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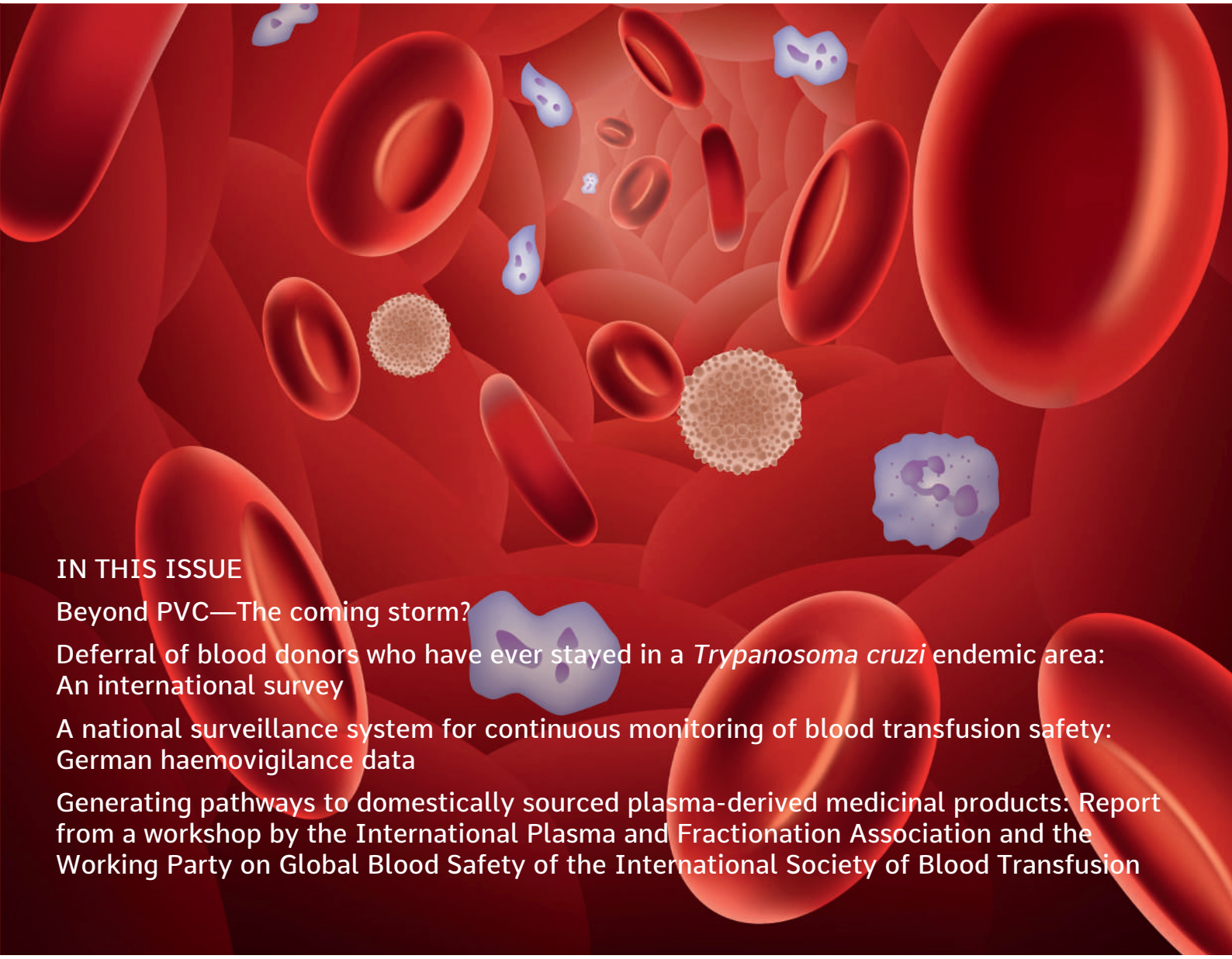

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Vox Sanguinis

International Journal of Blood Transfusion

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3. Transfusion-transmitted Disease and its Prevention: Identification and epidemiology of infectious pathogens transmissible by blood; Donor testing for transfusion-transmissible infectious pathogens; Bacterial contamination of blood components; Pathogen inactivation.
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5. Haemovigilance: Near misses, adverse events and side effects throughout the transfusion chain; Monitoring, reporting and analysis of those adverse events and side effects; Activities aiming at increasing the safety of the whole transfusion chain; Standardization of the definition of adverse events and side effects.
6. Patient Blood Management: Caring for patients who might need a transfusion; Transfusion indication decision-making process; Search for the optimal patient outcomes; Study of transfusion alternatives; Autologous blood transfusion.
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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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COMMENTARY

Vox Sanguinis ISBT International Society of Blood Transfusion

Beyond PVC—The coming storm?

INTRODUCTION

Blood collection packs made from polyvinylchloride (PVC) were introduced in 1950, and PVC has remained the material of choice for over 60 years. However, environmental and health concerns, currently focused on the phthalate plasticizer used with the PVC, have led to regulatory action, which is driving a move away from the current materials [1].

Replacement of the Di(2-ethylhexyl) phthalate (DEHP) plasticizer in PVC blood packs has been seen as the end game for blood establishments (BEs) in Europe and those relying on European manufacturers. However, forthcoming regulatory revisions make it clear that this is the starting gun for a revolution in chemical regulation, not the finishing line. This will inevitably affect medical devices in general and blood packs in particular.

CURRENT BLOOD PACKS

Blood packs have remained essentially unchanged in materials and solutions since the early 1970s with DEHP-plasticized PVC, citrate–phosphate–dextrose (CPD) anticoagulant and saline–adenine–glucose–mannitol (SAGM) red cell additive. DEHP migrates from the PVC into cell membranes, which it stabilizes. Storage of SAGM red cells in DEHP-PVC for 42 days has been proven to be acceptable in terms of quality and clinical outcome [2]. The original work was placed into the public domain, allowing development and routine use of numerous interchangeable products. Despite the availability of many arguably better alternatives, the European-influenced transfusion community has stayed with this combination. Now that DEHP must be replaced, we find ourselves in the regrettable position where many years of lack of consensus, collaboration or sufficient action by BEs and manufacturers have left us with a difficult and urgent issue to address.

BEYOND DEHP

Replacing DEHP can be achieved via several options. One option is to replace DEHP with something less toxic. The choice of alternative plasticizers is constrained by the requirement for their inclusion in the European Pharmacopoeia (EP), which lists four alternatives. However, all plasticizers have an environmental impact through the complexity of their supply chain and 'regrettable substitutions' of hazardous chemicals with alternatives can bring alternative risks [3]. A second option is to use PVC with zero migration of plasticizer, but this has proven to be prohibitively expensive [4].

European BEs are likely to adopt a range of different combinations of plastic–plasticizer–additive solution offered by the remaining European-based blood pack manufacturers, replacing the single de facto standard and effectively confining each BE to a single-source supply. While each proposed solution may have robust supporting data, the question of how these differing products can exist interchangeably in the complex scenario of blood collection, processing, distribution and transfusion remains to be answered [5].

A more strategic approach would be to move away from PVC altogether, as the requirement to remove DEHP does not mark the end of environmental regulation. The EU restrictions roadmap is part of the chemical strategy for sustainability towards a toxic-free environment. It classifies chemicals into three pools based on the priority for regulation and the work undertaken so far [6]. This will have a significant impact on blood pack manufacture.

PVC—A MATERIAL WHOSE TIME IS RUNNING OUT

PVC is an extremely useful and cheap material with diverse applications. For blood bag manufacture, plasticized PVC is ideal as it is flexible, can withstand extremes of temperature during steam sterilization and flash freezing, enables radio frequency sealing of the bag films, and allows for chemical bonding. However, it is an environmental contaminant, challenging to dispose of and has a substantial carbon footprint [7]. It is manufactured from carcinogenic vinyl chloride monomer [8] and 60% chlorine. Chlorine is obtained from seawater in a high-energy process using either mercury cells, asbestos diaphragms or membranes containing perfluoroalkyl and polyfluoroalkyl substances (PFAS). Classification of PFAS, known as 'forever chemicals' in the highest priority group of the restrictions roadmap, has the implied impact of banning PVC manufacture in the European Union. Further, the presence of PFAS in blood packs has not yet been fully described, but initial indications are that they are present in filters and in machinery used in blood pack manufacture. A few PFAS are already banned, but a proposal for a complete ban is under consideration. Under the proposal, the use of PFAS in medical devices would cease by 2042, with significant implications. While exemptions for medical devices may be made, the cycle of regulation and deferral seen with DEHP seems set to start again.

The roadmap also contains an entry for 'PVC and its additives' in the second priority group. The European Union has previously considered that the lack of end-of-life options for PVC prioritizes it for restriction [9]. Sustainable or recycled PVC is not viable due to cost and the poor quality of recycled resin, before consideration of contamination with blood. Its incineration produces dioxins, polychlorinated biphenyls and other harmful substances [10, 11]. Environmental groups within the European Union have called for a complete phase out of the plastic by 2030.

PVC-FREE BLOOD PACKS

There have been previous attempts to develop PVC-free blood packs. Polyolefin packs with alternative additive solutions were successful for red cell concentrate manufacture but with a reduced shelf-life. Sealing of the bags using standard equipment was not possible and the project ended without a commercial product being produced [12].

More recently, a PVC-free pack replicated the properties of current blood packs, including sterilization, cold storage and welding [13, 14]. The physical parameters of the pack compared favourably with DEHP-PVC; however, the pack was not used to store blood components, so no direct comparison has been performed yet. This work may provide a less environmentally damaging plastic pack with comparable properties to current packs; development would require collaboration between BEs, funding bodies and manufacturers.

LESSONS LEARNED FROM DEHP REGULATION

The history of DEHP-free blood packs provides lessons relevant to the inevitable regulation of all parts of the PVC supply chain under the European Green Deal. DEHP-PVC-SAGM provided a single combination for BEs and blood pack manufacturers, but the approach to removal of DEHP relied on manufacturers to develop alternatives in isolation and in a competitive market. The outcome of at least two different combinations introduces the need for multiple clinical evaluations and validation processes. Despite the best efforts of collaborative groups such as the European Blood Alliance to facilitate mutual recognition of validation results [15], this will be onerous and costly. The reliance on market forces to drive innovation and the competitive procurement process may have led to a more complex situation, placing a higher burden on BEs.

The development of a non-PVC alternative will be a lengthy process, and it is important that the DEHP scenario is not re-played. BEs must take ownership of this process—they are accountable for the provision of a safe and sustainable supply of blood components, whereas manufacturers are likely to prefer maintaining the *status quo* unless they can derive a competitive advantage. Faced with this regulatory imperative, a new approach is required, with an alliance of BEs and manufacturers agreeing upon a single combination that is available to all, sharing the implied costs between the manufacturers and the healthcare systems they support.

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The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

Gillian Grafton[1]
Stephen Thomas[2]

[1]*NHS Blood and Transplant, Birmingham, UK*
[2]*NHS Blood and Transplant, London, UK*

Correspondence
Gillian Grafton, NHS Blood and Transplant, Vincent Drive, Edgbaston, Birmingham B15 2SG, UK.
Email: gillian.grafton@nhsbt.nhs.uk

ORCID

Gillian Grafton https://orcid.org/0000-0002-6752-7742
Stephen Thomas https://orcid.org/0000-0001-7761-7138

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REVIEW

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Does high body mass index (>25 kg/m^2) or weight (>80 kg) reduce the effectiveness of anti-D prophylaxis in Rh(D)-negative pregnant women? A systematic review and meta-analysis

C. B. M. Ngan | R. Kaur | Denise E. Jackson

Thrombosis and Vascular Diseases Laboratory, School of Health and Biomedical Sciences, STEM College, RMIT University, Bundoora, Victoria, Australia

Correspondence
Denise E. Jackson, Thrombosis and Vascular Diseases Laboratory, School of Health and Biomedical Sciences, STEM College, RMIT University, Bundoora, Victoria, Australia.
Email: denise.jackson@rmit.edu.au

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Abstract

Background and Objectives: Haemolytic disease of the foetus and newborn (HDFN) occurs when maternal antibodies, often triggered by foetal antigens, destroy foetal and neonatal red blood cells. Factors like antibody strength, quantity and gestational age influence HDFN severity. Routine antenatal anti-D prophylaxis (RAADP) has significantly reduced HDFN cases. However, the effect of overweight/obesity (body mass index [BMI] > 25/30 kg/m^2) on anti-D prophylaxis efficacy remains unclear. This systematic review will examine the impact of BMI on anti D prophylaxis effectiveness in Rh(D) negative pregnant women.

Materials and Methods: We conducted a systematic review and meta-analysis following Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols. We searched databases from 1996 to 2023, focusing on studies exploring the link between high BMI/weight and anti-D serum levels in Rh(D)-negative pregnant women with Rh(D)-positive foetuses. Ten eligible studies were included, three suitable for meta-analysis. Study quality was assessed using the Strengthening the Reporting Observation Studies in Epidemiology (STROBE) checklist. Statistical analyses included Pearson correlation coefficients and risk differences.

Results: Our meta-analysis revealed a significant negative correlation ($r = -0.59$, 95% confidence interval [CI]: −0.83 to −0.35, $p = 0.007$) between high BMI/weight and serial anti-D levels in in Rh(D)-negative pregnant women with Rh(D)-positive foetuses. High BMI/weight had lower odds of serial anti-D level exceeding 30 ng/mL (arcsine risk difference [ARD] = 0.376, 95% CI: 0.143–0.610, $p = 0.002$). Heterogeneity among studies was low ($I^2 = 0$).

Conclusion: While our analysis suggests a potential linkage between high BMI/weight and reduced efficacy of anti-D prophylaxis, caution is warranted due to study limitations. Variability in study design and confounding factors necessitate

careful interpretation. Further research is needed to confirm these findings and refine clinical recommendations.

Keywords
anti-D prophylaxis, BMI, haemolytic disease of the foetus and newborn, meta-analysis, obesity in pregnancy, Rh(D) alloimmunization

Highlights

- There is a significant negative correlation between high body mass index (BMI)/weight and lower serial anti-D level in Rh(D)-negative pregnant women with Rh(D)-positive foetuses.
- High BMI/weight was associated with lower odds of RhD immune globulin RhIg (RhIg) prophylaxis serial anti-D level exceeding 30 ng/mL in Rh(D)-negative pregnant women.
- Obesity may reduce anti-D RhIg prophylaxis efficacy, increasing the risk of haemolytic disease of the foetus and newborn.

INTRODUCTION

Haemolytic disease of the foetus and newborn and Rh(D) alloimmunization

Haemolytic disease of the foetus and newborn (HDFN), alternatively referred to as alloimmune HDFN or erythroblastosis fetalis, is resulted from the lysis of foetal and neonatal erythrocytes by maternal immunoglobulin G (IgG) antibodies [1]. In particular, the development of maternal antibodies triggered by the foetal antigen is known as isoimmunization [2]. The antibodies are generated when the foetal red blood cells (RBCs), which express specific RBC antigens that are absent in the maternal system, traverse the placenta and enter the maternal bloodstream [3]. The antibodies have the potential to lead to foetal red cell destruction, consequently triggering various clinical severity from anaemia and hyperbilirubinemia, to kernicterus and death [4]. The clinical sequela is contingent upon a spectrum of factors such as the strength and amount of maternal antibody production and the foetus's gestational age [5].

It was found that approximately three to eight individuals per 100,000 patients were affected by HDFN annually [6]. Specifically, anti-D is responsible in majority of these cases, with anti-E, anti-K, anti-c and the MNS system antibodies contributing subsequently [7]. Despite the majority cause of the Rhesus system to HDFN, the Rh incompatibility illustrates variability across different racial backgrounds, ethnicities and distinct risk profiles [8]. Rh(D)-negative phenotypes are prevalent in White races at a frequency of 15%–17%, while it is less common among Black individuals with an occurrence of 8% subsequent to the rarest frequency of East Asians (1%) [9]. When considering the risk factor, a positive relationship was presented in the correlation between the magnitude of blood volume exposure and alloimmunization propensity [10]. Particularly, various pregnancy complications have been considered as a potential risk factor for foetal–maternal haemorrhage (FMH) such as preterm labour and vaginal bleeding [11]. Remarkably, alloimmunization could be induced by an allogeneic blood volume as minimal as 0.1 mL, emphasizing the notably low threshold for the immunological response [12]. Following the initial sensitization and primary immune response, a repeat exposure during the later pregnancy could initiate a significantly robust secondary immune reaction [13].

Rh(D) prophylaxis (intramuscular and intravenous administration)

In the early 1970s, the administration of anti-D prophylaxis was initiated to diminish the alloimmunization prevalence in pregnant women to the D antigen, which resulted in a substantial reduction from 14% to 1% [13, 14]. Most importantly, the consecutive establishment of routine antenatal anti-D prophylaxis (RAADP) has then significantly minimized the sensitization rate to relatively 0.4% in Rh(D)-negative women who delivered Rh(D)-positive foetuses [15]. While anti-D exerts a potent immunosuppressive effect, its dose appears to completely ablate the ability to mount a secondary response upon re-exposure to the D antigen. However, the secondary response may be diminished or modulated if no anti-D was administered initially [16]. Different mechanisms have been posited to elucidate the effectiveness of the prophylaxis, which include expedited elimination of D-positive cells, epitopes concealment, eradication attributed to antibodies targeting FcγRIIb and anti-idiotype 44, immature dendritic cell impediment and the suppression of B-cell clones directed towards the D antigen [17–21].

The prophylaxis could be administered via intramuscular or intravenous injection to Rh(D)-negative mother, whereas a full dose of anti-D prophylaxis (300 μg or 1500 International Units [IU]) provides protection from encountering up to 15 mL of Rh(D)-positive RBC (equivalent to 30 mL of whole blood) [22, 23]. RAADP protocols contain variability among different nations, which could be extended from two doses of anti-D administration containing a minimum of 500 IU at 28 and 34 weeks of gestation to a 1500 IU single injection at the 28th week [24]. The current recommendation in Australia stipulates the administration of two doses comprising 625 IU at both 28 and

34 weeks of pregnancy [25]. These two protocols exhibit merits and limitations. Despite the better cost efficiency and compliance (as the patients need to be administrated two times in a two-dose regimen) of a single dose, it demonstrates a decreased rate of anti-D detectability (22% compared to 61%), which was considered to be insufficient in the protection against sensitization during the third trimester [16, 26].

Obesity in pregnancy (high body mass index)

Body mass index (BMI) was widely utilized as a valuable measure for evaluating obesity, which contains a straightforward means to assess the weight-to-height ratio in adults who could hence be classified into categories such as underweight, overweight or obese [27]. The BMI is computed via a mathematical calculation involving the division of an individual's weight in kilogrammes by the square of his/her height in metres (kg/m^2) [28]. Additionally, overweight is defined by a pre-pregnancy BMI of 25–30 kg/m^2 while BMI higher than 30 kg/m^2 is considered to be obese [29].

The global incidence of overweight and obesity has rapidly risen over the last 30 years, encompassing approximately 19 billion overweight and 650 million obese adults [30]. In Australia, studies reported that approximately half of the population (women) who commence pregnancy demonstrate overweight or obesity [31]. Moreover, pregnant with obesity was shown to illustrate an elevated risk of maternal mortality and complications such as gestational hypertension and gestational diabetes mellitus (GDM) during the course of pregnancy and labour [30, 32–33].

Scope of review

Alloimmunization could not only occur in the blood transfusion but, most importantly, could be found in Rh(D)-negative mothers who carry an Rh-(D)-positive foetus, which provokes the sensitization, leading to anti-D production [34–36]. Despite no immediate detrimental health complications for the mother and the first baby by the occurrence of sensitization, it could contribute to haemolytic disease in later gestation with Rh-positive foetuses [37]. Anti-D prophylaxis may rectify the complications. With the increased trend of obese pregnancies, anti-D efficacy has not been fully understood in these groups of individuals. Some studies have linked pregnant obesity with alloimmunization. Therefore, pregnant obesity could be a potential risk factor for the reduction of anti-D prophylaxis efficacy upon sensitization.

This study evaluates the anti-D prophylaxis efficacy in high BMI (>30 kg/m^2) in Rh(D)-negative pregnant women who carry a Rh(D)-positive baby. The primary aim of this study is to perform a meta-analysis investigating the correlation between the anti-D serum level and high BMI (>30 kg/m^2) in Rh(D)-negative pregnant women carrying a Rh(D)-positive baby for present research. Second, to identify other risk factors, such as the way of injection, that is, intravenous and intramuscular, and the current dosage recommendation, that may also alter the efficacy of the prophylaxis in the population.

MATERIALS AND METHODS

Study design

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocols were performed to evaluate the relationship between the efficacy of Rh(D) prophylaxis and high BMI Rh(D) mother carrying Rh(D)-positive foetus [38]. This study focused on the impaired effectiveness of Rh(D) prophylaxis in high BMI Rh(D) mother carrying Rh(D)-positive foetus.

Literature search strategy

A systematic exploration of pertinent scientific literatures was undertaken across diverse digitalized bibliographic databases: Scopus, ProQuest, Embase and PubMed from 1 January 1966 to 1 August 2023. Different text keywords were utilized to conduct the searching including 'Anti-D prophylaxis', 'Pregnant Obesity' and 'Rh (D) alloimmunisation'. American English spelling of the keywords (i.e., alloimmunization) and alternative permutation of these phases (using 'and' and 'or') were also integrated into the search process to maximize the comprehensiveness of the results. Additional papers were discovered via manual searches, which included sources that were not originally located through database searcher. Google Scholar was used in the identification of these papers. The quantity of publishment encompassed in this study was illustrated in PRISMA flowchart.

Inclusion and exclusion criteria

The initial screening of articles was accessed through the search strategy, which involves evaluation of their titles to exclude other articles that did not exhibit a significant relevance to the objective of the meta-analysis. Articles that study the correlation between high BMI and anti-D concentration/titre in pregnant women were deemed eligible. The publications' abstracts were examined subsequently in which articles that were identified as conference proceedings, literature reviews or meta-analyses were excluded from the selection process. Exclusion was also focused on the articles that were non-English and translated versions.

Data extraction

Data from the included studies were extracted and stratified into tables comprising the primary author, year of publication, location of the studies, population size, design characteristic (prospective or

retrospective) and method used to quantity anti-D concentration. The suitability for the meta-analysis of each study was assessed via the Strengthening the Reporting Observation Studies in Epidemiology (STROBE) checklist [39].

Statistical analysis

In this research, data were collected to examine the relationship between BMI/weight and anti-D serum level. The association between BMI/weight and anti-D serum level was assessed using Pearson correlation coefficient (r) with 95% confidence intervals (95% CIs). From the selected studies, the random-effects meta-analysis method utilizing the maximum likelihood model approach was selected to estimate the effect size as a correlation coefficient with a 95% CI and to assess heterogeneity. Statistical significance was assessed using the p-value, with a threshold of $p \leq 0.05$ considered as indicating statistical significance. We evaluated the heterogeneity among the selected studies using statistical methods including chi-square-based Q test and I^2 statistic to assess the heterogeneity and degrees of freedom, respectively, where the significance level was set at $p \leq 0.05$ to determine statistical significance in our analyses. In our analysis, we employed a predefined threshold for assessing the heterogeneity degree: (1) Heterogeneity levels between 0% and 40% were considered of minimal significance; (2) values falling within the 30%–0% range suggest moderate heterogeneity; (3) a range of 50%–90% indicates substantial heterogeneity; and (4) heterogeneity is deemed considerable when the I^2 statistic falls within the 75%–100% range.

All statistical analyses were performed by the R project for statistical computing (Version 4.3.1. R Core Team, 2021) to examine the association between BMI/weight and anti-D serum levels in Rh(D)-negative pregnant women and OpenMeta (version 12.11.14, Brown university, 2023) to examine the arcsine risk difference (ARD) between high BMI/weight and normal BMI/weight in serial anti-D level.

RESULTS

Selection process and features of the encompassed research

Between the years 1966 and 2023, a cumulative count of 5444 published in the relevant databases was compiled. This includes 5442 articles obtained from four distinct databases and an additional 2 articles identified through manual retrieval methods. Out of this total, 5434 articles were subjected to exclusion based on the criteria delineated in Figure 1. Subsequently, a total of 10 articles met the eligibility criteria, which were included in the systematic review. Out of the 10 eligible articles, only 3 demonstrate an analysis of BMI/weight level in Rh(D)-negative mothers carrying a Rh(D)-positive foetus, specifically addressing their anti-D serum level. These three studies were hence incorporated into the meta-analysis (Figure 1).

The three included studies illustrate the analyses on the anti-D serum level in individuals with corresponding BMI or weight [40–42]. Particularly, two of the studies [41, 42] exhibit adequate data for analysing the relationship between BMI and anti-D serum level, whereas one study [40] presents data pertaining to the individual's weight in relation to the anti-D serum level. Table 1 encapsulates the pertinent information and principal findings drawn from the trio of studies, which was encompassed in our systematic review and subsequent meta-analysis. All of the studies included in this analysis were performed exclusively in either Sweden ($n = 2$) or Brazil ($n = 1$). These studies specifically focused on individuals who were Rh(D)-negative pregnant women. Additionally, all patients received anti-D prophylaxis at a dosage ranging from 1250 to 1500 IU during the gestational period between Weeks 28 and 32. The studies exhibited diversity in the anti-D serum levels that were linked to the patient's BMI/weight. Serial plasma anti-D quantitation was conducted in a range of periods from 0 to 84 post-injection using flow cytometry [40, 42] and gel microcolumn assay (GMA) [41] (Table 2). The population size of Tiblad et al. [40], Silva et al. [41] and Wikman et al. [42] was 15, 27 and 38, respectively. The table also presented the divided cohort of each group in accordance with the individuals' BMI or weight. BMI lower than 25 kg/m^2 or weight lower than 80 kg was classified as normal BMI/weight group while BMI equal to or higher than 25 kg/m^2 or weight equal to or higher than 80 kg was classified as high BMI/weight group. While the method of serial plasma anti-D quantitation varied among the studies, the anti-D levels were unified for meta-analysis.

Quality assessment of studies

The quality of the three eligible studies was evaluated and assessed in accordance with the STROBE standards as part of the meta-analysis process. Table 3 condensed overviews of the critical aspects within each research domain explored in the conducted studies, as determined by the author's perspective. The criteria incorporated into the assessment were derived from the following sections of each study: (1) introduction, (2) methods, (3) results and (4) discussion. In these four criterion areas, the assessment of study quality was contingent upon the following aspects: (1a) clarity of the rationale provided; (1b) specification of well-defined objective along with a hypothesis; (2a) explicit eligibility criteria for patients; (2b) clear definition of outcomes and identification of potential confounders; (2c) comprehensive description of all statistical methods employed; (3a) reporting the number of individuals at each stage of study; (3b) presentation of adjusted estimates; and (4a) articulation of limitations associated with the study. The quality assessment of each study was conducted by categorizing the criteria as either 'Yes' or 'No'.

Both rationale and objectives were well addressed in all of the included studies. When examining the methodology section, one of the studies [42] demonstrated a deficiency in providing information regarding potential study bias. Only one study [41] stated the 95% CI while the remaining two did adequately address the CI according to the statistical methods utilized.

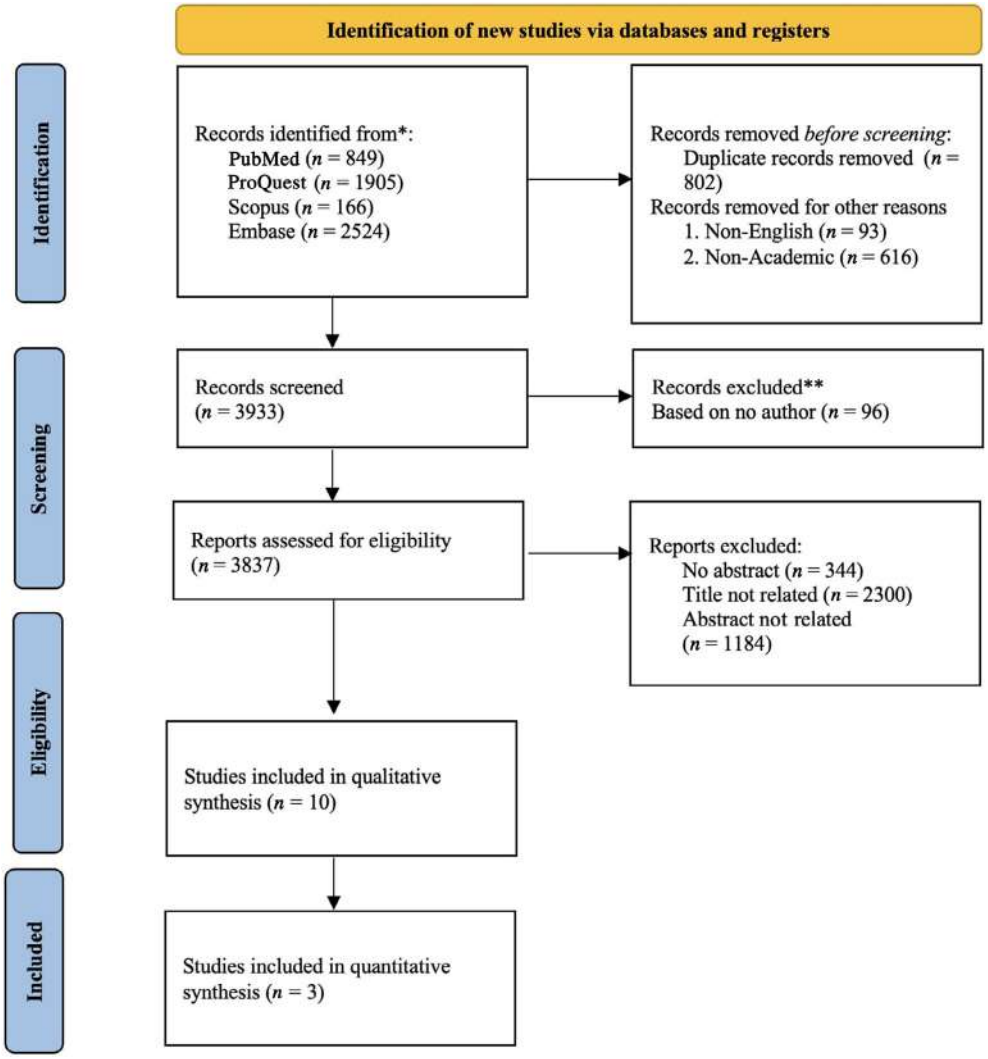

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart. Between 1966 and 2023, we compiled 5444 articles, including 5442 from four databases (Scopus, ProQuest, Embase and PubMed), and found two more through manual searches using Google Scholar. Of these, 5434 were excluded based on criteria outlined in this figure. We identified 10 articles meeting eligibility criteria for our systematic review, with 4 of them included in our meta-analysis. We conducted a comprehensive search across databases using keywords such as 'Anti-D prophylaxis', 'Pregnant Obesity', and 'Rh(D) alloimmunisation', including American English spellings and alternative permutations. Additional papers were found through manual searches. This figure illustrates our publication selection process. *Records identified by database searches. **Records excluded by title and abstract.

Data analysis association

Meta-analysis relating to anti-D threshold

A meta-analysis was performed and a forest plot was generated to assess the association between the BMI/weight and serial anti-D level, as shown in Figure 2. Figure 2a exhibits the two-arm proportion analysis, revealing that a high BMI exhibited an overall significant reduction in serial anti-D levels in Rh(D) mother carrying a Rh(D)-positive foetus. The ARD was found to be 0.376, while the 95% CI was 0.143–0.610 and the *p*-value was 0.002. The heterogeneity between the studies was not important ($I^2 = 0\%$; $p = 0.978$). For better demonstration, Figure 2b,c illustrates the divided version of the two-arm analysis. In Figure 2b (normal BMI/weight group), the ARD was observed to be 0.646, while the 95% CI was 0.487–0.790, and the *p*-value was less than 0.001. The heterogeneity between the studies was not important ($I^2 = 0.02\%$; $p = 0.158$). Figure 2c (high BMI/-weight) presents the ARD of 0.346 (95% CI: 0.110–0.632, $I^2 = 71.14\%$; $p = 0.031$).

Meta-analysis of correlation coefficients

Another meta-analysis was also conducted, and a forest plot was drawn to investigate the correlation between BMI/weight and serial anti-D level. Figure 2 demonstrates the ARD of the two-arm proportion analysis, as the individuals were divided into two groups by their BMI/weight, whereas Figure 3 illustrates the association

TABLE 1 Summary of studies included in the meta-analysis on BMI/weight associated with serial plasma level of anti-D.

Study	Study design	Country	Population	Gender (condition)	Study period	Mode of prophylaxis administration	Administration week (GA)	Data collection time (GA)	Prophylaxis dosage
Tiblad et al. [40]	Prospective	Sweden	Swedish	Female (Rh(D)-negative pregnant)	2011–2012	Intramuscular	28–30	0, 3, 10 ± 2, 14 ± 2, 28 ± 2, 42 ± 2, 56 ± 2, 63 ± 2, 70 ± 2, 77 ± 2 and 84 ± 2 post administration	250 μg (1250 IU)
Silva et al. [41]	Prospective	Brazil	Brazilian	Female (Rh(D)-negative pregnant)	2020–2021	Intramuscular	28–32	Days 3, 7, 21, 42, 63, 84 post administration	300 μg (1500 IU)
Wikman et al. [42]	Prospective	Sweden	Swedish	Female (Rh(D)-negative pregnant)	2020–2021	N/A	28 first dose, 38 second dose	Pre at 38, weekly monitor until 43[a]	300 μg (1500 IU)

Abbreviations: BMI, body mass index; GA, gestational age; N/A, not specified.
[a]Anti-D levels are analysed from a pre-administration of the second dose at GA 38, followed by weekly monitoring until GA 43.

TABLE 2 Summary of studies reporting number and frequency of high BMI/weight and normal BMI/weight Rh(D) negative women associated with their serum plasma anti-D level.

Study	Sample size	Patient cohort[a]	Method of anti-D quantitation
Tiblad et al. [40]	15	8−/7+	Flow cytometry
Silva et al. [41]	27	5−/27+	Gel microcolumn assay
Wikman et al. [42]	39	23−/16+	Flow cytometry

Abbreviation: BMI, body mass index.
[a]− indicates individuals who were categorized in the group of normal BMI/weight, that is, BMI < 25 kg/m^2 or weight <80 kg. + indicates individuals who were categorized in the group of high BMI/weight, that is, BMI ≥ 25 kg/m^2 or weight ≥80 kg.

between BMI/weight and serial anti-D level. The meta-analysis of correlation coefficients presents a significant negative correlation between BMI/weight and serial anti-D level. In other words, there was a trend showing a higher BMI/weight will have a lower serial anti-D level. The correlation coefficient (r) was found to be −0.59, while the 95% CI is −0.83 to −0.35 and the p-value was 0.007. The heterogeneity between the studies was not important ($I^2 = 0$; $p = 0.43$).

DISCUSSION

Rh(D) alloimmunization has the potential to result in HDFN, and in severe instances, it could lead to foetal demise. Particularly, HDFN can manifest when an Rh(D)-negative pregnant woman experiences a sensitizing event during her pregnancy, triggering the establishment of anti-D antibodies in which these antibodies could target and destroy the foetal RBCs. Antenatal anti-D prophylaxis was implemented to reduce the prevalence of Rh(D) alloimmunization among pregnancy. This intervention has led to a significant decrement, which lowers the incidence from 14% to 0.4% [13–15]. The actual mechanism of this potent immunosuppressive immunoglobulin, however, remains unclear, which requires further investigation. Given the rising prevalence of pregnant obesity, the effectiveness of anti-D prophylaxis has not been comprehensively elucidated. Some studies have suggested a potential association between obesity during pregnancy and the occurrence of alloimmunization [45]. Consequently, it is plausible that pregnant obesity might serve as a potential risk factor that could compromise the anti-D prophylaxis efficacy upon sensitization [45].

The present systematic review and meta-analysis focused on investigating the relationship between BMI/weight and serial anti-D levels in Rh(D)-negative pregnant women who carry an Rh(D)-positive baby from both Brazil and Sweden. All three included studies investigated the efficacy of anti-D immunoglobulin in Rh-D-negative pregnant women in a variety of weight/BMI. Paper 1 (Tiblad et al.) observed that a majority of women exhibited detectable anti-D levels at delivery when administered around Weeks 28–30, albeit raising concerns regarding its sufficiency at

TABLE 3 STROBE checklist for evaluating the relevance and quality of studies across various study aspects in meta-analysis.

	Introduction		Methods				Results		Discussion
Study	Rationale explained	Objectives specified with hypothesis	Patient eligibility provided	Outcome and potential confounders defined	Bias addressed	Describes all statistical methods	Number of individuals at each stage reported	Give adjusted estimates (95% CI)	States limitations
Tiblad et al. [40]	Y	Y	Y	Y	Y	Y	Y	N	Y
Silva et al. [41]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Wikman et al. [42]	Y	Y	Y	Y	N	Y	Y	N	Y

Abbreviations: CI, confidence interval; N, no; STROBE, Strengthening the Reporting Observation Studies in Epidemiology; Y, yes.

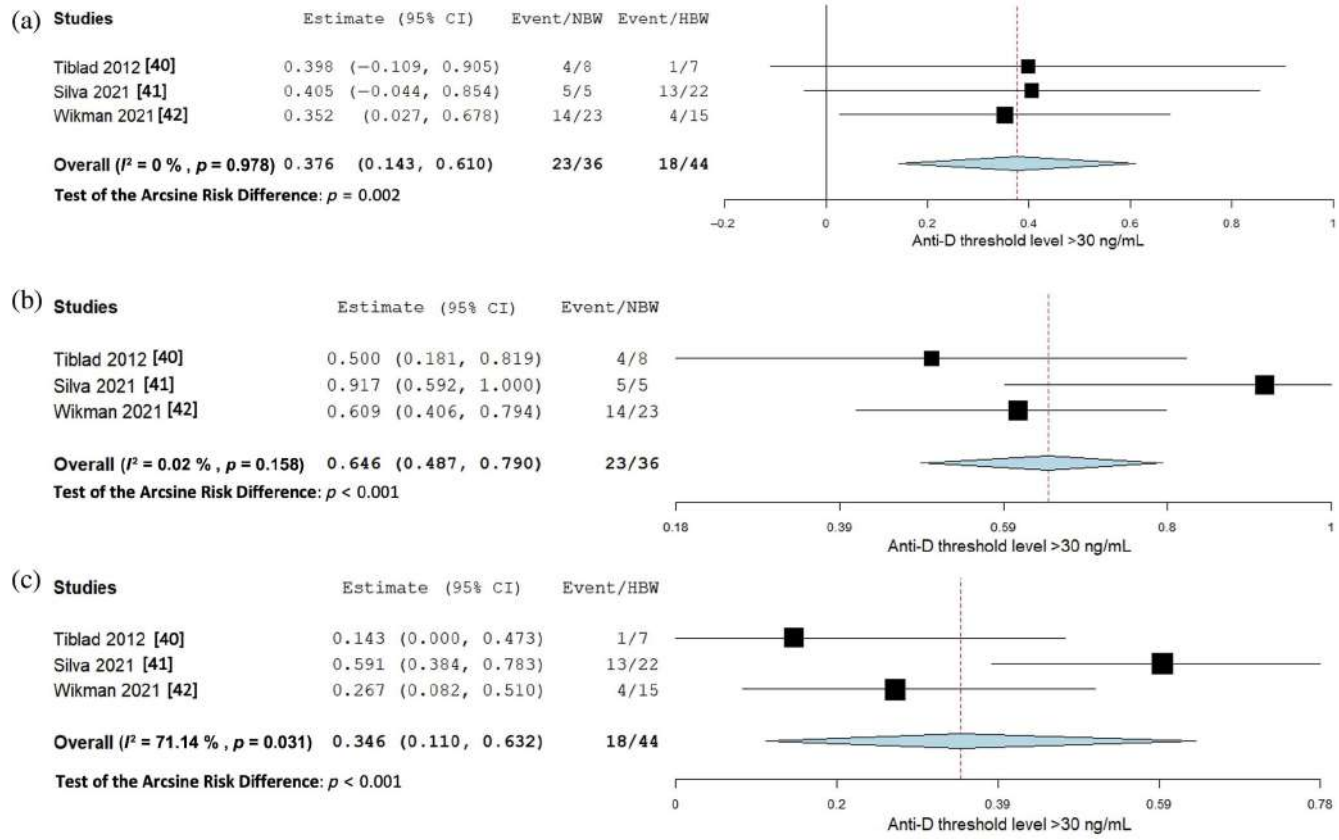

FIGURE 2 (a) Forest plot of the two-arm arcsine risk difference (ARD) between high body mass index (BMI)/weight and normal BMI/weight in serial anti-D level. (b) Forest plot of the one-arm ARD for normal BMI/weight in serial anti-D level. (c) Forest plot of the one-arm ARD for high BMI/weight in serial anti-D level. The outcome was presented as ARD along with 95% confidence intervals (CIs). The random-effects model maximum likelihood (ML) method was employed to calculate the overall difference. For assessing heterogeneity among the studies, the Mantel–Haenszel method (M–H) was utilized. The statistical significance of the forest plot was conveyed through the *p*-value. Heterogeneity was assessed using the I^2, and a separate *p*-value was used to determine the corresponding statistical significance. Event, event positive for a threshold of a serial anti-D level higher than 30 ng/mL; HBW, patients whose BMI or weight is higher than 25 kg/m^2 or 80 kg; NBW, patients whose BMI or weight is lower than 25 kg/m^2 or 80 kg.

term. Paper 2 (Silva et al.) echoed similar findings, noting that anti-D was undetectable in 41% of participants following administration at Week 28. Supporting these concerns, Paper 3 (Wikman et al.) indicated that 20% of women lacked detectable levels at terms with a single dose. Collectively, these studies underscore the necessity for further exploration of alternative strategies, potentially including the administration of repeated doses during pregnancy to ensure adequate anti-D protection for Rh(D)-positive offspring. [40–42].

