBE on clinical and laboratory characteristics in critically ill infants with malignant pertussis.

CASES SERIES

From January 2001 to December 2021, 60 patients were admitted to the unit for a *Bordetella* spp. severe infection, and 9 patients (5/9 male) who received MBE therapies were isolated between the year 2006 and 2021. The MBE patients had a median age at admission was 43 days (range: 13–80 days), and the median weight was 3.5 kg (range: 2.9–5.3 kg). At their admission, the median leukocyte count was 66.8 G/L (range: 23–109.1 G/L). All patients needed to be mechanically ventilated with a mean duration of ventilation of 6 days (range: 2–38 days), and 6/9 patients needed high-frequency oscillation ventilation during their stay. Pulmonary hypertension was present in 7/9, with four patients having echocardiographic signs of pulmonary hypertension at their admission. Length of stay in PICU was 8.5 days (range: 1–52 days), and eventually, 6/9 patients died after a mean time of 9 days (range: 1–38 days). Table 1 summarizes further details on patients' demographics and PICU evolution.

The decision of blood exchanges was the presence of hyperleukocytosis (>50 G/L in all patients) associated with organ failure. The mean time between admission and first MBE was 28 h (range: 2.5–89 h). Additional MBE may have occurred, according to attending physician decision in presence of insufficient reduction or re-aggravating hyperleukocytosis and persistent haemodynamic and respiratory failure. A total of 16 MBE were performed with one exchange in three patients, two exchanges in five patients and three exchanges in one patient. The median volume of MBE was 550 mL (142 mL/kg) (range: 300–800 mL) with a mix of 2/3 of packed red blood cells and 1/3 fresh-frozen plasma. Blood exchange consisted in successive removal of a small amount of blood (5 mL/kg every 2–5 min) and replacement with reconstituted whole blood. The total duration of MBE varied between 1 and 2 h. The evolution of clinical and biological characteristics is summarized in Table S1. MBE resulted in a significant reduction of leukocyte count and an improvement of both oxygenation and decarboxylation parameters (Figure 1). As expected, MBE significantly impacted haemoglobin, thrombocytes and ionized calcium (Figure 1). The reduction of leukocyte count between patients with one MBE and those with ≥2 MBE (Figure S1) was not significantly different, with similar leukoreduction of the first blood exchange.

Ethics

The study was approved by the ethical committee from the French Society of Intensive Care (CE SRLF 23–074). The study has been registered at the 'Commission Nationale de l'Informatique et des Libertés' corresponding to the reference methodology (MR-004). The processing of the data was carried out following European legislation. A note informed patients and their families in the welcome booklet that their child's clinical data could be collected for research purposes and of their right to decline such research.

DISCUSSION

Hyperleukocytosis associated with severe *Bordetella pertussis* infection negatively affects the prognosis [6, 10]. We showed that MBE is

TABLE 1 Demographics and PICU evolution of included patients.

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9
Age (days)	43	59	17	80	13	75	56	18	24
Sex	M	M	F	M	M	M	F	F	F
Vaccination	No	No	No	No	No	No	No	No	No
Cardiac Echo at admission	PAH	PAH	PAH	No PAH	PAH RVF	Normal	Normal	Normal	PAH RVF
ATB	Josamycin	Clarythromycin	Clarythromycin	Clarithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin	Azithromycin
IVIG	N/A	IVIG	N/A	N/A	N/A	N/A	IVIG	IVIG	IVIG
Mec vent (days)	1–3	1–36	2–3	1–38	1	1–6	2–5	3–7	1–3
ECMO	N/A	Yes	Yes	N/A	N/A	N/A	N/A	Yes	Yes
CRRT	Yes	Yes	N/A	N/A	N/A	N/A	N/A	Yes	N/A
BE timing (hours)	48	24	40	4	2	12	32	89	3
MBE number	2	2	1	3	1	2	2	1	2
Outcome	Death	Alive	Death	Death*	Death	Alive	Alive	Death	Death

Abbreviations: ATB, antibiotic; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; F, female; IVIG, intravenous immunoglobulin; N/A, not administered; M, male; MBE, blood exchange; Mec vent, mechanical ventilation; PAH, pulmonary arterial hypertension; PICU, paediatric intensive care unit; Pt, patient; RVF, right ventricular failure; Ttt, treatment.
*Alive to ECMO weaning, deceased following a septic shock.

an effective therapy to reduce the leukocyte count and improve oxygenation/decarboxylation parameters. It should be underlined that a clinically significant reduction of thrombocytes was also noted, mostly in the context of blood dilution, and monitoring of such parameters should be recommended.

In the context of *B. pertussis* infection, the very high number of leukocytes could have dreadful consequences as they aggregate in lung micro-vasculatures and promote pulmonary hypertension and cardiac and respiratory failure [2, 8, 10]. In such conditions, leukoreduction therapies have been proposed to prevent those consequences. However, leukoreduction therapies could be challenging to perform in small children, a point to underline as most severe pertussis are reported in infants weighting <5 kg, and it may not be available during the night or in case of emergency [2, 5]. The use of MBE for leukoreduction was primarily described in leukaemia. It could be performed in general PICUs without an apheresis team, in infants, and with the requirement of blood products and a central venous access. Those characteristics make MBE an attractive therapeutic option for pertussis-induced hyperleukocytosis, especially in population with limited access to immunizations. The use of MBE has been described in this setting [2, 5, 11, 12]. We found a dramatic decrease in the leukocyte count, underlining its role as leukoreduction therapy, as proposed in the literature reviewed by Chantreuil et al. [2]. Our data underscore the effectiveness of MBE. It is suggested that MBE should be performed early as it may prevent the evolution of pulmonary hypertension and organ failure [5, 9–11]. Hereby, we described the improvement of oxygenation and decarboxylation, as recently reported by Son et al. in four patients [12]. The conditioning of blood replacement is frequently discussed. We used a mixture of whole blood using packed red blood cells and fresh-frozen plasma for blood exchange, using the previously described procedure [2, 11]. We did find a slight increase of haemoglobin with questionable clinical impact, an important point to underline as a case of an essential rise of haemoglobin after blood exchange [2]. However, thrombocyte count and ionized calcium level were both significantly reduced. Both will need close monitoring and replacement if needed during the procedure and in the hours after. Although this report does not allow to interpret safety of MBE, it has been recently discussed the potential association between MBE and secondary clinical degradation. It is currently accepted that hyperleukocytosis >50,000 G/L in critically ill children with pertussis is an indication for MBE, but those criteria were defined retrospectively and should be interpreted cautiously.

Our report has several limitations, including its monocentric and retrospective design, on a limited number of cases. Criteria to perform MBE were not fully standardized. In addition, our study was not design to assess the impact of MBE on patient evolution in PICU but rather the impact of such procedure on numerous biological and clinical variables.

Our experience confirms the effect of MBE in malignant pertussis with decreased leukocyte count and improvement in oxygenation. Results of the first MBE did not seem to predict the need of additional MBE.

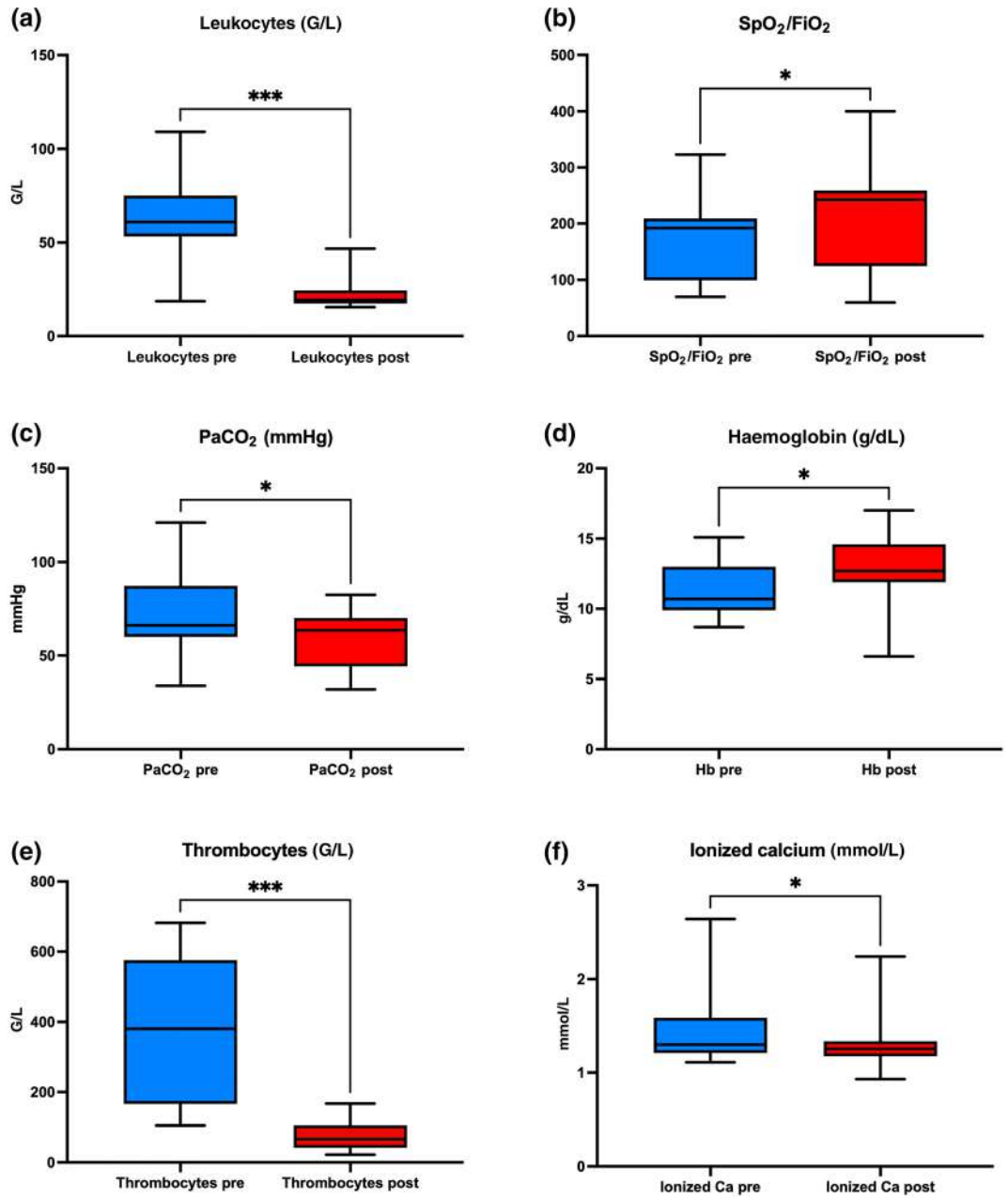

FIGURE 1 Significant biological parameter evolution, pre–post manual blood exchange. Evolution pre–post blood exchange of leukocyte count (G/L), oxygenation (SpO_2/FiO_2), decarboxylation ($PaCO_2$ [mmHg]), haemoglobin (Hb) (g/dL), thrombocytes (G/L) and ionized calcium (mmol/L). $p < 0.05$ ***$p < 0.001$.