Upon review and meta-analysis, one has provided confirmation that being overweight (both BMI and weight) could lead to a low serial anti-D level when compared with normal individuals. This study also found that a higher BMI/weight could lead to a lower anti-D level according to the negative correlation coefficient. These observations

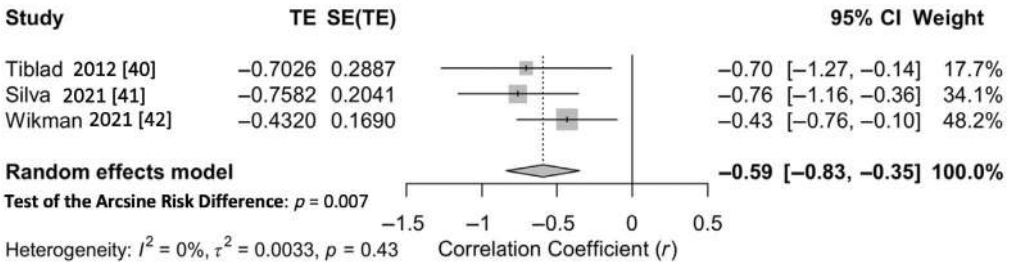

FIGURE 3 Forest plot of the correlation coefficient (*r*) between body mass index (BMI)/weight and serial anti-D level. The outcome was presented as correlation coefficient (*r*) with 95% confidence intervals (CIs) The random-effects model maximum likelihood (ML) method was employed to calculate the overall difference. For assessing heterogeneity among the studies, the Mantel–Haenszel method (M–H) was utilized. The statistical significance of the forest plot was conveyed through the *p*-value. Heterogeneity was assessed using the I^2, and a separate *p*-value was used to determine the corresponding statistical significance. Heterogeneity was assessed using the I^2, and a separate *p*-value was used to determine the corresponding statistical significance. The weight was expressed as a percentage, relative to the size of each study. SE, standard error; TE, treatment effect, the correlation coefficient of each study.

have illuminated the concept that the efficacy of anti-D prophylaxis is not exclusively linked to the dosage (i.e., single or double dose) and the administration method (i.e., intravenous and intramuscular injection) but is also impacted by the individual BMI/weight status that contributes to the anti-D serum level.

Despite different anti-D quantification (flow cytometry and GMA) and detection level (C_{max} [maximum serum concentration] and IU) from the selected studies, they were all unified into the same unit for better investigation. More importantly, the correlation coefficient (*r*) meta-analysis was also utilized to clarify the inconsistency of the data from ARD as the r is centralized for every study. The study could hence be more thoroughly investigated.

INTERPRETATIONS

Risk difference between normal and high BMI/weight groups

The study's findings indicate that the high BMI/weight individuals (BMI > 25 kg/m^2 or weight >80 kg) (Rh(D)-negative mother who carry Rh(D)-positive foetus) exhibit reduced odds of serial anti-D level detected of the threshold of 30 ng/mL when contrasted with individuals who are within the normal BMI/weight level. An odds ratio (OR) of 0.376 illustrates statistical significance that indicates a diminished likelihood of serial anti-D level being detected in the threshold of 30 ng/mL among individuals who had high BMI/weight ($p = 0.002$). The observed heterogeneity lacks significance ($I^2 = 0$), suggesting that the variations among the studies are attributed to random sampling errors. The observation is consistent in both the overall analysis and the subgroup analysis for the normal BMI/weight group (Figure 2a,b). Despite the higher degree of heterogeneity (71.14%) in high BMI/weight group, which may suggest that other factors contribute to this phenomenon (Figure 2c), this finding provides assurance that the BMI/weight status of the individuals may alter the anti-D efficacy for the protection of alloimmunization. These results are further supported by the subsequent investigation of the correlation coefficient (*r*).

Negative correlation between BMI and anti-D serum levels

As shown above, the forest plot using the correlation coefficient was also generated. The study findings indicate that the BMI/weight is negatively correlated with the individuals' serial anti-D level, which could further support that the higher BMI/weight will exacerbate the decrement of anti-D serum level, as shown in Figure 1. The overall correlation of −0.59 with statistical significance ($p = 0.007$) could support the above statement (Figure 2). The observed heterogeneity lacks significance ($I^2 = 0$), suggesting that the variations among the studies are attributed to random sampling errors.

Implication for clinical practice

The findings may affect the clinical decision with regard to the anti-D prophylaxis administration in pregnant women. It suggests that obese individuals may be at a higher risk of inadequate anti-D prophylaxis levels and response, which potentially causes the increased risk of haemolytic disease of the newborn or transfusion reactions. Therefore, healthcare providers may need to consider adjusting the anti-D prophylaxis dosage based on a patient's BMI or weight. Obese patients may thus require a higher dose to achieve the same protective effect as individuals with normal BMI/weight.

In obese individuals, the process of absorption at the injection site may exhibit delays. This delay could potentially be attributed to factors such as inadequate needle penetration into the more vascularized muscular tissue, which contributes to a prolonged residence of immunoglobulins within the adipose tissue [43]. Furthermore, it is pertinent to contemplate the fact that a notable percentage of obese individuals often partake in fewer physical activities in comparison with their non-obese counterparts. This diminished level of physical activity could potentially be a leading factor to the observed deceleration in absorption kinetics at the injection site [44].

Effective communication with patients regarding the potential impact of obesity on anti-D antibody levels is crucial. While patient

understanding and adherence to treatment regimens are critical for achieving optimal outcomes, health intervention measures such as addressing obesity through lifestyle modification and weight management strategies are crucial long-term conditions that could ultimately rectify overall health outcomes [46, 47].

Lastly, updating clinical guidelines and conducting risk assessments based on the negative correlation between BMI/weight and anti-D serum levels is of paramount importance in ensuring safe and effective patient care. These crucial clinical implications could establish a standardized framework for healthcare providers to follow, incorporating high BMI/weight as a risk factor in assessing the potential for inadequate anti-D antibody levels. For instance, Ramsey [48] suggested an anti-D prophylaxis dose calculator, which would calculate the prophylaxis amount/dose needed for the individuals according to the imported weight and weight. Healthcare professionals could therefore tailor their interventions and monitoring strategies to the specific needs of individuals with higher BMI/weight, which could hence minimize the risk of complications associated with subsequent Rh(D) sensitization and blood transfusions [48]. These implications could not only enhance patients' safety, but more importantly, could contribute to the overall quality of healthcare delivery, ensuring that individuals receive the most appropriate and effective care based on the BMI/weight and associated risks.

LIMITATIONS

The limitations of this meta-analysis must be considered when interpreting the findings. First, The scarcity of studies in this particular field necessitated the inclusion of only three papers, all of which present relatively small sample sizes. This limited dataset may not fully represent the diversity of patients or scenarios in the broader population, and the generalizability of the results should be viewed with caution. Second, different confounding variables could also be potential sources of influence on the relationship between BMI/weight and serial anti-D levels. In particular, age, the number of previous transfusions, race and external factors were not uniformly accounted for in the selected studies, which may have impacted the observed variations in the results. These uncontrolled factors can introduce bias and limit the ability to establish a clear cause-and-effect relationship between BMI/weight and anti-D levels. It is of most importance to note that the lack of thorough reporting on bias in some of the selected studies is another constraint. The potential for publication bias or selective reporting thus could not be fully examined, which may affect the overall validity of the meta-analysis. Finally, in the prospective part of Wikman et al.'s study, the follow-up samples included women who were no longer pregnant and thus had no risk of new FMH. This is a significant limitation, as our meta-analysis focuses on pregnant women. The inclusion of these follow-up samples introduces a potential bias in our analysis, given that Wikman et al.'s study constitutes almost one third of our meta-analysis.

In light of these limitations, while the findings demonstrate valuable insights, further research with larger, more diverse samples and standardized data collection methods is warranted to refine the understanding of the complex relationship between BMI/weight and serum anti-D level and to better account for potential confounding factors.

CONCLUSION

This systematic review and meta-analysis provide valuable insights into the relationship between BMI/weight and serum anti-D level in Rh(D)-negative pregnant women carrying an Rh(D)-positive foetus. The study reveals that high BMI/weight individuals exhibit a significant reduction in serial anti-D levels, suggesting potential implications for the efficacy of anti-D prophylaxis. These findings emphasize the importance of considering BMI/weight when administering anti-D prophylaxis and the need for potential dose adjustment in obese individuals. While this research sheds light on an important clinical aspect, it acknowledges limitations such as small sample sizes and uncontrolled confounding variables. Further research is warranted to validate and expand upon these findings for more precise clinical guidelines. Particularly, further studies should explore the long-term clinical outcomes of altered anti-D prophylaxis dosing based on BMI/weight. Additionally, investigating the mechanism underlying the observed relationship between BMI/weight and anti-D levels would provide valuable insights.

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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.

ORCID

Denise E. Jackson https://orcid.org/0000-0001-9044-8009

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Iron deficiency among Japanese whole-blood donors measured by serum ferritin

Takeshi Odajima[1] | Nelson H. Tsuno[1,2] | Fumihiko Ishimaru[3] | Rie Okubo[4] | Junko Murakami[5] | Kaori Kitsukawa[2] | Katsuya Ikuta[6] | Koji Matsuzaki[7] | Kazuo Muroi[2] | Masahiro Satake[1] | Shuichi Kino[3]

[1]Japanese Red Cross Central Blood Institute, Tokyo, Japan

[2]Japanese Red Cross Kanto-Koshinetsu Block Blood Center, Tokyo, Japan

[3]Japanese Red Cross Blood Service Headquarters, Tokyo, Japan

[4]Kanagawa Red Cross Blood Center, Yokohama, Japan

[5]Nagano Red Cross Blood Center, Nagano, Japan

[6]Hokkaido Red Cross Blood Center, Sapporo, Japan

[7]Japanese Red Cross Kyushu Block Blood Center, Kurume, Japan

Correspondence
Nelson H. Tsuno, Japanese Red Cross Kanto-Koshinetsu Block Blood Center, Tokyo, Japan
Email: h-tsuno@ktks.bbc.jrc.or.jp

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Abstract

Background and Objectives: A more restrictive blood donation criterion has been applied in Japan, with a maximum volume of whole blood (WB) donation of 400 mL, allowing twice a year for female donors and thrice a year for male donors. However, iron deficiency was as high as 20.5% among female donors prior to donation, increasing to 37.7% after blood donation. More than 20 years have passed since then, so we set out to investigate the present situation.

Materials and Methods: A total of 2659 (male/female: 1496/1163) donors of 400 mL WB who gave informed consent to join the study were enrolled. Serum ferritin (sFer) of first-time/reactivated (FT/RA) donors were compared with those of repeat donors, according to gender and age; those who returned for subsequent donations during the study period were also followed up.

Results: About one-third of FT/RA female donors had iron deficiency, possibly reflecting its high incidence among the general population. Interestingly, although sFer levels were low among pre-menopausal FT/RA female donors, these values were not much different in repeat donors, whereas significant differences were observed between FT/RA and repeat donors among post-menopausal females and in most age groups among males. As expected, donors with a normal initial sFer (≥26 ng/mL) recovered faster than those with a low initial sFer.

Conclusion: Female donors, especially, have iron deficiency even before donation, and the rate increased compared to what was found previously. Measures to prevent iron deficiency of blood donors is required, and studies are going on in Japan.

Keywords

iron deficiency, serum ferritin, whole-blood donation

Highlights

- The rate of donors with low serum ferritin levels seemed lower in Japan compared to most Western countries.
- This might be attributed to the existence of more restrictive blood donation criteria in Japan.
- However, there is an urgent need to evaluate the iron stores of blood donors in Japan to ensure that the donors are managed appropriately and safely.

INTRODUCTION

Iron-deficiency anaemia (IDA) is a nutritional and health-related issue worldwide, especially among pre-menopausal women, and it is not an exception in Japan. Among junior high school girls in a rural area of Japan (Ibaraki prefecture), 5.73% had mild anaemia, with the highest prevalence among second- and third-year junior high school girls (approximately 1 in 10) [1]. Among apparently healthy women, anaemia (defined as haemoglobin [Hb] < 12 g/dL) was present in 17.3% (2331/13,147), severe anaemia (defined as Hb < 10 g/dL) in 3.3% (438/13,147) and microcytic anaemia (defined as mean corpuscular volume [MCV] < 80 fL) in 5.2% (700/13,147). Especially among women younger than 50 years of age, anaemia was observed in 22.3%, and among them, 25.2% had severe anaemia [2], revealing that anaemia and severe anaemia are highly prevalent among young women in Japan. More recently, an analysis of apparently healthy women aged 20–49 years in Tokyo ($n = 10,598$) revealed that 17.1% had anaemia (defined as Hb < 12.0 g/dL) [3]. However, Hb is considered a poor surrogate of iron depletion because anaemia is a late manifestation of iron deficiency, and evaluation based on a more reliable surrogate is required.

Iron deficiency is reported to affect between 25% and 35% of regular blood donors worldwide [4, 5]. In Japan, more than 90% of donated blood comes from repeat or committed donors, with a male predominance (about 72%); however, the issue of iron deficiency has not been appropriately addressed among blood donors in Japan. Low Hb is the major contributor of deferral among female donors [6]. More than 20 years ago (1996), the storage iron—estimated by Hb concentration, transferrin saturation and serum ferritin (sFer)—was investigated in Japanese blood donors, enrolling 26 males and 196 females who donated 400 mL whole blood (WB), and it was found that 20.5% of female donors were in a state of negative iron balance prior to donation and this increased to 37.7% after donation. Interestingly, however, they did not find a significant decrease in storage iron by repeated blood donations [7]. On the other hand, repeat apheresis donors had lower storage iron values compared to 400-mL repeat WB donors and normal subjects, and a negative iron balance was found in 12.2% of males and 45.7% of females even prior to donation [8].

sFer has been investigated as the surrogate of IDA in blood donors in various countries and strategies to mitigate IDA have been implemented in some countries, including changes in the donation criteria, such as the extension of the interval between donations and the increase of Hb level requirement [9], donor deferral [10, 11] and iron prescription. In Japan, where a more restrictive blood donation criterion compared to other countries is applied, the situation of IDA among blood donors has not been investigated for more than 20 years.

In an attempt to understand the present situation of iron deficiency among the blood donors in Japan, and prepare data to serve as the basis to discuss the need to implement strategies to mitigate it, we conducted this prospective study enrolling WB donors who donated blood to the Japanese Red Cross Blood Services (JRCBS), who consented to be enrolled. This is the first large cohort study on sFer measurement of blood donors in Japan.

MATERIALS AND METHODS

Blood donation in Japan

As mentioned, in Japan a more restrictive blood donation criterion compared to other countries is applied. The maximum volume of WB collection is 400 mL, allowing half-volume (200 mL) donation for first-time teenage donors and females with lower body weight (BW). JRCBS, which is the sole blood agency in Japan, collects blood from around 5.0 million donors yearly, with more than 90% repeat blood donors and less than 10% first-time donors. For 400-mL donation, a minimum BW of 50 kg is a requirement for both males and females. Males need to be at least 17 years old, with a minimum Hb of 13.0 g/dL, whereas females need to be at least 18 years old, with a minimum Hb of 12.5 g/dL. Both males and females can start donating at the age of 16 years but only half the volume (200 mL), and the Hb requirements are lower than that for 400 mL, that is, 12.5 g/dL for males and 12.0 g/dL for females. Males are allowed to donate a maximum of 1200 mL WB in a year, with an interval of 12 weeks between donations, whereas females can donate a maximum of 800 mL with an inter-donation interval of 16 weeks. Presently, teenagers represent about 5% of the total donor population, and small-volume (200 mL) donation also represents about 5% of the total WB donation.

Donor enrolment

Informed consent was obtained from all donors enrolled in the study.

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

The study aimed to enrol 100 repeat donors from each age group (teenagers and those in their 20s, 30s, 40s, 50s and 60s) and from both genders, totaling 1200 repeat donors. Additionally, it sought to enrol 100 FT/RA donors from each age group, with a particular emphasis on teenager donors (16, 17, 18 and 19 years old), aiming for 100 donors from each teen year, in a total of 1800 donors. These donors were monitored during their subsequent blood donation visits. Donors who visited our blood collection rooms in Tokyo, Kanagawa prefecture or Nagano prefecture for WB donation during the period 2 July 2018 to 30 March 2020 were explained the study details, and those who consented to join were enrolled. Blood donors were approached by various personnel, especially medical doctors and nurses, during their visit to the blood donation room, during non-peak times, and only those who understood the aim of the study and agreed to join were enrolled. The majority of the donors agreed for participation. One of the main reasons of non-agreement was the non-accessibility to the results. Data from a total of 2977 donations (male/female [M/F]: 1601/1376) were obtained. The study encountered difficulties in recruiting FT teenager donors. To prevent

selection bias, we invited consecutive donors during their visits to the blood donation room. Data of a total of 2659 (M/F: 1496/1163) 400-mL WB donations were evaluated, after excluding those who donated only a small volume (200 mL) WB (318 cases [M/F: 105/213]). Repeat donors were defined as those who donated 400 mL WB at least twice in the period 1 April 2017 to 31 March 2018 (defined as fiscal year [FY] 2017) and first-time donors as those who donated for the first-time, including reactivated donors who had not donated in the previous 2 years, in FY 2017. It is noteworthy that this group of repeat donors would be expected to have lower sFer due to a more intensive donation pattern.

In addition to the routine blood samples for blood group typing, infectious marker screening, haemogram and a sample to be stored 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. For all donations, the following tests are routinely performed: blood group typing (ABO and Rh(D)), markers of transfusion-transmitted infectious diseases (TTIDs), including serological testing and individual nucleic acid test (NAT) (hepatitis B virus [HBV], hepatitis C virus [HCV] and human immunodeficiency virus [HIV]), complete blood counts and biochemical testing. HEV NAT was implemented only in August 2020, so our study cases were not screened for HEV. For those donors who agreed to receive a notification, test results, except for HIV, are sent with the aim to help them manage their health as a public health service.

sFer and haemogram measurement

sFer was measured in an automated biochemical analysis system (LABOSPECT 008; Hitachi, Tokyo, Japan) using the FER-Latex (X2) CN SEIKEN (Denka Seiken, Tokyo, Japan) kit.

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

sFer recovery analysis

Donors enrolled in the study were not requested to return at fixed intervals, but many of them had returned for subsequent donations at their own discretion, and additional sFer measurements were conducted during the study period. The sFer data collected on the subsequent donations were used for the analysis of the period required for sFer recovery, according to gender and age (teenagers vs. those in their 20s–60s for males, and teenagers vs. those in 40s [pre-menopausal] and 50s–60s [post-menopausal] for females) and according to the initial sFer value (normal range [≥26 ng/mL] vs. iron deficiency [<26 ng/mL]). In the first analysis, Kaplan–Meier curves of male and female donors according to age were drawn, showing to what extent (rate of the initial sFer value) the donors had recovered their sFer. sFer recovery here was defined as the recovery to 90% of the initial sFer levels. In the second analysis, Kaplan–Meier curves of male and female donors according to their initial sFer levels (normal sFer: ≥26 ng/mL or low sFer: <26 ng/mL) were drawn to show the rate of donors who had recovered sFer to normal values (≥26 ng/mL) [15]. In this part, sFer recovery was defined as sFer levels ≥26 ng/mL.

Donor data and statistical analysis

Data from donors were extracted from the donor management system of the JRCBS. The following data were collected for all donors: gender, age, height, BW, body mass index (BMI), total blood volume (TBV), complete blood counts (RBC, red blood cell count; Hb; MCV; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; WBC, white blood cell count; PLT, platelet count), donor status (first-time/reactivated [FT/RA] or repeat: see below) and sFer. TBV (L) is calculated by the following formula: $TBV = 0.168H^3 + 0.050W + 0.444$ for an adult male, and $TBV = 0.250H^3 + 0.0625W - 0.662$ for an adult female, where H is the height (m) and W is the body weight (kg), as previously reported [12].

WB 200-mL donations were excluded from the analysis because it is limited to donors in the younger age and female donors with lower BW, and a different variation in sFer is expected. Thus, only 400-mL WB donation were included.

Using descriptive statistical analyses, age, sex, BMI, TBV, RBC, Hb, sFer and donation status (FT/RA or repeat) were analysed as subgroups for evaluating the baseline characteristics of blood donors. We employed ANOVA with post hoc Tukey–Kramer tests to explore age discrepancies in sFer within both the FT/RA donor and repeat donor groups. Participants were stratified into male and female subgroups for this analysis.

Donors were divided into five groups according to the sFer levels (<12.0, 12.0–25.9, 26–49.9, 50.0–449.9, ≥450 ng/mL) and according to gender and donation status.

Logistic regression was used for the multivariate analysis, and the presence or absence of absent iron store (AIS; sFer < 12 ng/mL) [5] or iron-deficient erythropoiesis (IDE; sFer < 26 and ≥ 12 ng/mL) [13] as the dependent variables; independent variables were divided into two groups according to the median values. Confounding factors including age group and other significant variables were used for adjustment to calculate the odds ratio (OR) and the 95% confidence interval (95% CI), according to gender.

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

RESULTS

Comparison of sFer levels, TBV and age of FT/RA versus repeat blood donors, according to gender

As shown in Table 1, among males, the mean ± SD of sFer was 139.2 ± 96.43 ng/mL for FT/RA donors and 109.1 ± 94.66 ng/mL for repeat donors, which represented a 21.62% lower mean sFer level among repeat donors compared to FT/RA ones. Similarly, among females, the mean ± SD sFer was higher among FT/RA than repeat donors (51.0 ± 63.10 vs. 48.6 ± 41.86 ng/mL).

TABLE 1 Comparison of the first-time/reactivated donors and repeat donors according to gender.

	First-time/reactivated donor					Repeat donor				
	N	Mean ± SD	Median	Min	Max	*N*	Mean ± SD	Median	Min	Max
Male	460					1036				
Age (y.o)		24.2 ± 11.6	19	17	64		43.7 ± 14.5	44	17	69
BMI		22.3 ± 3.2	21.9	15.7	45.3		24.0 ± 3.3	23.7	16.4	42.0
TBV (L)		4579 ± 529	4521	3607	7998		4808 ± 570	4751	3644	7859
Hb (g/dL)		15.4 ± 0.9	15.3	13.1	18.7		15.1 ± 1.0	15.1	12.8	20
RBC ($\times 10^4/\mu L$)		510.6 ± 33.3	511	402	658		495.2 ± 37.9	495	373	628
sFer (ng/mL)		139.2 ± 96.4	115.6	7.0	828.6		109.1 ± 94.7	77.2	3.8	763.2
Female	275					888				
Age (y.o)		26.7 ± 12.7	19	18	64		46.0 ± 13.2	48	18	69
BMI		22.5 ± 2.8	21.9	17.9	36.2		23.1 ± 3.1	22.6	17.3	37.0
TBV (L)		3996 ± 504	3885	3219	6090		4078 ± 524	3968	3297	6844
Hb (g/dL)		13.6 ± 0.7	13.5	11.7	16.5		13.7 ± 0.8	13.6	11.9	16.6
RBC ($\times 10^4/\mu L$)		453.7 ± 24.9	452	383	539		454.7 ± 28.6	453	359	581
sFer (ng/mL)		51.0 ± 63.1	38.9	4.2	681.9		48.6 ± 41.9	37.5	0	388.2

Abbreviations: BMI, body mass index; Hb, haemoglobin; RBC, red blood cell; sFer, serum ferritin; TBV, total blood volume; y.o, years old.

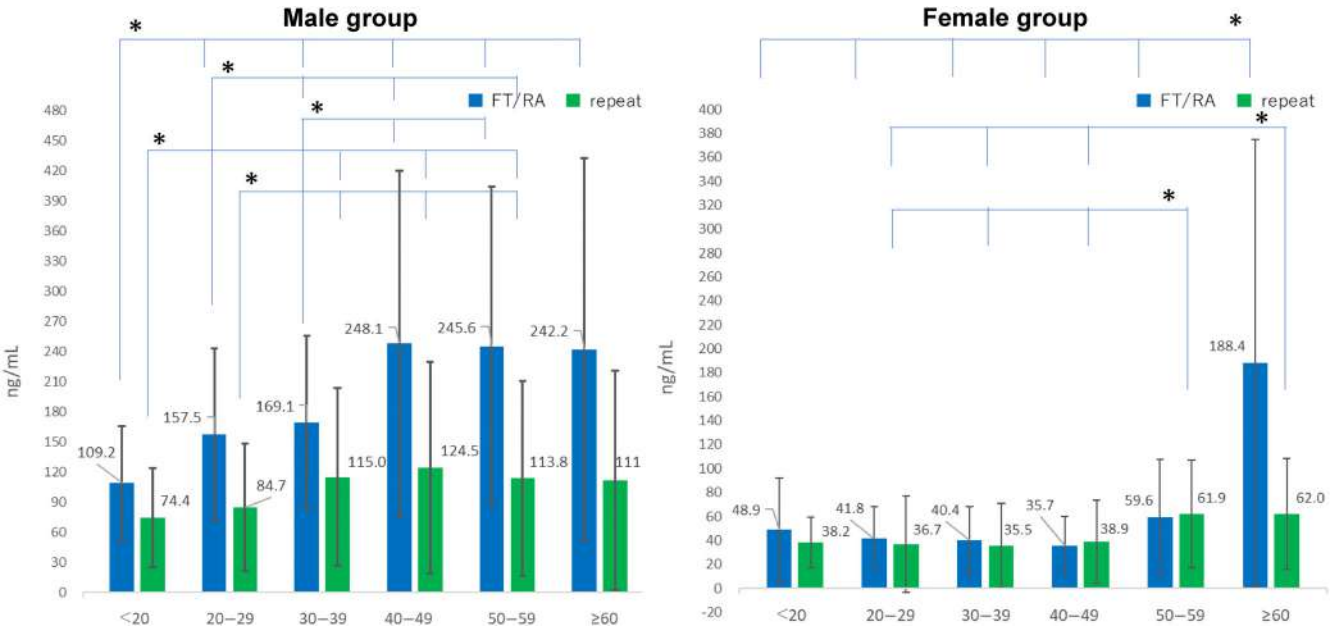

FIGURE 1 Mean serum ferritin (sFer) in male first-time/reactivated (FT/RA) (dark grey bars) and repeat (light grey bars) blood donors, according to age. In general, FT/RA blood donors have higher mean sFer compared to repeat donors (left). Mean sFer in female FT/RA (dark grey bars) and repeat (light grey bars) blood donors, according to age. Although the mean sFer levels were not different between FT/RA and repeat donors among pre-menopausal females, the difference was significant among post-menopausal females (right). *Statistical significance.

Comparison of sFer levels according to gender and age

Among males, FT/RA teenagers had the lowest sFer level (mean: 109.2), increasing with increasing the age, and reaching a plateau after reaching their 40s (mean: 248.1), as shown in Figure 1a. The sFer levels of repeat donors were significantly lower than that of FT/RA in all age groups (range of means: 74.4–124.5). Among females, as shown in Figure 1b, sFer levels were in general low among teenagers compared to those in the 40s (range 35.7–48.9), with a small range of variation among them, increasing in those in their 50s (59.6 ± 47.79), and further increasing in those in their 60s (188.4 ± 186.65), who had values comparable to males. sFer levels of female repeat donors in the age range between teenagers and those in their 50s showed a small difference compared to FT/RA

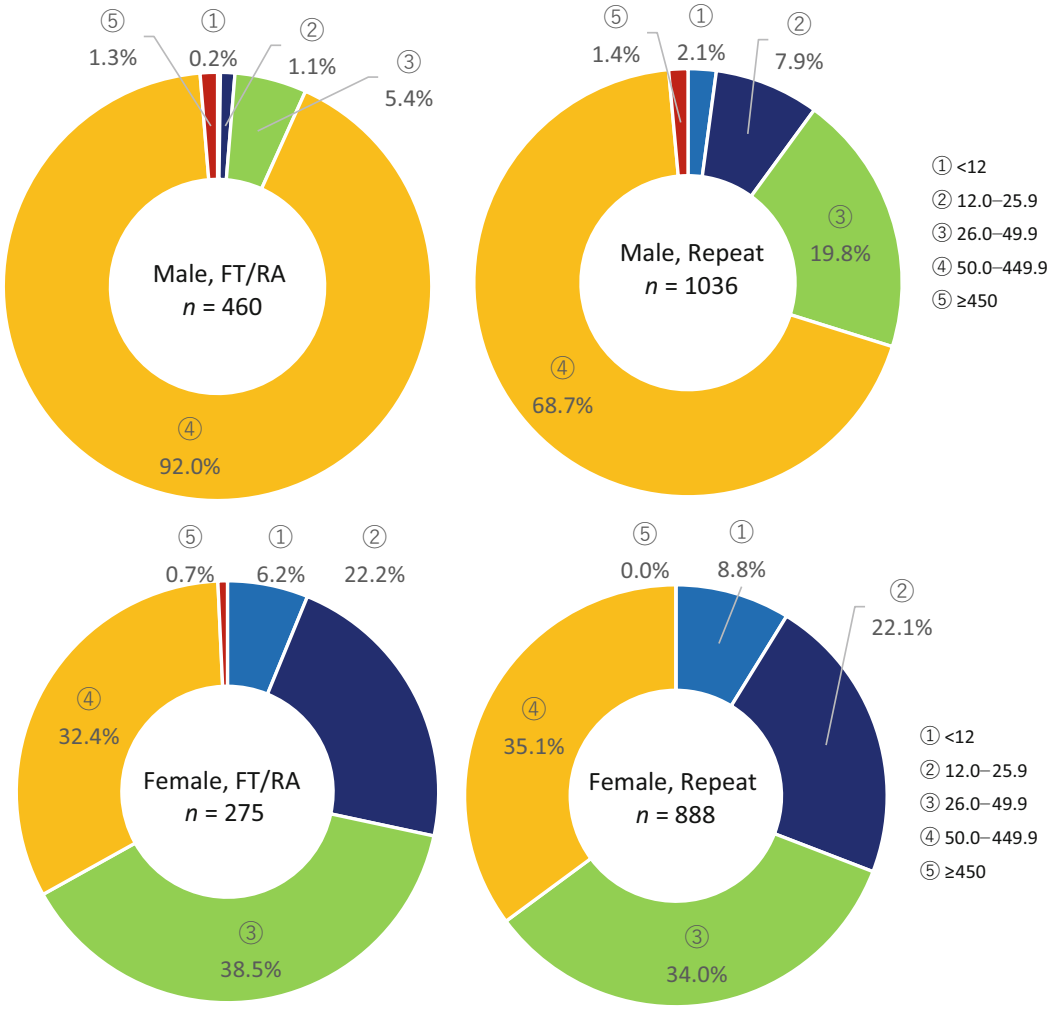

FIGURE 2 Distribution of absent iron store (AIS) (serum ferritin [sFer] < 12) (1), IDE (sFer ≥ 12 and < 26) (2), normal sFer (sFer ≥ 26 and < 50) (3), high sFer (sFer ≥ 50 and < 450) (4) and very high sFer (sFer ≥ 450) (5) among male first-time/reactivated (FT/RA) donors (a), male repeat donors (b), female FT/RA donors (c) and female repeat donors (d). Iron deficiency (AIS + iron-deficient erythropoiesis [IDE]) is rare among male FT/RA donors, accounting for only 1.3%, but higher (10.0%) among male repeat donors. Among female FT/RA donors, about one-third (28.4%) had iron deficiency, whereas it was 30.9% among female repeat donors.

donors, and the greatest difference was observed among those in their 60s.

Rate of donors with AISs (sFer < 12 ng/mL) and IDE (sFer < 26 ng/mL) among blood donors, according to gender and donation status (FT/RA or repeat)

As shown in Figure 2, among male FT/RA donors, the rate of iron depletion was low, with 0.2% presenting with AIS and 1.1% with IDE, in a total of 1.3% with iron deficiency. These values were higher among male repeat donors, with 2.1% presenting with AIS and 7.9% with IDE, in a total of 10% iron deficiency. Among female donors, these rates were higher, with 6.2% and 22.2% AIS and IDE, respectively, for FT/RA donors (total of 28.4% iron deficiency) and 8.8% and 22.1%, respectively, for female repeat donors (total of 30.9% iron deficiency). These numbers indicate that about 10% of male donors and 31% of female repeat donors are in a status of iron deficiency.

sFer recovery among blood donors, according to gender and donation status

In general, among male blood donors, the sFer recovery after donation was faster among repeat donors than FT/RA, and among teenagers compared to the other age groups (20s–60s).

As shown in Figure 3a, among FT/RA male donors, teenagers recovered faster than those aged 20s–60s, but 450 days (about 64 weeks) was required for 90% of teenagers to recover to 90% of the original sFer levels. The recovery of teenagers was significantly faster ($p < .05$) compared to the other age groups. Among male repeat donors (Figure 3b), however, there was no significant

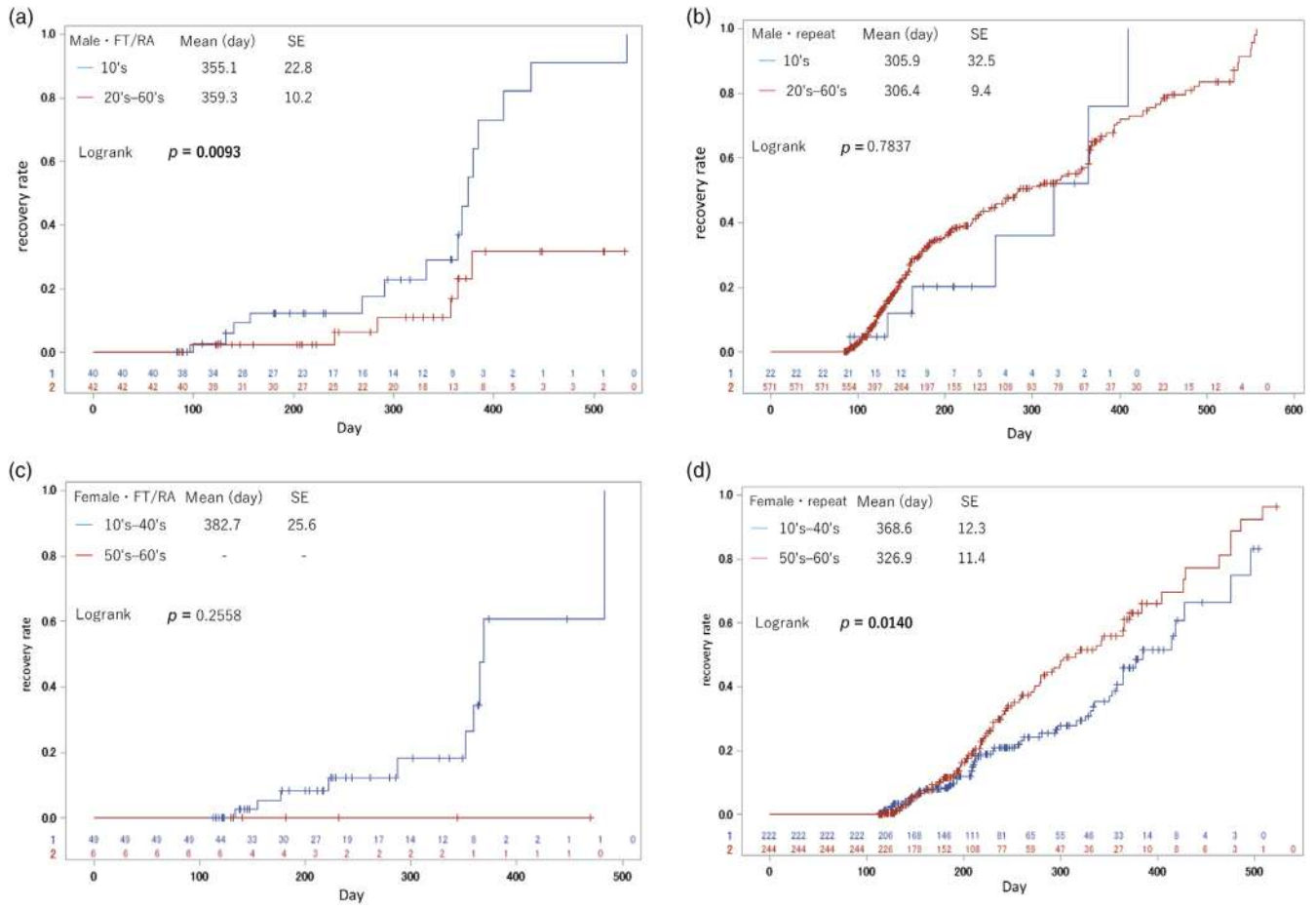

FIGURE 3 (a) Time to recovery of serum ferritin (sFer) to 90% of the pre-donation value among male first-time/reactivated (FT/RA) donors. Teenagers recovered sFer significantly faster than donors in other age groups. (b) Time to recovery of sFer to 90% of the pre-donation value among male repeat donors. There was no significant difference in the time of sFer recovery between teenagers and the other age groups. (c) Time to recovery of sFer to 90% of the pre-donation value among female FT/RA donors. Apparently, pre-menopausal female recovered faster than post-menopausal donors, but due to the small number of cases that could be followed, conclusion cannot be drawn. (d) Time to recovery of sFer to 90% of the pre-donation value among female repeat donors. Post-menopausal donors recovered significantly faster than pre-menopausal donors.

difference in the sFer recovery between those in their 20s–60s and teenagers.

Similarly, among females, repeat donors showed better recovery than FT/RA donors. As shown in Figure 3c, among FT/RA female donors, pre-menopausal (teenagers to those in their 40s) donors had apparently faster recovery than post-menopausal ones. In comparison, among repeat female donors, post-menopausal donors showed a significantly faster recovery ($p < .05$) than pre-menopausal ones, as shown in Figure 3d.

When FT/RA male donors with normal initial sFer levels (≥26 ng/m) were compared with those with low initial sFer levels (<26 ng/mL), in both male and female donors, those with initial normal sFer levels (≥26 ng/mL) recovered faster than those with initial low sFer (<26 ng/mL) (see Figure S1).

DISCUSSION

JRCBS, the sole blood business operator in Japan, applies a more restrictive practice of blood donation, allowing collection of lower volumes at lower frequency compared to other countries. Although criteria of blood donation include Hb values, the iron stores of blood donors in Japan have not been evaluated for more than 20 years [7].

It was evident that especially Japanese female donors, including FT/RA and repeat donors, are in a higher state of iron depletion (28.4% vs. 30.9%, respectively), defined as sFer < 26, compared to apparently healthy Japanese women (17.3%, anaemia defined as Hb < 12.0 g/dL) and among women aged 20–49 years, who attended the annual health check-up at a hospital in Tokyo [3].

While direct comparisons are hindered by varying standards across countries (Table 2), it is evident that AIS (sFer < 12 or < 15 ng/mL) were notably uncommon among male FT/RA donors, aligning with findings from other countries [15, 16]. Iron deficiency (sFer < 26 or < 30, depending on the country) was also less prevalent among male FT/RA donors in Japan compared to Canada [9] and the Netherlands [10].

However, this value was higher among Japanese female FT/RA and repeat donors, albeit with lower AIS rates compared to their counterparts in the United States [15], Australia [16] and pre-menopausal women in Denmark [14]. Approximately one-third

TABLE 2 Comparison of serum ferritin (sFer) deficiency among blood donors in different countries.

	Iron deficiency status	Australia	Canada	The Netherlands	US	Japan
Male FT/RA	AIS (sFer < 12 or 15)	1.30%	NA	0.10%	0.00%	0.20%
	AIS + IDE (sFer < 26 or 30)	NA	2.90%	1.60%	NA	1.30%
Male repeat	AIS (sFer < 12 or 15)	6.30%	NA	9.40%	16.40%	2.10%
	AIS + IDE (sFer < 26 or 30)	NA	41.60%	42.00%	65.10%	10.00%
Female FT/RA	AIS (sFer < 12 or 15)	12.00%	NA	5.30%	NA	6.20%
	AIS + IDE (sFer < 26 or 30)	NA	32.20%	25.00%	NA	28.40%
Female repeat	AIS (sFer < 12 or 15)	26.40%	NA	15.00%	27.10%	8.80%
	AIS + IDE (sFer < 26 or 30)	NA	65.10%	53.00%	93.20%	30.90%
Reference (*n*)		Salvin et al. [16]	Goldman et al. [9]	Vinnkenoog et al. [10]	Cable et al [15]	Present study (Odajima T et al.)

Note: Data from Japan includes only whole-blood donors (200 WB and 400 WB).
Abbreviations: AIS, absent iron store; FT/RA, first-time/reactivated; IDE, iron-deficient erythropoiesis; NA, not available.

(28.4%) of our female FT/RA donors exhibited iron depletion, surpassing the 20.5% reported in Japan in 1996 [7]. The absence of differences between FT/RA pre-menopausal donors in Japan could be attributed in part to the lengthy mandatory inter-donation intervals for both genders, particularly for females, who are only permitted to donate WB twice a year with a minimum interval of 16 weeks. Additionally, women may elect out of donation when their haemoglobin levels drop, and this population could benefit from iron supplementation. Furthermore, it is worth mentioning that the maximum volume of WB donation allowed in Japan is 400 mL, whereas many Western countries allow up to 500 mL.

Comparing with the earlier study in Japan over 20 years ago, the iron depletion rate among female FT/RA donors has increased from 20.5% in 1996 to 28.4% in the present study. Intriguingly, iron depletion among female repeat donors decreased from 37.7% to 30.9%. This might be attributed to the assessment of both sFer and iron storage (mg) for iron depletion evaluation, with diagnoses based on iron stores. Despite utilizing sFer < 12 to define iron deficiency, all except one female donor fell within the normal range [7], rendering direct comparisons challenging. Nonetheless, it appears that iron deficiency has increased in the general population, necessitating government and donor awareness, along with strategies to bolster iron stores. Targeted interventions are crucial not only for healthcare management but also to ensure the safe continuation of blood donation among this population. Iron deficiency among female donors was reported at 32.2% [9] in Canada, 31.1% in the United States [15] and 25% in the Netherlands [10], and these high numbers can importantly affect blood donation.

In Japan, more than 90% of the 5.0 million donations are from repeat donors, compared with about 70% of the 6.85 million blood donors in the United States, who donated in 2013. Repeat donors are at a higher risk of iron deficiency due to the progressive blood loss [17]. Especially in the present study, we selected a cohort of repeat donors who had donated at least twice in the previous year (1 April 2017–31 March 2018), who are expectedly at a higher risk of lower sFer due to a more intensive donation pattern.

Studies have demonstrated the efficacy of iron administration in improving iron stores post blood donation [13, 18, 19], and the results of an ongoing large scale study at Sanquin [20] are awaited. A randomized clinical trial [13] involving blood donors stratified by ferritin level, sex, and age assigned participants to receive oral iron supplementation after WB donation or not. Results showed that donors receiving iron supplementation achieved iron store recovery within a median of 76 days, whereas those without supplementation required a median recovery time exceeding 168 days (24 weeks), with 67% failing to restore iron stores by 168 days. Another study revealed minimal effects of oral iron on storage and RBC iron recovery among donors with baseline sFer levels ≥50 ng/mL, whereas significant effects were observed when sFer levels were <50 ng/mL [21]. This suggests that individuals with lower sFer levels prior to blood donation could benefit from iron supplementation. Unfortunately, robust reports on iron supplementation among pre-menopausal females in Japan are lacking, necessitating the wait for results from our ongoing study.

In our series, we confirmed that FT/RA male teenagers, regardless of iron supplementation, recovered faster than the other age groups, but sFer recovery of teenaged repeat donors was not different from that of the other age groups. On the other hand, female post-menopausal repeat donors recovered faster than pre-menopausal ones, but the recovery of FT/RA female donors could not be appropriately evaluated due to the small number of cases. Thus, we can speculate that iron supplementation would help further accelerate sFer recovery in both male and female donors as well as FT/RA and repeat donors.

Asian populations, including Japanese, generally have smaller body sizes than Caucasians [23–25], leading to stricter blood donation criteria in Japan. Comparisons between Japanese and Americans reveal that the latter typically have greater height, weight and limb lengths, with every limb girth measurement significantly larger among Americans [26]. Similar disparities are seen in studies comparing young Japanese and Australian Caucasian adults [27], as well as various other Asian populations [23], who tend to have higher body fat

percentages at lower BMI levels compared to Caucasians. These ethnic-specific differences highlight the inadequacy of universal BMI cut-off points for assessing obesity prevalence across ethnic groups [28] and possibly in estimating maximum blood donation volume. Consequently, a study comparing blood collection practices across Asia was deemed necessary, revealing varying practices and criteria among Asian countries [29]. Notably, Japanese donors in the present study generally exhibit lower BMI, height and BW compared to Danish [14] and US [15] donors.

Measurement of sFer offers a practical method to estimate the risks associated with blood donation. The application of this parameter in blood donation decision making, such as implementation of deferral policies [10, 11] or extension of the inter-donation interval [9], is crucial, as evidenced by previous studies from different countries. These policies have an impact on blood donor recruitment. In Canada, it is predicted that red cell collections would decline by at least 3.1% and even by as much as 19.2% after ferritin testing is implemented [21]. A simulation study from France [22] also showed that testing policy in delayed donations for iron-deficient donors would significantly impact the number of donations, although effectively reducing risk of IDA. At Sanquin [10], they have confirmed that among donors returning after a 6-month deferral due to low sFer, 88% of females and 99% of males, and after a 12-month deferral, 74% and 95%, respectively, had recovered their sFer levels. So, these policies would be effective in protecting the health of blood donors, but might have an impact on blood recruitment.

Our study's limitations include excluding donors who contributed a small volume (200 mL) of WB, focusing solely on those who donated 400 mL, which could introduce bias. However, we excluded these donors because of the expected association between small-volume donation and a lesser decrease in sFer levels. 'Repeat donors' here were defined as individuals who donated WB at least twice in the previous year, likely resulting in lower sFer levels due to more frequent donation. Involvement of various personnel in donor recruitment, including medical professionals, during non-peak hours, may have potentially affected donor selection. Despite JRC receiving approximately 5 million donations annually, and 913,840 donations were received at the three prefectures in FY 2018, our study included 2659 donations, a number that, however, greatly exceed the number in previous studies conducted over 20 years ago.

Our present results confirmed that in spite of the restrictive donation criteria applied in Japan, congruent with the small size of our donors, a substantial proportion of them are in an iron-deficient condition. Especially female donors require iron management even after the first donation, which suggests a relatively high incidence of iron depletion among the general female population in Japan. Implementation of donation criteria based on sFer measurement will certainly impact donor recruitment, but healthcare management of blood donors need to be prioritized. Measures need to be urgently implemented to evaluate and appropriately manage iron stores of our blood donors, and studies are ongoing.

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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.

ORCID

Nelson H. Tsuno https://orcid.org/0000-0002-7619-6500
Fumihiko Ishimaru https://orcid.org/0000-0002-7668-6083

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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

Deferral of blood donors who have ever stayed in a *Trypanosoma cruzi* endemic area: An international survey

Antoine Lewin[1] | **Laura Tonnetti**[2] | **Christian Renaud**[1] | **Steven J. Drews**[3] | **Evan M. Bloch**[4] | **Sheila F. O'Brien**[5] | **on behalf of the Parasite and Surveillance Risk Assessment and Policy Subgroups of the ISBT Working Party on Transfusion-Transmitted Infectious Diseases**

[1]Medical Affairs and Innovation, Héma-Québec, Montreal, Quebec, Canada

[2]Scientific Affairs, American Red Cross, Rockville, Maryland, USA

[3]Canadian Blood Services, Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton, Alberta, Canada

[4]Division of Transfusion Medicine, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[5]Epidemiology & Surveillance, Canadian Blood Services, Ottawa, Ontario, Canada

Correspondence
Antoine Lewin, Medical Affairs and Innovation, Héma-Québec, 4045 Boulevard de la Côte-Vertu Ouest, Montréal, QC H4R 2W7, Canada.
Email: antoine.lewin@hema-quebec.qc.ca

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Abstract

Background and Objectives: *Trypanosoma cruzi* is the etiologic agent of Chagas disease (CD), an anthropozoonosis from the American continent that progresses from an acute phase to an indeterminate phase, followed by a chronic symptomatic phase in around 30% of patients. In countries where *T. cruzi* is not endemic, many blood transfusion services test blood donors who have stayed in an endemic country ('at-risk stay')—even if they do not present with other risk factors. However, the efficiency of this approach has been questioned.

Materials and Methods: On 18 September 2023, a worldwide survey was distributed among employees of blood transfusion services. The questions mainly pertained to CD's endemicity in the blood services' region, the current testing policy for *T. cruzi* and the number of confirmed positive results among donors with a prior at-risk stay *alone* (i.e., without other risk factors for *T. cruzi* infection).

Results: Twenty-six recipients completed the survey. Of the 22 (84.6%) blood services that operated in a non-endemic region, 9 (42.9%) tested donors for *T. cruzi*, including 8 (88.9%) that considered the travel history or the duration of the stay (*alone*) in their testing algorithm ('study blood services'). Over 93 years of observation among all study blood services, 2 donations from donors with an at-risk stay *alone* and 299 from those with other risk factors were confirmed positive for *T. cruzi*.

Conclusion: The study findings question the utility of testing blood donors who have stayed in an endemic country without other risk factors.

Keywords

Chagas disease, donor testing policy, non-endemic, risk factors, *T. cruzi*, transfusion-transmitted infections

Highlights

- Only eight (36.4%) of the 22 participating blood services that operated in a non-endemic region reported testing donors for *Trypanosoma cruzi* if the donor had an at-risk stay *alone*, that is, without other risk factors.
- Over a cumulative total of 93 years of observation, only two confirmed *T. cruzi* infections were identified among donors with an at-risk stay *alone*, while 299 were identified among those with other risk factors.
- The results of this survey question the utility of testing blood donors who have ever stayed in an area where Chagas disease is endemic, in the absence of other risk factors.

INTRODUCTION

More than 6 million people may be infected with *Trypanosoma cruzi*, a parasitic protozoan that causes Chagas disease (CD) [1–3]. CD is endemic to many parts of Latin America, although vector control programmes have significantly reduced the risk in this region. The natural history of CD includes an acute phase that lasts 2–4 months and is characterized by high parasitaemia, followed by an asymptomatic indeterminate phase that may last decades (or even a lifetime) and is characterized by low or undetectable parasitaemia along with seropositivity [1, 2]. Only ∼30% of patients enter a chronic symptomatic phase ∼10–30 years after infection, which complicates early diagnosis and treatment as treatment effectiveness seems to decline with time post-primary infection [1, 2].

The modes of transmission of CD differ between endemic and non-endemic regions. In endemic regions, the disease is generally acquired through exposure to triatomine bites in sub-standard housing conditions [1, 2]. In non-endemic regions, the rare cases that have been described were either imported (i.e., ascribed to a previous long-term stay in an endemic area) or acquired through congenital or transfusion transmission [1, 2].

Very few cases of transfusion transmission have been reported in non-endemic countries [4]. Nevertheless, non-endemic countries may host a number of *T. cruzi* carriers [5], the number of which is poised to grow with increasing immigration and international travel.

Therefore, blood services have implemented measures to mitigate the risk of *T. cruzi* transmission by transfusion [6]. In endemic countries, many have implemented universal screening test for *T. cruzi* [7]; however, the cost-effectiveness of this approach is suboptimal in non-endemic countries [8]. Alternatively, at-risk blood donors may be deferred based on risk factors for *T. cruzi* infection, which is currently the preferred approach in many European conditions with smaller immigrant populations [6]. However, this strategy lacks specificity and may defer safe donors [9–11].

Another approach currently used by some non-endemic countries is selective testing [11], whereby only donors who are deemed to be at risk for *T. cruzi* are tested. Blood donors may, for example, be tested for *T. cruzi* if they report being born in an endemic country, having a mother or grandmother born in an endemic country, or having a history of a prolonged stay in an endemic country.

However, a controversial aspect of selective testing concerns the utility of testing donors who have ever stayed in an endemic country *alone* (i.e., with no other risk factors). Indeed, many studies have reported a weak or absent association between a stay in an endemic country and the risk of *T. cruzi* infection [11, 12]. Furthermore, the risk of acquiring *T. cruzi* is likely limited in the urban areas of endemic countries. Yet, the donor health questionnaire (DHQ) used in most blood services does not capture this level of detail.

A previous international survey described the strategies used by non-endemic countries to mitigate the risk of *T. cruzi* transmission [6], but did not explore the utility of testing donors with a history of a prolonged stay in an endemic country (at-risk stay) *alone*. Therefore, this study evaluated the relevance of testing donors with an 'at-risk stay' *alone*. Specifically, the study described the current practices regarding the screening of donors with risk factors for *T. cruzi* infection and assessed the risk of *T. cruzi* positivity among at-risk donors.

MATERIALS AND METHODS

Participating blood services

This was a worldwide survey developed in English and sent to members of the International Society of Blood Transfusion (ISBT) — Transfusion Transmitted Infectious Diseases (TTID) Working Party. All survey recipients were senior employees of blood transfusion services located anywhere throughout the world. Participants could complete the survey online through a survey tool (i.e., Microsoft Forms) or manually using a fillable Word document.

Survey

The survey was sent on 18 September 2023 to employees of blood services on behalf of the parasitology and surveillance, risk assessment and policy (SRAP) subgroups of the ISBT-TTID Working Party. The survey questions pertained to (1) the endemicity of CD in the blood service's region; (2) whether a blood service tested blood donors for *T. cruzi* based on the duration of a previous at-risk stay; (3) the number of years of *T. cruzi* testing; (4) the testing and confirmation tests used; (5) the number of tests that had been performed since

implementation; and (6) the number of confirmed-positive donations among donors with an at-risk stay *alone* and those with other risk factors.

RESULTS

Twenty-six recipients—including 5 (19.2%) in Africa, 4 (15.4%) in Asia, 9 (34.6%) in Europe, 3 (11.5%) in North America, 1 (3.8%) in Oceania and 4 (15.4%) in South America—completed the survey among 38 countries screened (Table 1). Twenty-two (84.6%) operated in a non-endemic region.

Current practices for testing donors with an at-risk stay

Fourteen (63.6%) of the blood services operating in a non-endemic region did not test blood donors with an at-risk stay *alone* (Table 1). These blood services cited the following as the three most common reasons for not testing these donors: travelling is not a significant risk factor for *T. cruzi* infection ($n = 9$ [64.3%]), lack of screening test ($n = 4$ [28.6%]) and the lack of human or financial resources ($n = 3$ [21.4%]). Nine (42.9%) blood services operating in a non-endemic country tested donors for *T. cruzi*. Eight (88.9%) of these blood services used a testing algorithm that factored in the duration of the stay or the travel history (*alone*) in an endemic country (study blood services), and one reported testing all blood donors once, regardless of their travel history.

Among the study blood services, the following length of stays (in consecutive days) in an endemic country qualified a donor for *T. cruzi* testing: ≥180 days ($n = 4$ [50.0%]), ≥120 days ($n = 1$ [12.5%]), ≥28 days ($n = 2$ [25.0%]) and <28 days ($n = 1$ [12.5%]). The median year of introducing the criterion for at-risk stays was 2010 (range = 2006–2016). All used enzyme-linked immunosorbent assay (ELISA) for testing, but the methods for confirmatory testing were more heterogeneous and included nucleic acid tests, ELISA, western blot, indirect immunofluorescence and line immunoblot assay.

TABLE 1 Characteristics of participating blood services, and use of deferrals for at-risk stays in *Trypanosoma cruzi* endemic countries.

Blood service	Country (region)	Endemic region	Deferral for at-risk stays *alone*[a]
American Red Cross	United States	No	No
Australian Red Cross Lifeblood	Australia	No	No
Babcock University Teaching Hospital Ilishan Remo	South West, Nigeria	No	No
Blood Services Group, Health Sciences Authority	Singapore	No	No
Blood transfusions	Iran	No	No
Canadian Blood Services	Canada (except Québec)	No	Yes
Centro de Transfusión de la Comunidad de Madrid	Spain (Madrid)	No	Yes
Etablissement Français du Sang	France	No	Yes
Fundação Pró-Sangue Hemocentro de São Paulo	Brazil	Yes	Yes
German Red Cross Baden-Wuerttemberg—Hesse gGmbH	Germany	No	No
Héma-Québec	Canada (Québec)	No	Yes
Hopsital materno-Infantil Ramón Sardá	Argentina (Buenos Aires)	Yes	No
Hospital Sirio-Libanes Blood Bank	Brazil	Yes	Yes
Instituto Nacional de Salud	Colombia	Yes	Yes
Interregional Blood Transfusion SRC	Switzerland (Vaud, Valais and Bern Cantons)	No	Yes
Irish Blood Transfusion Service	Ireland	No	No
Japanese Red Cross Society	Japan	No	Yes
Korean Red Cross Blood Services	Republic of Korea	No	No
National Blood Service, Ghana	Ghana	No	No
National Blood Services	Egypt	No	No
NBTS Cameroon	Cameroon	No	No
Pirogov National Medical Surgical Center	Russia	No	No
Red Andaluza de Medicina Transfusional, Tejidos Y Células.	Spain (Andalusia)	No	Yes
Red Cross Flanders, Blood Service	Belgium (Flanders)	No	Yes
Sanquin	The Netherlands	No	No
South African National Blood Service	South Africa	No	No

[a]Where *alone* means without other risk factors, such as birth in an endemic country.

Confirmed *T. cruzi* positives

Overall, the eight study blood services tested donations from donors with risk factors for *T. cruzi* infection over 93 years of observation, reporting two confirmed positives among the donors with an at-risk stay *alone* (Table 2). By contrast, 299 confirmed positives were identified among donors with other risk factors.

DISCUSSION

The results of this survey question the utility of testing donors who have ever stayed in an endemic country unless they present with other risk factors for *T. cruzi* infection (e.g., birth in an endemic country, having a mother or maternal grandmother born in an endemic country). Only 8 of the 22 participating blood services that operated in a non-endemic region reported testing donors with an at-risk stay *alone*—that is, without other risk factors. The most commonly cited reason for not testing blood donors with an at-risk stay *alone* was that it is not a significant risk factor for *T. cruzi* infection. Consistent with this view, over 93 years of observation, the study blood services reported only two confirmed *T. cruzi* infections among donors with an at-risk stay *alone*, while they reported 299 among those with other risk factors.

Our findings are consistent with prior studies that reported at-risk stays to be weakly associated (if at all) with the risk of acquiring a *T. cruzi* infection. In one study of 1570 French soldiers who served in French Guyana (an endemic region for CD) during 11 months, none tested seropositive upon their return to metropolitan France [12]. In a Canadian study, 13 out of 7255 at-risk donors (risk factors included birth in Latin America [50.6%], having a mother or maternal grandmother born in Latin America [28.0%], and spending ≥6 months in Latin America [19.0%]) were confirmed *T. cruzi* positives, and none reported an at-risk stay as the sole risk factor [11]. In a study in the United States, the odds of confirmed *T. cruzi* positivity differed minimally, whether an at-risk stay of 2 weeks, 1 month, 3 months or 1 year was considered [13], suggesting other risk factors are more significant than the duration of an at-risk stay. Moreover, to the best of our knowledge, no documented cases of transfusion transmission have been caused by a *T. cruzi*-positive donor with an at-risk stay *alone* [4, 14–17].

Our results suggest donors with an at-risk stay *alone* may not need to be tested for *T. cruzi* infection. Besides cost savings, such a change would minimize donor time spent answering these questions and personnel time spent ascertaining the donor's responses through in-person interviews. This approach could improve efficiency, allowing for the collection of more donations. Additionally, for blood services that rely on donor deferral instead of selective testing, removing the deferral for at-risk stays would increase the inclusiveness of blood donation and may significantly expand the donor base.

In the current survey, one participating blood service (Red Cross Flanders, Blood Service, Belgium) reported using a different approach. Specifically, for the travel-related risk factor, the donors are tested not only if they had spent >180 consecutive days in an endemic country, but also if they had ever slept in primitive accommodations in the jungle or dilapidated houses in the slums of large cities in Latin America (independent of the number of nights). This blood service

TABLE 2 Tested donations and confirmed *Trypanosoma cruzi* positives at the study blood services.

Blood service (country or region)	*n*
Canadian Blood Services (Canada, except Québec)[a]	
Total number of tested donations	138,536
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	33
Centro de Transfusión de la Comunidad de Madrid (Spain)	
Total number of tested donations	190,000
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	130
Etablissement Français du Sang (France)	
Total number of tested donations	334,205
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	3
Héma-Québec (Canada, Québec)[a]	
Total number of tested donations	32,763
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	14
Interregional Blood Transfusion SRC (Switzerland)	
Total number of tested donations	11,812
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	0
Japanese Red Cross Society (Japan)	
Total number of tested donations	85,158
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	5
Red Andaluza de dedicima transfusional, Tejidos y Células (Andalusia, Spain)	
Total number of tested donations	-
Confirmed positives due to an at-risk stay *alone*[b]	0
Confirmed positives due to other risk factors	112
Red Cross Flanders, Blood Service (Flanders, Belgium)	
Total number of tested donations	11,008
Confirmed positives due to an at-risk stay *alone*[b]	2
Confirmed positives due to other risk factors	2[c]

[a]Chagas testing was implemented in 2010, but the two types of risk factors (i.e., at-risk stay *alone* vs. other risk factors) were not assessed in separate questions until 2015. As a result, data are only available from 2015 through 2020 for Canada.
[b]Where *alone* means without other risk factors, such as birth in an endemic country.
[c]The participant reported that one confirmed positives was identified with a separate question that asked donors whether they ever slept in primitive accommodations in the jungle or in dilapidated houses in the slumps of large cities in Latin America (independent of the number of nights).

identified four confirmed positive cases, including two tested due to an at-risk stay *alone*, one due to an at-risk stay and having a mother born in an endemic country, and one due to a night spent in primitive accommodations. Albeit preliminary, this observation suggests the sensitivity of the screening question on at-risk stays may be improved by specifying substandard housing conditions associated with CD.

Pathogen reduction technologies (PRTs) may eventually obviate the need to question donors about CD risk factors, including those unrelated to at-risk stays. The technology thus holds promise for expanding the donor base, but no PRT is currently licensed for RBCs. Therefore, donor questioning will likely remain in effect in most blood services, at least in the short term.

This study is subject to some limitations. Despite its international scope, the survey covered relatively few countries, and the few blood services that operated in low- and middle-income countries were excluded from the analysis as they did not test donors based on at-risk stays. Moreover, as with all surveys, the accuracy of the findings depends on participant responses.

Overall, these results question the utility of testing donors for *T. cruzi* based on at-risk stay *alone* in an endemic country *alone*—that is, in the absence of other more significant risk factors for *T. cruzi*. Therefore, many countries may consider abandoning this practice, which should not affect the safety of the blood supply.

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CONFLICT OF INTEREST STATEMENT

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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.

ORCID

Antoine Lewin https://orcid.org/0000-0003-1748-4198
Christian Renaud https://orcid.org/0000-0001-5685-5380
Steven J. Drews https://orcid.org/0000-0003-2519-1109
Evan M. Bloch https://orcid.org/0000-0001-8181-9517
Sheila F. O'Brien https://orcid.org/0000-0002-5332-2789

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ORIGINAL ARTICLE

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New tatt? We're ok with that! Relaxing the tattoo deferral for plasmapheresis donors maintains safety and increases donations

Claire E. Styles[1] | Veronica C. Hoad[1] | Robert Harley[1] | John Kaldor[2] | Iain B. Gosbell[1,3]

[1]Donor and Product Safety Unit, Australian Red Cross Lifeblood, Melbourne, Australia

[2]The Kirby Institute, University of New South Wales, Sydney, Australia

[3]School of Medicine, Western Sydney University, Penrith, Australia

Correspondence
Claire E. Styles, 290 Wellington St, Perth, Western Australia 6000, Australia.
Email: cstyles@redcrossblood.org.au

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Abstract

Background and Objectives: Tattooing is one of the leading donor deferral reasons in Australia. Until September 2020, donors were deferred from all donation types for 4 months after a tattoo. At this time, our guideline changed such that donations of plasma for further manufacture were accepted immediately, provided the tattoo was administered in a licensed or regulated Australian establishment. We examined the effects of this change.

Materials and Methods: Donors with a tattoo deferral in the 2 years before or after the guideline change were identified and followed up until 3 November 2022. Between the two periods, we compared blood-borne virus (BBV) incidence, donor return, and the number of donors and donations regained after deferral.

Results: The incidence of BBV infection in donors after a tattoo deferral was zero in both periods. To exceed a residual risk of 1 in 1 million for hepatitis C virus, 190 donors would need to be infected yearly from a tattoo. Donors returned to donate significantly faster after the change (median return 85 days compared with 278 days). An extra 187 donations per 10,000 person-years of observation were gained, yielding a total of 44,674 additional plasma donations nationally 0–4 months after getting a tattoo.

Conclusion: Allowing plasma donations immediately post-tattoo resulted in a substantial donation gain with no adverse safety effect. Lifeblood subsequently reduced the deferral for transfusible component donations to 7 days for tattoos in Australian licensed/regulated establishments.

Keywords

blood donor return, blood-borne virus, deferral, residual risk, tattoo

Highlights

- The risk of viral infection in the plasma supply did not increase by allowing donors who received a tattoo in a licensed or regulated Australian establishment to donate plasma for further manufacture with no waiting period.
- This guideline change significantly increased the proportion of donors who returned to donate after a tattoo as well as reducing their time to return, and almost doubled the number of donations contributed post-tattoo.
- Lifeblood subsequently reduced the waiting period for donations intended for transfusion to 7 days after receiving a tattoo in Australia in licensed or regulated premises.

INTRODUCTION

Tattooing has dramatically increased in popularity over recent years, with approximately 10%–20% population prevalence in most countries; there is a trend towards higher frequency in each successive generation [1, 2]. This pattern is also seen in Australia, with 19.9% prevalence in 2021 [3]. Analysis of blood donation eligibility criteria in 17 countries across 5 continents in 2008 found that most blood services applied a tattoo deferral of either 6 or 12 months because of the perceived risk of acquiring a transfusion-transmissible infection; only the United States made an exception based on where the tattoo was performed, with no deferral for tattoos applied by state-regulated entities with sterile needles and single-use ink [4]. It is well known that temporary deferral has a significant detrimental effect on donor return [5]. This is even more pronounced for tattooing/piercing, as shown by a study of eight blood centres from Belgium, Brazil, Canada, Malta, the Netherlands and the United States [6]. Consequently, there is a large potential gain for blood services if deferral from donation following tattooing can safely be relaxed or removed.

Historically, tattoos have been associated with blood-borne viruses (BBVs), specifically hepatitis B and C viruses (HBV, HCV) and human immunodeficiency virus (HIV) [7, 8]. This correlation was likely due to historically poor infection prevention and control practices [9], plus a higher frequency of tattooing in people with other behaviours associated with these infections [10]. Tattoos applied in prison or by friends were more likely to be associated with HCV than those done professionally [10].

Studies that focus specifically on BBVs in relation to tattoos received recently, or in licensed or regulated settings, have found a very low risk. A critical review of studies specifying the venue of tattooing showed no evidence for increased risk of HCV infection when the procedure was performed in a professional setting [10]. We have previously reported a BBV incidence rate of 4.4 cases per 100,000 person-years of observation (PYO), all of which were HCV infections, among Australian donors who had a recent tattoo deferral and no reported history of the major risk factors injecting drug use or sexual partner with known infection [11]. The total HCV residual risk was estimated at 1 in 34 million if there was no deferral after a tattoo [11]. Further evidence of low risk came from a national survey of public health units, none of which had any record of BBV cases for which the attributed cause was a tattoo in a licensed establishment in Australia (unpublished data).

At the time of the earlier report, Australian donors were deferred from any type of donation for 4 months after receiving a tattoo in any location. Based on the model and other evidence outlined above, Australian Red Cross Lifeblood (hereafter 'Lifeblood') changed the guideline on 27 September 2020 to allow apheresis donations of plasma for further manufacture immediately after receiving a tattoo, provided it was performed at a licensed or regulated establishment in Australia. This study analysed whether the revised guideline was associated with any difference in BBV risk or rate of return to donation following a tattoo.

MATERIALS AND METHODS

Setting and definitions

Lifeblood is the sole blood operator in Australia, collecting around 1.6 million donations per year from approximately 500,000 donors. Donors may donate fresh (transfusible) components via whole blood and apheresis, or plasma exclusively for fractionation/further manufacture into plasma products. Collection type at each donation is determined by eligibility and other factors and may be changed up until the completion of the pre-donation interview.

Both outright deferrals and donation restrictions to plasma for further manufacture are controlled via deferral codes in Lifeblood's national blood management system, ePROGESA (MAK-SYSTEM, France), and hereafter will be referred to collectively as 'deferrals'. Deferrals may be applied because of the donor's answers to the pre-donation questionnaire or donor self-report. For some deferrals (including tattooing), donors received email communications about their eligibility at the beginning and near the end of the deferral period.

The time periods of this study consisted of the pre-change period (27 September 2018 to 26 September 2020) and post-change period (27 September 2020 to 7 October 2022), with 3 November 2022 representing the end of follow-up (Figure 1). The 'study period' refers to the entire period from 27 September 2018 to 3 November 2022.

Tattoo deferrals

The change to the tattoo deferral was promoted with a standard marketing campaign, 'New tatt? We're ok with that!' and the online

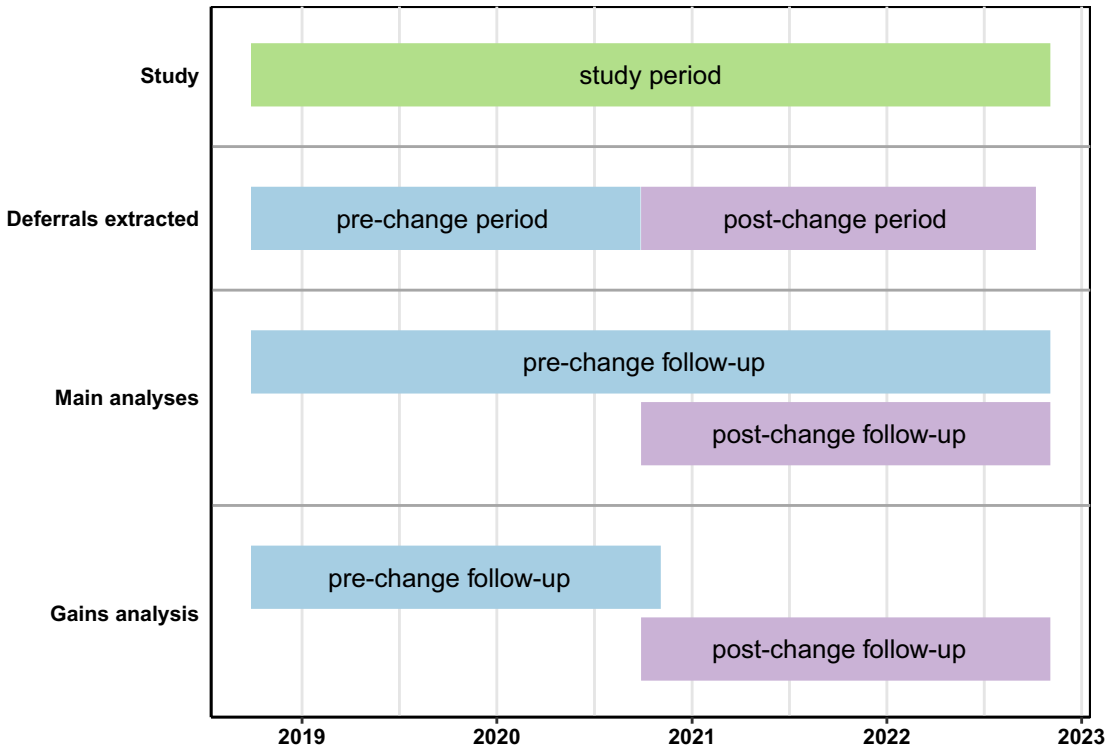

FIGURE 1 Timeline of study events.

eligibility quiz and appointment booking prompts were updated. The pre-donation questionnaire continued to ask about tattooing in the previous 4 months, with tattoos received in licensed/regulated establishments in Australia differentiated by further questioning if they answered 'yes' and indicated by a new deferral code allowing donation of plasma for further manufacture. Donors who still had an active deferral from the pre-change period were not individually contacted but could donate plasma for further manufacture of their own accord.

Data for all tattoo deferrals applied during the pre-change period or the post-change period were extracted. The associated donor ID, age, sex and donation history from prior to deferral to the end of follow-up was also extracted.

Donation testing for BBVs

During the study period, the serology suite of assays changed from PRISM chemiluminescent immunoassays to Alinity s assays, both from Abbott Diagnostics, Illinois, USA, on 26 October 2020. Donations were screened for anti-HIV-1/2, anti-HCV and hepatitis B surface antigen.

Between 31 May and 6 July 2021, the Ultrio Plus multiplex and discriminatory nucleic acid testing (NAT) assays on the Procleix Tigris platform were replaced with the Ultrio Elite assays on the Procleix Panther platform (all from Grifols Diagnostic Solutions Inc., Emeryville, CA). Donations were screened for HCV RNA, HBV DNA and HIV RNA (HIV-1 only on Ultrio Plus, HIV-1/2 on Ultrio Elite). Samples were tested individually except those from donations of plasma for further manufacture collected after May 2021, which were tested in minipools of 16.

All positive results were referred externally for confirmatory testing. Positivity was determined by a confirmed discriminated NAT result and/or positive serology on sequential immunoassays and confirmed by immunoblot for HIV and HCV.

Rate of BBV infection

From the infectious disease testing data for the entire donor population, a list of donors with confirmed HBV, HCV or HIV infection on donation screening was compiled for the period 27 September 2018 to 3 November 2022 and compared with the list of donors with a tattoo deferral. For donors appearing on both lists, further information from post-test discussion, such as clinical history and risk factors, was examined to determine the plausibility of the tattoo having been the cause of the infection. The rates of BBV infection among donors with tattoo deferrals were obtained from infections plausibly attributable (by case review) to a tattoo as numerator, and BBV PYO for each period, defined as follows. For donors with donation-related BBV test results before the end of the follow-up period, the observation time for each deferral instance was the number of days between receiving the tattoo and their next donation. These were adjusted if needed when donors had more than one deferral to ensure that each day of observation was contributed only once.

Hepatitis C risk assessment

As the BBV, which has historically had the strongest association with tattooing, HCV was selected for additional risk assessment. The previously described assessment of HCV risk related to tattooing [11] was updated using revised estimates from data collected in the post-change period. In brief, the observed rates of tattoo deferral and HCV incidence in the post-change period (including upper 95% confidence limit for sensitivity analysis) were applied to the overall proportion of all donors who gave fresh component donations. The resulting estimate of the number of tattoo-related infections was added to the baseline number of donors with incident HCV infection from the most recent 2-year period to estimate HCV residual risk using the Weusten model [12]. The incidence of tattoo-related HCV required to breach residual risk of 1 in 1 million, the Lifeblood threshold for a negligible risk, at the post-change rate of tattoo deferral was also estimated.

Return to donation after tattoo deferral

This analysis excluded retrospective deferrals, that is, deferral codes that were applied more than 4 months after the tattoo was performed (in error or for recall purposes). A donor was considered to have returned after a tattoo if they progressed to any type of collection after the date the deferral was applied (i.e., not on the same day) and before the end of the follow-up period. The number of returns and the return PYO for each period were used to obtain rates of return. The observation time from each deferral instance was the number of days between the date the deferral was applied and the date of return or the end of follow-up, whichever occurred first. As for BBV PYO, observation times were adjusted where needed to take account of multiple deferrals for an individual. Return behaviour was compared between the two periods.

Donor and donation gains

For this analysis, retrospective deferrals were excluded, and the pre-change period plus follow-up was limited to 768 days to match the post-change period and follow-up. For each period, the number of donors regained after deferral was the number who returned before the end of the relevant follow-up period, and the number of donations regained was the sum of all donations given by these donors after deferral and before the end of the relevant follow-up period. The donor/donation gain of the change was the difference in regain rates between the pre- and post-change periods. Donations of plasma for further manufacture that were collected during the 4 months after tattooing in the post-change period comprise the 'yield' of the change, as they could not have been collected under the pre-change guidelines. Donation gains and yields were also estimated for the subgroups shown in Table 1.

Statistics

R Statistical Software v4.0.2 [13] was used for all data cleansing, analysis and visualization.

Binomial proportion 95% confidence intervals (CIs) derived from the Wilson score interval are presented for BBV rates.

Return to donation was compared using Poisson regression, with the subgroup characteristics from Table 1 as covariates, and survival analysis using two different measurements for time to return. 'Overall return' commenced from the date the deferral was applied, which includes the length of the deferral and reflects the overall impact of the change. 'Eligible return' commenced from the date the donor became eligible for any donation type after a tattoo, which is independent of the length of deferral and reflects outcomes during the eligible period only. The R package 'survival' [14] was used to plot and compare the Kaplan–Meier survival curves using the log-rank test.

RESULTS

During the pre-change period, 24,485 tattoo deferrals were recorded for 21,680 donors, followed by a total of 26,624 deferrals for 21,579 donors in the post-change period. Tattoos in licensed/regulated establishments in Australia represented 24,793 (93.12%) of the post-change deferrals. A small proportion of deferrals (1.37%) was associated with therapeutic or autologous donors during the study period. The characteristics of donors with tattoo deferrals are shown in Table 1.

BBV infections and risk assessment

A total of 694 donors tested positive for at least one of the specified BBVs during the study period, with HBV, HCV and HIV representing 55.6%, 41.2% and 3.2% of infections, respectively. Only one donor with a tattoo deferral tested positive. This donor first donated in the post-change period and was confirmed positive for HBV. It was later identified that HBV infection had been diagnosed many years earlier and thus was definitively unrelated to the recent tattoo. The number of BBV infections attributable to a tattoo was therefore zero among 12,334 PYO of the pre-change donor cohort and 5573 PYO of the post-change cohort. This equated to incidence rates of 0 (95% CI: 0–0.311) and 0 (95% CI: 0–0.689) BBV infections per 1000 PYO in the pre- and post-change periods, respectively.

There has been no meaningful change in the BBV incidence in donors since the change in the tattoo deferral, with all risks remaining negligible. For HCV, the baseline (most recent routine calculation of) residual risk for a transfusion-transmitted infection event in 2020–2021 was 1 in 40,489,789 per unit transfused, derived from five donors with seroconversion for HCV. As there were no BBV infections among the tattoo cohort, the estimated risk for transfusible components incorporating tattooing remains the same, should these donors be allowed to donate such components. Using the upper 95%

TABLE 1 Characteristics of donors with tattoo deferrals.

Period	Subgroup	Level	Deferrals, *n* (%)	Donors, *n* (%)
Pre-change	Total		24,485	21,895
	Sex	Female	16,449 (67.18)	14,883 (67.97)
		Male	8036 (32.82)	7012 (32.03)
	Donor status	Repeat	23,220 (94.83)	20,636 (94.25)
		New	1265 (5.17)	1259 (5.75)
	Age	<20	1745 (7.13)	1582 (7.23)
		20–29	11,429 (46.68)	10,050 (45.9)
		30–39	5700 (23.28)	5123 (23.4)
		40–49	2865 (11.7)	2607 (11.91)
		50–59	1925 (7.86)	1776 (8.11)
		60–69	744 (3.04)	682 (3.11)
		70+	77 (0.31)	75 (0.34)
Post-change	Total		26,624	22,087
	Sex	Female	18,772 (70.51)	15,786 (71.47)
		Male	7852 (29.49)	6301 (28.53)
	Donor status	Repeat	23,165 (87.01)	18,649 (84.43)
		New	3459 (12.99)	3438 (15.57)
	Age	<20	2240 (8.41)	2002 (9.06)
		20–29	12,726 (47.8)	10,436 (47.25)
		30–39	5925 (22.25)	4844 (21.93)
		40–49	2955 (11.1)	2425 (10.98)
		50–59	1923 (7.22)	1631 (7.38)
		60–69	760 (2.85)	665 (3.01)
		70+	95 (0.36)	84 (0.38)

confidence limit for BBV incidence resulted in an additional 8.7 infected fresh component donors over 2 years; the total HCV risk was then 1 in 14,732,960 per unit transfused. To reach a total HCV risk of 1 in 1 million from baseline would require 191 donors per year to be infected from a tattoo, which at the current rate of tattoo deferral would require 1.56% of all tattoo deferrals to result in HCV infection.

Donor return behaviour

Among the pre-change donor cohort, return to donation following tattoo deferral was observed for 16,642 donors over 32,942 PYO, giving a rate of 50.5 returns per 100 PYO. Although donors from the post-change cohort were observed for a shorter period of 10,431 PYO, more returned ($n = 17{,}781$ donors), giving a rate of 170 returns per 100 PYO.