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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.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

A novel *cisAB* allele with a missense variant (*c.971T>C*) in the *ABO* gene of a Brazilian family

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Abstract

Background and Objectives: Missense variants in exon 7 of the *ABO* gene can lead to the formation of *cisAB* alleles. These alleles encode glycosyltransferases (GTs) capable of synthesizing both A and B antigens. In this study, we report the discovery of a novel *cisAB* allele and characterize it at molecular, protein and serological levels.

Materials and Methods: Blood and DNA samples from the proband and seven relatives were examined using standard and modified ABO phenotyping, polymerase chain reaction-restriction fragment length polymorphism and *ABO* gene sequencing. We assessed the impact of the p.Leu324Ser variant on the protein structure of the mutant GT using bioinformatics tools.

Results: Molecular tests revealed a c.971T>C (p.Leu324Ser) variant in the *ABO* gene in five of the eight individuals. This variant results in a GT that produces more A antigens and fewer B antigens. Bioinformatics analysis suggests that the amino acid substitution (p.Leu324Ser) could potentially affect enzymatic activity and specificity of the GT.

Conclusion: We identified a novel *cisAB* allele resulting from a c.971T>C variant in the *ABO* gene. This variant led to the expression of an AB_{weak} phenotype.

Keywords

ABO blood group, ABO genotyping, *cisAB* allele

Highlights

- This study shows that the p.324Ser variant is associated with changes in glycosyltransferase activity and specificity.
- This is the first report of a *cisAB* allele that lacks one or more of the four amino acid changes present in the *ABO*B.01* allele.
- Some clones of anti-B antisera were unable to identify the B antigen produced by the novel *cisAB* allele.

INTRODUCTION

The *ABO* gene encodes glycosyltransferases (GTs), which vary according to the *A* (GT-A), *B* (GT-B) and *cisAB* or *B(A)* (GT-AB) alleles. These GTs convert the precursor H antigen into A, B, or both A and B antigens. The distinction between the GT-AB encoded by the *cisAB* and *B(A)* alleles is made through ABO phenotyping. The *cisAB* allele is considered if the A antigen reacts more strongly, and the *B(A)* allele is considered if the B antigen has the strongest reactivity [1, 2]. This genetic complexity highlights the diversity of the ABO blood group system.

Six *cisAB* alleles (*ABO*cisAB.01-6*) are recognized by the International Society of Blood Transfusion (ISBT). Each of these alleles has missense variants in exon 7 of the *ABO* gene, which result in amino acid alterations when compared to the reference allele, *ABO*A1.01*. These alleles share one or more of the four amino acid changes (p.Arg176Gly; p.Gly235Ser; p.Leu266Met; p.Gly268Ala) that characterize the *ABO*B.01* allele [3]. These genetic correlations underscore the crucial amino acid alterations at these positions.

In this study, we evaluated eight individuals and identified a missense variant (c.971T>C) in the *ABO* gene of five of them. This variant resulted in the formation of a mutated GT-AB(p.Leu324Ser), which led to the expression of the cisAB phenotype and the discovery of a novel *cisAB* allele. The objective of this study was to characterize the new allele and determine its phenotypic expression.

MATERIALS AND METHODS

Casuistic and ethical aspects of the research

Peripheral blood samples from a blood donor (46.1), his wife (46.2), his two children (46.3 and 46.4), his father (46.5), his mother (46.6) and his two brothers (46.7 and 46.8) were collected and sent to our immunogenetics laboratory to clarify a discrepancy between the current result of the ABO phenotyping of the proband (phenotype AB) and his previous donation history (phenotype A). This study was approved by the Research Ethics Committee of Faculty of Medicine of São José do Rio Preto (FAMERP) (CAAE 34163114.6.0000.5415). All participants provided informed consent authorizing the research.

Serological investigations

Direct ABO phenotyping was performed using three methodologies. Column agglutination technology (CAT): automated method (IH-500, Bio-Rad, Switzerland), using three commercial cards containing anti-A (clones: A5 and LA-2) and anti-B antibodies (clones: G1/2 and LB-2). Tube test: using anti-A (clones: 9113D10, A003, Birma-1 and 11H5), anti-B (clones: 9621A8, B005, LB-2 and 6F9) and anti-A,B antisera (clones: 9113D10+152D12, ES-1+LB-2+Birma-1, ES-4+ES-15-+Birma-1, BS63+BS85 and 5E10+2D7) from six different manufacturers (Fresenius, Prothemo, Ebram, Brazil; Lorne, United Kingdom; Bio-Rad, Switzerland; and Immucor, Germany). CAT with neutral gel (CAT-NG): semi-automated method, using the same monoclonal antisera as the Tube test. All antisera were previously titrated, and A_1, A_2, B and O red blood cells (RBCs) (Bio-Rad, Brazil) were used for reverse ABO phenotyping. The A_1 and H antigen tests were performed with anti-A1 (Dolichos biflorus) and anti-H (Ulex europaeus) lectins (Fresenius, Brazil) in the Tube test and CAT-NG methods. We employed the technique of separating RBCs by mixed-field (MF) agglutination to remove non-agglutinated cells using anti-A1 lectin. Following the separation, non-reactive RBCs were prepared and subjected to further testing with anti-A1 lectin [4]. Lewis phenotyping was performed using CAT. The RBCs of the individuals were prepared in two suspensions, one with the ID-Diluent-1 and the other with ID-Diluent-2 (Bio-Rad, Switzerland). These were tested simultaneously using the Tube test and CAT-NG techniques with the previously mentioned monoclonal antisera.

Molecular investigations

Genomic DNA was isolated from peripheral blood using commercial kits (QIAGEN, Germany). Determination of *ABO* genotypes and alleles was performed by polymerase chain reaction-restriction fragment length polymorphism and sequencing, according to the protocol of Miola and collaborators [4]. Furthermore, we sequenced exon 1 and the promoter region of the *ABO* gene, using the following primer sequences (5′–3′) ABOp1ex1-F: GAACGCGAAGGTTCCTCAGTCT and ABOp1ex1-R: GCGGTAGGTGCTGAAAATAGCAG, under the same conditions as described in our previous report [4]. The sequencing covered all exons, introns, splicing sites and the promoter region (from −545 to the beginning of the GT translation site) of the *ABO* gene.

In silico investigations

The SWISS-MODEL (http://www.swissmodel.expasy.org) was utilized to construct the three-dimensional (3D) protein structure of the mutated GT-AB (p.Leu324Ser) and GT-B, using the reference sequence (GT-A, P16442). The Swiss-PdbViewer (version 4.1.0) was employed to compare these structures (Figure 1). The MutPred2 web application (http://mutpred.mutdb.org/) was used to predict the potential impact of the p.Leu324Ser variant on GT activity.

RESULTS

Serological analysis

By ABO phenotyping, the proband and four relatives exhibited standard reactivity with anti-A (4+) and variable reactivity with anti-B antisera. These results ranged from non-reactive (clones: LB-2 and B005) to reactive with weak (1+), intermediate (2−3+) and strong (4+, except 46.3) intensities, depending on the clone, antiserum titre and type of RBC suspension. The A_1 antigen was detected in all cisAB individuals, including in the non-reactive RBCs of the proband. To confirm the presence of the A_1 antigen in these non-reactive RBCs, they were separated from the MF and re-tested, obtaining the same pattern as had been observed before their separation [4]. Only anti-B antibodies were detected in the serum. The Lewis phenotyping varied among these individuals; it was Le(a+b−) in the proband, Le(a−b+) in 46.3 and 46.5, and Le(a−b−) in 46.7 and 46.8. The serological results are presented in Table 1.

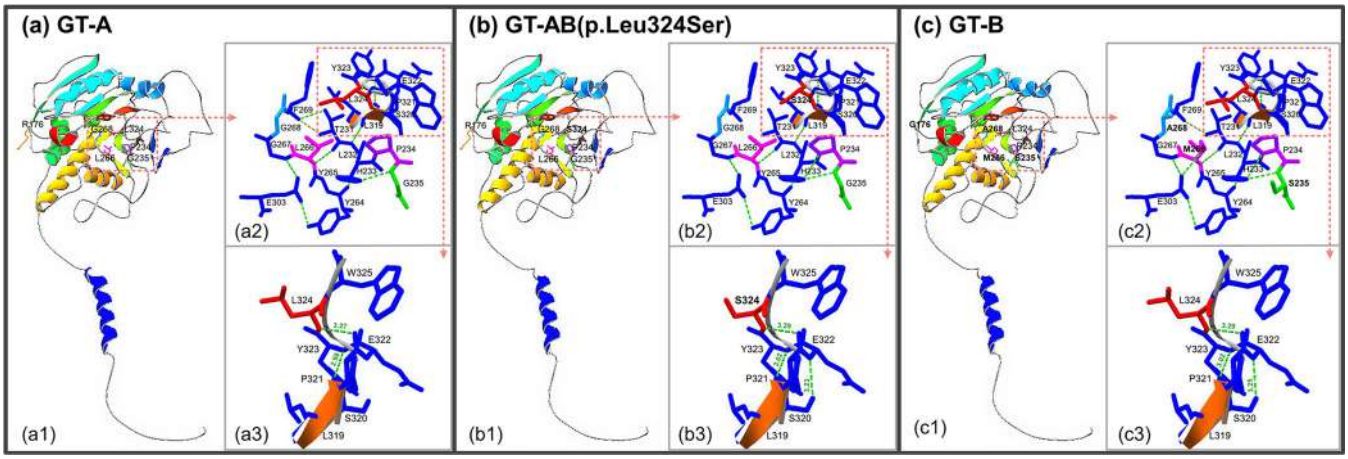

FIGURE 1 The 3D structures of the enzymes GT-A (a), GT-AB(p.Leu324Ser) (b) and GT-B (c), with enlarged sections (2 and 3) that expose the regions that present differences and equalities in hydrogen bonds between the amino acids of these three molecules. GT-AB(p.Leu324Ser) differs from GT-A in: F269-T231, H233-P234 and S320-E322; and from the GT-B in: F269-T231, and M266-E303 regions. The amino acids at positions 176, 234, 235, 266, 268 and 324 are represented by orange, purple, green, pink, light blue and red, respectively.