Return to donation remained significantly more frequent in the post-change period after adjusting for potential confounders (Table 2). Repeat donors, therapeutic/autologous donors and those in older age groups were the most likely to return after deferral across the study period, with no meaningful difference by sex.

The survival analysis demonstrated that return to donation was faster among the post-change cohort, regardless of how time to return was calculated. The outcomes of both calculation methods are shown in Table 3, while the Kaplan–Meier plot in Figure 2 shows only the 'Eligible return' method. The difference in return pre- and post-change was significant for both methods (method 1 $\chi^2_{(1)} = 4624$, $p < 0.001$; method 2 $\chi^2_{(1)} = 1298$, $p < 0.001$).

Donor and donation gains

Among 21,476 donors identified in the pre-change period, 12,222 (56.9%) were regained and donated a total of 42,971 donations by 3 November 2020. Appreciably more donors—13,865 (65.5%) of 21,158—were regained after deferral in the post-change period, but donations represented the most substantial change, with 84,971 regained donations being almost double those in the pre-change period. This equated to gains of 26 donors and 187 donations per 10,000 PYO. Some regained donations were not suitable for allogeneic transfusion, but the majority (42,000 from the pre-change period and 79,668 from post-change) were obtained from donors who were not donating for therapeutic or autologous purposes.

The yield of the change was 44,674 donations in total. Donation gains (Figure 3) and yield were highest for repeat donors, men and older donors.

TABLE 2 Predictors of return before the end of follow-up among donors deferred for tattoo.

Covariate	Level	aIRR	*p* value
Period	Pre-change	1 [ref]	
	Post-change	3.62 (95% CI: 3.55–3.70)	<0.001*
Status	Repeat	1 [ref]	
	New	0.429 (95% CI: 0.410–0.448)	<0.001*
Type	Allogeneic	1 [ref]	
	Therapeutic/autologous	1.57 (95% CI: 1.44–1.71)	<0.001*
Sex	Female	1 [ref]	
	Male	1.06 (95% CI: 1.03–1.08)	<0.001*
Age	<20	1 [ref]	
	20–29	1.02 (95% CI: 0.974–1.06)	0.459
	30–39	1.06 (95% CI: 1.02–1.11)	0.009*
	40–49	1.28 (95% CI: 1.22–1.35)	<0.001*
	50–59	1.50 (95% CI: 1.42–1.58)	<0.001*
	60–69	1.58 (95% CI: 1.47–1.70)	<0.001*
	70+	1.44 (95% CI: 1.20–1.72)	<0.001*

Abbreviations: aIRR, adjusted incidence rate ratio; CI, confidence interval.
'*' indicates statistical significance, ie. $p < 0.05$.

DISCUSSION

This study evaluated the revised eligibility guidelines for tattooing in Australia by analysing data from before and after a change allowing immediate donation of plasma for further manufacture. In total, the data covered 4 years, 51,109 deferrals and 41,209 unique donors. No risk of tattoo-associated BBV was detected in either period, and in the post-change period, a higher proportion of donors deferred for tattoo returned in a shorter time after deferral. This resulted in a substantial gain in the number of donations and shows that accepting blood donations after tattooing, when performed in a controlled setting, is both safe and worthwhile from a sufficiency perspective.

As no BBV infections following tattoo were observed in either the pre-change or post-change period, it is estimated that the HCV residual risk for transfusible components would have remained unchanged had the tattoo deferral been removed for these donations. Even assuming a tattoo-related HCV incidence at the upper confidence limit, the risk would remain well below the negligible threshold; to exceed it would require an unrealistically high incidence rate. Although the upper confidence limit of the BBV incidence rate was higher in the post-change period, this is an artefact of the lower PYO, which itself is due to the donors in this period having a shorter window of follow-up but also returning more quickly. This is consistent with findings from a large study of Dutch blood donors, where there was no association between reporting a recent needle-related event (including tattoo) and subsequent BBV-positive result during a 10-year period [15]. Additionally, only two of 287 BBV-positive donors reported a recent tattoo, which was not the most likely route of transmission in either case [15].

We also found that among donors subjected to a plasma-only restriction rather than an outright deferral after a tattoo, the rate of return to donation was significantly higher and the median time to return was reduced by almost 200 days overall and more than 100 days once they were eligible to donate. This is likely because donors' donation habits were not disrupted by waiting for the 120-day deferral period to elapse. The return rate in the post-change period among new and repeat donors was 47.0% and 69.1%, respectively, which compares favourably with the return rates reported in the study of eight blood centres previously described [6].

Many more donations were contributed after a tattoo deferral in the post-change period than in the pre-change period. We were unable to examine how many of these donations were intended for manufacture into fresh components, but the improved retention of donors benefits supply generally because it is easier to convert donors to the desired donation type than to recruit new donors or reactivate lapsed donors. In addition, the new policy directly enabled the collection of 44,674 donations of plasma for further manufacture during the 4-month period immediately after tattooing. The higher donor return and donation rates from progressively older donors are consistent with donor return and donations in the general donor cohort; older donors are more likely to return and donate more often.

Since our last publication [11], some additional literature relating to infectious complications of tattooing has been published, mostly case reports of known bacterial risks such as non-tuberculous mycobacteria [16, 17]. The most significant development was the global outbreak of mpox, with person-to-person transmission of the virus. This outbreak included the first known cases associated with tattooing and piercing, with most occurring in a clinic with multiple infection control violations [18, 19]. It is unclear whether these mpox cases would still have occurred in the presence of reasonable infection control measures, but there have been no reports of ongoing transmission within regulated premises, and the mpox outbreak is no longer an

TABLE 3 Survival analysis comparing return to donation before and after tattoo deferral change.

Method	Period	Records	Returns observed	Returns expected	Median days to return
1 (return since deferral date)	Pre-change	24,218	16,642	22,439	278 (95% CI: 268–287)
	Post-change	26,286	17,781	11,983	85 (95% CI: 84–88)
2 (return since date eligible)	Pre-change	24,218	16,642	19,812	191 (95% CI: 183–200)
	Post-change	26,286	17,781	14,610	78 (95% CI: 76–82)

Abbreviation: CI, confidence interval.

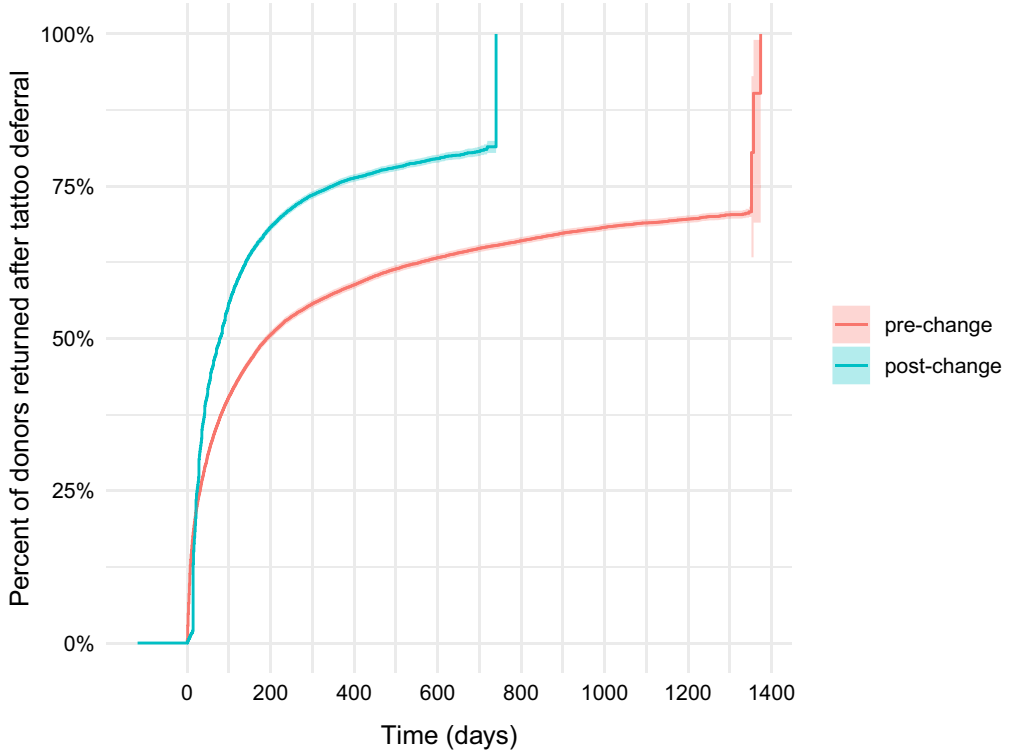

FIGURE 2 Time to return to donation once eligible after tattoo deferral: reversed Kaplan–Meier curves.

emergency. Within this context, the risk of transmitting monkeypox virus via a tattoo in a licensed clinic in Australia is negligible.

Based on the results of this period of data monitoring and updated literature review (unpublished), the Australian regulator approved the further relaxation of the tattoo deferral to allow fresh components to be manufactured from donations given 7 days or more (to cover the risk of short-term bacteraemia) after receiving a tattoo at a licensed establishment in Australia. This change was implemented on 26 June 2023, with no change to the donor questionnaire. The impact of this most recent change cannot be directly measured, as the relevant question (henceforth 'the percutaneous question') applies to tattooing, ear/body piercing and acupuncture together, and a deferral code will only be applied at interview if a donation restriction or deferral is required. However, indirect measures can be obtained. During the calendar year 2022, the percutaneous question was answered 'yes' at 49,780 attendances, and 15,528 deferrals for tattoo at a licensed establishment in Australia were applied. We therefore assume that approximately 31.2% of percutaneous 'yes' answers represent tattoos received in licensed establishments in Australia, and that this proportion remained the same once the fresh product deferral for tattoos was reduced to 7 days. During the first 4 months (26 June 2023 to 27 October 2023), 14,167 donors answered 'yes' to the percutaneous question at 18,178 donation attendances. We estimate that 4419 of these donors and 5670 of the attendances were associated with licensed Australian tattoos. Among these attendances, 2423 resulted in a donation of fresh components for allogeneic use, which could not have been collected under the previous guideline, and 2536 in a donation of plasma for further manufacture. In addition, the next iteration of our residual risk estimates, which included the year 2023, showed considerably lower risks for all BBVs, indicating no safety signals, as expected, from this change.

In conclusion, the lack of BBV infections observed after tattooing during the study period and our revised risk assessment demonstrate that there is negligible BBV risk associated with tattooing in licensed or regulated premises. Given the very high number of tattoo deferrals

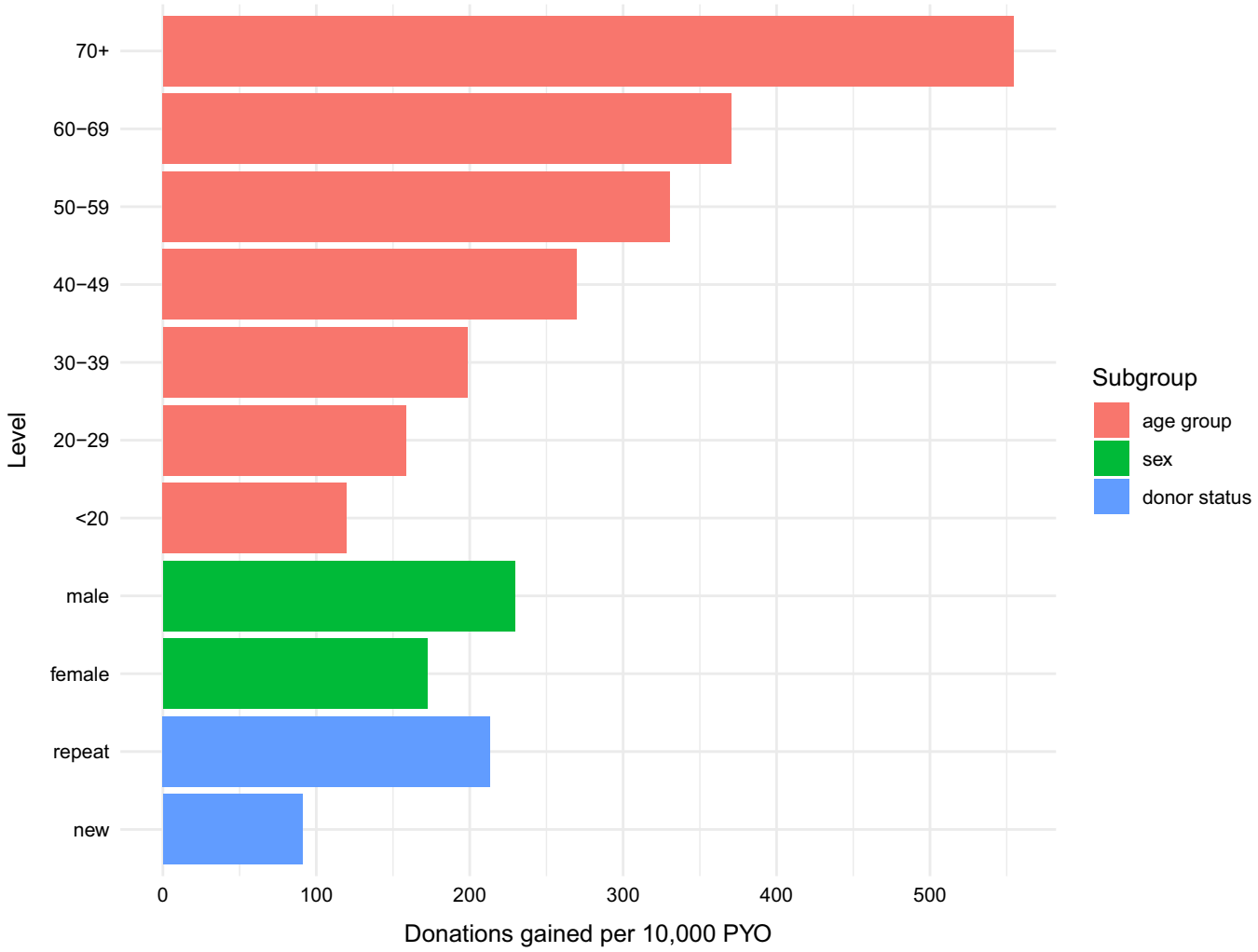

FIGURE 3 Donation gain rate for various donor subgroups. PYO, person-years of observation.

applied per year, we were able to recoup a substantial number of donations by allowing collection of plasma for further manufacture with no waiting period. These data supported Lifeblood's successful application to reduce the deferral period for all other components to 7 days and thus also gain fresh components.

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C.E.S. performed the analysis and wrote the first draft of the manuscript; V.C.H. and C.E.S. developed the method; V.C.H., R.H., I.B.G. and J.K. enabled the eligibility guideline change on which this analysis is based; all authors reviewed and edited the manuscript and approved the final version.

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.

ORCID

Claire E. Styles https://orcid.org/0000-0002-3840-847X
Veronica C. Hoad https://orcid.org/0000-0002-7827-3661
Iain B. Gosbell https://orcid.org/0000-0001-5245-5152

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ORIGINAL ARTICLE

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Optimal malarial screening strategy in Australian blood donors: A cost-effectiveness analysis

Qinglu Cheng[1] | Veronica C. Hoad[2,3] | Peter Bentley[2,4] | Robert Harley[2] | Katia Schenberg[4] | Virginia Wiseman[1,5]

[1]Kirby Institute, UNSW Sydney, Sydney, Australia

[2]Australian Red Cross Lifeblood, Melbourne, Australia

[3]School of Population and Global Health, University of Western Australia, Perth, Australia

[4]UWA Medical School, The University of Western Australia, Perth, Australia

[5]Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK

Correspondence
Veronica C. Hoad, Australian Red Cross Lifeblood, Melbourne, Victoria, Australia.
Email: vhoad@redcrossblood.org.au

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Abstract

Background and Objectives: The risk of transfusion-transmitted malaria (TTM) infections is extremely low in Australia, and the cost-effectiveness of the current screening strategy has not been assessed. This study aims to conduct a cost-effectiveness analysis of different malaria screening strategies in blood donors as part of the risk-based decision-making framework.

Materials and Methods: A decision tree model was developed to assess the cost-effectiveness of five alternative malaria screening strategies from a healthcare sector perspective. Screening strategies combining total or partial removal of malaria testing with different deferral periods were considered. The probabilities of developing severe and uncomplicated TTM were based on a literature review of cases in non-endemic areas since 2000. The health outcomes were quantified using disability-adjusted life years. The costs of non-returning donors due to deferral were also included. Deterministic and probabilistic sensitivity analyses were conducted to account for data uncertainty.

Results: The residual risks for all strategies were so low that the costs, mortality and morbidity associated with TTM are almost negligible. The overall costs were predominantly influenced by the costs of non-returning blood donors. As a result, removal of malaria testing and applying a 28-day deferral for at-risk donors were the least costly and most cost-effective of all the options considered.

Conclusion: The current screening strategy for malaria in blood donors in Australia is not an efficient use of healthcare resources. Partial or total removal of malaria testing would bring significant cost savings without significantly compromising blood safety.

Keywords

blood donor testing, blood safety, cost-effectiveness, malaria

Highlights

- Australia tests for malaria antibodies in both travellers returning from and former residents of malaria-endemic areas.
- Current malaria screening strategy in blood donors in Australia does not prevent any significant morbidity in recipients but uses significant resources.
- Partial or total removal of malaria testing would bring significant cost savings without significantly compromising blood safety.

INTRODUCTION

Malaria is an acute febrile illness caused by *Plasmodium* parasites, which infect people through infected mosquitoes. Malaria parasites invade and multiply in red blood cells and therefore can also be transmitted by transfusion containing red cells; however, the risk is negligible in well-screened donors. In Australia, the last reported case of transfusion-transmitted malaria (TTM) occurred in 1991 [1]. Australian Red Cross Lifeblood (Lifeblood), which is responsible for the collection and distribution of blood and biological products in Australia, estimates the current risk of TTM to be less than 1 in 1 million per unit transfused [2]. Almost all TTM cases are associated with donors born in or having resided in malaria-endemic areas (categorized as 'residents' by regulatory standards). Such individuals are often termed 'semi-immune' and can maintain very low parasite loads, without symptoms, years after their last exposure [3].

Although the risk of acquiring TTM is extremely low, it can cause severe outcomes, especially among individuals from non-endemic areas without immunity. Transfusion recipients, often with underlying medical conditions, are vulnerable. The chance of delayed or missed TTM diagnosis is high in non-endemic areas [4], which contributes to morbidity. The costs of managing a TTM case have never been evaluated; however, some TTM patients have required lengthy intensive care unit admissions [5–7].

Australia has comprehensive blood safety policies. Donors at risk of malaria include travellers or past residents of endemic regions and people who have had malaria. These donors are currently restricted to plasma for fractionation, unless negative on immunological testing at least 120 days post-return or post-treatment and recovery [8]. Although the current malaria screening strategy in blood donors permits earlier eligibility for fresh component manufacture than allowed by regulatory standards without testing, its cost-effectiveness is challenged by changes to international donor eligibility guidelines. Due to the extremely low residual risk of TTM, both the United States and Canada have recently shortened their deferral for visitors to malaria-endemic areas from 12 to 3 months without testing [9, 10], shorter than the 120-day period before testing is permitted for visitors in Australia. There is a lack of economic evidence informing the optimal strategy for malaria screening in donors; therefore, this study aims to conduct a cost-effectiveness analysis of potential malaria screening strategies in Australia to provide a complete blood safety risk-based decision-making assessment as per the Alliance of Blood Operators [11, 12].

MATERIALS AND METHODS

Alternative malaria screening strategies

'At-risk' donors refer to all donors disclosing an increased risk of malaria (i.e., both 'visitors' to endemic areas and 'residents', defined as those who have spent more than 6 months in malaria-endemic areas). The five strategies evaluated were as follows:

1. Status quo: At-risk donors are restricted from donating transfusible components for 120 days. Following this period, a negative malaria serology test is required to allow transfusible component release.
2a. No malaria testing: At-risk donors are restricted to plasma for fractionation donation but eligible to donate fresh components after 28 days.
2b. No malaria testing: At-risk donors are restricted to plasma for fractionation donation but eligible to donate fresh components after a 120-day deferral for visitors and a 3-year deferral for residents.
3a. Residents are restricted to plasma for fractionation donation but eligible to donate fresh components if they test negative for malaria after a 120-day deferral. For visitors, no testing is required. They are restricted to plasma for fractionation donation but eligible to donate fresh components after 120 days.
3b. Residents are restricted to plasma for fractionation donation but eligible to donate fresh components if they test negative for malaria after 28 days. For visitors, no malaria testing is required. They are restricted to plasma for fractionation donation but eligible to donate fresh components after 28 days.

Decision-analytic modelling

A decision tree model was developed to assess the cost-effectiveness of five alternative strategies. The pathway of malaria screening and treatment is depicted in Figure 1. Following the malaria screening strategy, blood safety would be achieved if blood donations were made by individuals without a risk of exposure to malaria, or if blood donations were made by at-risk donors but did not contain malaria parasites. However, there was also a residual risk that the donation contained malarial parasites. The probability that the contaminated blood donations were transfused was defined by the transfusion–donation ratio, noting that plasma for direct transfusion was included

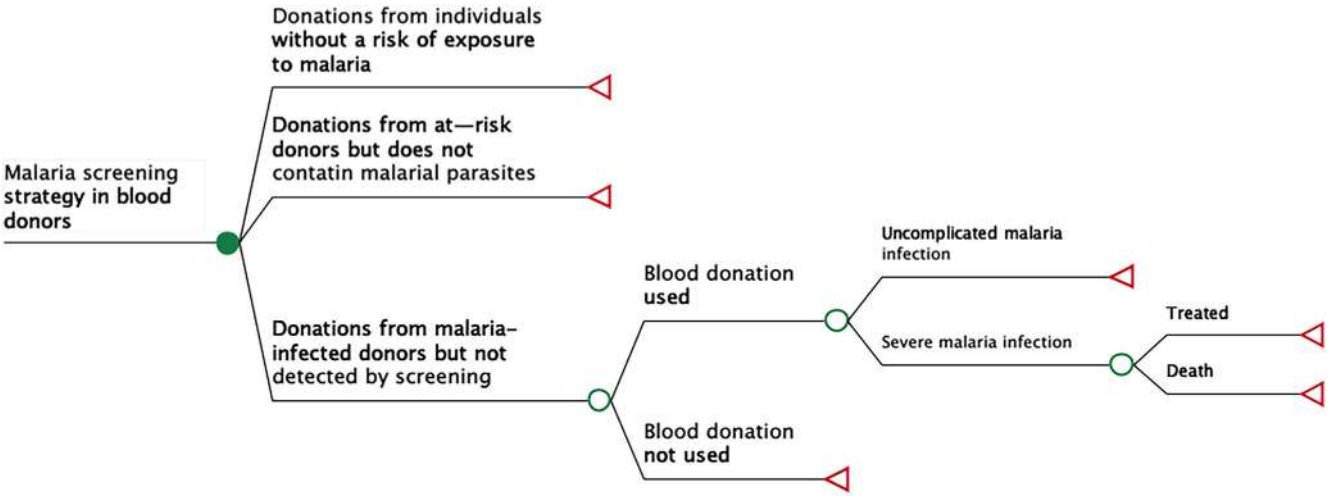

FIGURE 1 Decision tree model structure for malaria screening in blood donors.

TABLE 1 Residual risk of malaria infection following each screening strategy.

Residual risk[a]	Most plausible	Worst case (95%)	Sensitivity worst case (99%)
1. 120-day deferral and testing for all	1 in 68 million	1 in 25 million	1 in 19 million
2a. 28-day deferral for all; no testing	1 in 2 million	1 in 1 million	1 in 0.8 million
2b. 120-day/3-year deferral for visitors/residents; no testing	1 in 14 million	1 in 4 million	1 in 3 million
3a. 120-day deferral for all; testing for residents	1 in 68 million	1 in 10 million	1 in 8 million
3b. 28-day deferral for all; testing for residents	1 in 11 million	1 in 9 million	1 in 7 million

[a]The residual risks were estimated by Lifeblood using an in-house purpose-built risk model [11]. In the probabilistic sensitivity analysis, residual risks were assinged uniform distributions varying between values under the most plausible scenario and the worst case (99%) scenario.

despite it being unlikely to be infectious for malaria. It was conservatively assumed that once the blood transfusion recipient received the contaminated blood products, they would be infected. The infection would be either uncomplicated or severe. It was assumed that all uncomplicated cases of malaria would be treated with successful outcomes, while severe malaria infections would be treated, leading to symptom resolution or resulting in death.

Model parameters

Risk of TTM infection

In this study, the residual risk refers to the risk that a donation from a malaria-infected donor is not detected by screening. The residual risk for different screening strategies was estimated based on a purpose-built risk model that is published separately [11]. The 'most plausible' estimates were used in the baseline analysis (Table 1).

Transition probabilities

The proportions of fresh component donations were taken from Lifeblood 2020 donation data (Table 2). Due to the lack of published evidence on the probability of developing severe TTM, a review of the literature on TTM cases in non-endemic areas since 2000 was conducted (Table S1) [5–7, 13–39]. For each study, the following data were extracted: country, year, malaria species, age of blood transfusion recipient, symptoms, treatment setting, length of stay in hospital and treatment outcome. Severe malaria was defined according to the WHO criteria 2022 [40]. The proportion of severe TTM was calculated by dividing the number of severe TTM cases by the total number of TTM cases in non-endemic areas. Mortality following uncomplicated and severe TTM was also informed by the literature review.

Resource use and costs

This cost-effectiveness analysis was conducted from a healthcare sector perspective. All cost items were valued in 2020 AUD. Malaria testing was estimated to cost 7.50 AUD per test as a rolled-up test cost, including staffing. This does not include costs to maintain instrumentation. In 2018–2019, the total cost of treating malaria infections in Australia was 2.1 million AUD and included costs incurred in community and hospital settings. None of the notified malaria cases in Australia were TTM. Moreover, the literature review on TTM cases in non-endemic countries suggested that the treatment of TTM cases all occurred in the hospital setting. Thus, in this study, the costs of

TABLE 2 Model parameters.

Model parameters	Value	Range	Distribution	Reference
Transition probabilities				
Transfusion–donation ratio	0.75	0.60–0.90	Beta ($\alpha = 119, \beta = 40$)	Lifeblood internal data
Severe malaria	0.55	0.46–0.70	Beta ($\alpha = 18, \beta = 13$)	Calculated based on literature review
Mortality following severe TTM	0.17	0.18–0.27	Beta ($\alpha = 4, \beta = 14$)	Calculated based on literature review
Cost (AUD 2020)				
Malaria testing (aggregated cost per donation)	7.5	5–10	Gamma ($\alpha = 44.44$, $\lambda = 5.926$)	Lifeblood internal estimate
Uncomplicated malaria	6783	4748–8818	Gamma ($\alpha = 44.44$, $\lambda = 0.007$)	AR-DRG T64C [41]
Severe malaria	33,984	23,789–44,180	Gamma ($\alpha = 44.44$, $\lambda = 0.001$)	AR-DRG T64A [41]
Non-returning donor	628	381–707	Gamma ($\alpha = 44.44$, $\lambda = 0.082$)	Shehata et al. [42]
Disability weight				
Uncomplicated malaria	0.006	0.002–0.012	Beta ($\alpha = 5.72$, $\beta = 947.52$)	Global Burden of Disease Study [45]
Severe malaria	0.133	0.088–0.190	Beta ($\alpha = 23.45$, $\beta = 152.88$)	Global Burden of Disease Study [45]
Disability days				
Uncomplicated malaria	4.6	2–8	Uniform	AR-DRG T64C [41]
Severe malaria	17.8	10–30	Uniform	AR-DRG T64A [41]
Age (years, median, severe TTM)	48			Calculated based on literature review
Median survival after transfusion (years, after discounting)	12.3			Lifeblood internal estimates; Borkent-Raven et al. [46]

Abbreviation: TTM, transfusion-transmitted malaria.

managing TTM in the community were not considered. In addition, it was assumed that both uncomplicated and severe TTM would be managed in hospital. The hospitalization costs were informed by the Australian Refined Diagnosis Related Groups (AR-DRG) cost weights [41]. No discounting was applied to costs as it was assumed that the time frame of acquiring TTM and receiving treatment would be within 1 year.

It is expected that screening strategies with a longer deferral would result in donor loss and vice versa. To account for this, the costs of a non-returning donor (recruitment costs) were included. In Australia, the costs associated with recruiting a new blood donor to recoup lost blood components are not explicitly calculated. Thus, recruitment costs from a Canadian study by Shehata et al. [42] were utilized. The costs were first converted to AUD using purchasing power parities published by the Organization for Economic Co-operation and Development [43] and then inflated to 2020 AUD using consumer price indices [44]. However, quantifying the benefits of donor gains, such as reduced spending on importing blood products to address shortfalls in domestic supply and production, is challenging without further information on the volume of blood products imported to Australia each year and the corresponding costs. To incorporate recruitment costs, the screening strategy with the highest incremental donor gains was used as the reference case to calculate the relative number of non-returning donors for other screening strategies. The total recruitment costs incurred by each screening strategy were then calculated by multiplying the relative number of non-returning donors by the unit cost of recruiting a new donor.

Health outcome measure

The impact of TTM infection was quantified using disability-adjusted life years (DALYs). DALYs are calculated as the sum of years of life lost (YLL) and years lived with disability (YLD). YLD was calculated using disability weights for different severity levels of malaria infections, published by the Global Burden of Disease (GBD) study [45]. For uncomplicated TTM and severe TTM that did not lead to death, DALYs were equal to YLD. For severe TTM that led to death, DALYs were calculated by adding YLL to the YLD. For patients with severe TTM, the median age reported in the literature was 48 years (Table S1). Based on the literature [46] and Lifeblood's internal calculations [47], the median survival for transfusion recipients aged 46–50 is 15 years. Thus, the YLL was assumed to be 15 years if the blood recipient died of TTM. YLL was discounted at a rate of 5% per year in line with Australian government guidelines [48, 49].

Model evaluation

Baseline analysis

Each pathway in the decision tree was associated with cost and health outcome (DALYs) pay-offs. The expected cost and health outcomes of implementing a screening strategy were computed by summing the costs and health outcomes, weighted by the probability of each outcome [50]. Incremental cost-effectiveness ratios (ICERs) were calculated using the following equation: $\text{ICER} = \frac{\text{Cost}_A - \text{Cost}_B}{\text{Effectiveness}_A - \text{Effectiveness}_B}$, where effectiveness was measured by DALYs and the ICER was expressed as the additional cost to avert one DALY. If the ICER falls below the cost-effectiveness threshold, then the screening strategy is considered cost-effective. In Australia, there is no explicit cost-effectiveness threshold using cost per DALY averted. Daroudi et al. reported that, on average, the cost per DALY averted threshold was 1.46-fold the Gross Domestic Product (GDP) per capita in countries with a very high Human Development Index [51]. With a GDP per capita of 94,001 AUD [52], 137,241 AUD per DALY averted was used as the cost-effectiveness threshold in this analysis.

Sensitivity analysis

Uncertainty in the model parameters was accounted for by deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA), to assess the impact of varying parameter values on model outputs. A tornado plot was used to present the multiple one-way sensitivity analyses results. A Monte Carlo simulation of 10,000 model runs was conducted in the PSA. Key model parameters were assigned distributions from which random values were drawn in each model run. The results of the PSA were summarized using a cost-effectiveness acceptability curve to illustrate the probability of each screening strategy being cost-effective at varying willingness-to-pay thresholds. Moreover, threshold analyses were conducted to identify under which circumstances the screening strategies that were not cost-effective in the baseline analysis would become cost-effective with a willingness-to-pay threshold of 137,241 AUD per DALY averted. All analyses were conducted using TreeAge Pro 2021 [53].

RESULTS

Baseline analysis

The number of donors gained or lost under each screening strategy is presented in Table S2. Using Strategy 1 (status quo) as the reference, implementing screening Strategy 2a (28-day deferral for all; no testing), 3a (120-day deferral for all; testing residents) or 3b (28-day deferral for all; testing residents) would result in gains of 1003, 79 and 419 donors, respectively. In contrast, implementing Strategy 2b (120-day/3-year deferral for visitors/residents; no testing) would lead to a loss of 8157 donors. Strategy 2a was then used as the reference strategy for calculating the relative number of non-returning donors. Table 3 summarizes the total costs, DALYs and disaggregated costs for malaria testing, TTM treatment and non-returning donors associated with each screening strategy in the baseline analysis. Based on 1,595,508 donations in 2020, Strategy 2b was not cost-effective compared with Strategy 1, as Strategy 2b would cost more and result in a greater loss of healthy life years due to TTM. Strategy 1 was not cost-effective compared with Strategy 3a, which would produce the same DALYs at a lower cost. Both Strategies 3a and 3b would not be cost-effective, as the ICERs lie above the cost-effectiveness threshold of 137,241 AUD per DALY averted. Therefore, Strategy 2a was the most cost-effective malaria screening strategy.

Sensitivity analysis

Variables such as the probability of severe malaria and the costs of treating TTM had minimal impact on the cost-effectiveness results (Figure 2). This was attributed to the extremely low residual risks, with total costs being predominantly influenced by recruitment costs. Sensitivity analyses using higher residual risk estimates are presented in Tables S3 and–S4. Strategy 2a remains the most cost-effective strategy. Strategies 1, 3a and 3b were not cost-effective at the 137,241 AUD/DALY averted threshold. Strategy 2b was not cost-effective due to its higher costs and increased DALYs compared with other strategies.

Threshold analysis demonstrated that Strategy 2a remains the only cost-effective strategy when the recruitment cost was 12 AUD per donor or above (Table S5). Strategy 2b would become cost-effective if the recruitment cost were reduced to 11 AUD per donor or lower. The residual risk of Strategies 2a, 2b, 3a and 3b was increased to find a scenario where the current strategy (Strategy 1) would become cost-effective (Table S6). The results indicate that for Strategy 1 to be cost-effective, the residual risks of other screening strategies would need to be at least 1 in 199,318. This threshold is significantly higher than the residual risk estimated by Lifeblood under a worst-case scenario.

The probabilities of each screening strategy being cost-effective at varying willingness-to-pay thresholds are depicted in Figure 3. Strategy 2a showed a 100% probability of being cost-effective until the willingness-to-pay threshold reached 100,000 AUD per DALY averted. Beyond this threshold, the probability of Strategy 2a being cost-effective decreased, while the probability of Strategy 3b being cost-effective increased. After the threshold of 400,000 AUD per DALY averted, Strategy 3b's probability of being cost-effective remained higher than that of other strategies. The probabilities of cost-effectiveness for Strategies 1, 2b and 3a remained at 0%.

DISCUSSION

This is the first Australian study to assess the cost-effectiveness of different malaria screening strategies in blood donors. The current

TABLE 3 Baseline analysis using 'most plausible' residual risk estimates.

Strategy	Cost (malaria testing)	Cost (TTM treatment)	Recruitment cost (non-returning donor)	Total cost (AUD)	DALYs	Incremental costs (AUD)	DALY averted	ICER (AUD/DALY averted)
2a: 28-day deferral for all; no testing	0	11,535.40	0	11,535.40	0.8128			
3b: 28-day deferral for all, testing for residents	233,355.00	2378.11	317,699.60	553,432.71	0.1676	541,897.31	0.6453	839,810
3a: 120-day deferral for all, testing for residents	232,312.50	396.83	502,661.70	735,371.03	0.0280	181,938.32	0.1396	1,303,194
1: 120-day deferral and testing for all	893,647.50	396.83	545,638.19	1,439,682.52	0.0280			Dominated
2b: 120-day/3-year deferral for visitors/residents; no testing	0	1938.11	4,983,096.53	4,985,034.64	0.1366			Dominated

Note: 'Dominated' means that the strategy is not cost-effective due to a higher cost and worse health outcomes compared to the next less expensive strategy.
Abbreviations: DALY, disability-adjust life-year; ICER, incremental cost-effectiveness ratio; TTM, transfusion-transmitted malaria.

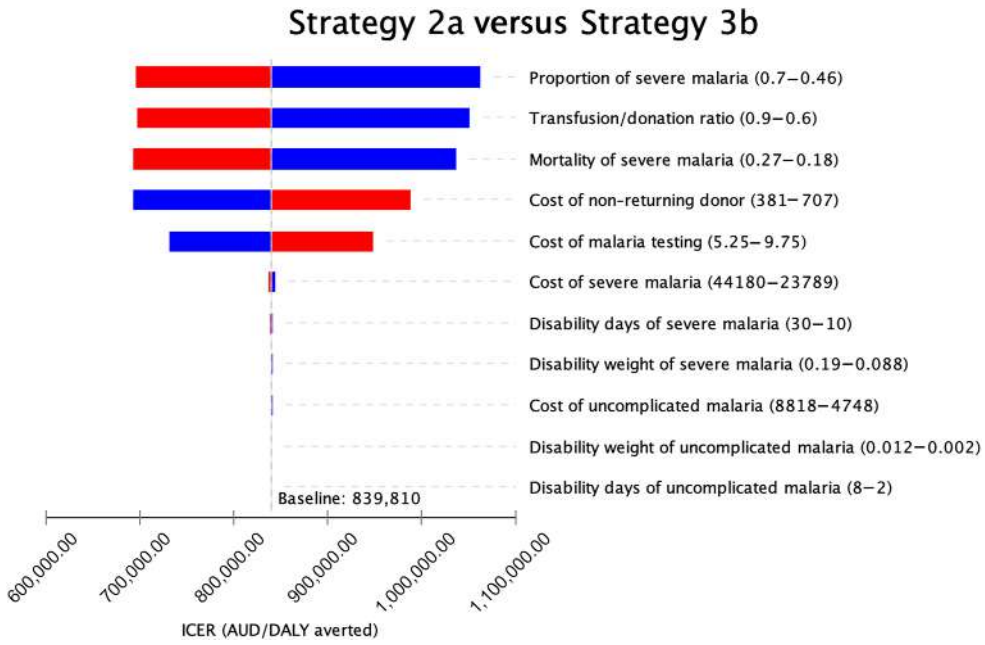

FIGURE 2 Tornado plot showing multiple one-way sensitivity analysis comparing Strategy 2a and Strategy 3b. DALY, disability-adjust life-year; ICER, incremental cost-effectiveness ratio.

screening strategy does not offer value for money from the healthcare sector costing perspective. Among all strategies, Strategy 2a (28-day deferral for all; no testing) emerged as the most cost-effective screening strategy. Our study findings were highly robust to parameter uncertainty, as the thresholds at which decisions changed lay far outside their plausible ranges. This study provides important economic evidence on the most cost-effective method to implement malaria screening in blood donors to help inform resource allocation decisions.

Our study found that while screening questions followed by malaria testing for all at-risk donors (Strategy 1) was not the most cost-effective strategy, it was less costly and caused less harm than screening questions alone with a long deferral (Strategy 2b). This aligns with the findings of a previous cost-effectiveness study in Canada [42], where Shehata et al. reported that adding PCR testing to standard screening questions was more cost-effective than using a standard screening questionnaire with a long deferral. However, our study's findings are not directly comparable to those of Shehata et al. as their study involved a considerably higher malaria prevalence of 0.0038%. Additionally, they did not evaluate a selective testing strategy or consider a shorter deferral period.

Our study demonstrates that the length of deferral is pivotal in determining the cost-effectiveness of alternative strategies. Our study considered a shortened deferral of 28 days, as well as the current minimum 120-day deferral in Australia. Shortening the deferral would

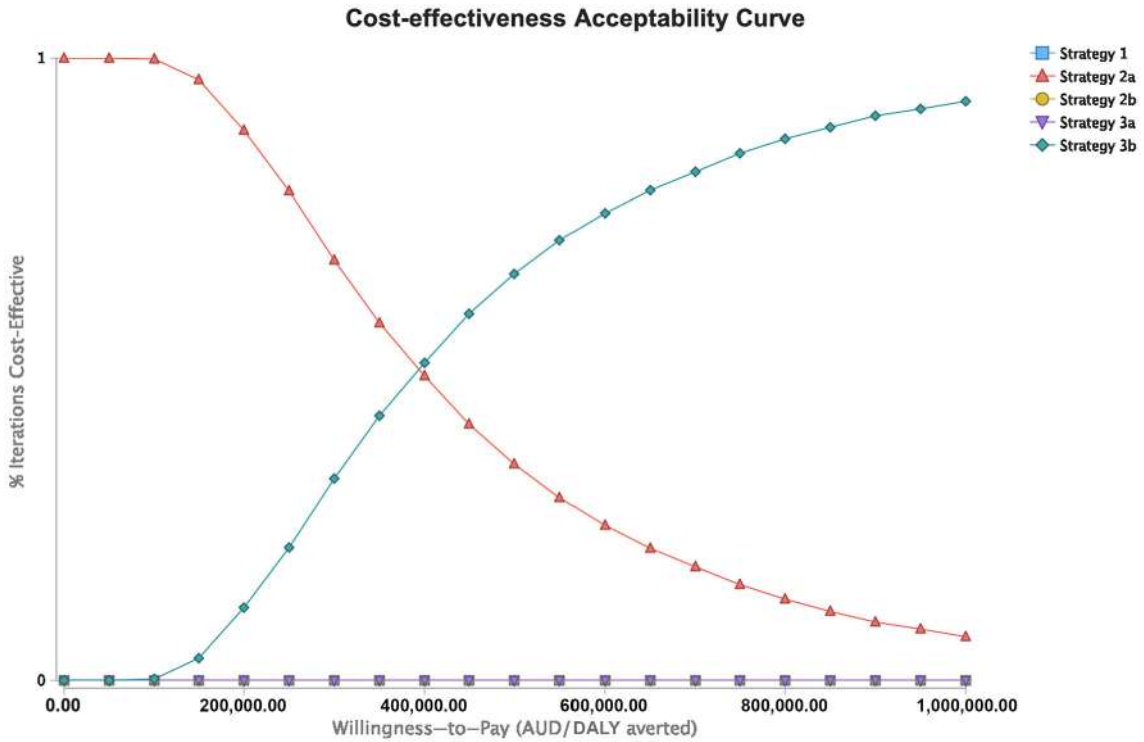

FIGURE 3 Cost-effectiveness acceptability curve comparing five malaria screening strategies. DALY, disability-adjust life-year.

increase the risks of TTM and lead to higher healthcare costs of managing TTM and more lives lost. However, due to the extremely low residual risks associated with alternative screening strategies, the impact of TTM was minimal on overall costs. On the other hand, a shortened deferral led to more donor gains, reducing the donor recruitment costs. It should be noted that our study did not consider blood collection, production or retrieval costs. Future policies considering shorter deferrals may need to weigh other costs and benefits.

A limitation of our study was the lack of data on the sequelae of TTM in Australia. As there are no TTM-specific management data, published hospital costs for infectious and parasitic diseases were used as a proxy. This may lead to an underestimate of costs as blood recipients usually have other underlying conditions impacting treatment costs. Given our reliance on TTM case reports, there may be potential for detection bias. Severe malaria cases are more likely to be identified than uncomplicated cases. However, the uncertainty in these parameters does not affect the cost-effectiveness results due to the very small risks of TTM. In the PSA, we assumed independence between the residual risks for the five screening strategies and assigned an individual uniform distribution to each residual risk. This approach ignored the strong correlation between the residual risks, resulting in an overestimation of uncertainty. Another limitation is the simplified assumption of a constant marginal cost of donor replacement, which may not hold true in practice. Further studies are needed to explore the actual costs associated with recruiting new blood donors in Australia.

In conclusion, the current malaria screening strategy in Australia is not cost-effective compared with no testing or selective testing with screening questions. In our low-prevalence population, partial or total removal of malaria testing would achieve significant cost savings without compromising blood recipient health. In addition to cost-effectiveness, the selection of the optimal strategy would also need to consider operational factors such as the impact on the sufficiency of blood components and process errors associated with system complexity.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Qinglu Cheng https://orcid.org/0000-0002-3701-8760
Veronica C. Hoad https://orcid.org/0000-0002-7827-3661
Peter Bentley https://orcid.org/0000-0001-8680-922X

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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

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Managing the risk of transfusion-transmitted malaria from Australian blood donations: Recommendation of a new screening strategy

Katia Schenberg[1] | Veronica C. Hoad[2,3] | Robert Harley[2] | Peter Bentley[1,2]

[1]Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia

[2]Australian Red Cross Lifeblood, Melbourne, Victoria, Australia

[3]School of Population and Global Health, University of Western Australia, Perth, Western Australia, Australia

Correspondence
Veronica C. Hoad, Australian Red Cross Lifeblood, Melbourne, Victoria, Australia.
Email: vhoad@redcrossblood.org.au

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Abstract

Background and Objectives: To reduce the risk of transfusion-transmitted malaria (TTM) from transfusible components, Australia tests for malaria antibodies in both travellers returning from and former residents of malaria-endemic areas. The testing is performed a minimum of 120 days after last potential exposure. TTM is an extremely rare event and managing the risk adds considerable complexity. The objectives of this study were to analyse various testing and deferral strategies, considering the risk, donation numbers and operational complexities.

Materials and Methods: A residual risk model was developed to calculate the risk of TTM in five testing/deferral strategies. Australian blood donor data from 2020 and 2021 were used and incorporated the incidence of parasitaemia, *Plasmodium* species and the malaria enzyme immunoassay test's failure rate. Donor and donation loss or gain and an operational assessment were performed.

Results: The current model's estimated risk of TTM is 1 in 67.9 million transfused units. Testing residents with a 120-day plasma restriction for visitors without testing was found to have the same estimated risk, with an expected increase of 342 donations per year, significant cost savings and a 62% reduction in the number of donors requiring assessment.

Conclusion: A strategy that involves testing residents of malaria areas only and a 120-day plasma travel restriction would not significantly increase the risk of TTM, is operationally simpler, costs less and results in a small increase in donations.

Keywords

blood donation testing, blood safety, transfusion-transmitted malaria

Highlights

- Previous residents of malaria-endemic areas constitute most of the transfusion-transmitted malaria risk.

- The optimal strategy for malaria risk reduction, in the context of available malaria testing, considering operational complexity and donation loss, is keeping a fresh component restriction of 120 days for all donors, selective testing of donors who have lived in an endemic area and ceasing testing in travellers.

INTRODUCTION

Malaria is a blood-borne disease caused by a protozoan parasite, *Plasmodium*, which in 2020 resulted in an estimated 241 million infections and 627,000 deaths worldwide, with nearly half the world at risk [1]. In Australia, there are approximately 300 cases of imported malaria annually, the top countries being Papua New Guinea (subject to separate risk management and excluded from the visitor testing regime [2]) and India [3].

Transfusion-transmitted malaria (TTM) in non-endemic countries, like Australia, is a rare but serious complication of blood transfusions, as individuals do not have significant immunity. TTM can result in significant morbidity and mortality, therefore blood operators, particularly in non-endemic countries, must develop effective risk management measures [4]. The Alliance of Blood Operators' Risk-Based Decision Making Framework determines the rate of transmission risk and cost-effectiveness as fundamentals in blood safety decision-making [5, 6]. Risk management measures should be considered in the context of the residual risk, cost-effectiveness of testing, sufficiency and operational complexity.

A systematic review identified 100 cases of TTM in non-endemic countries between 1911 and 2017 [7]. In Australia, the last reported case of TTM occurred in 1991 and prior to that in the 1960s [8]. A study from 1992 by Whyte, prior to malaria testing of donors, calculated an approximate risk of TTM in Australia to be 1 in 20 million [8].

In non-endemic malaria countries, TTM risk is managed by donor deferrals in at-risk donor populations, donor testing or a combination. To identify and exclude high-risk donors, Australian Red Cross Lifeblood (Lifeblood) uses a combination of product restriction (deferral from donations for transfusible components but allowing plasma for further manufacture) and testing of at-risk donors using the Trinity Biotech CAPTIA malaria enzyme immunoassay (EIA) (Alere, Brisbane, Australia) [9].

The Donor Questionnaire identifies exposure risk by identifying anyone who has either travelled to a malaria area in the last 3 years (visitors) or lived in an endemic country for at least 6 months consecutively (residents). Visitors and residents of malaria-endemic countries are deferred from donating transfusible components for 120 days following their return from those areas. After the 120 days, to prevent a 3-year post-travel restriction for visitors or an indefinite plasma restriction for residents, as required by Australian regulations [10], donors are no longer restricted to plasma but require a negative malaria EIA test to allow transfusible component release [11]. Residents are responsible for the overwhelming majority of TTM, as significant cumulative exposure may lead to asymptomatic infection. In this situation, immune control of the infection leads to a condition known as 'semi-immunity' [12].

Malaria-endemic countries are defined according to risk documented in the World Malaria Report [1], Health Information for International Travel [13] and via changes in risk identified through horizon scanning. Countries with historical malaria endemicity are included due to the risk of ongoing parasitaemia in semi-immune donors.

Testing in Australia, rather than prolonged plasma restriction, is justified as it allows earlier entry for transfusible components of otherwise ineligible donors and therefore a significant positive red blood cell inventory gain. When testing was introduced, it was estimated that a malaria deferral was impacting 5% of donors [14]. However, other blood establishments have malaria deferral periods that challenge the value of malaria testing for earlier donor re-entry. In 2020, the Food and Drug Administration (FDA) revised its previous recommendations [15], resulting in both the United States and Canada having a 3-month deferral period for visitors and no testing. This is shorter than the Australian 120-day period with testing. The FDA requires a 3-year deferral for 'residents', which they define as continuous residence of five or more years (as opposed to Lifeblood's 6 months).

Canada recently reported their first TTM case since 1997, in an eligible semi-immune donor [12, 14]. Data from the United Kingdom showed that 43% of positive donors had left the exposure area more than 2 years ago [16]. This demonstrates the ongoing TTM risk of residents due to semi-immunity.

Internal data document that malaria assessment in Australia is a leading cause of both donor and staff assessment errors, in part due to both donor failure to declare and process complexity.

Our study evaluated whether we could improve Australia's malaria strategy to balance risk, deferral length and testing.

This study models the residual risks, the number of donations gained or lost per year, operational complexity and also provided data for a cost-effectiveness study [17] for various malaria testing strategies in Australia's blood supply. The study compares the TTM risk of the current Lifeblood strategy with each of the alternative testing and deferral strategies to determine the optimal future strategy.

MATERIALS AND METHODS

See Appendix S1 for complete information.

Data collection

Australia transitioned to an electronic Donor Questionnaire (eDQ) in December 2019, which enabled data extraction of attendances

associated with a declared malaria exposure event between 1 January 2020 and 31 December 2021 from Lifeblood's National Blood Management System, ePROGESA (MAK-SYSTEM, France). The answers to the eDQ were used to classify donors into 'visitors' or 'residents'. Donor demographics, donation type and return data were also extracted. The data were extracted on 25 March 2022 and retrospectively analysed.

Selection of testing and/or deferral strategies

Five strategies, including Lifeblood's current regime, were selected for risk and economic modelling, the economic companion paper is published separately [17] based on expected risk and international practice. We analysed two non-testing and two selective testing models.

Strategies

Current regime (1)

The current Lifeblood regime restricts all visitors and residents of malaria-endemic countries from donating transfusible components for 120 days. Following this period, a negative EIA test is required to allow transfusible component release.

No testing (2a, 2b)

Strategy 2a does not differentiate between residents and visitors. All donors who have been present in a malaria-endemic area are deferred from donating transfusible components for 28 days from date of last exposure, with no testing required. The standard travel deferral for other travel-related infections such as a flavivirus risk is 4 weeks and hence was chosen for operational simplicity. Most cases of malaria would be evident within 4 weeks as incubation periods are typically 10–14 days for *Plasmodium falciparum*, 2–3 weeks for *Plasmodium vivax* and *Plasmodium ovale*, and 18 days or longer for *Plasmodium malariae* [18].

Strategy 2b defers visitors for 120 days and residents for 3 years from the date of their last exposure after leaving an endemic area. This is based on the international standard, where there is no testing [15] and Lifeblood's previous deferral period prior to implementing malaria testing [19].

Selective testing (3a, 3b)

In the two selective testing strategies, both visitors and residents are restricted to donating plasma. After the deferral period, only residents are tested. Strategy 3a defers visitors and residents for 120 days, while strategy 3b defers for 28 days. Semi-immune donors, the main risk, are outside the antibody window period when they leave the area.

Donor testing

The malaria EIA was estimated to cost Lifeblood $894,000 in 2020 as a rolled-up cost. Malaria testing was introduced in Australia in 2005, with EIA-positive donors being tested by a malaria polymerase chain reaction (PCR) [19, 20]. Lifeblood discontinued PCR testing in 2018 due to lack of a testing platform that complied with regulatory requirements.

RISK MODEL

A published Lifeblood mathematical model [19] was adapted to estimate the TTM risk for each testing/deferral strategy. The proportional risk was subdivided into four components:

1. Incidence of malaria in blood donors (I).
2. Test failure rate (T).
3. *Plasmodium* species proportion (S).
4. Adjustment factor (A).

$$\text{Risk} = (I \times T \times S \times A).$$

Due to model uncertainty, a sensitivity analysis was incorporated. The most plausible risk used the most likely estimates. The moderate- and high-risk estimates were used as the two upper estimates, which were based on uncertainty (as described in the parameter methodology). To ensure safety in decision-making, the model concentrated on pessimistic scenarios and, therefore, lower confidence intervals (CIs) were not used.

Incidence

The previous incidence of confirmed parasitaemia in EIA-tested donations was used. From July 2005 to December 2016, there were four PCR-positive donations from 1,106,795 total tests. This total figure did not differentiate the denominator of visitors and residents, as this was unavailable prior to electronic records. All four positives met the 'resident' definition.

To estimate the proportion tested for each cohort, the first half of 2020 visitor and resident proportions were assumed as the denominator (i.e., 79.5% of total tests were visitors and 20.5% were residents). This found four PCR test-positive donors from an estimated 226,893 residents and zero PCR test-positive donors from an estimated 879,902 visitors. This was used as the baseline plausible risk estimate. If the PCR missed 50% of parasitaemic donations, the risk would be double the plausible risk.

The most plausible risk was calculated using these proportions for all strategies, except for visitors in 2a and 3b. Visitors in 2a and 3b assumed a parasitaemic risk of one PCR positive rather than zero (1/879,902), to account for both the reduction in visitor deferrals

from 120 to 28 days and the increased possibility of donating during the incubation period. This assumption was necessary to ensure the risk model had an above zero risk.

For the moderate- and high-risk estimates, baseline risk for visitors was calculated by the resident parasitaemia risk, adjusted by the proportion of visitors compared with residents, who tested EIA positive. Using the upper 95% and 99% CIs, the number of parasitaemic residents estimated by the model in 2020 was 1.38 and 1.83, respectively. Further adjustment was performed using the estimated false-positive test rate. The false-positive rate was calculated using data from visitors who had only visited Bali, Indonesia, with the assumption that this was a true-negative population. The false-positive rate was calculated at 0.20%. This was used to calculate the number of visitors and residents expected to be false positive and the true-positive rate ratio in the 2020 data. In 2020, visitors were estimated to have 42.8-fold lower true antibody positivity than residents. This was used to determine the two upper plausible incidence risks of the donation of an asymptomatic parasitaemic visitor (i.e., 0.09 and 0.12 parasitaemic donations in 2020).

Test failure rate

A review of the sensitivity of the EIA demonstrated limited literature [21–26], including the product specification, which used small sample sizes [23], a sensitivity of 100% and wide CIs for *P. vivax*, despite known test failures [2]. Therefore, the sensitivity of the EIA testing at Lifeblood (using Trinity Biotech CAPTIA) used calculations from Kitchen et al. [22]. This paper found that the EIA detected 95.7% of *P. falciparum* on follow-up of clinical samples. The sample size for *P. vivax* was inadequate, and therefore the *P. falciparum* sensitivity was used for all malaria. In Australia, 32% of malaria is due to *P. vivax* and 10% is due to other non-*falciparum* species [3]. The product insert states that the kit uses *P. falciparum* and *P. vivax* antigens only, but, due to antigenic similarity, all species can be detected. However, as only limited data were presented, with no sample size for the sensitivity of other species, our sensitivity assumption is uncertain and likely overestimated. Test failure rate is determined as follows:

$$(T) = 1 - \text{sensitivity} = 1 - 0.957 = 0.043,$$

where testing was not performed, a failure of 100% was given.

As with the incidence risk, the risk is proportional to the input parameter. If the true test failure was double, then the risk would increase twofold in the model where testing was performed.

Plasmodium species proportion

The probability that a donor was infected with either *P. falciparum* or *P. vivax* was derived. This was used to determine the appropriate adjustment factor by species due to different incubation periods and the possibility of prolonged infection.

Adjustment factor

An adjustment factor was incorporated to account for changes from the current strategy. This included adjusting for time to testing and the likelihood of someone being parasitaemic, either through an incubation period or clearance, with transfusible component donation. A literature review determined data on time to infection and natural clearance over time, in low- and high-prevalence populations [27–33]. This was combined with the proportion of donors who returned in the altered periods (see Table 1 and Appendix S1).

RISK TOLERABILITY ASSESSMENT

Lifeblood aims for a balance between providing an adequate number of blood donations, while keeping transfusion risks as low as reasonably achievable. The Alliance of Blood Operators Risk Based Decision Making Framework is used to determine the tolerability threshold of various blood-borne agents, such as malaria [6]. Lifeblood considers an upper tolerable risk level of less than 1 in 1 million transfusions for TTM. The risk modelling considered this level and uncertainty when assessing each strategy.

NUMBER OF DONATIONS GAINED OR LOST

The estimated number of net donations was determined by calculating the percentage of 2020 donors who returned to donate whole blood and plasma. This also considered whether a malarial deferral restricted donors to plasma only. If testing was removed, then the model considered donors would donate with no plasma restriction. If the deferral length was increased to 3 years, donors were restricted for this period at a plasma-restricted donation rate. This was applied to the strategies to calculate the donation loss or gain.

OPERATIONAL ASSESSMENT

For each strategy, donor declaration requirements and recalls, staff training and assessments and total assessment numbers were considered.

RESULTS

In 2020, out of 1,595,508 donations, 119,153 were EIA malaria tested. Of those tested, 88,178 were categorized as visitors and 30,975 as residents. Two hundred and eighty-three (0.23%) visitors and 1612 (5.2%) residents were EIA reactive. India was the top country of tested residents (24%) and accounted for 69% of all positive tests in residents.

The study data were applied to the model to estimate the proportional risk that a donor would donate while infected in each strategy.

TABLE 1 Adjustment factor data and results with status quo as baseline.

Strategy	Visitor/resident status and species	Plausible adjustment	Adjustment source (see Appendix S1)
(2a) No testing, 28-day deferral[a]	Visitors *Plasmodium falciparum*	1.084	[32]
	Visitors *Plasmodium vivax*	1.355	[33]
	Residents Both species	1.035	[32]
(2b) No testing, 3-year residents deferral and 120-day visitor deferral	Visitors Both species	1	No adjustment required
	Residents Both species	0.210	[15]
(3a) Selective testing, 120-day deferral and testing residents only	All	1	No adjustment required
(3b) Selective testing, 28-day deferral and testing residents only	Visitors	As per 2a	
	Residents both	1	No adjustment, long term infection expected

[a]Deferral in all tables refers to a fresh component deferral but allows plasma donation.

TABLE 2 Modelled transfusion-transmitted malaria risk under different donor testing strategies.

Testing strategy	Most plausible risk estimate (moderate and upper plausible range) – 1 in	Proportion of risk contributed by resident (upper estimates)	Number of donations expected to be lost/gained per year
1. Current regime	67.9 million (24.8–19 million)	100% (93.8%)	0
2a. No testing, 28-day deferral	2.3 million (1.1–0.8 million)	83%[a] (93.1%)	3904
2b. No testing, 3-year residents deferral and 120-day visitor deferral	13.9 million (4.1–3.1 million)	100% (76.1%)	−20,019
3a. Selective testing, 120-day deferral and testing residents only	67.9 million (10.4–7.9 million)	100% (39.3%)	342
3b. Selective testing, 28-day deferral and testing residents only	11.3 million (9.4–7.2 million)	16.7%[a] (35.6%)	1409

[a]Partly because of the non-zero parasitaemia risk given to visitors.

The most plausible risk estimates of TTM per component transfused ranged from 1 in 67.9 million in the current regime (Strategy 1) and the selective testing with 120-day deferral and testing residents only (Strategy 3a), to 1 in 2.3 million in no testing with 28-day deferral (Strategy 2a). All five strategies were below the TTM tolerable risk level of less than 1 in 1 million transfusions, except for the upper estimates in Strategy 2a. The modelled proportional risks are summarized in Table 2, with the net donation gained or lost for a 1-year period. The operational assessment is presented in Table 3.

DISCUSSION

As per current regulations [10], Australia currently requires malaria testing to prevent a 1- to 3-year visitor plasma restriction and indefinite resident plasma restriction. Our risk assessment of the current regime demonstrates a negligible risk of 1 in 68 million. Our model is conservative and shows that other strategies are superior.

Removing testing, with a 28-day overseas deferral for all donors (Strategy 2a), resulted in a tolerable risk estimate for the most plausible risk (1 in 2 million). The 28-day overseas deferral for this strategy is consistent with other travel risk reduction. Additionally, it had the highest donation gain of over 3900 donations per year and was the simplest operationally. This strategy was also the most cost-effective [17]. However, there is considerable uncertainty in our model, and the upper residual risks were above the tolerable risk. The model assumes that a donor would only cause a TTM event once, be detected and then removed [12]. Due to the model's uncertainty, tolerable risk thresholds for Strategy 2a could not be reached.

Accepting residents without a prolonged deferral was not considered an acceptable risk management option due to the known risk of TTM in this population, which is not international practice.

Removing all testing with a 120-day deferral period for visitors and 3 years for residents (2b) resulted in an acceptable residual risk and sensitivity analysis, while noting a worst-case result of a TTM case every few years. In countries that have adapted this strategy,

TABLE 3 Operational assessment.

Testing strategy	Visitors assessed for deferral or testing	Residents assessed for deferral or testing	Total	Different assessment for residents and visitors	Different deferral for residents and visitors	Number of recalls (components) [% recalls of status quo]
Status quo	97,404	35,636	133,040	Yes	No	482 (2374)
2a	3045	380	3425 (2.57%)	No	No	27 (84) [5.6%]
2b	14,840	28,204	43,044 (32.35%)	Yes	Yes	199 (982) [41.3%]
3a	14,840	35,636	50,476 (37.94%)	Yes	Yes	204 (1004) [42.3%]
3b	3045	35,636	38,681 (29.07%)	Yes	Yes	109 (535) [22.6%]

occasional transfusion-transmitted cases occur [12, 34]. Our study demonstrated that, in Australia, even allowing plasma donation would result in a donation loss of over 20,000 donations per year. Blood services that do not collect significant plasma donations could have a far larger donation loss. In Australia, even with a plasma donation, this is an unacceptable donation loss, due to the cost of recruiting and retaining donors, and therefore was not supported by the cost-effectiveness analysis [17].

Testing residents after 28 days instead of 120 days (3b) is not expected to change risk as semi-immunity is due to chronic exposure, and therefore antibody positivity would be established. However, a 28-day restriction period for visitors and no testing is less than most international practice. Strategy 3b does not cover all incubation periods and therefore was not considered acceptable, even though the risk was less than the tolerable threshold.

Strategy 3a, a 120-day restriction for all donors with resident testing, is not the most cost-effective option; however, it is the optimal Australian future strategy. It is expected to deliver a similar residual risk as the current regimen, with a small annual donation gain and reduced testing costs. In addition, it is expected to decrease donor malarial assessments by almost two-thirds and decrease recalls by more than half. Other countries have shorter than 120-day deferrals with no testing, and therefore, this strategy would be considered positively when requesting an exemption to regulatory standards.

The limitations of the model include the uncertainty of parameters such as EIA and PCR sensitivity, the variable duration of parasitaemia in donors and human error during the collection of donor information. The risk modelling does not include the leucodepletion risk reduction of TTM, performed since 2008 [35]. The model only considered *P. falciparum* and *P. vivax*, which account for 87% of cases in Australia [36], although the model parameters are applied to all malaria species. Additionally, the data used in the study were from 2020 and the COVID-19 pandemic affected donor travel. However, in 2019, malaria deferrals were only 8% higher, and in the first 6 months of 2023, testing was approximately two-thirds of that in our risk model, indicating a likely small impact. Some countries are only considered malaria prone in certain seasons and in specific areas, and this was not accounted for when assessing risk status, which is done on a country-wide basis.

Our proposed strategy does not retest residents if they return overseas once cleared by a negative antibody test, as on return they would be considered a visitor. While it has been documented that seroreversion occurs after completion of treatment for an episode of malaria [37], the TTM risk is from semi-immune individuals who retain antibody for clinical protection [9, 38]. Therefore, individuals most at risk of causing TTM are expected to be continually antibody positive. This is not expected to significantly change our risk estimates.

It is noted that while our antibody screening permanently restricts positive donors to plasma, the majority are not currently infected or at risk of transmitting. PCR methodology has been considered insensitive to detect the highest risk semi-immune donors [34, 39] with low parasite loads. While the potential for malaria nucleic acid test (NAT) has recently been evaluated [37], due to acceptable risk reduction from antibody testing, the absence of a licenced NAT test for blood donor screening in Australia and potential NAT insensitivity, we have no immediate plans to evaluate NAT as an alternative strategy.

Our risk modelling provides an alternative deferral and selective malaria testing strategy to the existing regimen. The preferred strategy (3a) results in reduced testing costs by approximately 75%, increases the number of acceptable donations, does not affect the residual risk of TTM and improves operations. Therefore, we have submitted an application to our regulator for a change. While Australia's unique geography and demography affect malaria risk, the evidence that visitors to malaria-endemic countries pose an extremely low risk is likely to be applicable to other countries' strategies for reducing malaria risk in blood safety.

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K.S. performed the risk assessment research and wrote the first manuscript draft; P.B., R.H. and V.H. designed the study; all authors reviewed the manuscript; V.H. and P.B. supervised the research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Veronica C. Hoad https://orcid.org/0000-0002-7827-3661
Peter Bentley https://orcid.org/0000-0001-8680-922X

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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 national surveillance system for continuous monitoring of blood transfusion safety: German haemovigilance data

Philipp Berg | **Margarethe Heiden** | **Susanne Müller** | **Britta Meyer** | **Cornelia Witzenhausen** | **Gabriele Ruppert-Seipp** | **Sarah Kehr** | **Markus B. Funk**

Division Safety of Biomedicines and Diagnostics, Paul-Ehrlich-Institut (PEI), Langen, Germany

Correspondence
Markus B. Funk, Division Safety of Biomedicines and Diagnostics, Paul-Ehrlich-Institut, Paul-Ehrlich-Str. 51-59, Langen, Germany.
Email: markus.funk@pei.de

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Abstract

Background and Objectives: Haemovigilance (HV) systems aim to improve transfusion outcomes in patients and donor safety. An important question for blood regulators is how to ensure an effective HV system.

Materials and Methods: We retrospectively analysed the HV reports submitted to Paul-Ehrlich-Institut over the last two decades.

Results: Between 2011 and 2020, 50.86 million units of blood components were used, and 8931 suspected serious donor and recipient adverse reactions (SARs), 874 serious adverse events (SAEs) and 12,073 donor look-backs were reported. Following implementation of specific risk-minimization measures (RMMs) between 2000 and 2010, SAR reporting rates decreased for transfusion-transmitted viral infections (TTVIs), transfusion-related acute lung injury (TRALI) and transfusion-transmitted bacterial infections (TTBIs), while increasing for other serious adverse transfusion reactions. Within this decade, the overall blood component use decreased.

Conclusion: Long-term data collection forms the basis to establish trends and changes in reporting and to evaluate the effect of RMM. Standardized criteria for reaction types, seriousness and imputability assessments and availability of a denominator are important elements. Central data collection and independent assessment allow for monitoring HV data in a nationwide context over time. Stakeholder involvement and transparent feedback on the benefit of RMM will help to achieve the objectives of HV.

Keywords

adverse reactions, blood safety surveillance, haemovigilance, transfusion complications

Highlights

- The aim of haemovigilance (HV) is to ensure transfusion safety; while the approach to achieve this can vary in different countries, some elements appear to be key to success.

- Pre–post comparison of HV data confirmed significant reductions in transfusion-transmitted bacterial infections, transfusion-related acute lung injury and hepatitis B virus transmission reports following the introduction of specific risk-minimization measures in Germany.
- Consistent long-term data collection forms a basis for establishing changes in reporting over time and to evaluate the effect of risk-minimization measures.

INTRODUCTION

Blood transfusions are life-saving therapies, and it has been estimated that globally more than 300 million units of blood for transfusion are needed every year [1]. Transfusion-associated adverse reactions can cause morbidity and mortality [2–4] and necessitate continuous donor and recipient haemovigilance (HV) to safeguard transfusion safety [5]. Risks can originate either from the blood component itself or from process-related problems, affecting the quality or adequate administration. Investigation of adverse reactions and events is key to identify contributing factors as well as clinical relevance, and, if avertable, to prevent occurrence or recurrence [6, 7].

HV systems aim to improve transfusion outcomes in patients and donor safety, but their organizational set-up and mode of operation differ considerably between countries. The first such systems were introduced in the 1990s [8], and well-established systems have evolved in several countries, including Japan (Japanese Red Cross Society), France (National Agency for the Safety of Medicines and Health Products), Germany (Paul-Ehrlich-Institut [PEI]), United Kingdom (Serious Hazards of Transfusion), Canada (Transfusion Transmitted Injuries Surveillance System) and Australia (National Blood Authority). Of note, the individual system set-up varies and can be centralized or decentralized, governed by a competent authority, a professional body or an independent organization, may be passive or active, reporting may be mandatory or voluntary, and it may cover all reactions that occur or only those classified as serious [8–11]. Several countries pursue the development of HV systems or have recently implemented one, including the populous countries India and China [12, 13]. However, globally less than half of all countries have a national HV system in place, and of those, not even all collect data on adverse reactions or events [5]. In some cases, the implementation and performance of systems are still in the early stage and may even lack adequate legal foundations [14].

Comparisons of HV data revealed variable reaction reporting rates between countries that may be a result of differences in reporting, classification and assessment practices [15–17]. A comparison of national reporting rates of serious adverse transfusion reactions is therefore only possible to a limited extent.

An important question for blood regulators is to ensure that an HV system is effective. A functioning HV system aims to surveil the entire transfusion chain (vein-to-vein) to facilitate the effective use of blood components and minimize the risks of adverse reactions. We present an analysis of continuous HV data monitoring in Germany and highlight the elements considered critical for the functioning of the HV system.

MATERIALS AND METHODS

Regulatory framework

The national HV system in Germany is based on the German Medicinal Products Act (AMG) and the German Transfusion Act (TFG), which are consistently aligned with the European legislation. PEI as the national competent authority (NCA) is responsible for regulatory oversight, including central data collection, analysis and evaluation. Blood establishments (BEs) need a manufacturing licence from federal authorities and have to implement a vigilance system for documentation and reporting. Moreover, blood components are considered proprietary medicinal products (red blood cells [RBCs]; platelet concentrates [PCs]; plasma for transfusion) and require a marketing authorization by the PEI. Hospitals and other transfusion institutions need to have a quality assurance system in place. Reporting is mandatory and covers all suspected serious adverse reactions (SARs) as well as serious adverse events (SAEs) at the donor and patient side, as defined in Article 3 of the European directive 2002/98/EC. An SAE is any untoward occurrence that might lead to death or life-threatening, disabling or incapacitating conditions or which might result in or prolong hospitalization or morbidity; an SAR is an unintended response in a donor or patient, which is fatal, life-threatening, disabling, incapacitating or which results in or prolongs hospitalization or morbidity [18]. In addition, reporting of donor-triggered look-back procedures is required if there is a risk of transmission [19].

Data collection, standardization and evaluation

BEs are obliged to report all suspected SAEs and reactions according to the AMG [20]; treating physicians have to report suspected SAR according to the TFG [21] to the PEI as responsible authority. In addition, PEI needs to be informed about all donor-triggered look-back procedures, whose correct realization is controlled by the local authorities of federal states. PEI provides standardized reporting forms on its website and captures all reports in a national database. If relevant information for case assessment is missing, the reporters are requested to provide additional details, for example, on the patient, the reaction(s) or the involved blood component(s).

Classification of serious transfusion reactions follows the definitions proposed by the Haemovigilance Working Party of the International Society of Blood Transfusion (ISBT). The imputability evaluation follows the criteria as required for SAR and SAE (SARE) reporting by the European Commission (2005/61/EC) and is also employed for PEI

HV reports [22]: an SAR is considered as confirmed if it has been categorized as certain or likely/probable in cases of transfusion-related acute lung injury (TRALI), transfusion-transmitted bacterial infection (TTBI), transfusion-transmitted viral infection (TTVI) or incorrect blood component transfused (IBCT). For acute allergic and anaphylactic transfusion reactions (ATRs), febrile non-haemolytic transfusion reactions (FNHTRs), and partly also for haemolytic transfusion reactions (HTRs) and transfusion-associated circulatory overload (TACO), unique laboratory parameters are missing that unambiguously provide proof for the causal relationship between an SAR and the transfusion. Therefore, these reactions are categorized as confirmed if the connection with the transfusion was considered possible. For HTR, case reports assessed as possible were attributed to confirmed SAR until 2019; since 2020, this was limited to reports categorized as certain or likely/probable. Reported deaths are only recorded as transfusion-associated if the clinical course, additional laboratory parameters or post-mortem findings point to a certain or likely/probable causal relationship with the blood component transfused.

We retrospectively analysed the HV reports submitted to PEI between 2011 and 2020. Donor SARs were categorized in line with the ISBT 2014 Standard for Surveillance of Complications Related to Blood Donation as outlined previously [22]. For data presentation purposes, transfusion reactions assigned to ATR, HTR, IBCT, TACO, TRALI, TTBI or TTVI were included in a more detailed analysis. Moreover, HV data between 2000 and 2010 were presented to show the effectiveness of risk-minimization measure (RMM), issued in a graduated plan procedure by PEI after consultation with stakeholders, in particular the BE (Table S1).

Data presentation and statistical analysis

Within the scope of a descriptive statistical analysis, absolute and relative frequencies were calculated for qualitative data. To calculate reporting frequencies, the numbers of confirmed adverse reactions were correlated with the numbers of blood components transfused in Germany [23]. Reporting rates are presented as the number of confirmed SAR reported per 10^6 transfused or donated blood component.

Ethics statement

The reporting of SAR and SAE involving blood components is required by German law. Data collection and analysis, as well as its publication in an anonymized form, are covered by the legal mandate of the German competent authority, the PEI.

RESULTS

HV reporting between 2011 and 2020

HV reports are centrally collected by PEI as the NCA; reporting is mandatory and covers all suspected SARs, as well as SAEs and notification of donor-triggered look-back procedures (Figure S1). The total number of annual HV reports submitted to PEI has increased from 1341 in 2011 to 5237 in 2020, representing a factor increase of 3.9 (Figure 1). At the same time, the use of blood components for transfusion has steadily decreased, from 6.07 to 4.40 million units of RBCs, platelets and plasma (Figure 1). The rise in the number of reports differed between the types of reports and has been paralleled by changing requirements with regard to donor testing and reporting. One change in regulation was the introduction of a reporting obligation for donor SAR (introduced in 2012) as reflected by respective reports received with a small delay since 2015. A large share of HV reports corresponds to donor-triggered look-back investigations, which accounted for 55.2% of all reports in the past 10 years. In 2017, PEI initiated a scientific discussion (graduated plan procedure) about donor hepatitis E virus (HEV) testing in Germany, which coincides with the start of look-back reporting related to HEV. The number of these reports has increased considerably since 2019, the same year that PEI announced that HEV testing will become mandatory. The number of reported SAEs has increased 8-fold from 22 in 2011 to 176 in 2020, and that of suspected SAR increased 1.8-fold from 516 to 923 reports.

Transfusion reactions reported and confirmed/distribution of adverse transfusion reactions by type of SAR

Altogether, 6044 suspected cases of SARs were reported between 2011 and 2020 (27.6% of all reports), of which 2177 were not confirmed, either because an association with the transfusion was considered unlikely or at least not evident based on the available information. A causal connection with the administration of blood components was confirmed in 3867 cases, and the number of confirmed SARs increased constantly over the years, from 248 in 2011 to 624 in 2020. Reports on reactions with arguable severity, mainly ATR and FNHTR, accounted for 34% (1303) of the confirmed reports but had been omitted from further analysis. Of the 4479 reported, well-defined serious cases of SAR, 2564 were confirmed to be causally related to the transfusion and 54 confirmed SARs resulted in fatal outcome (Figure 2). Severe ATR accounted for the majority of confirmed SARs (56.1%). TTVI, TTBI and TRALI accounted for 2.9%, 4.4% and 4.5% of confirmed reports per year, respectively. More reports concerned HTR and TACO, accounting for 10.9% and 20.2% of confirmed SARs, respectively. IBCT accounted for 8.2% of the confirmed SARs, increasing by a factor of 6.8 from 4 reports in 2011 to 27 reports in 2020. The relative share of confirmed and not confirmed reports varied between different types of SARs and a causal link between a transfusion, and reaction was most frequently confirmed for IBCT. Cases of IBCT, which always occur due to human error and include AB0-incompatible transfusions, accounted for a disproportionate share of fatal SARs (18.5%). A considerable number of fatal SARs were due to HTR (22%), TACO, (20%) and TTBI (14.8%). ATR also caused fatal SARs (20%), but with a relatively smaller frequency considering these reactions were the most frequently confirmed SARs.

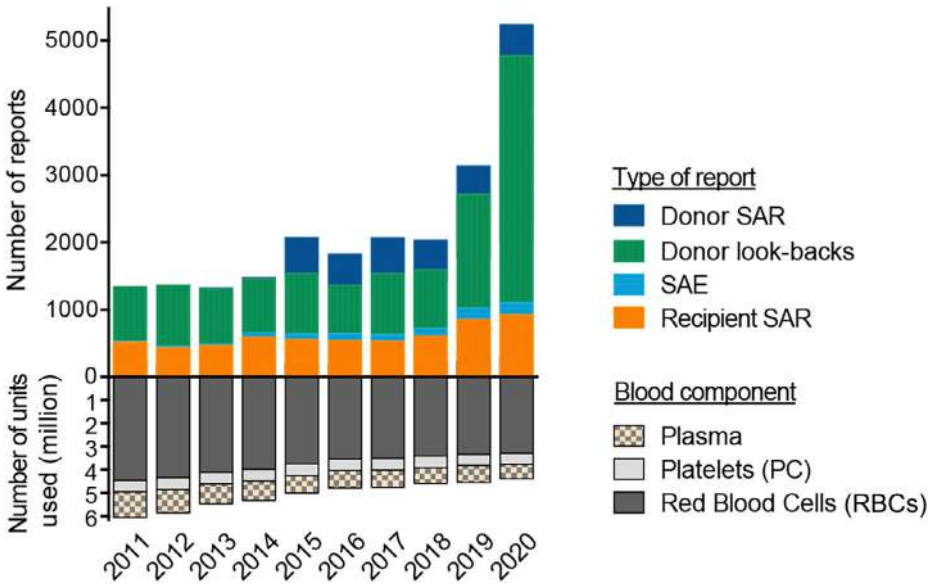

FIGURE 1 Haemovigilance reporting and use of blood components in Germany. SAEs, serious adverse events; SARs, serious adverse reactions.

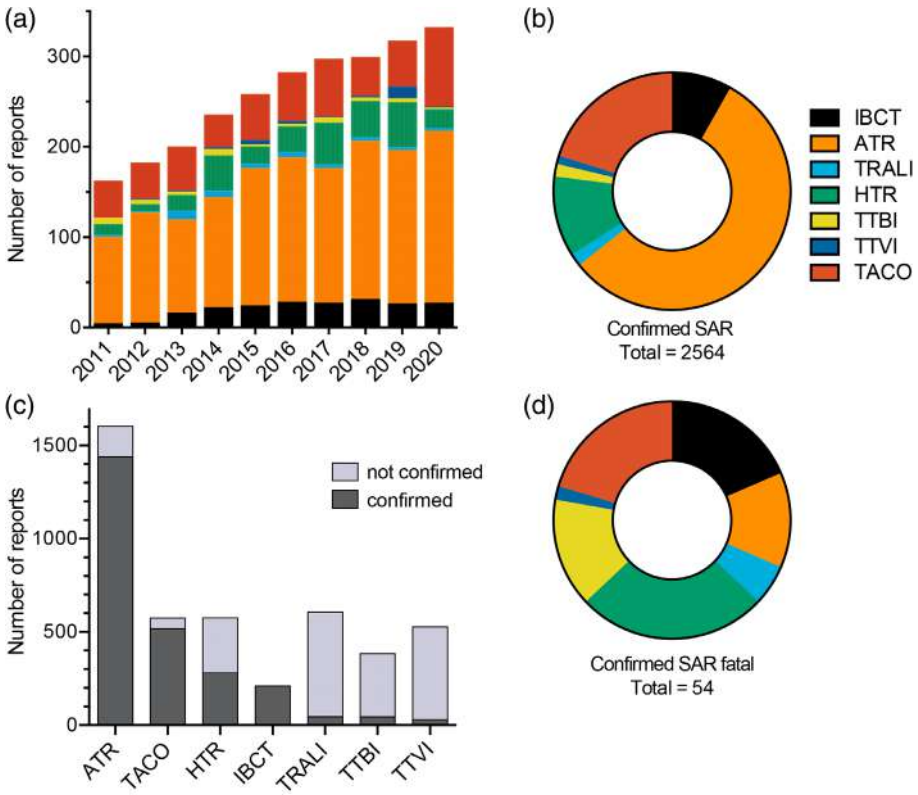

FIGURE 2 Confirmed serious adverse reaction (SAR) reports by time and type. ATR, acute allergic and anaphylactic transfusion reaction; HTR, haemolytic transfusion reaction; IBCT, incorrect blood component transfused; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; TTBI, transfusion-transmitted bacterial infection; TTVI, transfusion-transmitted viral infection.