TABLE 1 Phenotyping and genotyping data of family members.

	ABH RBC phenotyping					Serum antibody				Phenotype ABO	Phenotype Lewis	Genotyping ABO	
Case	A	B	AB	A_1	H	A_1	A_2	B	O			c.261G	Alleles
46.1	4	0–4[a]	4	MF	2	0	0	4	0	cisAB	Le(a+b−)	G/delG	*ABO*cisAB(c.971T>C)/O.01.68 (+c.542G>A)*
46.2	4	0	4	4	1	0	0	4	0	A	Le(a−b+)	G/delG	*ABO*A1.01/O.01.01*
46.3	4	0–2[b]	4	4	1	0	0	4	0	cisAB	Le(a−b+)	G/G	*ABO*A1.01/cisAB(c.971T>C)*
46.4	4	0	4	4	1	0	0	4	0	A	Le(a−b−)	G/delG	*ABO*A1.01/O.01.68(+c.542G>A)*
46.5	4	0–4[a]	4	1	2	0	0	2	0	cisAB	Le(a−b+)	G/delG	*ABO*cisAB(c.971T>C)/O.01.01*
46.6	0	0	0	0	4	4	4	4	0	O	Le(a−b−)	delG/ delG	*ABO*O.01.01/O.01.68(+c.542G>A)*
46.7	4	0–4[a]	4	1	2	0	0	2	0	cisAB	Le(a−b−)	G/delG	*ABO*cisAB(c.971T>C)/O.01.01*
46.8	4	0–4[a]	4	w	2	0	0	2	0	cisAB	Le(a−b−)	G/delG	*ABO*cisAB(c.971T>C)/O.01.68 (+c.542G>A)*

Note: 0 = non-reactive; w, 1, 2, 3 and 4 = reactive.
Abbreviation: MF, mixed field.
[a]Reactive with clones G1/2 (Reactive 1–2+), 9621A8 and 6F9 (2+, titres: 512/1024). RBCs suspended in ID-Diluent-1 showed stronger reactions (3/4+).
[b]Reactive with clones G1/2 (1), 9621A8 and 6F9 (2, titres: 512/1024) only with RBCs suspended in ID-Diluent-1.

Molecular analysis

The c.261delG variant was identified in four of the five individuals with a suspected cisAB phenotype. Sequencing revealed four alleles: two common alleles (*ABO*A1.01 and ABO*O.01.01*) and two novel alleles. One of the novel alleles contained the variant of the *ABO*O.01.68* allele plus c.542G>A, named *ABO*O.01.68(+c.542G>A)* in this paper; the other contained only one missense variant (*c.971T>C*—rs2118940134) that differs from the reference allele (*ABO*A1.01*), named *ABO*cisAB(c.971T>C)* in this paper. The protein sequence of this *cisAB* allelic variant was deposited in GenBank (OR829321). Table 1 illustrates the allelic composition.

In silico analysis

The c.971T>C variant resulted in the substitution of the amino acid leucine (nonpolar) by serine (polar) at position p.324 of the encoded GT-AB. The analysis performed with the SWISS-MODEL and Swiss-PdbViewer tools revealed differences in the interatomic interactions between GT-AB(p.Leu324Ser) and GT-A so that it resembles GT-B (Figure 1). The MutPred2 algorithms assigned a probability score of 0.752, suggesting that the amino acid substitution (p.Leu324Ser) has the potential to affect enzyme activity and specificity. Moreover, this programme identified potential mechanisms that could influence the phenotype (p-values: <0.05). These mechanisms include the following:

altered ordered interface (which could influence GT interactions and modify antigen conversion), gain of strand (potentially affecting GT folding, stability and enzyme activity), altered transmembrane protein (with implications on GT localization and antigenic expression), loss of pyrrolidone carboxylic acid at Gln328 (altering protein function and antigen conversion) and gain of sulfation at Tyr323 (modifying protein properties and GT activity or substrate specificity) [5].

DISCUSSION

This study describes an intriguing case of a blood donor whose ABO blood group results were different from his previous tests. To further our investigation, we invited the donor's relatives to participate in the study. We obtained the consent of eight members, representing three generations (Figure 2). Using serological and molecular methods, we identified two novel alleles of the *ABO* gene. The first, named *ABO*O.01.68(+c.542G>A)*, encodes a non-functional GT. The second, *ABO*cisAB(c.971T>C)*, leads to the formation of a GT that can add both A and B antigens (GT-AB). Additionally, we performed an in silico analysis of the protein structures, revealing the similarities and differences among GT-A, -B and -AB(p.Leu324Ser) (Figure 1).

The variation observed in the results with the anti-B monoclonal antibodies and the B antigen formed from the *ABO*cisAB(c.971T>C)* allele demonstrated two main characteristics. The first, linked to cell clones, showed reactivity with clones G1/2, 9621A8 and 6F9, but did not react with LB-2 and B005. The second characteristic was related to its ability to potentiate the reaction. Both RBCs treated with a proteolytic enzyme (ID-Diluent-1, bromelain) and using reagents at high titres intensified the reaction. However, this intensification did not occur with the anti-B antibodies of clones LB-2 and B005, suggesting the absence of the antigen-binding sites for these clones. The non-reactivity with these clones could be due to the difference in the precursor structure to which galactose is added. This structural difference also explains the presence of anti-B antibodies in the serum of these individuals [6]. The study did not analyse the type of precursor used by GT-AB(p.Leu324Ser), which is acknowledged as a limitation of this study.

All individuals carrying the *ABO*cisAB(c.971T>C)* allele exhibited the same serological pattern in direct ABO phenotyping, except for 46.3, who showed weaker reactivity with anti-B antiserum. This is explained by the presence of the trans-acting allele *ABO*A1.01*, which encodes a GT-A that outcompetes GT-AB(p.Leu324Ser) in the competition for the H antigen precursor [2]. This allele also explains the strong reactivity with anti-A1 lectin in this case, while weaker reactivity was observed in the other individuals who carry the *ABO*O* allele in trans with *ABO*cisAB(c.971T>C)*. Furthermore, the distinct Le^a and Le^b phenotypic compositions in individuals carrying the *ABO*cisAB (c.971T>C)* allele obviated the need for secretor status investigation, which could otherwise influence the expression of ABO antigens [2]. These observations suggest that the encoded GT-AB(p.Leu324Ser) can synthesize small amounts of A_1 antigens, and a larger quantity of A antigens. Additionally, it can synthesize B antigens, capable of promoting moderate reactivity (2+) in routine tests, limited to certain clones of anti-B antiserum.

The c.971T>C variant, identified in the proband and in four of his relatives, is registered in dbSNP (rs2118940134). As the nucleotide sequence containing this variant was not found in the GenBank database, we have submitted it (OR829321). In addition, another unmatched allele identified on the ISBT website, which is composed of a variant of the *ABO*O.01.68* allele plus c.542G>A, has not been submitted to GenBank. However, we identified two novel allele

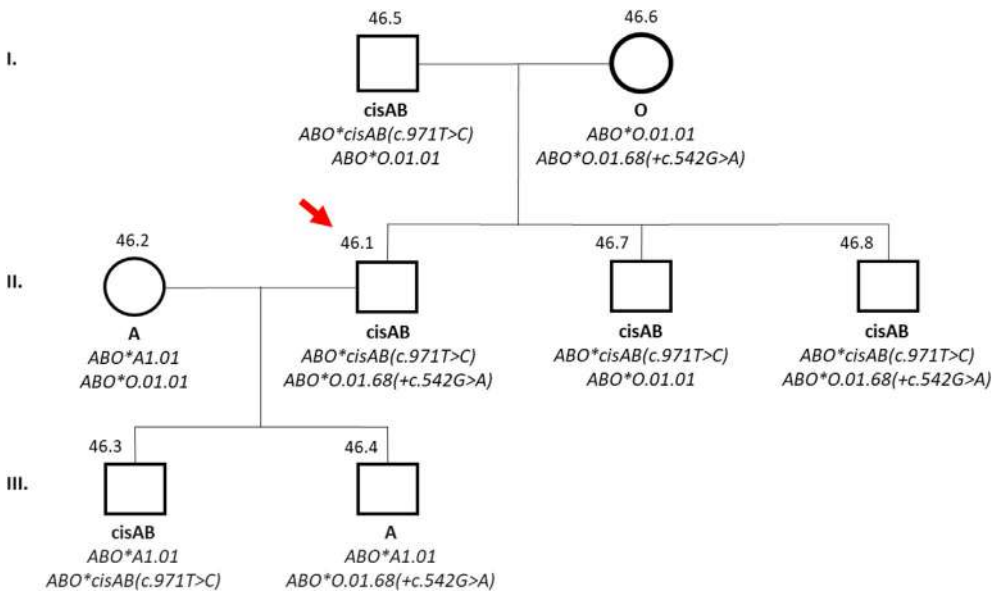

FIGURE 2 Pedigree of the studied family showing the inheritance of the *ABO*cisAB(c.971T>C)* allele and the phenotypic composition of the ABO system.

variants, one variant of the *ABO*cisAB* allele and the other of the *ABO*O.01* allele.

The GT was studied using 3D modelling of GT-AB(p.Leu324Ser) encoded by the *ABO*cisAB(c.971T>C)* allele. This revealed that the amino acid substitution (p.Leu324Ser) resulted in changes to hydrogen bonds, differentiating it from the GT-A and GT-B proteins (Figure 1). These interatomic changes occurred due to the substitution of a hydrophobic molecule with a nonpolar and aliphatic-branched side chain (R-group), by a hydrophilic molecule with hydroxyl, polar and uncharged side chain. The p.Leu324Ser substitution was analysed using the MultPre2 programme, which indicated that this substitution has the potential to affect the activity and/or specificity of the enzyme, which would have an impact on the phenotype. Among the significantly associated molecular mechanisms, the sulfation of tyrosine residues at position 323 of the protein stands out. This modification has several functional implications, such as a modification of electrical charge and activity regulation [7]. In addition, serine is frequently found in catalytic sites of enzymes, with the capacity to modify interactions with the surrounding environment and promote significant changes in enzyme conformation and function [8].