Donor-triggered look-back procedures by pathogen

Donor-triggered look-back investigations represented a large share of all HV reports. A retrospective investigation (look-back) needs to be initiated if a previously unrecognized infection is suspected in a blood donor that in consequence could indicate a potential transmission risk through previous donations. The process involves the identification of components from a particular donor and removing or recalling

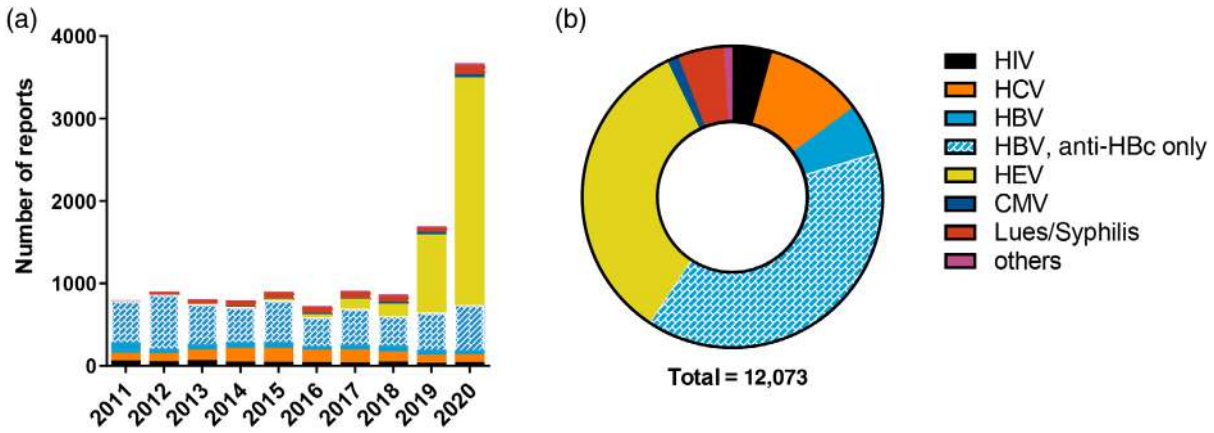

FIGURE 3 Donor-triggered look-backs by time and pathogen. CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus.

potentially harmful components from the BE inventory or hospitals. Moreover, retain samples from previous donations are tested to identify potentially unrecognized TTVI. Over the past 10 years, the highly transfusion-relevant viruses human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) accounted for 7158 or 59% of look-backs reported to PEI (Figure 3). During the same period, very few actual transmissions were confirmed (0 HIV, 2 HBV, 2 HCV), which were all related to very low virus titre blood donations in the window period of the applied test systems. HBV-related look-backs constituted almost half of all procedures reported, of which a considerable fraction was due to isolated anti-HBc-positive test results. An increasing relevance of HEV for transfusion recipients in Germany has been recognized, which led to the 2019 decision to introduce HEV donor screening as evidenced by a sharp increase of look-back procedures. In total, HEV-associated look-backs accounted for 34% of all look-backs since 2011 and for 75% of all look-backs in 2020. Between 2011 and 2020, a total of 25 transfusion-transmitted HEV infections were confirmed. Reports related to syphilis (*Treponema pallidum*) accounted for 5%, and those related to human cytomegalovirus (CMV) accounted for 1.2% of all look-backs. Look-backs due to other pathogens (e.g., Parvovirus B19, West Nile virus [WNV], hepatitis A virus [HAV]) were rarely reported and accumulated to less than 1% of all reports. Nevertheless, 22 of all 28 (79%) look-backs related to the emerging WNV were reported in 2020, while no transfusion-transmitted WNV infections have been reported. In rare instances, donor infections with pathogens of unclear relevance for transfusion safety were reported (e.g., *Borrelia*, *Burkholderia cepacia*, Usutu virus). Such agents are not covered by existing look-back guidelines, and thus no formal look-back investigations are required or have been performed.

Characterization of SAEs

SAEs are incidents that have the potential to cause an SAR in the donor or recipient and may occur at any step in the transfusion chain (collection, donor testing, processing, storage, distribution, use). They can be categorized by the underlying cause, for example, a technical error such as a defective material or a human error. Reporting of SAEs became mandatory in 2012, and the first consolidated data were obtained with some delay. Therefore, we summarize reporting over the past 5 years. Human errors accounted for the majority of SAEs in the past 5 years (Figure 4) and include errors during component selection or issue. In 2020, this led to 76 events, which could have resulted in IBCT or resulted in IBCT without a transfusion reaction (IBCT-SAE). In the latter case, severe transfusion reactions were mainly avoided by the accidental compatibility of ABO blood groups of intended and actual recipient. An additional group of SAE refers to donor exclusion criteria that became known in retrospect (post-donation information [PDI]), for example, due to the diagnosis of an infectious disease shortly after donation. Since 2016, technical errors accounted for 153 (20%), human errors for 409 (54%) and PDI for 190 (25%) of all SAEs reported to PEI.

SAR reporting rates for different blood components

Different blood components inherit different risk potentials due to their distinctive characteristics and storage conditions (Figure 5). Plasma and RBC are stored frozen or at 4°C, respectively, thereby inhibiting or diminishing bacterial growth in case of an undetected contamination. Since 2000, a relatively low number of TTBI reports were related to RBCs (40) and only 1 with plasma transfusions, resulting in reporting rates of 0.47 and 0.05 per million transfused units. For PC, on the other hand, TTBI reporting rates were above 10 between 2000 and 2007 and at around 5 thereafter.

In recent years, ATR reporting rates for plasma and RBC were similar (plasma: 27.1; RBC: 27.5), while ATR was reported about 3.4-fold as often in association with PC transfusions (92.5 reports per million transfused units). A continuous increase in ATR reports was evident across all blood components, probably reflecting a growing awareness of adverse reactions and readiness to report them.

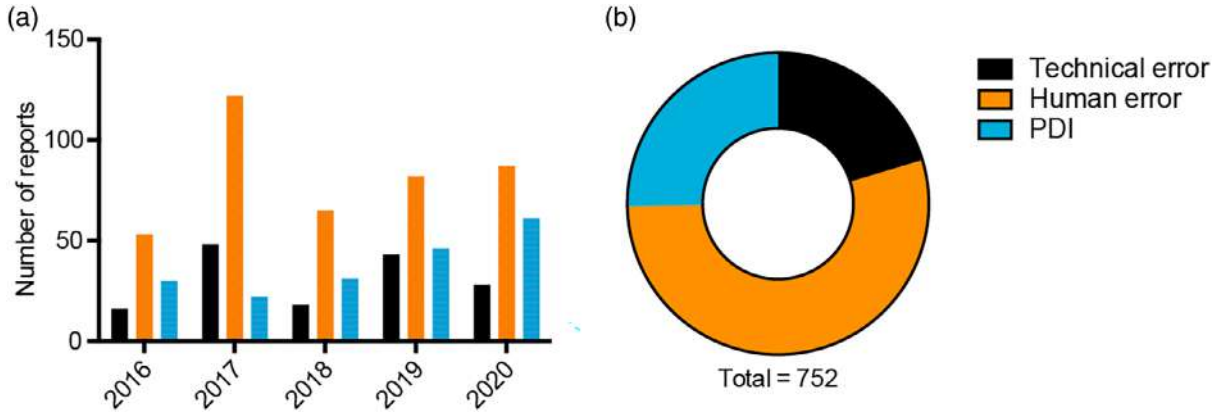

FIGURE 4 Serious adverse event reporting and distribution by cause. PDI, post-donation information.

Reporting rates for TACO, HTR and IBCT have also increased in recent years, most noticeably in relation to RBC transfusions. It should be noted that TACO recording started in 2009 and a reporting obligation for IBCT was introduced in 2012. Reports of TRALI were mainly associated with plasma transfusion in the past but decreased in number after the introduction of RMMs in 2009. However, a slight increase in the TRALI reporting rate was observed in view of PC transfusions, which contain plasma as well. As a result of donor selection and screening, confirmed reports of viral transmissions represented rare exceptions in the past 20 years. A slight increase in the reporting rate more recently was caused by HEV transmissions, which reached its peak with 10 confirmed HEV-TTVI in 2019.

Comparison of SAR reporting rates before and after risk mitigation

In order to investigate the effectiveness of RMMs introduced for TTBI relating to platelets, for TRALI relating to plasma and for HBV transmission relating to all components, we compared respective reporting rates before and after implementation (Table S2). This pre–post comparison confirmed a significant reduction in relative TTBI, TRALI and HBV transmission reports (Figure 6a). Hence, the composition of SAR reports changed, which was most prominent for plasma-associated reports. While TRALI accounted for 72% of all SAR reported in association with plasma transfusion between 2001 and 2008, it represented only 3.1% of such reports between 2010 and 2020, reflecting the relative reduction in TRALI reports and the overall increase in SAR reporting over time. Similar changes were evident for TTBI and HBV transmissions, although less marked (Figure 6b).

Adverse reactions related to blood donation

A legal obligation to report SAR during or after the donation of blood was introduced in Germany in 2012, and reliable data exist since 2015. From 2015 to 2020, a total of 2847 SARs in blood donors have been reported, a mean of 474 reports per year. During this time, vasovagal reactions (VVRs) without or with loss of consciousness (LOC) were the most frequently reported donor SARs followed by local symptoms due to venipuncture. Donor SAR occurred most frequently with platelet apheresis (the largest part of cell apheresis by far), followed by whole blood donation, and least frequently with plasmapheresis. The distribution of the type of donor SAR and the type of donation is shown as an example for 2019 in Table 1.

Although a majority of donors recover without sequelae, falls due to LOC can result in injuries including teeth and bone fractures in individual cases. In 2019, for example, 67 severe injuries due to VVR-caused falls were reported, which required medical interventions [22].

DISCUSSION

The data collected over time showed a reduction in SAR reporting referring to TTVI (HBV, HCV, HIV), TRALI and TTBI, as well as an increase in ATR and IBCT and a less pronounced increase in TACO, HTR and HEV-related TTVI reporting. A general upward trend of SAR reporting, in particular of ATR, may reflect an increased willingness to report suspected transfusion reactions. Important cornerstones to encourage reporting readiness might be the availability of feedback, for example, using annual HV reports, and a non-punitive reporting environment. This applies particularly to errors that lead to the mix-up of blood components (IBCTs) and often result in ABO-incompatible transfusions with severe and life-threatening reactions. Continuous data monitoring is essential for an effective HV system, and consistency in the presentation of reporting data is beneficial (e.g., reporting rates as SAR per 10^6 transfused units), as this provides a baseline to allow for the evaluation of RMM that have been implemented. The marked reduction in TRALI reporting rate demonstrates that the RMM introduced in 2009 [24] concerning plasma for transfusion from female donors with a history of pregnancy was highly effective. RMM to prevent clinically relevant TTBI was also effective in reducing the number of reports. However, septic transfusion reactions and fatal outcomes are not completely prevented by these steps [25] and a

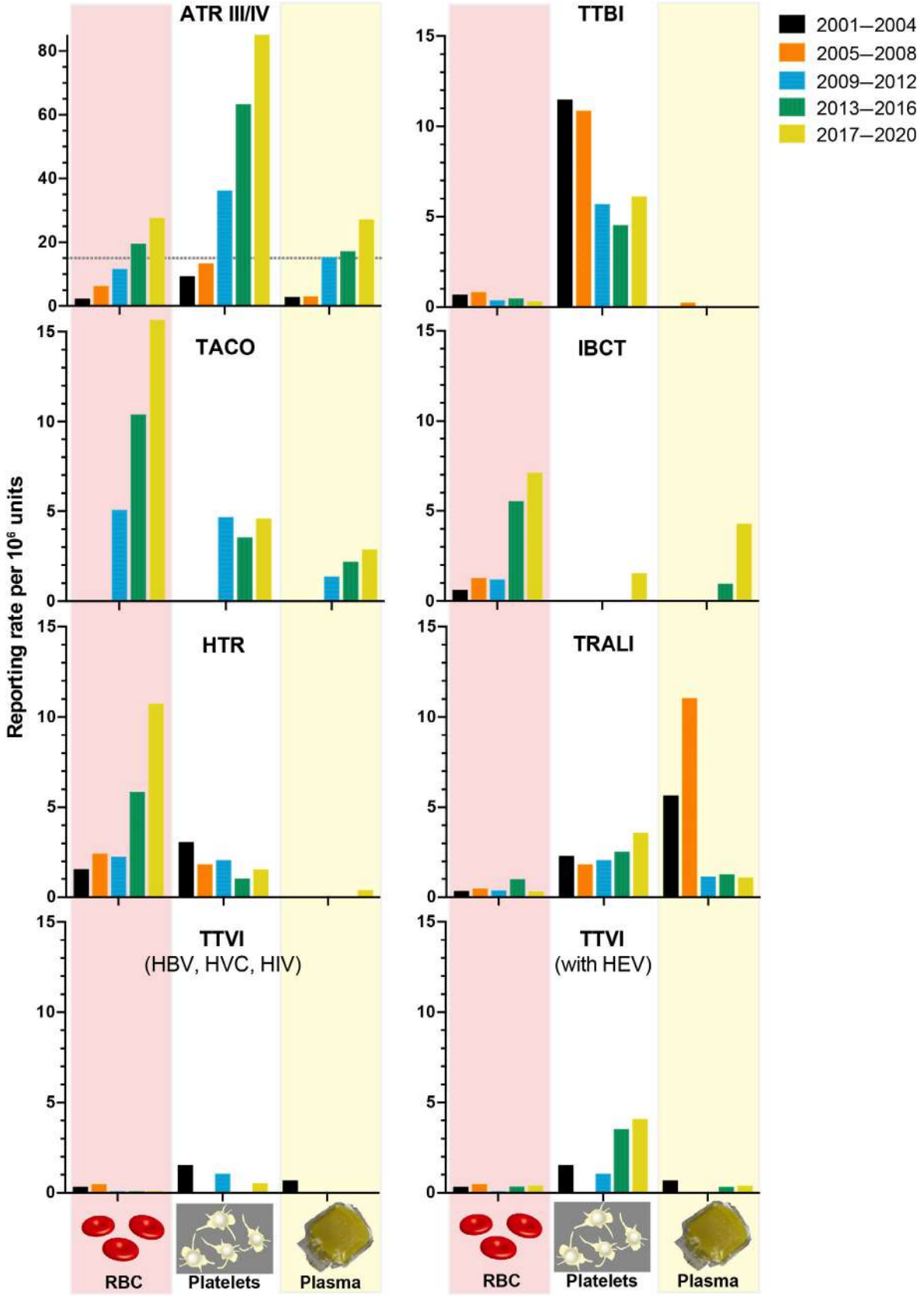

FIGURE 5 Reporting rates of serious adverse reactions attributed to blood components transfused between 2011 and 2020. The dashed line in the top left graph highlights a reporting rate of 15, which is used in all other graphs as *Y*-axis maximum. ATR, acute allergic and anaphylactic transfusion reaction; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HTR, haemolytic transfusion reaction; IBCT, incorrect blood component transfused; RBC, red blood cell; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; TTBI, transfusion-transmitted bacterial infection; TTVI, transfusion-transmitted viral infection.

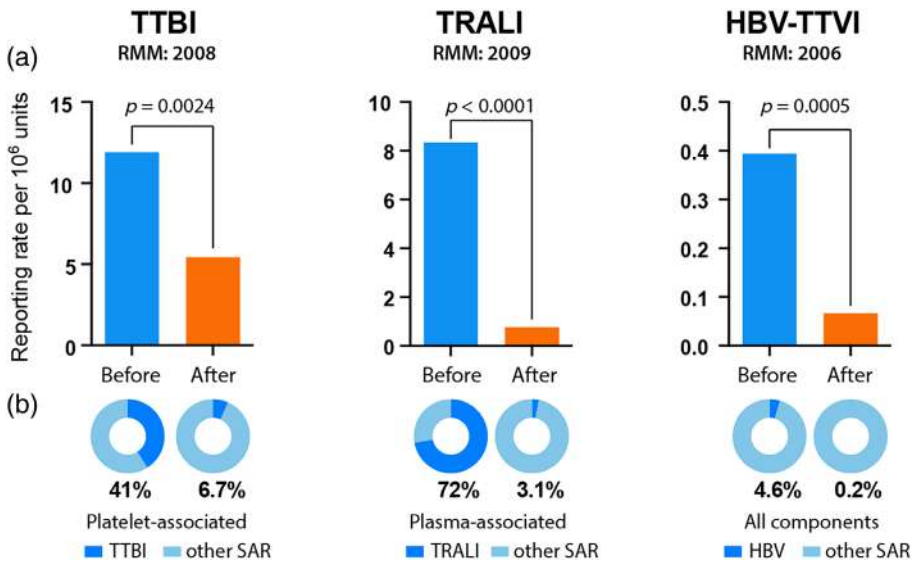

FIGURE 6 Evaluation of risk mitigation. (a) Reporting rates demonstrate a reduction in transfusion-transmitted bacterial infection (TTBI), transfusion-related acute lung injury (TRALI) and hepatitis B virus transfusion-transmitted infections (HBV-TTVI) following the implementation of risk-minimization measures (RMMs). (b) Serious adverse reaction (SAR) reports composition changed and the relative share of TTBI, TRALI and HBV transmissions decreased. Reporting data associated with platelets were used for TTBI in line with the RMM, with plasma for TRALI, and across all blood components for HBV-TTVI. Chi-squared test with Yates' correction was used to compare reporting rates.

TABLE 1 Donor SAR in Germany 2019 by type of donation.

	WB donations	Cell apheresis	Plasmapheresis	Sum	%
Haematoma	49	6	5	60	
Arm pain	55	5	1	61	
Local inflammation	7	2	0	9	
Other vessel diseases	0	0	1	1	
Sum local reactions	111	13	7	131	31.0
VVR w/o LOC	32	7	12	51	
VVR with LOC at donation	32	15	2	49	
VVR with LOC post donation	147	17	3	167	
Sum VVR	211	39	17	267	63.1
Citrate reactions	0	1	3	4	
Cardiovascular reactions	5	4	0	9	
Other	3	9	0	12	
Sum further reactions	8	14	3	25	5.9
Total no. SAR	330	66	27	423	100
No. of donations	**3,728,767**	**158,597**	**2,617,505**	**6,504,869**	
SAR per 10^6 donations	88.5	170.2	25.2	65.0	

Note: Cell apheresis summarizes platelet, granulocyte, red blood cell and multicomponent apheresis.
Abbreviations: LOC, loss of consciousness; SAR, serious adverse reaction; VVR, vasovagal reaction; WB, whole blood.

further risk-minimizing action may be needed. Measures aiming to protect transfusion recipients from HBV, HCV and HIV transmissions were implemented in multiple steps [26] and have evidently reduced such risk. Once a key reason to establish HV activities, viral transmissions have become rare exceptions in the past 10 years. In total, 2 HBV, 0 HIV, 2 HCV and 25 HEV transmissions were reported within the period studied and 50.86 million units of blood components were used during this time, resulting in a cumulative reporting rate of 0.02 per million transfused units or one per 25.43 million units for HBV and HCV, a reporting rate of less than 0.01 per million transfused units or one per 50.86 million units for HIV. Nevertheless, this risk inherent to blood components requires constant attention as evident

by false-negative results that triggered screening assay improvements [27, 28]. Risk from infectious diseases can be dynamic, as their emergence and spread are affected by global changes [29], and new testing requirements were introduced in response to emerging pathogens. The expanding distribution of WNV has led to precautionary measures to ensure blood safety [30], including new testing requirements in Germany as of 2020 almost simultaneously to mandatory HEV screening. For HEV, the reporting rate was higher, with 0.5 per million transfused units or one per 2.03 million units, although the reported transmissions took place prior to the introduction of a mandatory HEV testing. Regulatory provisions may not only reduce risks but also affect the number of reports received by the NCA as seen following the introduction of reporting obligations for SAE and donor SAR. The most striking effect in terms of absolute number of reports was associated with the introduction of mandatory HEV donor screening. The number of notifications of look-back procedures had been consistent over many years, followed by a 4.2-fold increase from 2018 to 2020 in the number of look-backs with the introduction of HEV donor screening.

The HV data presented illustrate that blood components have reached high safety with regard to infectious agents, which is in line with other countries' risk prevention due to effective donor screening [3, 16]. However, risks inherent to blood components and considered non-preventable, as well as human errors, remain common causes of adverse reaction reporting in Germany and other HV systems [31, 32]. When improving blood transfusion standards, it is important to consider the data and experiences of other HV systems. Additionally one should take into account the practicability of establishing specific measures within the country-specific context and the national specifics of blood transfusion and HV system. As a lack of timely blood transfusion can contribute to unfavourable patient outcomes and many countries lack sufficient blood supply [1], lack of blood for transfusion might be defined as an adverse event term to be reported in countries with a high need-to-supply ratio to collect HV data that may help to identify relevant factors and evaluate the benefits of actions for improvement.

The involvement of all relevant stakeholders in a transparent process to develop and implement risk mitigation measures is important. The German Graduated Plan Procedure ('Stufenplan') is a legally defined multi-step process that specifies the cooperation and coordination between the authorities and concerned parties when addressing a new risk and risk mitigation. Providing aggregated feedback and recommendations to the community by means of annual HV reports [22] is done by several national HV systems and is also recommended by WHO [10]. The benefits of the measures introduced should therefore be reviewed to ensure an evidence-based, efficient and cost-effective system [33].

The limitations of a passive HV system that relies on spontaneous reporting include heterogeneity in data quality, incomplete clinical information that can impede case evaluation, underreporting and limited personnel resources at reporting institutions. However, as such limitations apply constantly, long-term HV data are still considered highly informative regarding changing trends and can serve as a basis to assess blood safety standards.

In conclusion, consistent long-term data collection forms an important basis to establish changes in reporting, identify new risks and to evaluate the effect of RMMs. In this context, a clear allocation of roles and responsibilities, mandatory reporting and standardized criteria for reaction types, seriousness and imputability assessments, as well as availability of a denominator (number of units transfused), are requirements ensuring comparability over time in Germany. Central data collection and independent assessment taking place at the NCA allow for evaluating HV data in a nationwide context and monitoring over time. Stakeholder involvement and transparent feedback on transfusion safety and the benefit of RMMs help to achieve the aims of HV, that is, ensuring the safety and availability of blood components for transfusion now and in the future.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in haemovigilance reports at www.pei.de/haemovigilance-report.

ORCID

Philipp Berg https://orcid.org/0000-0003-0674-9031
Gabriele Ruppert-Seipp https://orcid.org/0000-0002-6141-1386
Sarah Kehr https://orcid.org/0000-0003-0271-2629
Markus B. Funk https://orcid.org/0000-0001-8642-1276

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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

Blood transfusion dynamics in Colombia: Unveiling patterns, reactions and survival rates in multitransfused patients

María-Isabel Bermúdez-Forero[1] | **Michel-Andrés García-Otálora**[2]

[1]Coordinación Red Nacional Bancos de Sangre y Servicios de Transfusión, Instituto Nacional de Salud (INS), Bogotá, Colombia

[2]School of Medicine and Health Science, Public Health Research Group, Universidad del Rosario, Bogotá, Colombia

Correspondence
Michel-Andrés García-Otálora, School of Medicine and Health Science, Public Health Research Group, Universidad del Rosario, Cra. 24 #63C-69, Bogotá, Colombia.
Email: michel.garcia@urosario.edu.co

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Abstract

Background and Objectives: There is no consensus on a universally accepted threshold to categorize a patient as multitransfused. In 2019, Colombia established the definition of a multitransfused patient as someone who has received six or more blood components, irrespective of the time frame. This study aims to delineate the characteristics, adverse transfusion reactions (ATRs, definitions according to the International Society of Blood Transfusion [ISBT]) and survival rates in this population.

Materials and Methods: We performed an analysis from the data of all institutions engaged in blood component transfusions at the national level who notified events to the National Information System of Haemovigilance (SIHEVI-INS), from January 2018 to December 2022. The selection criteria focused on individuals who not only exhibited ATRs but also received six or more blood components.

Results: Among the 1,784,428 patients who received 6,637,271 blood components, an average of 3.7 components per patient was noted. Concurrently, 8378 ATRs were reported (12.6 ATRs/10,000 transfused components). Within this cohort, 691 patients met the criteria for multitransfusion. Predominantly women (51.8%), these individuals received between 6 and 14 blood components. Out of the 691 multitransfused individuals who experienced ATR, 541 had an allergic reaction. Conversely, out of the 6479 non-multitransfused individuals who experienced ATR, 3835 had an allergic reaction (odds ratio: 2.49, 95% confidence interval: 2.06–3.0). Notably, 271 multitransfused individuals (39.2%) were documented as deceased, with 76% succumbing within 12 months of encountering their most recent ATR.

Conclusion: Multitransfused individuals in Colombia, being a high-risk group, exhibit a heightened susceptibility to allergic reactions, surpassing the frequency observed in other transfusion populations. This underscores the necessity for tailored medical care specific to this group.

Keywords

adverse transfusion reaction, blood components, blood transfusion, haemovigilance

Highlights

- The rate of documented adverse reactions (ATRs) in Colombia from 2018 to 2022 was 12.6/10,000 components transfused. Of the patients experiencing an ATR, 691 (9.0%) met Colombian multitransfusion criteria and experienced mainly allergic ATRs (78.3%).
- Four out of every 10 multitransfused patients who experienced ATR were diagnosed with thrombocytopaenia, and a majority (78.7%) received a single type of blood component.
- Of the 691 multitransfused patients, 271 individuals were reported deceased; 56% of them died within 138 days following the notification of the last ATR.

INTRODUCTION

The terms 'poly' and 'multi' originate from different languages, with 'poly' coming from the Greek word 'πολύς' (polys), meaning 'many' or 'several', and 'multi' deriving from the Latin word 'multus', which also signifies 'many' or 'various'. As of 8 February 2024, a PubMed search revealed 651 results for 'multitransfused' and 358 results for 'polytransfused', reflecting their usage in medical literature. There is no universally agreed-upon threshold for defining a patient as such, with definitions varying from receiving ≥2 blood units to ≥10 units [1–6]. In 2019, Colombia, with an estimated population of 51,682,692 inhabitants [7] and 78,785 hospital beds (equating to 1.5 beds per 1000 inhabitants) [8], established the definition of a multitransfused patient as an individual who has received at least six blood components, irrespective of the time frame [9].

Individuals transfused for thalassaemia, haemophilia, haemodialysis [10–12], sickle cell disease, acute bleeding [13], neoplasms [12, 13], myelodysplastic syndromes [14] and liver disease [3] are often categorized as multitransfused. Within this group, there is a higher prevalence of hepatitis B, C, D and G viruses and human immunodeficiency virus (HIV) compared to non-transfused individuals [4, 5, 9, 10], although no such association has been found with *Trypanosoma cruzi* [1, 15].

It has been established that the accumulation of iron, due to repeated erythrocyte unit transfusions, significantly elevates the risk of failures of the heart, liver and haematopoietic, endocrine [14] and immune systems [12], particularly in thalassaemia and myelodysplastic patients. The use of iron chelation therapy has been shown to reduce the risk of multiple organ failure in multitransfused patients [14, 16].

Currently, there is limited information available regarding the characteristics, transfusion patterns, adverse transfusion reactions (ATRs) and survival rates of multitransfused patients in Colombia. Since 2018, the National Information System of Haemovigilance (SIHEVI-INS) has served as the central repository for data encompassing blood donors and recipients of blood components nationwide [17]. The aim of this study was to outline the characteristics, occurrences of ATRs and survival rates within this demographic group.

MATERIALS AND METHODS

We conducted an analysis by collating the number of patients documented by 669 healthcare institutions reporting to SIHEVI-INS during 1 January 2018–31 December 2022 [18–21]. We acknowledge that there could be patients who fit the Colombian definition of multitransfusion but not included in this work. This limitation arises from the fact that the institutions responsible for transfusing patients in the country are not mandated to provide the specific identification details of each transfused patient. It is important to note that only individuals who experienced ATRs had their data nominally recorded within SIHEVI-INS. Consequently, there was accessible information only regarding the total number of blood components administered to these specific patients. The selection criteria focused on individuals who exhibited ATRs and received six or more blood components in the SIHEVI-INS database.

The Administrator of the Resources of the General Social Security Health System (ADRES) obtains information from individual healthcare service providers, including their status such as active, deceased, retired or suspended. Everyone is assigned a unique identification number, which can be associated with a range of identification documents, including citizenship cards, among others. To determine the status of multitransfused patients, their SIHEVI-INS identification numbers were cross-referenced with the ADRES, with this comparison extending until 25 August 2023. To calculate the time elapsed between a patient's reported death and the most recent report of an ATR, the two variables were subtracted from each other. Any cases resulting in negative values (indicating a prior declaration of death followed by a subsequent ATR report) were excluded from the analysis.

Colombia has adhered to the event definitions, imputability criteria and severity assessments established by the International Society of Blood Transfusion (ISBT) [22] since 2016, which were subsequently updated in 2019 [23].

RESULTS

There were 1,784,428 patients receiving 6,637,271 blood components as reported to SIHEVI-INS, resulting in an average of 3.7 blood components per patient. During this period, 8378 ATRs were documented by 474 clinics, equating to a rate of 12.6 ATRs per 10,000 transfused blood components (Figure 1). Among patients with ATRs, 691 met the criteria for multitransfusion, with 19 of them being foreign citizens. This translates to an estimated 1 multitransfused patient for every 2582 transfused patients in the country. Remarkably, 93.6% of these patients received between 6 and 14 blood components (median: 6.0; interquartile range: 6.0–8.0). Among the multitransfused

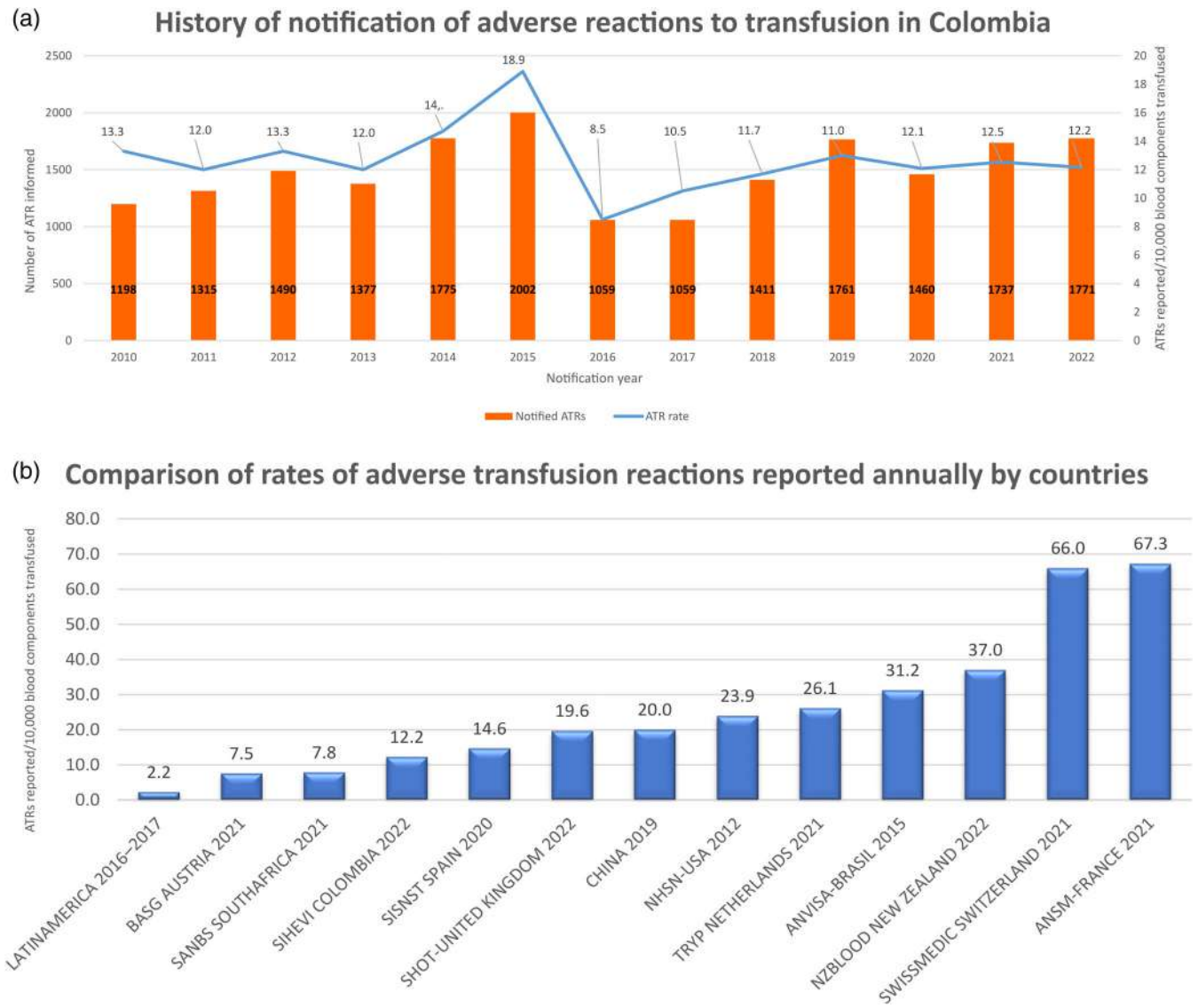

FIGURE 1 (a) Adverse transfusion reactions (ATRs) recorded by the Colombian National Institute of Health from the inception of the programme in 2010. (b) Comparative analysis of ATR rates per 10,000 blood components transfused among countries with recent public haemovigilance reports [24–35].

patients, 51.8% (358 individuals) were women, resulting in a national multitransfusion rate of 13.5 women per million inhabitants (Table 1). When considering age groups, the male population between 71 and 80 years of age exhibited the highest multitransfusion rate at 44.7 individuals per million inhabitants (Table 1 and Figure 2). Interestingly, the rate of multitransfused women was 21% higher among individuals aged 11–50 compared to the male population, a period that coincides with potential obstetric adverse events in women. Conversely, the rate of multitransfusions in women was 25.5% lower among those aged 51–90 compared to men.

The distribution of ABO blood groups among multitransfused individuals showed that 63.0% were blood type O, followed by 27.2% with blood type A, 8.0% with blood type B and 1.7% with blood type AB. These percentages closely align with the distribution observed among Colombian blood donors [36]. Additionally, 93.3% of multitransfused patients were classified as RhD positive, a statistic that mirrors closely the 92.1% reported among blood donors.

Among the total reported ATRs in multitransfused individuals, 78.3% were of an allergic nature, with febrile non-haemolytic transfusion reaction (FNHTR) for 8.4% and transfusion-associated circulatory overload (TACO) making up 4.8% (Table 2). Notably, 81.2% of patients experienced one ATR, while 16.8% reported between two and three ATRs and 2.0% encountered four to five ATRs. In terms of imputability, 93.2% of ATRs were categorized as definite (37.2%), probable (34.0%) or possible (22.0%). The majority (89.9%) of ATRs were non-severe, while 7.1% were severe, 2.2% reached life-threatening levels and 0.9% resulted in death.

To test the hypothesis that the frequency of allergic reactions was higher in the multitransfused population compared to the non-multitransfused population, we conducted a comparison of the

TABLE 1 Total number of multitransfused patients and the rate per million inhabitants depending on sex and age in Colombia.

	Men			Women		
Age range (years)	Multitransfused (*n*)	Inhabitants	Rate per million	Multitransfused (*n*)	Inhabitants	Rate per million
0–10	21	4,343,120	4.8	20	4,158,133	4.8
11–20	51	4,115,173	12.4	51	3,962,476	12.9
21–30	44	4,387,689	10.0	67	4,369,878	15.3
31–40	50	3,775,309	13.2	56	3,921,437	14.3
41–50	33	3,002,673	11.0	45	3,301,588	13.6
51–60	45	2,551,655	17.6	44	2,951,123	14.9
61–70	41	1,770,648	23.2	33	2,129,202	15.5
71–80	40	895,531	44.7	25	1,130,720	22.1
81–90	6	313,090	19.2	17	421,924	40.3
91–100	2	75,251	26.6	0	106,072	0.0
Total	333	25,230,139	13.2	358	26,452,553	13.5

number of reported allergic cases in both groups. Out of the 691 multitransfused individuals who experienced ATR, 541 had an allergic reaction. Conversely, out of the 6479 non-multitransfused individuals who experienced ATR with definite, probable or possible imputability, 3835 had an allergic reaction. The frequency of allergic reactions was estimated to be 2.49 times higher in multitransfused individuals compared to non-multitransfused individuals (odds ratio [OR]: 2.49, 95% confidence interval [CI]: 2.06–3.0).

A majority of multitransfused patients (78.7%) received one type of blood component, with platelets being the most common at 64.0%. Fresh frozen plasma accounted for 29.8% of the unique blood components, followed by cryoprecipitate at 5.0% and red blood cells (RBCs) at 1.3%.

Among multitransfused patients, 14.9% received a combination of two blood components. The most common pairing was RBC with platelets, accounting for 42.7% of cases, followed by RBC combined with fresh frozen plasma (24.3%), or cryoprecipitate along with platelets (13.6%). In the case of 5.1% of multitransfused patients, they required three blood components. Among these cases, the combination of RBC, platelets and fresh frozen plasma was the prevailing choice, constituting 65.7% of instances. Alternatively, the administration of cryoprecipitates with RBC and platelets, as well as cryoprecipitates with RBC and fresh frozen plasma, each represented 14.3% of the total. A smaller subset (1.3%) of all multitransfused patients required the administration of four or more blood components.

To investigate the potential correlation between the number of blood components received and mortality, we conducted a comparative analysis of the reported status of multitransfused patients in two distinct groups. The first group consisted of those who received between six and seven blood components ($n = 473$), while the second group included individuals who received eight or more blood components ($n = 218$). Upon examining the data, we observed that in the first group, there were 199 communicated deaths and 244 individuals reported as alive, while in the second group there were 72 reported deaths and 135 individuals informed as alive (OR: 0.65, 95% CI: 0.46–0.92). It is important to note that this analysis did not consider factors such as the causes of transfusion or the specific type of blood component administered, which could potentially act as confounding variables influencing the outcomes.

Table 3 provides a comprehensive summary of the underlying reasons for transfusions within the multitransfused population. Notably, 4 out of every 10 multitransfused patients were diagnosed with thrombocytopaenia. Among those diagnosed with adenomas/carcinomas, two-thirds of cases resulted in reported mortality. In the case of leukaemias or lymphomas, 52% were reported as deceased. Conversely, among all the considered diagnoses, the conditions associated with the lowest mortality rates were shock/haemorrhage and plasma exchanges.

We identified 10 patients who have been registered in the deferred donor registry (DDR) [17], a classification that permanently prohibits them from making blood donations due to being diagnosed with potentially transfusion-transmissible infections (TTIs). Among these 10 individuals, 4 had passed away. The remaining six individuals within this registry fall within an age range 14–62 years. Out of these cases, four were diagnosed with HIV, one with hepatitis B virus (HBV) and one with *T. cruzi*. Notably, five of these patients had been previously notified to the DDR before the most recent ATR was reported. However, in two cases, the report to the DDR occurred 369 and 492 days after the last recorded ATR which was not a TTI.

Similarly, our analysis revealed that 13 patients had a history of blood donation. Among them, 12 had donated blood prior to experiencing ATRs and becoming multitransfused. The median time elapsed between the registration of their last ATR and their last donation was −642 days (interquartilic range [IR]: −1137 to −390 days). Additionally, we identified another patient who donated whole blood on 27 October 2021. On 14 December 2021, a definitive, non-severe allergic reaction was reported to SIHEVI-INS following a transfusion due to acute myeloid leukaemia. This patient was reported as deceased on 1 December 2022 to ADRES.