When comparing the *cisAB* and *B(A)* alleles recognized by the ISBT (*ABO*cisAB.01-06*; *ABO*BA.01-06*), we observed that they share one or more of the four amino acid substitutions present in the *B* allele [3]. Additionally, none of these alleles have changes in the p.324 region. Recently, researchers identified the c.972G>T(p.Leu324Phe) variant in a blood donor who carries mutations of the *B* and *O* alleles. This variant was associated with the *B* allele, resulting in the formation of the B(A) phenotype [9]. Although not yet officially recognized by the ISBT, this variant aligns with our study, as the p.324 position is associated with the enzyme's catalytic site. Furthermore, these findings can be corroborated by studies that have shown that this region interacts with acceptor H and the monosaccharide donor of galactose [10]. In contrast, the novel allele, *ABO*cisAB(c.971T>C)*, differs from the others in that it lacks any of the four amino acid substitutions found in the *B* allele. Moreover, this study is the first to demonstrate that position p.324 is associated with the formation of the cisAB phenotype.

In conclusion, a novel *cisAB* allele variant was discovered, resulting from a c.971T>C variant in the *ABO* gene. This variant encodes a GT-AB(p.Leu324Ser) capable of synthesizing A and B antigens, expressing the AB_{weak} phenotype. Furthermore, the B antigen synthesized by this allele cannot be detected by the anti-B antiserum from clones LB-2 and B005.

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L.C.M. and M.P.M. designed the study, analysed and interpreted the data. M.P.M. performed the experiments and wrote the manuscript. L.C.M. reviewed the manuscript. C.L.P. and G.C. identified the case, collected the data and facilitated sampling. O.R.J. contributed essential reagents and tools. All authors approved the final manuscript. We gratefully acknowledge David A. Hewitt for the English language editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in GenBank at https://www.ncbi.nlm.nih.gov/nuccore/OR829321, reference number OR829321.

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SHORT REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Blood donor questionnaires and infectious disease screening in Latin American countries

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Abstract

Background and Objectives: Blood donor questionnaires are tools used to screen prospective blood donors to determine their eligibility. There are limited data regarding blood donor questionnaires and infectious disease screening of the blood supply in Latin American countries. This study aimed to survey donor centres in Latin American countries to learn more about blood donor screening and infection assessment.

Materials and Methods: An international team of transfusion medicine professionals including medical directors and supervisors who work or collaborate with Latin American donor centres, called '*Comité de Investigación en Medicina Transfusional*', designed a survey (16 questions) to characterize blood donor eligibility in Latin America.

Results: Eighty-two institutions from 14 Latin American countries responded to the survey. Most donor centres (66%; 54 of 82) had a donor deferral percentage between 5% and 25%, and the most common causes of deferrals were low haemoglobin and high-risk behaviour. Most donors in blood centres were directed family donors compared with voluntary donors. Infection evaluation included mostly serologic assessment (81%; 30 of 37) for human immunodeficiency virus (HIV), Hepatitis B, Hepatitis C, *Treponema pallidum* and *Trypanosoma cruzi* rather than nucleic acid tests (5%; 2 of 37).

Conclusion: Heterogeneity exists in donor selection and infectious disease screening in Latin American countries. This survey provides valuable information to understand Latin American blood centre practices.

Keywords

blood donor centres, global transfusion, infectious disease screening

Highlights

- This study highlights the heterogeneity that exists in donor selection and infectious disease screening in Latin American countries.
- Most donors in surveyed blood centres were directed family donors rather than voluntary donors.

- Infection evaluation included mostly serological assessment for human immunodeficiency virus, hepatitis B, hepatitis C, *Treponema pallidum* and *Trypanosoma cruzi* rather than nucleic acid tests.

INTRODUCTION

Blood donor questionnaires are essential tools used to screen prospective blood donors to determine their donation eligibility [1]. The assessment of donor suitability and deferral aims to exclude donations from individuals with a pre-existing medical disease, anemia or at risk of transfusion-transmitted infection (TTI), particularly from those with a recently acquired infection that may not be detected by routine screening tests or infections for which no effective blood screening tests are available [2]. Therefore, donor selection, use of sensitive screening tests and the application of a mandatory quality assurance system are important to maintain the safety of the blood supply. Different blood donor screening strategies are used in United States, Europe and the United Kingdom [3]. The World Health Organization (WHO), the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe, the Association for the Advancement of Blood & Biotherapies (AABB), Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee and other international bodies provide standards for Donor Health Questionnaires (DHQs). These standards aim to ensure comprehensive screening of blood donors for potential health risks that could affect the safety of blood transfusions. However, there are limited data regarding blood donor questionnaires and infectious disease screening of the blood supply in Latin American countries. This study aims to survey Latin American countries to learn more about the questions used to screen prospective blood donors and characterize blood donor eligibility in Latin America.

MATERIALS AND METHODS

An international team of transfusion medicine professionals including medical directors and supervisors working with Latin American donor centres, called '*Comité de Investigación en Medicina Transfusional*', designed a 16-question Spanish survey to investigate and characterize blood donor eligibility in Latin America. The survey was validated and piloted by the participating authors. The survey questions were modified according to feedback in multiple iterations, prior to deploying the survey. Questions were written in a structured response format with multiple-choice options or with a free text option where appropriate. The survey was created using a secure web-based survey platform (Qualtrics, Provo, UT), a secure web-based platform designed to create complex online surveys for secure research study collection and analysis. This survey was then distributed to 18 Latin American countries, with blood collection establishments and hospital transfusion medicine services in April and May 2023. The Qualtrics online survey was disseminated to different blood banks in Latin America, identified through contacts and professional groups associated with the '*Comité de Investigación en Medicina Transfusional*'.

The final 16-question survey included questions in Spanish regarding: (a) the location of institution; (b) the role in the blood centre/transfusion service; (c) the type of institution (blood centre or hospital or both); (d) the number of donors and estimated blood collection per year; (e) percentages of deferrals and reasons; (f) the type of donor; (g) who administers or performs the donor questionnaire to donors; (h) the estimated time for completion of donor questionnaire; (i) the questions used to screen donors; and (j) infectious disease testing performed to blood donation to reduce the risk of TTI (Appendix S1). The estimated time to complete the survey was 5–10 min. The study was approved by the Institutional Review Board (IRB) at the University of California San Francisco (UCSF) (study number 22-38186, approval date 24 February 2023).

RESULTS

Eighty-two institutions from 14 Latin American countries responded to the survey (Mexico, Guatemala, Nicaragua, Honduras, El Salvador, Panama, Colombia, Venezuela, Chile, Peru, Bolivia, Paraguay, Uruguay and Argentina; Figure 1). Most institutions (51%; 42 of 82) were donor centres, with a range of 250–100,000 donors. Many of the donor centres (66%; 54 of 82) had a donor deferral percentage between 5% and 25%, and the most common causes of deferrals were low haemoglobin (30%) and high-risk behaviour (28%), followed by medical condition (12%), underweight (1%), travel (1%) and others (10%). Most donors in blood centres were unpaid directed family donors compared with voluntary donors (Figure 2). The donor questionnaires were mainly administered by a medical director/physician (45%; 37 of 82) or medical technologist (32%; 26 of 82), and in most cases were performed within 10–15 min (85%; 70 of 82). Most (63%; 52 of 82) of the institutions asked about men who have sex with men (MSM), but fewer asked about HIV medications (30%; 25 of 82) or prophylaxis (32%; 26 of 82). Infection evaluation included mostly serologic assessment for HIV, Hepatitis B, Hepatitis C, *Treponema pallidum* and *Trypanosoma cruzi* rather than nucleic acid tests (Figure 3). Additional infectious disease testing was performed if high-risk medical history was detected for syphilis, HIV-1,2 Hepatitis B, Hepatitis C and Chagas disease.

DISCUSSION

The WHO Global Status Report on Blood Safety and Availability 2021 indicated that ≥118.5 million blood donations are collected annually

FIGURE 1 Number of surveys completed per country.

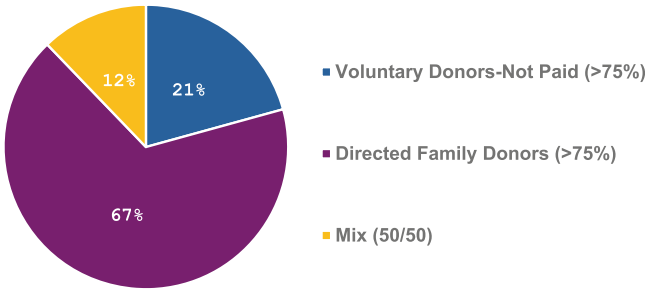

FIGURE 2 Types of donors in Latin American blood centres ($N = 82$).

from 171 different countries around the world [4]. The total deferral rates (the percentage of deferrals among all blood donor presentations) varied widely among countries, from less than 1% to over 67%. The median rate of total deferral was 13%. According to the 2021 report by the WHO, drawing on data from 110 countries, the primary reasons for deferral included low haemoglobin levels, high-risk behaviour, travel history and low weight. These percentages exhibited variation corresponding to the income levels of the respective countries. At least 11 million donors were deferred due to having the risk of infection that could be transmitted through blood, a pre-existing medical disease or anemia [5]. The survey from this study showed that significant heterogeneity exists in donor selection and infectious disease screening in Latin American countries. Most of the donor centres reported a donor deferral percentage range between 5% and 25%, which is comparable to what is reported in the WHO report for the Americas, with a mean of 20.3% and an interquartile range spanning from 15% to 27.7% [6]. This is also consistent with the 2020 Pan American Health Organization (PAHO) report of blood supply for transfusions in the countries of Latin America and the Caribbean 2016–2017, which reported a donor deferral of 10%–13% [7]. The three most common deferral reasons among the Latin American blood

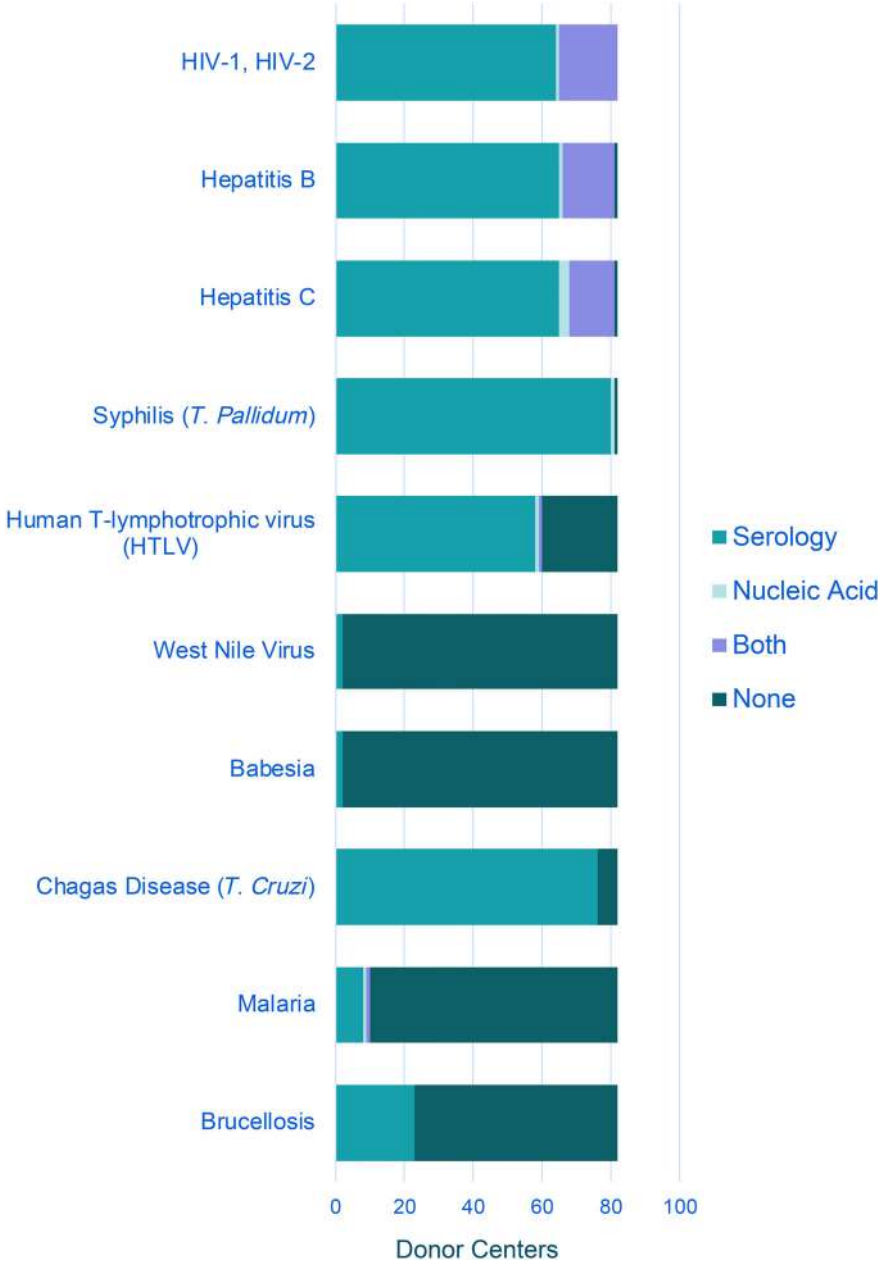

FIGURE 3 Routine infectious disease screening testing.

donor centres were low haematocrit/haemoglobin (30%), high-risk behaviour (28%) and medical condition (12%). Low haematocrit/haemoglobin was the major deferral overall compared with the reports in other studies. The wide deferral percentage range observed might be due to socio-economic status, the menstrual loss of blood in the childbearing age group or consumption of low-iron diet, among others [8]. More studies are needed to identify the barriers each country faces to collect sufficient blood from safe donors to meet national requirements.

Regarding the questions included in the donor questionnaires, the current survey showed that most institutions asked about MSM, but not all asked about HIV medications (30%; 25 of 82) or prophylaxis (32%; 26 of 82). A prior study found that MSM in three large cities in Canada demonstrated support for more individual behaviour-based screening that is gender-neutral and applied to everyone [9]. Therefore, it would be interesting to perform a more individualized risk assessment in the participating donor centres and evaluate the differences.

Another aspect that may affect access to donation is that donor questionnaires are administered by a medical director/physician (45%; 37 of 82) or medical technologist (32%; 26 of 82) instead of self-administration. There are data that suggest that self-administered surveys increase the elicitation of behaviours associated with the risk of TTI in donors. It also improves donor and staff satisfaction and reduces errors and omissions that frequently accompany traditional interviewing methods [10].

An adequate and reliable supply of safe blood can be assured by a stable base of regular, voluntary, unpaid blood donors. These donors are also the safest group of donors, as the prevalence of blood-borne infections is lowest among this group [11]. In 2020, PAHO reported that between 2016 and 2017, the percentage of unpaid voluntary donations in Latin America and the Caribbean averaged 46.1%. By sub-region, Mexico recorded the lowest percentage, with 4.8% in 2016 and 5.2% in 2017. Central America reported an average of 33.2% voluntary donations, followed by the Southern Cone, with 39.7% in 2016 and 41.3% in 2017. Data for the non-Hispanic Caribbean were similar, with 47.4% in 2016 and 44.9% in 2017. Conversely, the highest percentages of voluntary donations were observed in Brazil (62.1%), the Andean subregion (83.2% in 2016 and 67.3% in 2017) and the Hispanic Caribbean (81%). Our survey results showed that 67% of participants in Latin American countries persisted with a higher proportion of unpaid family-directed donations compared with voluntary donors. This raises questions about access to blood products and why donations come from directed family donations. The difference in the types of donors in Latin America may be due to decreased availability of donors and limited blood supply. Previous studies have reported that there is a marked difference in the level of access to blood between low income, lower middle income, upper middle income and high income [5].

WHO recommends that all blood donations should be screened for infections prior to use [2]. Screening for HIV, hepatitis B, hepatitis C and syphilis should be mandatory [12]. WHO states that while nucleic acid testing (NAT) can reduce the risk of transmitting infections during the window period, its actual advantage must be weighed against its complexity and high cost, including the necessary infrastructure [4]. The 2021 WHO report revealed that out of 171 countries surveyed, 166 reported implementing a policy to screen all blood donations for HIV. Similarly, 166 out of the 171 responding countries indicated having a policy to screen all blood donations for hepatitis B virus (HBV). Additionally, of the 171 countries surveyed, a total of 164 reported implementing a policy for serological testing of all blood donations for hepatitis C virus (HCV) [4]. Blood screening should be performed according to quality system requirements. Our survey results showed that the infectious disease evaluation in most of the donor centres surveyed in Latin America included serologic assessment for HIV, HBV, HCV, *T. pallidum* and *T. cruzi* rather than nucleic acid tests. Additional infectious disease testing was only performed in most countries if high-risk medical history was detected for syphilis, HIV-1,2, HBV, HCV and Chagas disease. However, nucleic acid screening is known to reduce the window period for TTIs like HIV and HCV [5]. The WHO recommends using the most sensitive assay available, whether it is a rapid diagnostic test or an enzyme immunoassay, in terms of analytical sensitivity and clinical sensitivity, for the detection of HBV and HCV. This acknowledges that in high-incidence countries NAT would benefit significantly as it identifies donors in their window period [13]. Nonetheless, access and cost may be barriers to implementing more routine NAT in Latin America. Therefore, further evaluation is needed to determine the barriers to NAT.

This study is limited by sampling method as it may not be representative of all countries. As participants were identified by '*Comité de Medicina Transfusional*' and their professional contacts, the results may be subject to selection bias. A unique strength of this study is that it provides data from Latin American blood centres and results came from an interdisciplinary international group rather than only from government data. Future directions include further studies to assess the reasons behind directed donor donation and blood availability in Latin American countries.

In conclusion, this survey highlights the heterogeneity that exists in donor selection and infectious disease screening in Latin American countries. Differences in types of donors and routine infection screening could be further studied to possibly establish new strategies to decrease directed donations across centres in Latin America. To this end, additional research on Latin American blood donor centre practices is needed to provide a better understanding of practices and increase the accessibility of safe blood products.

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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.

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REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Navigating the Asia-Pacific region plasma therapies landscape: Insights from the 2023 Asia-Pacific Plasma Leaders' Network meetings

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Abstract

The Asia-Pacific Plasma Leaders' Network (APPLN) plays a crucial role in addressing the regional shortage of plasma-derived medicinal products (PDMPs), particularly in low- and middle-income countries (LMICs). It provides a platform for experts to share their expertise and drive multi-stakeholder collaborations. While several PDMPs are acknowledged by the World Health Organization (WHO) as life-saving therapeutics on the Model List of Essential Medicine for treating various chronic and acute life-threatening diseases, there are still many inadequacies in the availability and affordability of PDMPs. These challenges arise from insufficient domestic supplies of plasma suitable for fractionation, as well as a lack of technical and financial capabilities to implement contract or domestic plasma fractionation programmes. At two separate dialogue forums organized by the APPLN in 2023, experts discussed the unmet needs of PDMPs for individuals living with haemophilia and immunodeficiencies in the region. They also highlighted the limited access to early diagnosis and patient-centred care in several LMICs. To address these issues, there is an urgent need to increase the availability of high-quality domestic plasma for fractionation. Adopting a stepwise approach to utilize unused recovered plasma and establishing contract fractionation programmes could be viable strategies to potentially enhance PDMP availability in LMICs. However, achieving this goal requires improving existing domestic infrastructures for blood collection, implementing adequate policy reforms and fostering competent local leadership. Ultimately, there is no 'one-size-fits-all' strategy for securing safe plasma proteins for all patients in need. Collaborative efforts are essential for achieving progressive self-sufficiency in PDMPs.

Keywords

fractionation, haemophilia, low- and middle-income countries, patients' needs, plasma, plasma-derived medicinal product, prophylaxis

Highlights

- Several plasma-derived medicinal products (PDMPs) have been classified as 'Essential Medicines' by the World Health Organization; however, access to therapies with these products is limited in many parts of world, particularly in low- and middle-income countries (LMICs).
- The reasons for the low availability of PDMPs in LMICs include limited public awareness and medical expertise, limited medical coverage, plasma quality that does not meet fractionation standards, lack of access to technology for fractionation and a lack of well-established and effective policies and regulations.
- Plasmapheresis is key to enabling the collection of larger volumes of plasma for fractionation, and the establishment of a contract fractionation programme could be a viable strategy to potentially increase the availability of PDMPs in LMICs.