In 2021, Colombia incorporated an immunohaematology database into SIHEVI-INS to monitor individuals with a transfusion history. We

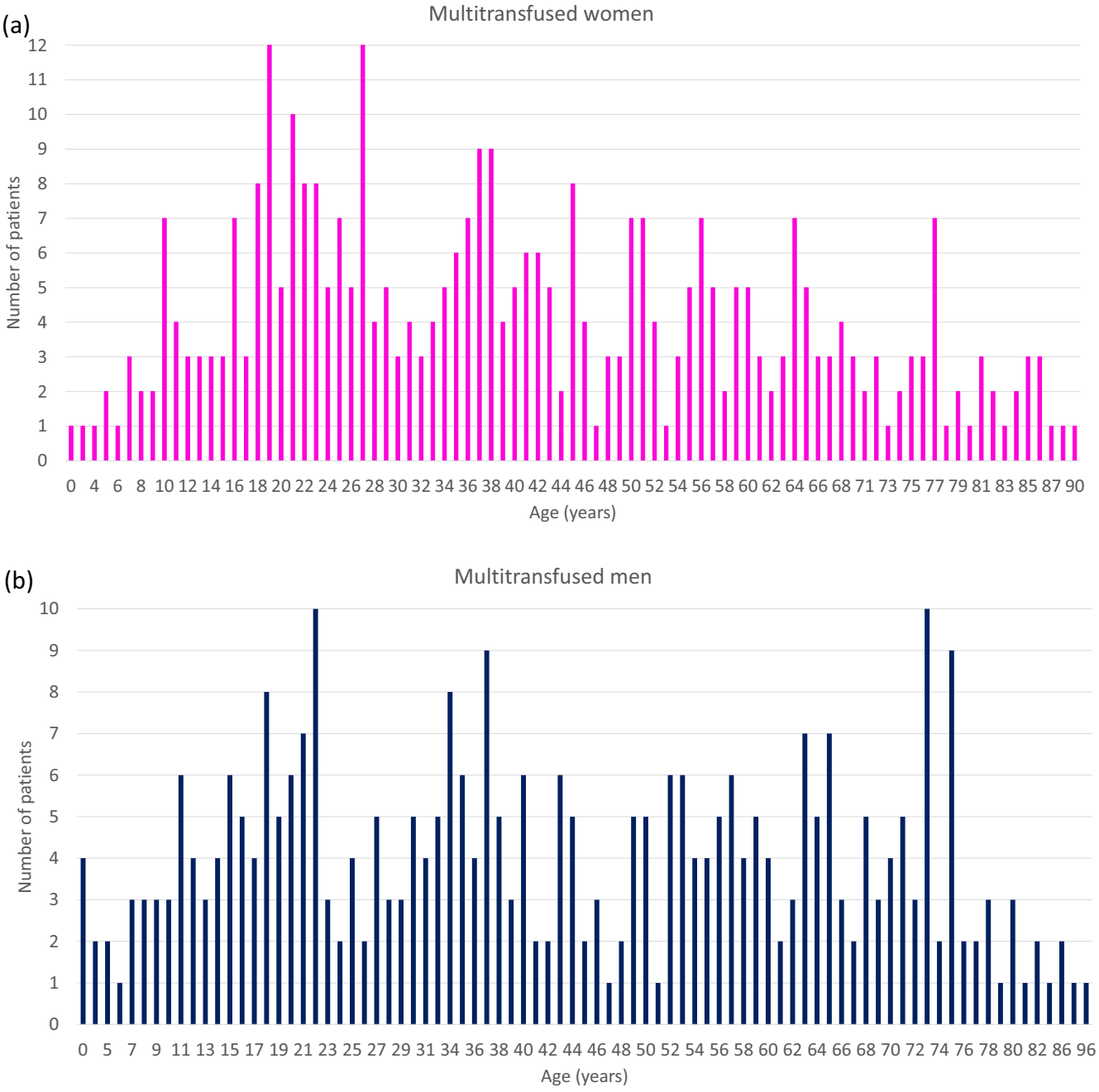

FIGURE 2 Histogram of multitransfused patients according to age: In magenta, female population; in dark blue, male population. The median age of female patients was 38 years (IR: 23–57), whereas for males it was 41 years (IR: 22–63) $p = 0.307$. The histogram for females showed a unimodal distribution with left skew, coinciding with their reproductive period. Conversely, in males, a bimodal distribution was identified between ages 17–21 and 73–75. This suggests that the factors contributing to Colombian females becoming multitransfused differ from those of males.

determined the count of multitransfused patients with an immunohaematological record. There were 98.7% of these individuals without an immunohaematological data.

There were 271 individuals (39.2%) documented as deceased according to ADRES. To explore the temporal relationship between the last reported ATR and the notification of their demise, Figure 3 has been provided. Our analysis of 232 multitransfused patients (excluding 39 individuals with records of adverse reactions after their death), 56% passed away within 138 days following the notification of the last ATR. Additionally, 76% of these patients were reported as deceased within a year or less after the last ATR notification.

DISCUSSION

Our research findings uncovered a contrast in the ATR rate per 10,000 blood components in Colombia when compared to countries such as Switzerland [24], France [25], New Zealand [26], and the

TABLE 2 ATRs described in the multitransfused population, according to the reported severity.

Classification of the ATR	Number	%	Severity			
			Non-severe	Severe	Life-threatening	Death
Allergic reaction	541	78.3	514	24	3	0
Febrile non-haemolytic transfusion reaction (FNHTR)	58	8.4	57	1	0	0
Transfusion-associated circulatory overload (TACO)	33	4.8	15	12	4	2
Transfusion-related acute lung injury (TRALI)	16	2.3	4	5	3	4
Unclassifiable complication of transfusion	11	1.6	9	1	1	0
Hypotensive transfusion reaction	9	1.3	8	0	1	0
Transfusion associated dyspnoea	7	1.0	4	3	0	0
Acute haemolytic transfusion reaction	3	0.4	1	0	2	0
Incidents[a]	3	0.4	3	0	0	0
Transfusion-transmitted infection (TTI): Parasitic	2	0.3	0	2	0	0
TTI: HIV	2	0.3	1	1	0	0
TTI: Bacterial	1	0.1	0	0	1	0
Near-miss	1	0.1	1	0	0	0
Non-immune haemolysis	1	0.1	1	0	0	0
Delayed haemolytic transfusion reaction	1	0.1	1	0	0	0
Delayed serologic reaction	1	0.1	1	0	0	0
Incorrect blood component transfusion[b]	1	0.1	1	0	0	0
Total	691	100.0	621	49	15	6

Abbreviations: ATR, adverse transfusion reaction; HIV, human immunodeficiency virus.
[a]An incident refers to a scenario in which a patient receives a blood component that fails to meet all the necessary criteria for a suitable transfusion for that specific patient, or which was designated for another patient. This encompasses transfusion errors and departures from standard operating procedures or hospital policies, resulting in incorrect transfusions. Whether or not it results in an adverse reaction is variable [22].
[b]Male patient, 63 years old, blood group A positive, diagnosed with prolonged coagulation times, who received six units of plasma. The reaction was classified as probable.

TABLE 3 Reasons for transfusion in multitransfused patients with ATRs.

Reasons for transfusion	Number	%	Live (%)	Death (%)
Thrombocytopaenia[a]	267	38.6	47.2	47.2
Others	110	15.9	59.6	32.5
Leukaemia/lymphomas	73	10.6	43.8	52.1
Coagulopathy-prolonged coagulation times	65	9.4	58.5	33.8
Shock/haemorrhage	55	8.0	74.5	16.4
Plasmapheresis	41	5.9	84.1	11.4
Anaemia	27	3.9	55.6	37.0
Not registered	24	3.5	45.8	45.8
Afibrinogenaemia or hypofibrinogenaemia	16	2.3	58.8	41.2
Adenomas/carcinomas	13	1.9	33.3	66.6
Total	691	100.0	54.8	39.2

Abbreviation: ATR, adverse transfusion reaction.
[a]Forty percent of the patients were diagnosed with primary immune thrombocytopaenia and 60% with secondary thrombocytopaenia. The main causes reported for secondary thrombocytopaenia were infectious, 24.5%; neoplasms, 17.6%; bone marrow aplasia/Fanconi anaemia, 17.6; systemic lupus erythematosus, 12.7%.

Netherlands [27] (Figure 1b). The data revealed a 3–5 times lower ATR rate in Colombia. This variance may be attributed to several factors, including the relatively shorter history of Colombia's national haemovigilance programme and potentially inconsistent adherence among the involved stakeholders (Figure 1a). For example, there was a noticeable decline in ATR notifications from 2015 to 2016 onwards. This decrease can be attributed to a modification in the reporting format mandated for completion by stakeholders. The revised format,

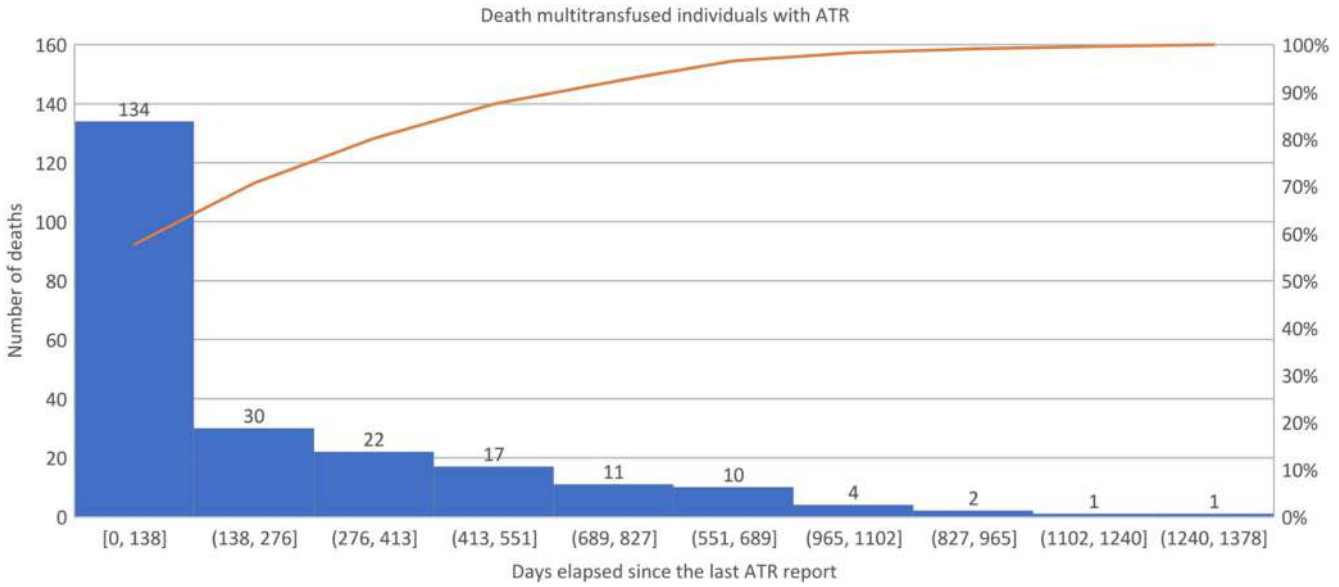

FIGURE 3 Pareto diagram illustrating data pertaining to multitransfused patients recorded in Administrator of the Resources of the General Social Security Health System (ADRES) as deceased individuals. In the diagram, the data distribution, shown in blue, is arranged in descending order based on the frequency of days elapsed between the date of the last adverse transfusion reaction (ATR) and the registration as deceased. The orange line represents cumulative data on the secondary axis as a percentage of the total number of deaths.

introduced in 2016, incorporated additional variables in accordance with recommendations from the Haemovigilance Working Party of the ISBT. However, this change brought about several challenges. It led to confusion among some individuals responsible for completing the format, resulted in the absence of notifications from certain stakeholders and caused incomplete or incorrect submissions. Consequently, there was a need to either reprocess the information or risk losing some reports altogether.

Our investigation uncovered a prevalence rate of ATRs as 13.4 per million inhabitants among multitransfused patients. Significantly, allergic reactions were the predominant ATR, followed by FNHTR and TACO. These findings diverge from those of haemovigilance studies in other countries [37–40], as well as from non-multitransfused patients in this study. In cases where crossmatch testing is conducted for multitransfused individuals, the standard practice typically centres on the assessment of ABO and RhD antigens. Because patients requiring platelet transfusions may not always receive ABO-compatible units, this could explain a higher occurrence of allergic reactions. For instance, Malvik and colleagues identified that transfusion of ABO-antigen-incompatible platelets showed the highest incidence of allergic transfusion reactions, with a rate 1.5–2 times higher than that of ABO-compatible transfusions [41].

Focusing solely on the ABO and RhD compatibility of the blood components to be transfused may overlook numerous other erythrocyte or human leukocyte and platelet antigens, which are also immunogenic [42]. Neglecting these antigens increases the risk of alloimmunization [6, 37], leading to platelet and erythrocyte incompatibility and potentially resulting in transfusion refractoriness and a heightened susceptibility to ATR [2, 6]. According to Cohn [38], platelet refractoriness can be non-immune (60%–80%) or immune (10%–25%). Currently, the definitions proposed by the haemovigilance working party of the ISBT do not consider platelet refractoriness as an ATR [22, 23], so stakeholders do not have the possibility of considering this diagnosis when reporting to SIHEVI-INS. Therefore, our current haemovigilance system has no way of determining this diagnosis or its aetiology.

Cytokines originating from residual white blood cells or recipient antibodies targeting donor antigens are commonly attributed to the onset of FNHTR [39]. FNHTR, typically, is an exclusion diagnosis. When encountering a patient manifesting fever in temporal proximity to a transfusion, considerations for underlying diseases, haemolytic transfusion reactions, septic transfusion reactions or transfusion-related acute lung injury (TRALI) are imperative within the realm of differential diagnosis. The likelihood of FNHTR occurrences decreases by approximately 50% when employing pre-stored leukoreduced RBCs compared to non-leukoreduced components [39]. In Colombia, only 17% of blood components undergo pre-storage leukoreduction [43]. Given the established association between leukoreduction and reduced FNHTR rates, the notably higher incidence reported in New Zealand [26] compared to Colombia hints at potential under-reporting in our country.

This investigation revealed that 1.3% of multitransfused individuals had undergone antibody screening, all with negative results. This contrasts with the observations made by Poornima et al. [6] that 6.4% of patients exhibited alloantibodies, while 1.6% displayed auto-antibodies. In another study, which involved 842 multitransfused, the detection of alloantibodies was 5.2% [3]. It is known that the prevalence of alloimmunization varied across different conditions [40]. For example, there are gender discrepancies, with 12.7% of females showing alloimmunization compared to 3.2% of males [3]. Another

study highlighted a higher incidence of RBC alloantibodies in female patients (63%) compared to males (37%) and a greater prevalence of alloantibodies among patients with non-haematological malignancies (14%) [40].

In this study, we found that 10 patients were documented in the DDR, with 6 of them still alive and infected with HIV, HBV and *T. cruzi*. Regrettably, we have not been able to ascertain whether these infections stem from transfusions. Despite improvements in screening tests and the introduction of mass hepatitis B vaccinations [44], it has become evident that multitransfused populations require more frequent vaccination compared to non-multitransfused individuals [12, 45–47]. Moreover, prevention efforts have fallen short, leaving most infected individuals with limited or no access to harm-reduction strategies [48]. This situation poses a considerable public health concern, as it has been observed that untreated infections can spread within families [13, 17, 18] through various transmission patterns, including maternal, paternal and sexual routes [49–51]. Therefore, it is important, as a public health imperative, to investigate the infection status of the relatives of multitransfused patients in this cohort. The ongoing evaluation underscores the importance of confirming infection status promptly and initiating treatment swiftly, while also monitoring progress as needed.

It is intriguing that since 2010, Colombia's haemovigilance programme has not reported any cases of hepatitis C virus (HCV) or HBV related to transfusion. This stands in contrast to reports from other countries suggesting a higher prevalence of these viruses in multitransfused patients [4, 5, 11, 12]. In 2022, Mongolia, Pakistan, Ukraine and Gabon reported HCV population prevalences of ≥3%, while in Colombia it remained at <1% [52]. Throughout 2022, in Colombia there were 3657 reported cases of hepatitis B, C and B-Delta co-infection at the national level [53]. The estimated incidence rate for hepatitis B was 5.0 cases per 100,000 inhabitants, whereas for hepatitis C, it was 2.1 cases per 100,000 inhabitants. In the first half of 2023, the incidence rates were reported at 3.07 per 100,000 inhabitants for HBV and 2.3 per 100,000 inhabitants for HCV [53], with genotypes 4 and 1b being the most prevalent [54]. Therefore, the lack of reported cases in Colombia may not be solely due to a lack of notification but possibly indicative of a low circulation of both viruses. In fact, the Colombian figures for 2023 suggest that the country has already achieved the World Health Organization (WHO)-defined goal for 2030, with rates of 2/100,000 for HBV and 5/100,000 for HCV [55].

Our study showed a 39% all-cause mortality rate among Colombian multitransfused individuals within 1 year of their last ATR. This increased mortality within the multitransfused population may be attributed to their initial condition, which tends to be more severe [56]. For instance, the transfusion of packed RBC has been linked to heightened mortality in non-cardiac surgeries due to its association with severe complications [57]. Additionally, in critically ill patients, transfusion of blood components has been correlated with an elevated risk of adverse events [58]. It is crucial to acknowledge that mortality rates can vary depending on individual pathology and age [59], potentially introducing selection bias in our methodological approach. For example, patients with neoplasms exhibited a mortality rate exceeding 52% (Table 3), yet they are less likely to experience ATRs due to their immunosuppressed state [60], possibly leading to under-reporting of ATRs even though they may have received many transfusions. Conversely, patients with severe trauma requiring massive transfusion protocols may be more susceptible to ATRs and mortality during trauma correction, thereby classifying them as multitransfused individuals after receiving numerous blood components. Remarkably, our analysis showed that patients experiencing haemorrhage and shock had the lowest mortality rate at 16.4%. Despite advances, transfusions remain an independent risk factor for increased major surgical and medical complications [57, 61], along with prolonged ventilatory support. Studies by Schack et al. demonstrate significantly higher mortality rates at 7, 30 and 90 days post-surgery among transfused patients compared to non-transfused ones, with age also influencing 30-day mortality [59]. Furthermore, the combination of various blood components poses an increased risk of mortality within 30 days post-surgery. Dorsey and Moritz [62] and Kamper-Jørgensen et al [63]. highlight declining survival rates over time following transfusion, underscoring the importance of cautious interpretation of these findings. Unfortunately, our study was unable to delve into these variables in depth, emphasizing the need for careful consideration when interpreting our results.

This study presents several limitations that require careful consideration. Firstly, it focused solely on multitransfused patients who experienced adverse reactions, which may result in an incomplete representation of the broader multitransfused population. For instance, an analysis of blood component data for Colombia in 2022 revealed that RBC units accounted for 58.94% of 1,456,845 transfused components, followed by platelet concentrates at 19.58% and fresh frozen plasma at 15.75% [43]. However, in this study we found that only 69 RBC units were individually administered to nine patients in the multitransfused population experiencing ATR, representing 1.3% of the total individuals studied. This discrepancy raises questions. Firstly, multitransfused patients who regularly receive erythrocyte units may not always develop adverse reactions, leading to under-reporting to SIHEVI-INS. It is crucial to note that our study could only capture data from patients who initially experienced an ATR, with subsequent selection of those who received six or more blood components. Secondly, although multitransfused patients regularly receiving RBC units may indeed experience ATR, these reactions might not always be severe and hence may not be reported to SIHEVI-INS. Moreover, significant gaps exist in our understanding of the status of these multitransfused patients, particularly regarding the presence of TTIs and their access to beneficial interventions such as iron chelation therapies for haematopoiesis improvement or hepatitis B vaccine boosters. Furthermore, uncertainty surrounds the potential transmission of infections to close relatives, given that patients themselves may be unaware of their disease status.

In conclusion, individuals in Colombia who have undergone multiple transfusions are at increased vulnerability to allergic reactions and higher probability of death, surpassing the prevalence observed in other populations. This increased mortality might be due to their initial

condition being more severe. This emphasizes the importance of providing customized medical care that is specifically designed for this group.

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M.-I.B.-F. and M.-A.G.-O. designed the study, performed the research and wrote the first draft of the manuscript, acquired and analysed the data, supervised the research and reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that 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.

ORCID

Michel-Andrés García-Otálora https://orcid.org/0000-0001-9637-8937

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ORIGINAL ARTICLE

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Management of massive haemorrhage in transfusion medicine services in the Middle East and North Africa

Arwa Z. Al-Riyami[1] | **Suha Hejres**[2] | **Sanaa Abd Elshafy**[3] | **Hind Al Humaidan**[4] | **Hanady Samaha**[5]

[1]Sultan Qaboos University Hospital, University Medical City, Muscat, Oman

[2]Department of Pathology, Blood Bank and Laboratory Medicine, King Hamad University Hospital, Al Sayh, Bahrain

[3]Department of Clinical Pathology, Faculty of Medicine, Beni Sueif University, Beni Suef, Egypt

[4]Blood Bank and Transfusion Medicine, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia

[5]Saint George Hospital UMC, Saint George University of Beirut, Beirut, Lebanon

Correspondence
Arwa Z. Al-Riyami, Department of Haematology, Sultan Qaboos University Hospital, University Medical City, P.O. Box 38, 123 Muscat, Oman.
Email: arwa@squ.edu.om

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Abstract

Background and Objectives: Massive transfusion protocols (MTPs) are critical in managing haemorrhage, yet their utilization varies. There is lack of data on the utilization of MTPs in the Middle East and North Africa (MENA) region. This study aims to assess the degree of utilization of MTPs in the region.

Materials and Methods: We conducted a survey to collect data on MTP use, inviting medical directors of transfusion services from various hospitals. Data were analysed to determine the prevalence of MTP utilization, their compositions, challenges in application and areas of future need.

Results: Eighteen respondents participated, representing 11 countries in the region. Thirteen hospitals implemented MTP, and eight included paediatrics. Eleven institutions used more than one definition of massive haemorrhage, with the most common being ≥10 red blood cell (RBC) units transfused for adults and replacement of >50% total blood volume in paediatrics. The majority of sites with MTPs utilized 1:1:1 RBCs:platelets:plasma ratio (70%). Variations were observed in the types and blood groups of components used. Two sites utilized whole blood, while six are considering it for future use. Utilization of adjunctive agents and frequency of laboratory testing varied among the sites. Challenges included the lack of medical expertise in protocol development, adherence and paediatric application. The need assessment emphasized the need for developing regional guidelines, standardized protocols and training initiatives.

Conclusion: Although several hospitals have adopted MTPs, variations exist in activation criteria, blood product ratios and monitoring. Challenges include the lack of medical expertise, protocol adherence and addressing paediatric needs. Standardizing protocols, enhancing training and paediatric application are crucial for improving massive transfusion management in the region.

Keywords
massive transfusion, plasma, platelets, red blood cells, trauma

Highlights

- There is a lack of consensus on the definition of adult and paediatric massive transfusion, content of massive transfusion packs, the use of adjunctive agents and laboratory monitoring in the Middle East and North Africa.
- There are several challenges in the implementation of massive transfusion protocols and their application in paediatric patients.
- There is call for harmonized definition, consensus protocols/guidelines and continued education for healthcare providers involved in massive haemorrhage management.

INTRODUCTION

Massive transfusion protocols (MTPs) play a crucial role in the management of major haemorrhage due to trauma, surgery, obstetrics or other emergencies. Prompt and effective administration of blood components during these emergencies can save lives. Acute traumatic coagulopathy significantly impacts the outcome of major trauma patients [1, 2]. Implementation of MTPs is associated with significant reduction in mortality [3]. A well-defined MTP, specifying quantities and ratios of red blood cells (RBCs), plasma and platelets, as well as the early use of cryoprecipitate/fibrinogen, can improve coagulopathy induced by haemorrhagic shock and enhance patient survival [2].

The development of MTPs has predominantly targeted the resuscitation of trauma patients. While massive haemorrhage is commonly defined as transfusion of 10 units of RBCs or more within 24 h [4], the definitions vary widely in the literature [5]. In a survey from the United States, most protocols administer predetermined quantities of blood components, targeting an RBC/plasma ratio of 1:1, and 68% include platelets [6]. This approach is supported by studies indicating that higher ratios of plasma and platelets in massive haemorrhage management are linked to improved outcomes in trauma patients [7, 8]. However, the ideal ratio for resuscitating trauma patients remains uncertain. In the PROPPR study, no significant differences in mortality at 24 h were detected in the 1:1:1 versus 1:1:2 (plasma: RBCs:platelets) groups of patients. However, exsanguination was significantly lower in the 1:1:1 group [7]. Moreover, different clinical scenarios, such as gastrointestinal haemorrhage and obstetric bleeding, might require tailored approaches and specific modifications to these protocols. For paediatric trauma patients, MTPs adjusted for weight-based transfusion volume have been implemented [9].

Understanding the variations in MTP utilization and the factors influencing its implementation is crucial for optimizing transfusion practices and enhancing patient care in critical situations. Despite the widespread adoption of MTPs, comprehensive research comparing their use across different medical centres is limited [10]. Most of the published literature on MTP implementation has originated from the Western world, including centres in North America, Europe and Australia [6, 7, 9–12]. There is a lack of data on the extent of MTP utilization in the Middle East.

The primary objective of this study is to explore various aspects of MTPs currently used in the hospitals in the Middle East and North Africa (MENA) and to provide a snapshot of the current management of massive transfusion in the region. Furthermore, the study aims to assess the challenges in the implementation of MTPs, as well as the obstacles preventing their application in hospitals that have not yet adopted the protocol. This survey was presented at the Arab Transfusion Forum 15 and International Society of Blood Transfusion (ISBT) highlight day meeting in Cairo, Egypt, in January 2024.

METHODS

A cross-sectional survey, designed with multiple-choice questions supplemented by open-ended and free-text responses, was conducted to explore the utilization of MTPs in various hospitals across the region (Supplementary Material). The initial survey was reviewed by the five research team members to ensure clarity, content validity, thereby ensuring it would capture the necessary information while minimizing bias. After multiple rounds of testing and editing, the electronic survey was piloted among the five members. Following the pilot phase, the survey was distributed via email to transfusion medicine directors (or designated representatives) working in different hospitals in the region.

The survey consists of four main sections: an introduction, demographics of the participants and their hospitals and details about the MTPs. This includes the number of annual activations, definitions used, indications, services/specialties utilizing it, scenarios that activate it, type of blood components and pharmaceutical agents used, blood product ratio, as well as strategies for activation, provision and laboratory monitoring of patients. In addition, information on how hospitals without the protocol manage patients with massive haemorrhage was also collected. Question skip logic was applied as appropriate.

An online survey was designed using Google Forms in English language. We invited 40 transfusion medicine medical directors (or their designates) working in different hospitals in the region to participate in this survey. Invitees were selected from the membership of the Arab Transfusion Forum and from their contacts. The survey link was

sent to the participants by email on 1 October 2023, with three reminders on 8th, 17th and 30th of the same month. Responses were collected up to 30 November 2023. Participation in this survey was voluntary, and consent by completion of the survey was implied. Participants were offered acknowledgment but were given the option to remain anonymous if they preferred not to disclose their details. Participants were allowed to include one more participants from their centre if needed (e.g., from other specialties). Descriptive statistics were used, and reported variables were expressed in numbers and percentages. Categorical variables were presented as proportions. Data were summarized in tables and pie charts as required. Additionally, we summarized the challenges in implementing MTPs, as well as the reasons for preventing their application in centres without such protocols.

This study received ethical approval from the Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University, Oman (REF. NO. SQU-EC/227\2023 MREC # 3120).

RESULTS

Eighteen out of 40 participants responded to the survey (response rate 46%). This included four hospitals from Saudi Arabia, three from Oman, two from Yemen and Lebanon and one each from the United Arab Emirates, Libya, Turkey, Bahrain, Tunisia, Egypt and Qatar (Figure 1, Table S1). Three of the authors contributed to the survey by representing their hospitals. The participants work in hospitals of different sizes, with more than 50% having more than 500 beds and transfusing more than 5000 RBC units per year (Figure 1, Table 1).

Most hospitals treat patients of all age groups, including trauma patients. Sixteen out the surveyed hospitals offer obstetrics and surgical care, while all hospitals have emergency and intensive care units. Furthermore, 16 hospitals have an onsite blood bank that collects blood from blood donors. Two-thirds of these hospitals rely on different types of donations such as voluntary, family replacement and directed donations, while 22% rely solely on voluntary donations. Eleven hospitals have access to other sources of blood, including national blood banks, private and governmental blood banks and the Red Cross. All hospitals have access to all blood components.

Thirteen hospitals reported having an MTP (72%, Table 2). The protocol is commonly owned by the blood bank or the hospital transfusion committee. Notably, two hospitals had been using the protocol for more than 10 years. The frequency of protocol activation per year is variable between the hospitals. Most hospitals have a general protocol for all indications of massive haemorrhage ($n = 10$). Three hospitals have one protocol that addresses each indication specifically.

Eleven hospitals use more than one definition of massive haemorrhage (range 2–5 definitions by site), with the commonest definition for adults being transfusion of 10 or more RBCs units in 24 h and

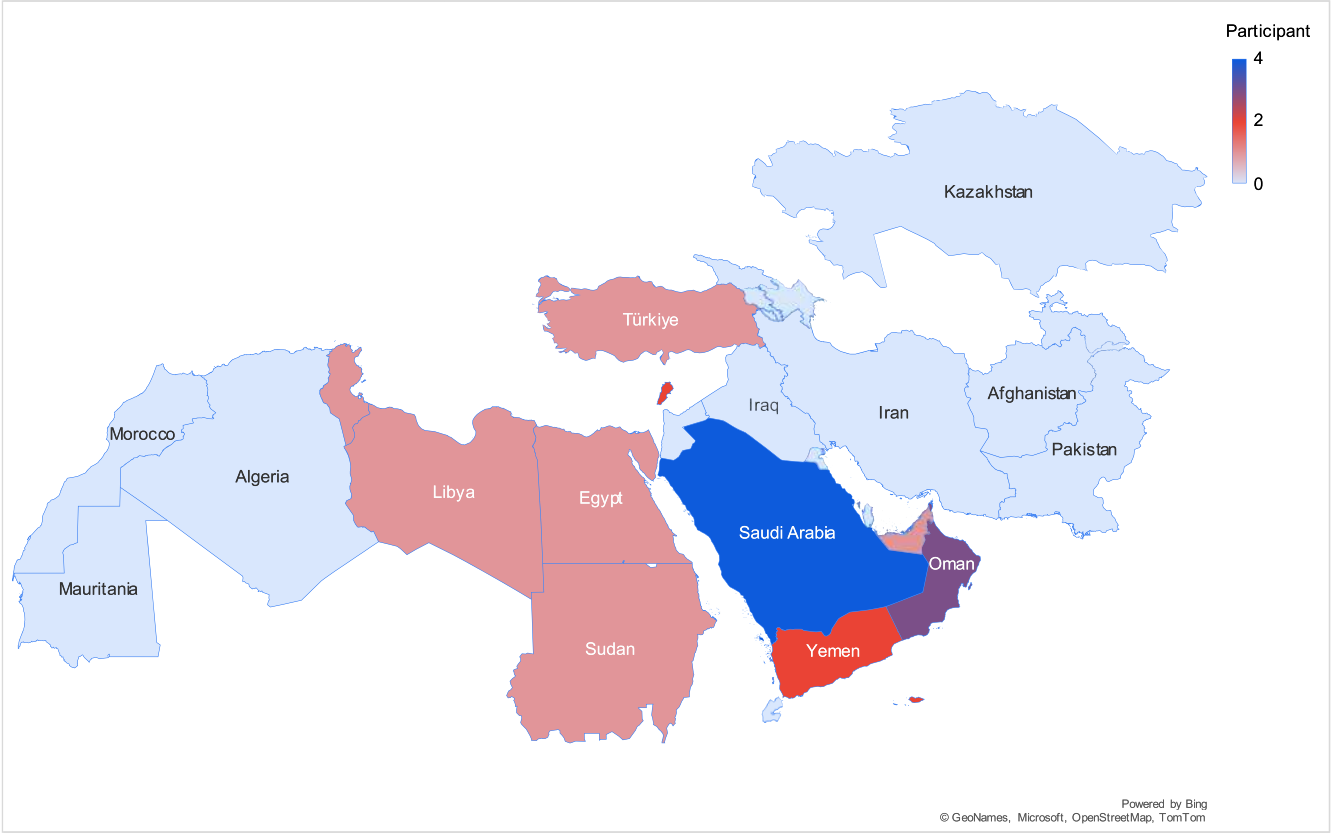

FIGURE 1 Participating countries in the survey.

TABLE 1 Demographics of institutions ($n = 18$).

Variable	N (%)
Hospital size (no. of beds)	
<200	2 (11.1)
200–499	6 (33.3)
500–1000	7 (38.9)
>1000	3 (16.7)
Age group of patients treated	
All age groups	15 (83.3)
Adults only	2 (11.1)
Paediatrics and neonates only	1 (5.6)
Number of RBC units issued per year	
<1000	1 (5.6)
1000–4999	5 (27.8)
5000–9999	3 (16.7)
10,000–49,999	5 (27.8)
>50,000	4 (22.2)

Abbreviation: RBC, red blood cell.

TABLE 2 Massive transfusion protocols ($n = 13$).

Variable	N (%)
Owner	
Blood bank	6 (46.2)
Transfusion committee	5 (38.5)
Emergency department	1 (7.7)
Anaesthesia	1 (7.7)
Number of years the protocol has been in use	
2–4	7 (53.9)
5–10	4 (30.8)
>10	2 (15.4)
Frequency of protocol activation per year	
<10 times	6 (46.2)
10–29 times	4 (30.8)
30–49 times	1 (7.7)
50–100 times	2 (15.4)
Specialities activating the protocol (multi-select)	
Anaesthesia	12 (92.3)
Emergency	12 (92.3)
Trauma team	10 (76.9)
Cardiac surgery	8 (61.5)
Internal medicine	4 (30.8)
Haematology	2 (15.4)
Others	7 (53.9)
Clinical scenarios of protocol activation	
Intraoperative bleeding during major surgery	13 (100)
Obstetric emergencies (e.g., postpartum haemorrhage)	11 (84.6)
Blunt trauma with significant blood loss (e.g., car accidents)	10 (76.9)
Penetrating trauma (e.g., gun shots)	9 (69.2)
Others[a]	4 (30.8)
Challenges in implementation	
Proper application and adherence to the protocol	8 (61.5)
Inconsistent deactivation of the protocol	8 (61.5)
Activation for un-indicated cases	6 (46.2)
Wastage of blood components that were not used	4 (30.8)
Implementation in paediatrics	2 (15.4)
Others[b]	3 (23.1)

[a]Gastrointestinal bleeding, bleeding while on extracorporeal membrane oxygenation (ECMO).
[b]Communication between staff and stakeholders, deviation from the protocol.

replacement of ≥50% of total blood volume (TBV) in 3 h (Table 3). Other definitions used are replacement of 50% TBV or more in 4 h, transfusion of 4 RBC units within 1 h and anticipated need for more and blood loss at a rate of 150 mL/min or more. Some hospitals utilize clinical definitions and risk assessment tool scores such as the Shock Index (SI), Assessment of Blood Consumption (ABC) score and Revised Assessment of Bleeding and Transfusion (RABT). Eight hospitals include paediatric patients in their MTPs, and three hospitals use more than one definition, with the commonest being the replacement of over 50% of TBV in 3 h (Table 3). Other common definitions used are bleeding that exceed 10% TBV/min ($n = 3$), blood loss of 40 mL/kg in 24 h ($n = 3$) and blood loss of 80 mL/kg in 24 h. Other less common definitions are blood loss of 40 mL/kg in 3 h or 80 mL/kg in 24 h and a bleeding rate of 2–3 mL/kg/min. One site uses clinical definitions that rely on haemodynamic changes compatible with hypovolemia accompanying evidence or suspicion of serious haemorrhage.

The MTPs are typically activated by anaesthesia, emergency and trauma teams, often for intraoperative bleeding, obstetric emergencies and blunt and penetrating trauma. Most hospitals employ phone notification for protocol activation ($n = 12$); while three use a paging system, one uses an electronic system and one uses overhead announcement. The majority of sites with MTPs employ a 1:1:1 RBCs:platelets:plasma ratio of blood components (9; 70%), while two utilize a 2:1:1 ratio (15%).

The types of blood components and corresponding blood groups in the packs vary significantly across hospitals (Figure 2), with all hospitals including RBCs and plasma in all the packs. For the first pack, hospitals use 4 units of either group O Rh negative (three sites), or a mix of O Rh positive and O Rh negative RBCs (three sites). Meanwhile, two centres use either group-specific or a combination of group O Rh negative and group-specific RBCs. The majority of the sites shift to 4 units group-specific RBCs in the second and third packs. With regard to platelets, all but one site include aphaeresis platelets, pooled platelets or whole-blood-derived platelet concentrates in the three packs. The number of whole-blood-derived platelet concentrates per pack ranges from 4 to 6 units. One site does not include platelets in first and second pack, and may include platelets in the third pack based on the thromboelastography results and the clinical condition

of the patient. As for plasma, most sites include 4 units of group AB, group A or group-specific plasma in the first pack (two sites each), with increasing use of group-specific plasma in the second (three sites) and third pack (five sites). Eight sites indicated that the protocol used for managing obstetric bleeding differ from that used for other causes of massive haemorrhage, including earlier provision of cryoprecipitate or fibrinogen, aiming for a higher fibrinogen level and replacing plasma with cryoprecipitate if fibrinogen level was low. Two hospitals utilize whole blood in their protocol, while six are considering implementation in the future.

Ten sites utilize tranexamic acid as part of the massive transfusion activation, four use fibrinogen concentrate, four use rFVIIa and one uses prothrombin complex concentrate (PCC). Two hospitals utilize satellite fridges with un-crossmatched group O RBCs in the emergency department, operating theatre, intensive care units and labour ward for immediate provision in cases of massive haemorrhage. None of the sites maintains an inventory of pre-thawed plasma, although one keeps a stock of liquid plasma for up to 5 days for massive haemorrhage activations.

Most of the sites employ multiple mechanisms to sustain sufficient inventory of blood components for MTPs. This includes regularly assessing and monitoring blood product levels ($n = 9$), allocating a stock of blood units for emergency use ($n = 8$), collaborating with neighbouring blood banks for emergency blood supply ($n = 7$) and maintaining a call list of walk-in donors in emergencies ($n = 7$). Patient monitoring is typically performed through clinical assessment of bleeding and laboratory testing (Figure 3). Testing is commonly performed using coagulation profile; rothrombin time (PT)/activated partial thromboplastin time (APTT) and international normalized ratio (INR), while thromboelastography or rotational thromboelastometry is used in only two sites. The frequency of laboratory testing varies between every 15 min to every 2 h. Adherence to the protocol is supported via the blood transfusion committee ($n = 9$), debriefing after every massive transfusion ($n = 4$) and regular multidisciplinary meetings ($n = 1$).

TABLE 3 Definitions of massive transfusion (multi-select).

Variable	*N* (%)
Adult patients ($n = 13$)	
≥10 RBC units in 24 h	10 (76.9)
≥5 RBC units in 4 h	3 (23.1)
Replacement of ≥50% TBV in 3 h	8 (61.5)
≥3 RBC units in 1 h	4 (30.8)
Excessive bleeding regardless of volume	6 (46.2)
Others	4 (30.8)
Paediatrics patients ($n = 8$)	
Replacement of >50% TBV in 3 h	6 (75)
RBC transfusion exceeding 10% TBV	3 (37.5)
>40 mL/kg in 24 h	3 (37.5)
Others	3 (37.5)

Abbreviations: RBC, red blood cells; TBV, total blood volume.

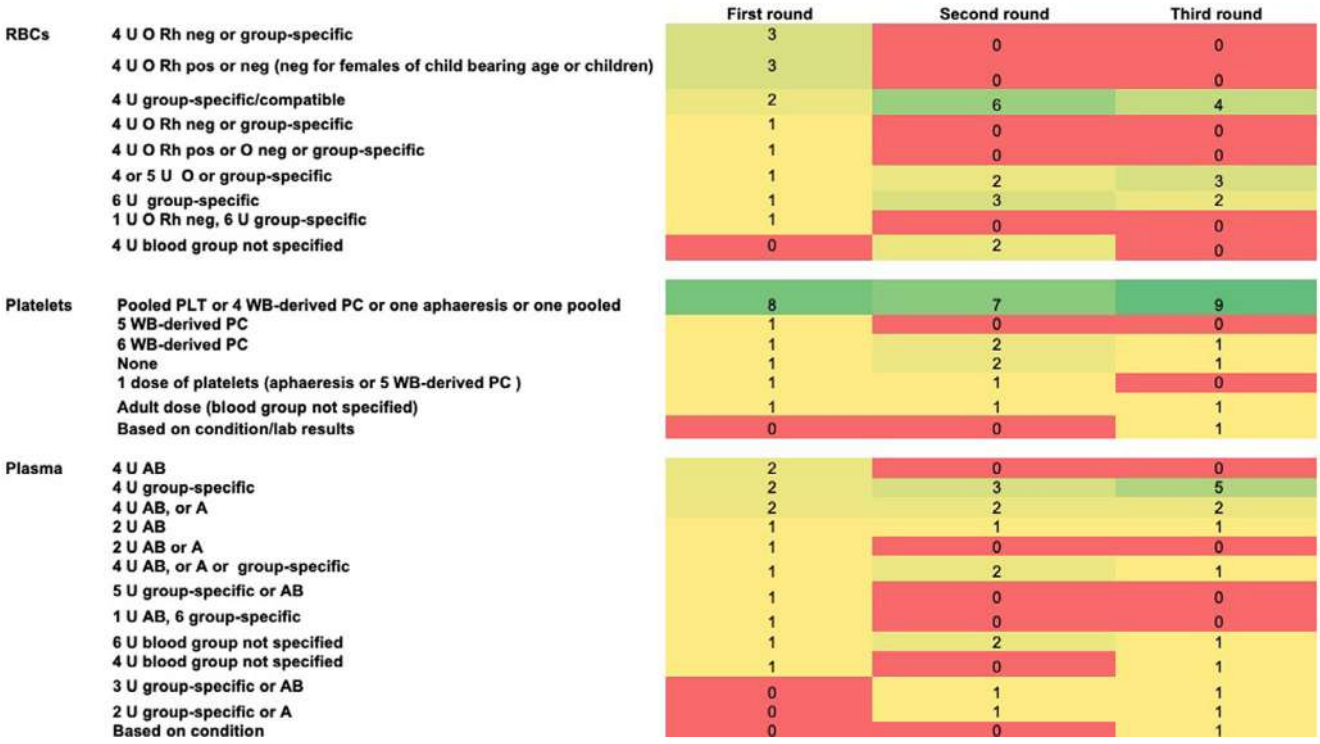

FIGURE 2 A heatmap of the composition of the packs used in massive transfusion protocols. Numbers reflect proportion of hospitals using the indicated blood components in the massive transfusion packs ($n = 13$). PC, platelet concentrates; PLT, platelets; RBCs, red blood cells; U, units; WB, whole blood.