INTRODUCTION

The Asia-Pacific Plasma Leaders' Network (APPLN) held two separate dialogue forums in 2023: the first was held virtually on 24 May, and the second was held on 21 September in Ho Chi Minh City, Vietnam, featuring lectures from prominent experts and leaders from the field of plasma and blood transfusion. The experts discussed the status of plasma and blood collection in the region, with an emphasis on current gaps and potential strategies to overcome challenges, with the shared goal of achieving self-sufficiency across the region to meet the patient needs. Both forums were chaired by Thierry Burnouf and co-chaired by Sonu Bhatnagar and were attended by around 150 healthcare professionals from 12 Asia-Pacific countries besides the speakers. This report provides excerpts from both the meetings.

In a welcome message for the 24 May meeting, Sonu Bhatnagar noted on the crucial role of healthcare professionals—from medical professionals to researchers, policymakers, regulators or representatives of a blood and plasma organization—in the life-saving endeavour of providing a safe and reliable supply of blood and plasma products. There are several challenges that need to be faced, from addressing the increase in demand for blood and plasma products while navigating the complexities of producing quality plasma for fractionation, mastering plasma fractionation technologies, facing global shortages, making products affordable and addressing emerging infectious diseases to evolving medical technologies and changing demographics. The APPLN serves as a platform for leaders and experts in the field to share their expertise that will improve and drive innovation of sustainable plasma collection, testing and fractionation programmes in the region. By enabling blood and plasma services across the region to share experiences and learn from each other, the APPLN hopes to drive Asia-Pacific countries towards progressive self-sufficiency and guarantee of supply in at least essential plasma-derived medicinal products (PDMPs) and fuel the future of all PDMPs in the region.

As chairperson, Thierry Burnouf acknowledged the lifesaving role of PDMPs for persons living with bleeding disorders, immune deficiencies and other pathologies based on hereditary and acquired deficiencies in plasma proteins, highlighting how it is of paramount importance that PDMPs reach the people in need in Asia Pacific and worldwide. There are mixed scenarios faced by the Asia-Pacific region—some countries doing well with their blood transfusion systems, obtaining every drop of plasma from whole blood and establishing efficient dedicated plasmapheresis collection systems, but others still working to establish and strengthen the building blocks of an efficient blood transfusion system. These disparities have resulted in a gap in access to PDMPs. The APPLN meetings serve as a platform to discuss strategies to bridge such gaps in a pragmatic and accessible way.

UNMET NEED FOR PDMPs IN THE ASIA-PACIFIC REGION: THE PRIMARY IMMUNODEFICIENCY PATIENTS' PERSPECTIVE

Johan Prevot shared that the International Patient Organisation for Primary Immunodeficiencies (IPOPI) is an association of national primary immunodeficiency (PID) patient organizations that is dedicated to improving access to early diagnosis and patient-centred care, building capacity and support for national member organizations, educating and promoting knowledge and data-sharing and strengthening multi-stakeholder cooperation. The key goal of the IPOPI is to improve the lives of people living with PID worldwide.

PIDs, sometimes referred to as inborn errors of immunity, are rare disorders. The understanding of these disorders has improved tremendously over the last few years and PIDs are no longer defined by a tendency for infections alone. The clinical presentation of PIDs is variable, and PID patients with non-infectious complications are increasingly recognized with features of immune dysregulation such as autoimmunity, inflammation, lymphoproliferation, allergy and malignancy.

Immunoglobulin replacement therapy (IRT) is a treatment with a polyvalent immunoglobulins (Ig) product given either intravenously (IVIG) or subcutaneously (SCIg) that needs to be provided on a lifelong prophylactic basis. Igs, which have been shown to decrease the incidence of infections and rate of hospitalization, prevent long-term deterioration in organ function and reduce mortality from acute bacterial infections [1], are classified as 'Essential Medicines' by the World Health Organization (WHO). These Ig products should not be

viewed as generic medicines, but rather as products with specific characteristics, specifications or modes of administration, leading to treatment options that could be tailored to suit patient needs and circumstances to provide optimal safety as well as medical and quality-of-life outcomes [1–3]. For PID patients, a personalized approach represents the gold standard approach to their care.

It is estimated that there are currently 6 million people globally living with PID, and an estimated 80% of PID patients worldwide do not have access to appropriate therapy [4]. There is a general imbalance in global Ig consumption—North America, for instance, represents only 5% of the world's population but consumes 48% of the world's Ig; whereas the Asia-Pacific region comprises 56% of the world's population but consumes only as little as 20% of global Ig [5, 6].

According to country-specific data on patient-reported challenges, which were shared at the IPOPI Regional Asian PID Meeting held in Kuala Lumpur, Malaysia, in November 2022, there are still relatively few PID experts in countries like China, and many doctors from the less developed cities have no experience with treating PID. Patients often cannot receive accurate and timely treatment, and commonly suffer repeated infections. Medical coverage for Ig therapy varies significantly across cities, with subsidies ranging from 10% to 90%. In certain hospitals, Igs are categorized as drugs that do not have direct therapeutic effects. While they may not directly treat the underlying condition, Igs play a crucial role in modulating the immune response or preventing infections. Consequently, patients may face restricted access or receive inadequate doses due to strict drug control policies. In Malaysia, intravenous Ig is available nationwide; however, dosages are often insufficient due to cost. IVIG treatment centres are typically found in major hospitals and cities. This treatment is also administered to patients who are not in a critical condition and whose clinical status lacks strong confirmation or evidence. SCIg treatment is not an available alternative and is currently being adopted only by university hospitals and Ministry of Higher Education facilities. Similarly, in Indonesia, there is limited access and support facilities for PID patients, in addition to low public, governmental and medical awareness of PID. Therapeutic options such as IVIG are limited, and bone marrow transplantation is unavailable. IVIG is only partially reimbursed but some progress has been made recently in obtaining full reimbursement at certain top referral hospitals. In the Philippines, it was reported that the current process to request for medical assistance from the government can be difficult and patients often must approach different individuals and agencies when seeking assistance from government hospitals. Access to treatment is often irregular and can be difficult for patients who live far away from hospitals. At present, both patients and doctors are pushing for a streamlined process that can help patients obtain uninterrupted regular assistance such as IVIG infusion. The IPOPI PID Life index available on IPOPI's website is a useful resource providing an overview of the PID environment in different countries [7].

When considering strategies on how to improve plasma availability, the needs of patients should play a key factor in determining the optimal collection of blood and plasma in order to maintain safe blood availability for transfusion while focusing on improving the plasma availability. There is a need to increase the availability of high-quality plasma for fractionation and also an urgent need to improve good manufacturing practice (GMP) practices so as to enable fractionation into products for patients. Plasmapheresis is key to collect larger volumes and has been the key contributor to the growth of collection of plasma for fractionation in the last few decades. For plasma availability to improve, it is also important to have multi-stakeholder collaborations and dialogue around key issues pertaining to regulations, legislation and policies and focus on patient-centred approaches. It is also important to recognize the valuable role of both public and private sectors in improving plasma availability.

IMPROVING STEPWISE SUPPLIES WITH SAFE PLASMA PROTEIN PRODUCTS IN RESOURCE-CONSTRAINED COUNTRIES

Jean-Claude Faber noted that the lack of therapeutic products for patients with bleeding disorders (inherited or acquired) in low- or middle-income countries (LMICs) often leads to inadequate treatment, pain and suffering, crippling, illness and, in some cases, premature death. While it is well known that in most LMICs there is insufficient supply of appropriate anti-hemophilic medicinal products, at the same time, large volumes of plasma are discarded. Several initiatives have been undertaken to address this, including WHO's 'Achilles Project', the World Federation of Hemophilia (WFH) Guidelines on the Management of Hemophilia and the International Coalition for Safe Plasma Proteins (ICSPP).

The WHO Achilles Project sought to increase the availability of safe blood-derived products for developing countries by supporting the implementation of nationally validated quality and safety standards for blood establishments using the expertise and experience from developed countries [8]. The initiative called upon member states to improve the quality and safety of blood and blood products, and to avoid wastage of plasma which can be used for fractionation of PDMPs. The third edition of the WFH Guidelines, which was published in 2020, highlighted that clotting factor concentrates (CFCs) are the treatment of choice for persons with haemophilia due to their safety and efficacy for the treatment and prevention of bleeds and that the use of non-pathogen-reduced cryoprecipitate can be justified only in situations where CFCs are unavailable. The guidelines also acknowledge that access to CFCs is limited in many parts of world [9].

The International Society of Blood Transfusion (ISBT) Working Party on Global Blood Safety initiated the creation of ICSPP as a global coalition to advance access to safe plasma and plasma proteins in LMICs. The main goal of the ICSPP is to address the insufficiency of PDMPs in many LMICs (due to unavailability or unaffordability) and the consequent suffering and early mortality of patients with bleeding disorders and immune deficiencies as a result of inadequate treatment [10]. The pilot project of the ICSPP—Local preparation of

pathogen-reduced cryoprecipitate at the National Blood Transfusion Center in Dakar, Senegal—which was started in July 2022, is ongoing and making good progress. This pilot project is expected to last until the end of 2024 and should produce evidence on the feasibility, safety, quality and efficacy of 'substitute' therapeutic products, as long as CFCs are not accessible. As part of the project's second phase, pathogen-reduced IVIGs will be produced and field-tested.

QUALITY PLASMA FOR FRACTIONATION IN EMERGING COUNTRIES

René Buechel highlighted that the production of plasma-derived therapies (PDTs) is a complex, lengthy and capital-intensive process requiring up to 12 months from plasma donation to product delivery. To date, most of the plasma for global manufacturing of PDTs is collected in the United States, and relatively little plasma for fractionation is collected in the Asia-Pacific region. All plasma for manufacturing, for example, in the European Union (EU) is required to meet the quality requirements that are stipulated in the Guideline on the scientific data requirements for a Plasma Master File (PMF) [11] on the following topics: blood establishments, epidemiological data, traceability of donations, details on serological and NAT testing of blood/plasma donations and plasma pools; and overall safety strategy including selection/exclusion criteria for donors, inventory hold period and look-back procedures. Additionally, manufacturers in the EU are required to comply with a large body of regulations at the EU level as well as those of the national member states.

Restrictive regulations and policies can hinder plasma donation in LMICs, which in turn hinders fractionation. There are several roadblocks to plasma donation including the lack of plasmapheresis infrastructure, lack of donor compensation (including non-monetary compensation for time and effort), limited donor outreach and awareness activities by public authorities and the limited value recognition of PDTs. Local health systems may be able to reduce the barriers to cross-regional cooperation on the collection and manufacturing of blood products via a strategic, regulatory and infrastructure three-pronged approach. Strategically, there is a need to deepen understanding of how improved access to PDMPs can positively impact health economics [12–14]. From a regulatory perspective, regulations need to be updated to meet internationally recognized quality standards for recovered plasma, in addition to introducing science-based regulations that will enable or improve cross-border movement of plasma, for example, for contract fractionation. From an infrastructure perspective, there is a need to deepen understanding of the patient need for PDMPs, improve donor management systems and facilitate logistics and resources.

The PIC/S (Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme) Good Practice Guidelines for the Blood Establishments and Hospital Blood Banks is a freely available guidance (most recently updated in 2021) that stipulates all quality measures from donation to GMP. By adopting PIC/S standards, countries can better comply with requirements from regulators as well as fractionators [15].

ENSURING A SAFE SUPPLY OF PDMPs IN LMICs

Yuyun Siti Maryuningsih reiterated that the WHO designated many blood products as essential medicines, as blood transfusions can save lives and patients around the world depend on transfusions and plasma products daily to stay healthy. In 2023, native and pathogen-reduced cryoprecipitate was added to the WHO Model List of Essential Medicines [16], a move that highlighted the importance of this product, when virus-safe, in LMICs where the best treatments may not always be available. The National Institutes of Health Clinical Center noted in their endorsement that while CFCs are the preferred products, the availability of pathogen-reduced cryoprecipitates in LMICs can provide patients with inherited and acquired bleeding disorders with alternative treatments when CFCs are unavailable or unaffordable [17].

There are several reasons for the low availability of PDMPs in LMICs, including insufficient plasma quality to meet fractionation standards, lack of technology for fractionation and the limited presence of plasma fractionators in Asia and Africa (an issue compounded by the fact that the establishment of a local plasma fractionation facility requires high investment). There are currently at least four World Health Assembly (WHA) Resolutions in place that are driving the WHO strategy in blood to address the issues around PDMP availability in LMICs: Resolution WHA 63.12 (2010) on the availability of safe and good-quality blood, blood components and PDMPs; WHA 67.20 (2014) on the strengthening of regulatory systems; WHA 72.6 (2019) on the global action on patient safety; and WHA 76.5 (2023) on strengthening diagnostic capacity. In 2022, it was requested that the Director-General (WHO) continue to report to the Health Assembly every 2 years until 2030 on the progress made in the implementation of Resolution WHA 63.12 (2010) on the availability, safety and quality of blood products.

Clinicians and other health personnel also play a key role in ensuring safe blood products and transfusions. They can do this by monitoring the storage and transportation of blood components, using blood components appropriately and based on clinical indications and monitoring transfusion adverse reactions through a haemovigilance system [18]. Another item to support the promotion of safety is the establishment of a hospital blood transfusion committee and implementation of patient blood management. Under patient blood management, there are three pillars that need to be taken into consideration: detection and management of anaemia and iron deficiency; minimization of blood loss and optimization of coagulation; and leveraging and optimizing patient-specific physiological tolerance of anaemia [19]. Clinicians can greatly influence the availability of PDMPs for treatment, as demand for PDMPs will ultimately drive the production of safe plasma protein products.

UNDERSTANDING THE CLINICAL NEED OF PATIENTS WITH BLEEDING DISORDER

In Vietnam, noted Bach Quoc Khanh, blood service centres are jointly managed by the country's Ministry of Health, the National Steering Committee for Voluntary Blood Donation (NSCVBD) and the Vietnam Red Cross Society (VRCS). In 2022, a total of 1,468,824 blood units (including 1,370,785 whole blood units and 98,039 platelet units from single donors) were collected, which was an 11% increase compared with the quantity collected in 2021. In the same year, 2,575,171 blood component units were produced and supplied to 684 healthcare departments, of which 52% were red blood cell (RBC) concentrates, 28.5% plasma, 6.5% pooled platelet, 5.2% cryoprecipitates and 4% single-donor platelets. Access to PDMPs in Vietnam could potentially be increased if there were a contract fractionation programme in place; however, this is currently not possible in Vietnam as it is an LMIC, and such a programme would require high investment. There is also a need to further develop GMP in Vietnam blood establishments as, at present, only one hospital in Vietnam carries out GMP plasma production.

Nguyen Thi Mai noted that the treatment of bleeding disorders would depend on the type of disorder and may include medicines (i.e., antifibrinolytic agents, desmopressin, immunosuppressive medicines, vitamin K, monoclonal antibodies) and factor replacement therapy (CFCs, fresh frozen plasma, bypassing agents). Different treatments may lead to different outcomes but, ultimately, a haemophilia patient who receives proper treatment may have a chance to lead a significantly better life.

Prophylaxis consists of regular administration of therapeutic products aimed at maintaining haemostasis to prevent bleeding. It is recognized as a key strategy to change haemophilia treatment history and can enable people with haemophilia to lead healthy and active lives like non-haemophiliacs [20]. Home-based prophylaxis programmes may increase compliance and allow people with haemophilia to live relatively normal lives. However, there are many challenges with prophylaxis, ranging from cost, reimbursement, patient ability and product availability. In limited-resource countries, cost is the biggest barrier. As home treatment is yet to be approved in Vietnam, 90% of haemophiliacs receive on-demand treatment at hospitals. Low-dose prophylaxis is an effective strategy and should be adopted in limited-resource countries such as Vietnam, with adequate adaptation of policies to help more patients to access treatment. A comprehensive care plan is also advised for haemophilia patients, covering routine screening for inhibitors and transfusion-borne viruses, genetic diagnosis and coordination with related specialties (i.e., rehabilitation, musculoskeletal, surgery, obstetrics).

STRATEGIES FOR DONOR RECRUITMENT AND SECURING SOURCE PLASMA IN JAPAN

Hideo Nakanishi and Masako Kataoka shared that, in Japan, the supply of albumin products has increased steadily since 2020. The supply of domestic Ig peaked in 2021 and has decreased since then; however, this decrease may be due to the temporary halting of production as a result of repairs at a domestic PDMP fractionation facility. In 2022, there were 2.52 million blood donors, of whom 2.32 million were whole-blood donors and approximately 340,000 were apheresis donors. Overall, the supply of red blood cell products in Japan has increased in recent years, alongside an increase in the amount of whole blood donated.

The Japanese Red Cross Society (JRCS) is, to date, the only blood collection service entity in Japan. The initiative for the establishment of a second blood collection entity was discussed when concerns were raised in the National Council by a group of international PDMP manufacturers that Japan may not be able to enjoy a sufficient supply of Ig products in the future, claiming that the JRCS alone may not be able to secure enough plasma for fractionation. The establishment of a new Blood Collection Consortium led by plasma fractionators and other companies was thus proposed, with the goal of stabilizing the future supply of Ig products. However, in response, the JRCS has reaffirmed its willingness and capability to secure plasma from blood donations. The JRCS also noted that the recruitment of apheresis donors (who cooperate frequently in blood donations with the JRCS) by other blood collection service entities may greatly affect the availability of blood for transfusion. Lastly, based on the proven results of the blood collection and the stable supply of blood in Japan over the past 60 years, the JRCS restated its mission to continue securing all the blood needed by the people in Japan and that it will do its best to secure it. This commitment has received support from the members of the National Council.

The JRCS has implemented several strategies to improve the efficiency of plasma collected for fractionation. To increase the volume of plasma collected per plasmapheresis donor, there are guidances on selecting donors with higher body weight for apheresis donation and strategies for retaining these donors for future collections. Appointments for blood donations and pre-donation check-ups can also be implemented via smartphones messages. Japanese PDMP manufacturers also carry out video campaigns to promote a better understanding of PDMPs and the necessity of these products.

In a pilot project aimed at meeting the growing demand for source plasma, a blood donation room dedicated to source plasma collection was opened at the Tokyo Railway Station in 2023. The goal of this new blood donation facility was to move away from the initial concept of simply collecting blood to a new concept where a private relaxing space was provided to donors at a convenient location. Donors are encouraged to take their time and make full use of the location's facilities, which include private workstations and refreshments. Early figures based on reservation rates indicate that the number of donors at the facility has increased steadily from May (106.75%) to August (128.7%) 2023.

Future initiatives to increase and improve the collection of source plasma in Japan include reinvigorating interest in blood donations which has waned since the COVID-19 pandemic; improving the accessibility of blood donation appointments by increasing awareness of the smartphone app; improving and broadening awareness of blood

donation among the younger generation; and easing restrictions on blood donation among the elderly. The JRCS also aims to establish more blood donation rooms dedicated for source plasma collection, trialling more efficient equipment and improving operational efficiency.

STRATEGIES TO ESTABLISH CONTRACT FRACTIONATION PROGRAMME

Thierry Burnouf stressed that the establishment of a contract fractionation programme is a viable strategy to potentially increase the availability of PDMPs in LMICs. He highlighted several important elements that could aid in the success of a contract fractionation programme, including governmental and regulatory support, support from blood donor organization, sufficient volume of quality plasma, GMP collection of plasma, auditing of the fractionator and a transparent process with public support and understanding.

There are several reasons why a contract fractionation programme is a reasonable step forward for LMICs. It enables access to a plasma fractionation facility without major capital investment while functioning on a relatively fast-track scenario to ensure product supply for patients using domestic plasma. It is a good testing and learning phase on the regulatory requirements of plasma fractionation and a way to better understand fractionation technology. In terms of cost and clinical value, the utilization of unused recovered plasma for fractionation is economically justifiable, as the cost of plasma makes up 40% of the cost of PDMPs [21]. A fractionation programme also provides some guarantee of supply that could aid in improved long-term strategic independence in the supply of PDMPs.

A viable strategy for initiating a plasma for fractionation programme in LMICs would be to start off with recovered (prepared from whole-blood donations) and concurrent plasma (plasma that is collected as a by-product of plateletpheresis collection), as this can avoid the risks of 'competition' between whole-blood and plasma donations while contributing to improving the GMP of blood component production. Plasmapheresis is a viable option if there is a need for additional plasma for fractionation. When referring to apheresis, it is important to keep in mind that there are two key types of plasma that can be collected by an apheresis procedure: standard plasma, which can be used to manufacture all PDMPs (including IVIG, Factor VIII, Factor IX, albumin, etc.), and hyperimmune plasma, which can be used to manufacture hyperimmune IgGs, several of which are listed as WHO essential medicines.

While this would vary according to country, there are several key items to keep in mind in a legal contract for plasma fractionation. Clear specifications about the quantity and quality of plasma, such as the volume and frequency of plasma supply and the quality standards the plasma, must be met. Details about delivery and transportation (including responsibility for transportation and specific conditions required), processing specifications and details on the expected product yield are also key items. The contract should outline clear terms regarding the cost of processing, including payment schedules, details about the ownership of fractionated products (especially if there are multiple products derived from plasma) and any clarification on liabilities and indemnities.

Ultimately, there is no 'one size fits all' when it comes to a strategy for securing safe plasma proteins for all patients in need, but contract plasma fractionation is a meaningful solution for paving the way to stepwise access to safe plasma proteins. We may conclude from the presentations and discussions at both meetings that APPLN is committed to working together to improve the safe supply of PDMPs in the region.

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All authors reviewed and edited summaries of their respective presentations, S.B. and T.B. edited and reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

S.B. is currently an Abbott employee and company shareholder. R.B. is currently a Takeda Pharmaceuticals employee. T.B. is the Secretary of the Working Party for Global Blood Safety of the International Society of Blood Transfusion and has received travel support from Abbott to chair the APPLN meeting. J.P. is Executive Director of IPOPI; IPOPI regularly receives support from a broad range of companies involved in the manufacture of immunoglobulin therapies and the field of primary immunodeficiencies. He has received financial support for this lecture from Abbott. J.-C.F., Y.S.M., B.Q.K., N.T.M., H.N. and M.K. have no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Vox Sanguinis ISBT International Society of Blood Transfusion

LETTER TO THE EDITOR

Non-neutralizing antibody profiles against hepatitis B virus: A comparative study of Japanese- and US-donor-derived intramuscular human hepatitis B-specific immunoglobulin preparations

Intramuscular preparations of human hepatitis B-specific immunoglobulin (HBIG) contain high titres of neutralizing antibodies specific to hepatitis B virus (HBV) surface antigens (anti-HBs antibodies), providing immediate passive immunity against HBV infection. Consequently, HBIGs are administered for prophylaxis against mother-to-infant HBV transmission, typically in conjunction with active immunization using the hepatitis B vaccine, following recommendations from the World Health Organization (WHO) [1]. Although mother-to-infant transmission of HBV is less prevalent in Japan compared with other Asian countries, it remains the primary route of HBV infection in newborns [2, 3]. This underscores the clinical significance of a combined prophylactic approach, given that approximately 90% of neonates infected with HBV develop chronic hepatitis B [1]. Nonetheless, this combination therapy does not ensure complete prevention of HBV transmission [2]. Therefore, serological testing remains essential for infants born to mothers with HBV infection, while acknowledging potential factors that can complicate the interpretation of test results.

Our pharmacovigilance department recently received case reports describing elevated levels of immunoglobulin G (IgG) antibodies against hepatitis B core antigen (anti-HBc) in infants who received HBIG prophylaxis. Although the presence of anti-HBc antibodies in certain commercially available intravenous immunoglobulins has been documented [4], limited information is available on the presence and variability of non-neutralizing antibodies against HBV in HBIG products. To address this gap, we evaluated the concentrations of anti-HBc antibodies and antibodies against hepatitis B early antigen (anti-HBe) in two HBIG brands currently available in Japan. These brands were manufactured from plasma that was collected in Japan (including both recovered plasma and source plasma) or in the United States (source plasma).

We conducted an analysis of five lots from each brand using one-step competitive enzyme immunoassay kits: E-test TOSOH II (HBcAb) and E-test TOSOH II (HBeAb) (Tosoh Corporation, Tokyo, Japan). Because anti-HBc and anti-HBe antibodies are not included in routine quality control examinations for HBIG products, we developed quantification methodologies in advance according to the Japanese regulations for biological pharmaceuticals [5]. The titres of each antibody were quantified using the WHO International Standard First International Standard for anti-HBc (code 95/522) and the WHO First International Standard for anti-HBe (code 129095/12).

Our analysis revealed the presence of anti-HBc and anti-HBe antibodies in both HBIG brands (Table 1). This finding suggests the potential for their detection by serological testing and raises concerns regarding iatrogenic positivity. Notably, products fractionated from domestic plasma (Brand A) exhibited significantly higher antibody content than those derived from US plasma (Brand B) (Table 1). This observation suggests that the origin of the antibodies detected during testing may not be solely limited to passively acquired maternal antibodies or those produced by the infants themselves, particularly when administering Brand A products.

Japan has a unique system in which a single organization, the Japanese Red Cross (JRC), oversees the entire blood donation process, including collection, testing and processing. In 1989, the JRC launched a nationwide HBV screening program employing a combined testing approach for both anti-HBc and anti-HBs antibodies. Since August 2012, blood units with positive anti-HBc levels have been deemed suitable for transfusion or as source material for plasma-derived therapeutic products, provided that the concentration of anti-HBs antibodies exceeds 200 mIU/mL [6]. This policy may have contributed to elevated levels of anti-HBc and anti-HBe antibodies in Brand A products. Conversely, the reasons behind the lower titres of anti-HBc and anti-HBe antibodies observed in Brand B products remain unclear. One possible explanation could be the higher prevalence of vaccination-induced immunity among US donors compared with their Japanese counterparts. This hypothesis is supported by specialized plasma donation programs implemented by certain manufacturers, which encourage donors to receive vaccinations against specific pathogens to increase hyperimmune globulin titres, thereby facilitating the collection of suitable source plasma for hyperimmune globulin production.

It is essential to acknowledge that the plasma utilized for both HBIG products is subjected to meticulous screening in both countries, encompassing serological assay and nucleic acid amplification test (NAT), to confirm the absence of detectable levels of hepatitis B surface antigen (HBsAg) and HBV DNA. In addition, the clearance of

TABLE 1 Anti-HBc and anti-HBe antibodies in two commercially available HBIG products.

Brand	Plasma collection	Lot	Unit	Antibody	
				Anti-HBc	Anti-HBe
Brand A	Japan	A-i	IU/mL	583.4 ± 27.7	47.0 ± 2.8
		A-ii		611.3 ± 16.0	45.1 ± 4.6
		A-iii		477.1 ± 12.5	36.1 ± 4.1
		A-iv		581.3 ± 28.9	47.8 ± 2.4
		A-v		666.5 ± 50.9	54.5 ± 1.8
Brand B	United States	B-i		2.0 ± 0.1	0.2 ± 0.0
		B-ii		2.1 ± 0.1	0.2 ± 0.0
		B-iii		14.3 ± 0.6	1.4 ± 0.1
		B-iv		14.7 ± 0.2	1.5 ± 0.0
		B-v		15.4 ± 0.5	1.5 ± 0.2

Abbreviations: Anti-HBc, antibodies against hepatitis B core antigen; Anti-HBe, antibodies against hepatitis B early antigen; HBIG, human hepatitis B-specific immunoglobulin.

TABLE 2 Measures implemented to prevent the transmission of HBV via two HBIG products.

Safety measures	Methods principles		Brand	
			Brand A	Brand B
Screening	Serological assay	HBs antigen	Not detected	Not detected
	NAT	HBV DNA	Not detected	Not detected
Viral clearance	Inactivation/removal		Ethanol precipitation Nanofiltration	Ethanol precipitation PEG precipitation Pasteurization Nanofiltration

Abbreviations: HBIG, human hepatitis B-specific immunoglobulin; HBs antigen, hepatitis B virus surface antigen; HBV, hepatitis B virus; NAT, nucleic acid amplification test; PEG, polyethylene glycol.

HBV during the manufacturing processes was estimated using appropriate model viruses (Table 2); the ethanol precipitation and nanofiltration processes, which are common to both products, were indicated to remove HBV with an adequate safety margin. Furthermore, the HBIG products contain highly concentrated anti-HBs antibodies, which are neutralizing antibodies that prevent HBV infection. Collectively, these facts render the risk of HBV transmission via these products virtually nonexistent, as no such case reports have been received by our pharmacovigilance department.

In conclusion, our study unveiled the presence of both anti-HBc and anti-HBe antibodies in HBIG products. Furthermore, we noted significant variations in antibody concentrations between the two brands, likely attributable to disparities in donation management practices between Japan and the United States. Our findings suggest that HBIG preparations could serve as a source of the identified antibodies, potentially complicating the interpretation of serological assays.

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T.M. and K.M. conceived the research; H.O. performed the experiments; H.O., S.H., T.M. and K.S analysed the data; T.M. wrote the manuscript; and K.M. supervised the research and reviewed 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 upon request from the corresponding author.

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ERRATUM

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Correction to 'Determining the impact of current Canadian stem cell registry policy on donor availability via dynamic registry simulation'

Blake J, Kanz G, Seftel MD, Allan D. Determining the impact of current Canadian stem cell registry policy on donor availability via dynamic registry simulation. *Vox Sang*. 2024;119:598–605. http://doi.org/10.1111/vox.13619

In paragraph 2 of the 'Non-Caucasian searches at historic rates (Patient Case P1)' section, the text 'Simulated patients were matched with simulated patients, assuming that the CBSSCR dynamically evolves over time' was incorrect. This should have read: 'Simulated patients were matched with simulated donors, assuming that the CBSSCR dynamically evolves over time'.

We apologize for this error.

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EVENTS

See also: https://www.isbtweb.org/events.html

11–14 November 2024	WHO Webinar: Strengthening Blood Systems Through Effective Blood Regulation. https://who.zoom.us/webinar/register/WN_tgccrtP8Sd-1Ko0hnuwjeg#/
13 November 2024	ISBT Corporate Partner Webinar: Could It Be Drugs? How to Differentiate AIHA from DIIHA. https://www.isbtweb.org/events/isbt-corporate-partner-webinar-could-it-be-drugs-how-to-differentiate-aiha-from-diiha.html
14–15 November 2024	BlooDHIT 2024. https://bloodhit.com/registration/
20–21 November 2024	RCPath & SHOT Advances in Transfusion Symposium. https://www.rcpath.org/event/advances-in-transfusion-medicine-2024-joint-rcpath-shot-symposium.html
21–23 November 2024	TRANSCON 2024. https://www.transcon2024.in/
28 November 2024	ISBT Corporate Partner Webinar: Strategies to Maintain a Sustainable Supply of Platelets. https://www.isbtweb.org/events/isbt-corporate-partner-webinar-strategies-to-maintain-a-sustainable-supply-of-platelets.html
14–15 January 2025	EDQM Blood Conference: Innovation in Blood Establishment Processes. https://www.edqm.eu/en/edqm-blood-conference