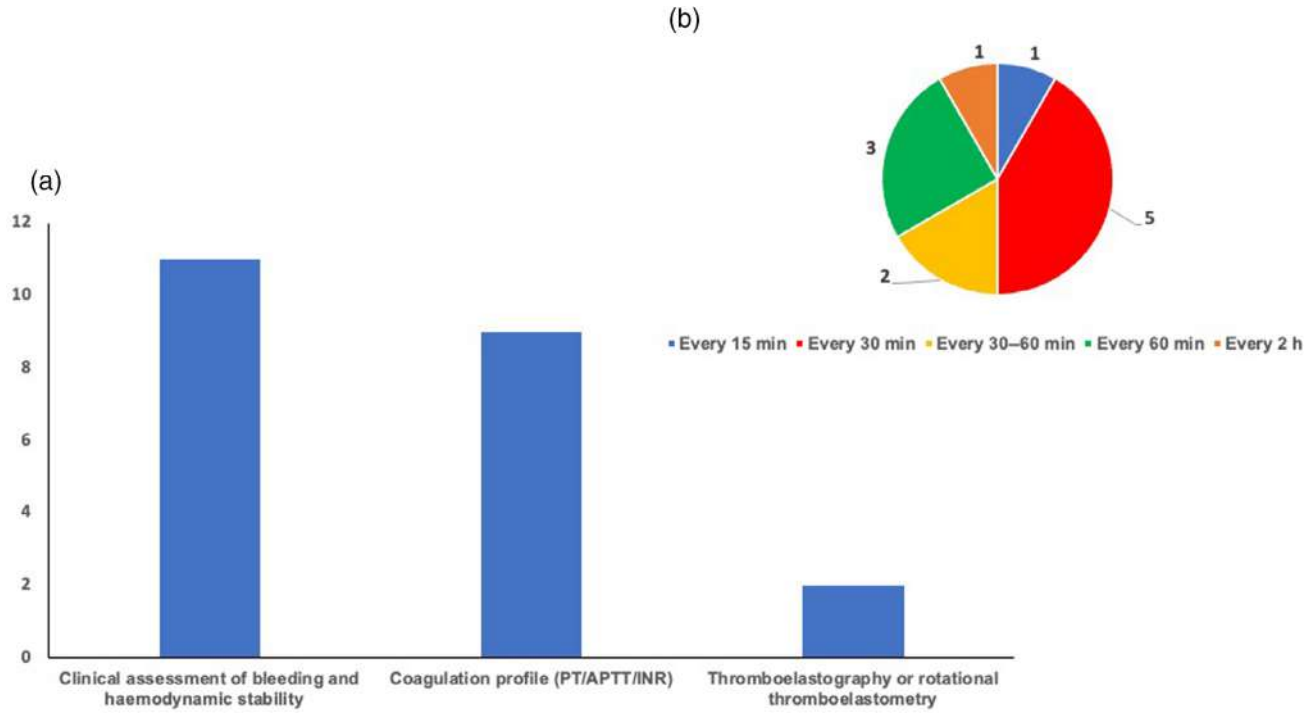

FIGURE 3 Patient monitoring in massive transfusion protocols. (a) Methodology used for assessment. (b) Frequency of laboratory testing. APTT, activated partial thromboplastin time; INR, international normalised ratio; PT, prothrombin time.

TABLE 4 Needs for the Middle East and North Africa region.

Category	Needs
Protocol development	Regional guidelines Standardized protocols Customizable protocol templates Data from civilian trauma
Application	Addressing paediatric transfusion Free pocket management software
Training	Sharing of experiences and best solutions among hospitals in the region Training courses for all stake holders (physicians, nurses, blood bank staff, transporters/runners and others) including use of simulation Conferences

Regarding education and training, most sites utilize lectures or presentations ($n = 12$), while three utilize simulation-based training.

Several challenges were reported in implementing MTPs (Table 2), including adherence, application in paediatric patients, communication between staff and stakeholders and inappropriate dosing of cryoprecipitate. Five sites do not utilize MTPs for reasons such as clinician and transfusion service preference for ordering individual components and the lack of medical expertise to develop the protocol. In these hospitals, individual component transfusion, RBCs or whole blood is typically used for resuscitation purposes.

The survey respondents highlighted the necessity for development of regional guidelines and standardized protocols, encompassing protocols for paediatric patients, as well as training and continuous education of healthcare professionals, including transporters/runners. They also emphasized the need for sharing experiences among hospitals (Table 4). Seventeen participants indicated the need for a regional conference on massive transfusion management.

DISCUSSION

Our survey provides insights into MTP implementation in the MENA region, given the scarcity of data [12]. It illuminates several key areas, including clinical practices for defining and managing massive transfusion, blood product ratios, patient monitoring, challenges encountered and potential areas for improvement.

Most hospitals surveyed manage their MTPs by the blood bank or the transfusion committee, underscoring the importance of multidisciplinary teams in establishing procedures to ensure safe and efficient protocol activation, patient resuscitation and performance improvement [13]. This study highlights variability in the duration of protocol use and the frequency of activation. A notable finding is the variability in the indications for activating MTPs, including operative, obstructive, blunt and penetrating trauma. This differs from Western literature, which predominantly reports penetrating trauma in massive haemorrhage in civilians [14]. The Middle Eastern countries exhibit the highest rates of mortality from road injuries [15], highlighting the need for studies to assess optimal treatment methods for these injuries, including pre-hospital resuscitation and the use of whole blood.

Challenges in implementing MTPs, especially for paediatric patients, were noted, along with variability in definitions used in both

adults and paediatric patients as reported in other literature [5, 6, 16, 17]. A systematic review identified 15 different definitions of massive transfusion in adult patients, the commonest being the transfusion of 10 RBC units within 24 h, as noted in our study [5]. For paediatrics, studies reported reliance on crude definitions based on the volume of blood product transfused over specified periods, such as 4, 12 and 24 h [18]. The inconsistency in defining massive bleeding could impact the efficacy and promptness of clinical responses [19] Some centres use validated clinical scores such as SI, which relies on clinical assessment, and the ABC score, which includes ultrasound findings [20]. The RABT score was reported to be more sensitive than the other two scores [21].

There was variation in the composition of the MTPs packs, including the type, blood group and number of blood components in the second and third packs. This aligns with other studies highlighting variability in the implementation and component ratio used in the MTPs internationally [12] including the United States [6, 16], China [22], Australia and New Zealand [23]. Using cryoprecipitate or fibrinogen to target higher fibrinogen levels is recommended in managing obstetric haemorrhage [24]. However, the use of fibrinogen concentrate in the surveyed hospitals in our study is limited, likely due to its cost compared to European countries, where it is less expensive and more easily administered [24]. The use of tranexamic acid also varied, similar to the findings in recent international studies [12].

Several survey respondents mentioned barriers to MTP application, such as a preference for individualized transfusion strategies and a lack of expertise or collaboration among different stakeholders. Some expressed the need for regional guidelines and standardized MTPs. However, this approach introduces additional challenges in ensuring utility and monitoring their effectiveness. Regular evaluation of MTP use and efficacy is necessary to ensure adherence and assess its impact on patient outcomes [25, 26]. Quality indicators for how well a MTP performs in a hospital may include the composition of MTP blood component types and ratios, use of adjunctive agents and laboratory monitoring, resource allocation and blood component wastage [26].

This study has several strengths, such as a notable response rate across a wide and diverse region, indicating significant engagement and interest. The survey was designed with clear objectives to address gaps in the literature and ensured the relevance of the data collected. However, there are limitations. The complex structure of the blood bank and transfusion services in the region, as well as the lack of a database of medical directors working in different hospitals in the region, limited the reach to study participants. It was particularly difficult to reach out to medical directors in countries with active humanitarian emergencies. Additionally, we did not assess whether the hospitals audited MTP activations and outcomes, or the impact of MTP implementation on the effectiveness of resuscitation, such as the time from MTP activation to blood arrival at the patient bedside, or on outcomes such as hospital stay length and mortality [26]. Finally, the availability of resources (such as cell salvage) was not assessed.

In conclusion, this survey provided insights into the current practices and challenges of MTPs use in hospitals across the MENA region. It underlines the widespread adoption of MTPs, with notable variability in the definition and blood component ratios, and the underutilization of tranexamic acid, reflecting the urgent need for standardized guidelines and practices. Inconsistencies and resource limitations in some hospitals suggest considerable room for improvement. The study highlights the pivotal role of the blood bank and hospital transfusion committee, as well as the importance of educational initiatives to ensure adherence to protocols, inform the improvement of transfusion practices and optimize patient outcomes [23, 27]. Moreover, it emphasizes the need to implement quality improvement initiatives to assess protocol adherence and track patient outcomes. The findings emphasize the necessity for regional cooperation, standardized practices and ongoing education to enhance MTP efficacy. Addressing these challenges and fostering a culture of collaboration and continuous improvement are essential steps forward.

Further efforts should focus on developing tailored, evidence-based protocols that can be effectively implemented across the region, ensuring timely and appropriate care of both adult and paediatric patients during massive haemorrhagic events. Initiatives such as conferences and training courses could help foster knowledge exchange and continuous improvement in massive transfusion practices across hospitals in the region, as advocated by others [19, 22, 28]. We also advocate for addressing resource constraints in some countries in the region to ensure equitable care delivery to all patients.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

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

ORCID

Arwa Z. Al-Riyami https://orcid.org/0000-0001-8649-0650

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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 retrospective analysis of postpartum red blood cell transfusions at a tertiary care obstetric centre

Ariane Lasry[1] | Samuel Adant[2] | Karen Farag[3] | Celya Tidafi[3] | Cassandra Wareham[3] | Mandy Malick[4] | Marie-Ève Roy-Lacroix[5] | Pierre-Aurèle Morin[2] | Nadine Sauvé[6]

[1]Department of Obstetrics and Gynecology, University of Sherbrooke, Sherbrooke, Canada

[2]Department of Medicine, Hematology-Oncology Division, University of Sherbrooke, Sherbrooke, Canada

[3]Faculty of Medicine, University of Sherbrooke, Sherbrooke, Canada

[4]Department of Medicine, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Canada

[5]Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Division, University of Sherbrooke, Sherbrooke, Canada

[6]Department of Medicine, Obstetrical and Internal Medicine Division, University of Sherbrooke, Sherbrooke, Canada

Correspondence
Nadine Sauvé, Department of Medicine, Obstetrical and Internal Medicine Division, University of Sherbrooke, 3001 12e Avenue Nord, Sherbrooke, QC J1H 5H3, Canada.
Email: nadine.sauve@usherbrooke.ca

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Abstract

Background and Objectives: Postpartum anaemia is a prevalent health problem. We aimed to determine the compliance rate for red blood cell (RBC) transfusion indication among postpartum women in a single tertiary care centre in Quebec, Canada.

Materials and Methods: Retrospective cohort study including all women ≥6 h postpartum who received ≥1 RBC transfusion during their delivery hospitalization between January 2005 and February 2022. We determined our centre's compliance rate by indication as compared to current society guidelines, all published after 2015 (Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis [NATA], Royal College of Obstetricians and Gynaecologists [RCOG], American College of Obstetricians and Gynecologists [ACOG]). We then explored predictors of guideline non-compliance and described transfusion practices in our centre.

Results: A total of 171 women were included. Our centre's compliance rate was 79.5% (95% confidence interval [CI] 72.7–84.8). Predictors of guideline non-compliance were maternal medical comorbidity or abnormal placentation, both limited by large CIs (odds ratio [OR] 2.26, CI 1.02–4.94, $p = 0.04$; OR 4.00, CI 1.31–12.06, $p = 0.01$, respectively). Postpartum haemorrhage was diagnosed among 68% of the cohort, mostly due to uterine atony (73.3%). Mean baseline and nadir haemoglobin were 111 g/L (±18) and 62 g/L (±7.7), respectively. Multiple unit initial transfusion was found in a majority of patients (63.7%). Iron therapy was administered to 51.5% of women in-hospital and 81.9% received an oral iron prescription at discharge. There were no differences in primary or secondary outcomes subsequent to relevant guideline publication.

Conclusion: Our centre's compliance rate for RBC transfusion indication meets current practice guidelines. Areas for improvement include single-unit initial transfusion protocols and adjuvant iron treatment. Antenatal optimization of haemoglobin and ferritin stores may limit postpartum transfusions.

Keywords
blood transfusion, postpartum anaemia, postpartum haemorrhage

Highlights

- The postpartum red blood cell (RBC) transfusion compliance rate in our centre approaches 80%, meeting current practice benchmarks.
- The majority of postpartum patients received multiple initial-unit RBC transfusions, while only half were treated with iron therapy in-hospital.
- Antenatal optimization of haemoglobin and ferritin stores may limit postpartum transfusions.

INTRODUCTION

In order to improve patient outcomes, patient blood management (PBM) is considered as standard of care. While the focus of PBM programmes in many institutions, including our own, is often on surgical patients, other populations may benefit from the application of these principles in their management, including obstetrical patients. Postpartum anaemia is a well-recognized health problem in the developed world, with an estimated prevalence as high as 50% in the 48 h following delivery [1]. Blood transfusions given during the postpartum period are often found to be inappropriate in retrospective audits [2–4]. Barring hemodynamic instability or active bleeding, liberal transfusion practices may potentially increase the risk of cardiovascular and thromboembolic disease without associated clinical benefit, as well as increase the risk of isoimmunization which may impact future pregnancies [5–7]. Across various clinical settings mostly outside of pregnancy, a recent Cochrane review of 48 trials similarly demonstrated that restrictive transfusion strategies limited to a haemoglobin of 70–80 g/L have no significant effect on 30-day mortality, overall mortality or acute morbidity [8].

This context prompted a 2017 Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) consensus statement on PBM in obstetrics [9]. The NATA guideline recommends a haemoglobin transfusion threshold of 60 g/L in haemodynamically stable and asymptomatic postpartum women in the absence of bleeding. At the time of literature review, available clinical guidelines published by obstetric societies on the management of acute postpartum anaemia dated to 2015 and 2017 by the Royal College of Obstetricians and Gynaecologists (RCOG) and the American College of Obstetricians and Gynecologists (ACOG), respectively [10, 11]. In contrast to NATA, both societies recommend a postpartum haemoglobin threshold of 70 g/L to consider elective transfusion.

Herein, we aimed to conduct a single-centre audit of all red blood cell (RBC) transfusions administered outside of the immediate bleeding setting to postpartum women hospitalized on our tertiary care maternity ward. Our primary objective was to determine our centre's compliance with society guidelines for transfusion indication. Our secondary objectives were to determine predictors of guideline non-compliance and to describe transfusion-related practices.

MATERIALS AND METHODS

We conducted a single-centre retrospective chart review of all RBC transfusions administered ≥6 h postpartum on the maternity ward of the CIUSSS de l'Estrie—Centre Hospitalier Universitaire de Sherbrooke (CHUS)—Hôpital Fleurimont. Our centre performs approximately 3000 deliveries per year, including high-risk obstetrics with a maternal–foetal medicine unit, an obstetric medicine consultation service and a neonatology unit receiving preterm babies as of 23 weeks. All RBC transfusions administered to postpartum women between 1 January 2005 and 1 February 2022 were identified using TraceLine (MAK-SYSTEM, Paris, France), the information database from the local blood bank. Eligibility was then determined through individual chart review. Women were included if they received ≥1 RBC transfusion during their initial postpartum hospitalization, regardless of delivery location, and delivered at a gestational age (GA) ≥ 23 weeks. Exclusion criteria were RBC transfusion received uniquely <6 h postpartum, as this was considered immediate postpartum haemorrhage management, and patients with a diagnosis of beta thalassemia major or sickle cell anaemia, who have unique transfusion requirements. In the absence of institutional guidelines, compliance was evaluated based on the previously mentioned society guidelines; an RBC transfusion indication was considered compliant if any of the following criteria were met: active bleeding with ongoing hemodynamic instability (systolic blood pressure <90 or heart rate >120), haemoglobin <60 g/L or haemoglobin between 61 and 70 g/L and significant symptomatic anaemia (asthenia, dizziness, dyspnoea precluding mobilization) or an underlying medical condition requiring a higher transfusion threshold (complex cardiovascular or pulmonary conditions). Study data were collected and managed using Microsoft Excel 2022. This study was approved by the ethics board of the CIUSSS de l'Estrie—CHUS (#2023-4697).

Statistical analysis

Compliance is described using frequencies (percentages) and 95% confidence intervals (CIs) according to Wilson method. Covariate analysis was then conducted using univariate logistic regression analysis to determine predictors associated with guideline non-compliance. Variables included in the analysis were primiparity, multiple gestation,

medical and pregnancy-related comorbidities, delivery type, chorioamnionitis, retained placenta, past history of postpartum haemorrhage, diagnosis of postpartum haemorrhage, blood loss >1500 mL, minimal haemoglobin level and treatment of postpartum haemorrhage with one of carboprost tromethamine, ergometrine or surgical management. Variables were chosen based on a combination of available literature and author consensus. Significant predictors ($p \leq 0.1$) were then included in the multivariate logistic regression. Results are presented as odds ratios (ORs) and 95% CI. Results were then stratified by the year 2015 (before and after or including), to evaluate if a change in practice could be found in relation to guideline publications. Significance level was set at $p < 0.05$. Description of transfusion practices is presented using means (standard deviations) or medians [interquartile ranges] according to distribution. Categorical variables are described using frequencies and percentages. Missing data are only reported. Analysis was performed using SPSS v.28.

RESULTS

There were 44,379 deliveries and a total of 280 patients who received a postpartum RBC transfusion during the study period (Figure 1). After chart review, 171 patients met inclusion criteria for receiving one or more RBC transfusions ≥6 h postpartum. Demographics are presented in Table S1. The majority (65.5%) of patients were primiparas, with a mean GA of 39.2 weeks. Two pregnancies were multiple gestations (1.2%). Mode of delivery was spontaneous vaginal (38.6%), urgent caesarean (25.7%), instrumented vaginal (20.5%) and elective caesarean (15.2%). Among our cohort, up to 14% had a hypertensive disorder of pregnancy, 10% gestational diabetes and 9% an abnormal placentation. The median estimated blood loss was 1000 mL. A diagnosis of postpartum haemorrhage was noted in 68% of the cohort, mostly due to uterine atony (73.3%). Mean baseline haemoglobin was 111 g/L and nadir postpartum haemoglobin 61 g/L (Table 1). Indications for RBC transfusion were haemoglobin <60 g/L (40.9%), symptomatic anaemia (38.6%), active bleeding with hemodynamic instability (2.3%) and none specified (16.4%). Obstetricians were most responsible for ordering transfusions (73.7%). Mean time to transfusion was 29 h postpartum. Most patients (63.7%) received greater than one unit of RBC initially and half received additional treatment with oral or parenteral iron. Among patients who received more than one unit of RBC transfusion initially, most (89.9%) were not re-evaluated between units. Six percent of our cohort experienced complications during their delivery hospitalization, with urinary tract infections being the most prevalent. There were no transfusion-related complications documented among our cohort.

Guideline compliance in our centre was 79.5% (CI 72.7–84.8). In the univariate analysis (Table 2), primiparity trended towards an odds of adequate guideline compliance, but this was not statistically significant (OR 2.11, CI 0.99–4.52, $p = 0.05$). Having a medical comorbidity or abnormal placentation significantly increased the odds of poor guideline compliance with large CIs (OR 2.26, CI 1.02–4.94, $p = 0.04$; OR 4.00, CI 1.31–12.06, $p = 0.01$, respectively). Specifically, asthma was associated with increased odds of poor guideline compliance (OR 5.42, CI 1.68–18.04, $p = 0.005$). None of the variables explored in the univariate analysis were retained for multivariate analysis. Primary and secondary outcomes were then stratified by before or after and including the year 2015 (Table S2). Guideline compliance

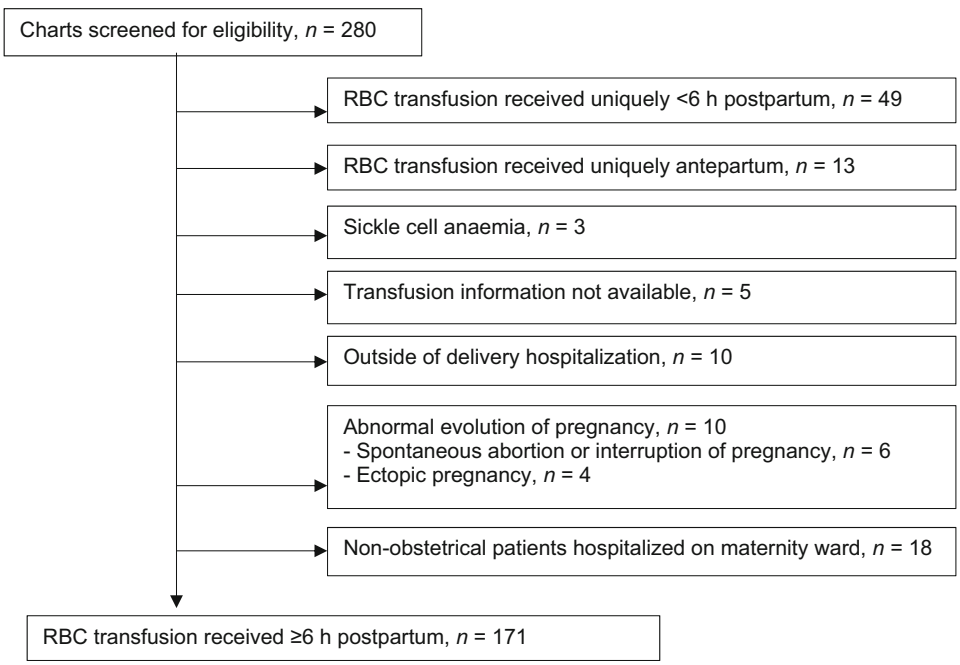

FIGURE 1 Flow diagram for patient inclusion. RBC, red blood cell.

TABLE 1 Transfusion characteristics.

Transfusion characteristics	Total ($N = 171$)
Transfusion indication	
Haemoglobin <60 g/L	70 (40.9%)
Symptomatic anaemia	66 (38.6%)
Haemodynamic instability	4 (2.3%)
Medical condition	3 (1.8%)
Not specified	28 (16.4%)
Ordering physician	
Obstetrician	123 (71.9%)
General practitioner (family MD)	40 (23.4%)
Anaesthesiologist	2 (1.2%)
Other (ICU, haematologist, unknown)	6 (3.5%)
Time to transfusion, hours	29.0 [20.0–46.3]
Haemoglobin at admission, g/L	111 (±18)
First postpartum haemoglobin, g/L	81 (±17)
Minimal postpartum haemoglobin, g/L	61 (±7.3)
Haemoglobin prior to transfusion, g/L	62 (±7.7)
Haemoglobin delta (admission to first postpartum)	30 [18–43]
Haemoglobin at discharge, g/L	82 (±12.1)
International normalized ratio	1.15 (±0.23)
Partial thromboplastin time, seconds	28 (±7.62)
Fibrinogen, g/L	4.08 [2.88–4.98]
Consent to transfusion documented	144/149 (96.6%)
Number of units transfused initially[a]	
1	62 (36.3%)
>1	109 (63.7%)
Re-evaluation between units if multiple initial-unit transfusion	109
Yes	11/109 (10.1%)
No	98/109 (89.9%)
Mean number of units transfused per patient	1.93 (±0.69)
Alternate treatment of anaemia in-hospital	88 (51.5%)
Intravenou iron	63/88 (71.6%)
Oral iron	25/88 (28.4%)
Iron prescribed at discharge	140 (81.9%)
Complications following transfusion	10 (5.8%)
Urinary infection	5/10 (50%)
DVT or PE	2/10 (20%)
SVT	1/10 (10%)
Wound infection	1/10 (10%)
Endometritis	1/10 (10%)
Transfusion-related reaction	0/10 (0%)
Readmission within 6 weeks	3 (1.8%)

Note: Results are expressed as counts with frequencies (%), means with standard deviation (±SD) or medians with interquartile range [IQR].
Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; SVT, superficial venous thrombosis.
[a]Before 2015: 1 unit = 29 (34.1%), >1 unit = 56 (65.9%). After 2015: 1 unit = 33 (38.4%), >1 unit = 53 (61.6%).

TABLE 2 Univariate regression analysis according to overall guideline compliance.[a]

Variable	Odds ratio	95% CI	*p*-value
Primiparity	2.11	0.99–4.52	0.05
Gravidity	1.15	0.93–1.43	0.18
Blood loss >1500 mL	1.26	0.48–3.03	0.61
Diagnosis of PPH	1.02	0.46–2.40	0.97
History of PPH	2.67	0.34–16.72	0.30
Medical comorbidities			
Hypertension	1.58	0.22–7.73	0.59
Diabetes	1.30	0.06–10.55	0.82
Asthma	5.42	1.68–18.04	0.01
Thyroid	0.69	0.10–2.73	0.64
Any one of above	2.26	1.02–4.94	0.04
Obstetrical comorbidities			
Gestational hypertension	1.03	0.32–2.80	0.96
Preeclampsia	0.33	0.05–1.21	0.15
HELLP	1.12	0.16–4.88	0.89
Gestational diabetes	0.82	0.18–2.69	0.76
Any one of above	1.76	0.83–3.76	0.14
Abnormal placentation	4.00	1.31–12.06	0.01
Placental abruption	2.92	0.92–8.76	0.06
Mode of delivery			
Instrumental vaginal	1.25	0.42–3.53	0.68
Elective caesarean	2.22	0.76–6.38	0.14
Urgent caesarean	1.29	0.47–3.42	0.61
Chorioamnionitis	0.21	0.01–1.08	0.13
Retained placenta	0.82	0.31–1.98	0.68
Treatment of PPH			
Carboprost tromethamine	0.55	0.21–1.43	0.22
Ergometrine	0.67	0.10–2.72	0.62
Surgical	0.50	0.16–1.30	0.19
Any one of above	0.59	0.23–1.56	0.27

Abbreviations: CI, confidence interval; HELLP, haemolysis, elevated liver enzymes and low platelet count; PPH, postpartum haemorrhage.
[a]Guideline compliance overall: 79.5% (CI 72.7–84.8); guideline compliance before 2015: 80.0% (CI 70.2–87.1); guideline compliance after and including 2015: 79.1% (CI 69.3–86.3).

rates were similar in both groups (80.0% CI 70.2–87.1 and 79.1% CI 69.3–86.3, respectively). Multiple unit initial transfusion rates were also comparable between groups (65.8% multiple units before 2015; 61.6% multiple units after or including 2015).

DISCUSSION

Compliance to guideline recommendations for RBC transfusion indication approaches 80% among patients ≥6 h postpartum in our centre. This compliance rate meets the Using Blood Wisely benchmark, aimed

to limit inappropriate transfusion practices in Canada [12]. This rate is also superior to those reported by international retrospective audits of postpartum blood transfusions, ranging between 53% and 69% [2–4].

Although our results seem satisfying, 16% of postpartum transfusions notably did not specify an indication. In addition, 64% of patients received an initial transfusion of multiple RBC units and only a minority were reassessed between each unit. Single-unit transfusion protocols promote fewer number of absolute unit transfusions without significant impact on patient morbidity in the obstetric population [9, 13]. Beyond limiting the risk of all transfusion-related complications, possible isoimmunization remains a consequential concern, particularly in the context of 65% of our cohort being primiparous.

We also noted that nearly 30% of patients receiving an RBC transfusion did not have a documented diagnosis of postpartum haemorrhage. Median blood loss at delivery was 1 L as estimated by the delivering physician. One explanation is inaccurate blood loss estimation, which is historically imprecise both for vaginal and caesarean deliveries [14]. Another possible explanation is unrecognized antenatal anaemia, defined as haemoglobin <110 g/L. A population-based study in British Columbia revealed rates of third trimester antenatal anaemia at 12.8%, associated with higher rates of postpartum anaemia and blood transfusions [15]. Even without overt anaemia in a majority of patients, iron deficiency was found in 91% of an outpatient obstetric population at a tertiary care centre [16]. Altogether, this highlights the need for pre-delivery haemoglobin and ideally ferritin optimization as recommended by current practice guidelines [17, 18].

Concerning iron treatment, the ACOG recommends individualizing treatment between transfusion, oral or parenteral iron in asymptomatic patients with haemoglobin below 70 g/L. Similarly, the Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends a threshold of 70 g/L for transfusion, tolerating a haemoglobin even as low as 50 g/L, with parenteral iron treatment of patients with haemoglobin below 80 g/L. The recommendations of obstetric societies seem to be largely extrapolated from the results of transfusion studies in other fields. Based on 31 randomized controlled trials (RCT), the American Association of Blood Banks recommends a restrictive RBC transfusion threshold of 70 g/L in haemodynamically stable patients [19]. In contrast, the NATA in collaboration with the International Federation of Gynaecology and Obstetrics (FIGO) recommends a haemoglobin threshold below 60 g/L for elective transfusion in non-bleeding and asymptomatic patients [9]. Their recommendation is based on the WOMB study, the only RCT investigating transfusion thresholds in obstetrics to date [7]. The WOMB study was a non-inferiority trial in women with acute asymptomatic anaemia (haemoglobin 48–79 g/L) 12–24 h postpartum randomized to non-intervention or RBC transfusion. Women allocated to RBC transfusion showed a small absolute difference, but no clinically significant difference, in physical fatigue scores compared to non-intervention. Overall, there were no significant differences in health-related quality of life nor in physical complications.

Our study included all postpartum RBC transfusions given outside of the acute bleeding episode, considered to be ≥6 h postpartum, over a 17-year period in a tertiary care centre. It is also one of the largest audits conducted on postpartum RBC transfusion appropriateness to date. Previous audits of this kind have investigated RBC transfusions in the immediate (in minutes) postpartum period and up to 24 h to 7 days postpartum over a 1-year period only [2–4]. The main limitations of this study are inherent to its retrospective design, as guideline recommendations and clinical practice are continuously evolving. While we stratified our outcomes by the year 2015 to try and account for practice changes following various guideline publication, we acknowledge that this strategy is imperfect. However, despite this stratification, we found compliance rates and tendency towards multiple unit initial transfusion to be similar.

One of the challenges we faced when assessing guideline compliance was how to objectively evaluate asthenia, which was the main indication for transfusion in our cohort. However, the SOGC is clear that fatigue alone is not a symptom that warrants RBC transfusion [18]. The evaluation of asthenia was at the discretion of the treating physician who ordered the transfusion. That is, there are currently no uniform clinical criteria to assess patients with acute anaemia reporting fatigue. As a result, the compliance rate in our centre may be lower than that reported if stricter clinical definitions were applied to these patients (e.g., asthenia being defined as fatigue or weakness too severe to care for oneself or one's newborn in the postpartum period).

Although the compliance rate for postpartum RBC transfusions in our centre is acceptable, there remain areas for improvement, particularly with respect to evaluation of transfusion indication and single-unit transfusion episodes. Greater emphasis on both antenatal and postpartum iron replacement, as well as a threshold haemoglobin below 60 g/L in symptomatic women, may limit postpartum transfusions in this population. The results of this study have been presented at departmental grand rounds and a protocol for the prevention, screening and management of antenatal and postpartum anaemia is currently being elaborated.

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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.

ORCID

Ariane Lasry https://orcid.org/0000-0003-2023-2338

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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

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Influence of donor age, sex and ethnicity on high-titre anti-A and -B: Review of 6 million donations from two national blood providers

Melanie Robbins[1] | Sian Huish[1] | Alexandra Griffiths[2] | Tanya Powley[3] | James Daly[3] | Rebecca Cardigan[1,4]

[1]Component Development, NHS Blood & Transplant, Cambridge, UK

[2]Statistics and Clinical Research, NHS Blood & Transplant, Cambridge, UK

[3]Clinical Services and Research, Australian Red Cross Lifeblood, Sydney, Australia

[4]Department of Haematology, University of Cambridge, Cambridge, UK

Correspondence
Melanie Robbins, NHS Blood & Transplant, Long Road, Cambridge CB2 0PT, UK.
Email: melanie.munro@nhsbt.nhs.uk

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Abstract

Background and Objectives: Some blood operators routinely screen blood donations for high-titre (HT) anti-A/B to reduce the risk of a haemolytic transfusion reaction due to out-of-group plasma-rich components. We assessed donor factors associated with an increased likelihood of screening positive and compared routine data between England and Australia.

Materials and Methods: Data were assessed from HT screening during 2018–2020 in Australia and 2018–2021 in England, totalling nearly 6 million blood donations. Screening was performed using a Beckman Coulter PK7300 analyser with a micro-titre plate saline direct agglutination test in both countries, although different reagent red cells were chosen. HT-positive was defined as testing positive at a titre of 128 or above.

Results: The likelihood of a donor testing HT-positive was greater for females than males, declined with age and was dependent on the ABO group. However, the proportion of donors testing HT-positive was consistently higher in Australia than in England: overall, 14% of group O donations and 5% of group A donations in England tested HT-positive, compared with 51% and 22%, respectively in Australia. English data also showed that donors from Black, Asian or mixed ethnic backgrounds were more likely to test HT-positive than White donors.

Conclusion: These data demonstrate that donor sex, age, ABO group and ethnicity affect the likelihood of testing HT-positive. Differences in testing methods likely had a significant impact on the proportion of donors testing as HT-positive or -negative rather than any differences in donor populations.

Melanie Robbins and Sian Huish contributed equally to this work and designated as co-first authors.

Keywords
blood donations, donor testing, high-titre (HT)-positive

Highlights

- Data demonstrate that donor sex, age, ABO group and ethnicity affect the likelihood of testing high-titre (HT)-positive.
- Differences in testing methods, however small, likely had a significant impact on the proportion of donors testing HT-positive.
- The likelihood of a given donor testing HT-positive or -negative tends to remain consistent over 2–3 years.

INTRODUCTION

Transfusion of ABO non-identical plasma or minor ABO-incompatible platelets (where the suspending plasma of the platelet concentrate is not compatible with the ABO group of the recipient's red cells) has been associated with increased risk of haemolytic transfusion reactions (HTRs) [1]. Therefore, the preference in many jurisdictions is to provide ABO-identical plasma-rich components [2]. However, this is not always possible in emergency situations when a patient's blood group is unknown. Moreover, transfusion of ABO-incompatible platelets may also be required to ensure the availability of platelets when needed without significant wastage of a product with a short shelf life (5–7 days in most countries). For this reason, transfusion of ABO-incompatible platelets is not an infrequent occurrence, and thus many centres have policies in place to mitigate risk to recipients. For platelets, this may include volume reduction or suspension of platelets in PAS to reduce the levels of anti-A/B, or screening of donations and selection of 'low-titre' units if ABO non-identical platelets are transfused [3]. In addition, the resurgence of interest in the transfusion of whole blood, where group O plasma may be transfused to non-O patients, also necessitates, ensuring that these units are low-titre to mitigate the risk of HTR [4].

Some blood providers routinely test either all donations, apheresis donors only or the final platelet component for high-titre (HT) anti-A/B. However, a recent international survey showed there is no international consensus regarding the HT screening methodology, with wide variation in the methods used and cut-offs regarded as HT and whether both IgM and IgG antibodies are screened for [3]. Therefore, ensuring that out-of-group plasma-rich transfusions are safe requires a careful balance between reducing risk and maintaining an adequate supply of components.

Previous small-scale studies, many performed decades ago, have identified key donor factors that may influence whether a donation tests positive for HT anti-A or -B including age and sex of the donor [5–8]. It has also been suggested that a donor's HT status may be consistent over time and questioned whether testing is needed for every donation or just once [9]. In addition, factors such as vaccination and the use of pro-biotics have been shown to increase anti-A/B titres [10], although this does not appear to be the case with more modern vaccines [11] including influenza [12]. Here we have analysed nearly 6 million test results from 2 to 3 years of data across two national providers, to assess the relationship between donor age, sex, ethnicity and likelihood of testing HT-positive for anti-A/B. Understanding these variables is key to being able to perform robust risk assessments in relation to risk-mitigation strategies for out-of-group transfusions of plasma, platelets and whole blood.

MATERIALS AND METHODS

Screening methods for anti-A and -B

England

A tube sample from the donor (EDTA plasma) is tested for HT anti-A and/or anti-B on every donation using a direct agglutination microplate method on a Beckman Coulter PK7300 analyser. Reagent red cells used are prepared in-house from A_2B donations. Random A_2B red cell concentrates ($n = 6$) are titrated against anti-A of known titre (Lorne Laboratories) and the two units with the lowest A antigen strength, which are not completely negative, are selected, pooled, aliquoted and allocated the expiry of the oldest unit used. Reagent red cells are washed and diluted to 1.4% solution in saline. Donor plasma is diluted at 1:32 ratio in 0.9% unbuffered saline, which has been validated to equate to a manual saline tube method of 128. A total of 15 µL dilute plasma and 25 µL dilute red cells were incubated at 30°C for 1 h and agglutination was assessed by digital image analysis. A positive and a negative control containing monoclonal anti-A and anti-B (ALBAcheck® BGS High Titre Controls Kit—Z257) are used for this assay, at 128 and 64 manual saline equivalents, respectively. Plasma and platelet components produced from donations that test negative using this screening method are labelled as HT negative. The choice of reagent red cell and test conditions was made to balance reducing the risk of an HTR, with the ability to supply sufficient components to meet demand. The effectiveness of testing, combined with clinical policies, is assessed by monitoring national haemovigilance data.

Australia

Screening for HT anti-A and -B was introduced in 2018 in Australia, based on the methods in England above.

A tube sample from the donor (EDTA plasma) is tested for HT anti-A and/or anti-B using a Beckman Coulter PK7300 along with the routine blood grouping (ABO and RhD) panel on every donation. Two different dilution ratios of the plasma in 0.9% unbuffered saline are tested in parallel: 1:32 (which approximates a conventional tube saline direct agglutination titre of 128, see Table S1) and 1:64 (which approximates a conventional tube saline direct agglutination titre of 256, see Table S1). The 128 titre is used to define low- and high-titre anti-A and/or anti-B. Blood components from donations that are negative at a titre of 128 are labelled as low anti-A/B. Apheresis platelet donations that test positive at a titre of 256 are further tested at a titre of 8000 to ascertain donations that may be exceptionally high for anti-A or -B (see Figure S1).

The diluted donor plasma is tested separately (using a Beckman Coulter PK7300) against a commercially available solution of 2% group A_1 or group B cells (Beckman Coulter PK System Reverse Grouping Cells—17318). The reported result is based on the combination of the results with the individual cells. Thus, in group O donations, it is possible to ascertain whether anti-A or -B or both are HT. Negative results must be obtained for both cell types for an overall negative result to be reported. Any other combination of results, including indeterminate or equivocal, is interpreted as positive. A positive and a negative control containing monoclonal anti-A and anti-B (ALBAcheck® BGS High Titre Controls Kit—Z257) are used for this assay. This negative control contains anti-A and anti-B, which may be detectable at a 1:64 dilution in manual titration (1:16 dilution in an automated system), and therefore may occasionally return a HT-positive result at a titre of 128 in some automated techniques.

DATA ANALYSIS

English data were extracted from NHSBT's PULSE database on all whole blood, apheresis platelet and plasma donations collected between 9 April 2018 and 16 May 2021, where an HT screening result was available. Indeterminate HT results were classed as positive. The donor's sex, age at donation, ethnicity (ONS 2011 Census categories) and ABO group were available.

Australian data summarizing HT results was extracted for the period 1 March 2018–31 January 2020, including donor sex, age and ABO group (but not ethnicity). This data set included all whole blood and apheresis platelet donations during the period, as well as all plasma donations from new donors or those returning after a long interval.

Subgroup-specific HT rates (% of donations screening as HT-positive) were calculated according to the following variables: donor sex and age group; donor ethnicity (England only); and month of donation. In each case, different ABO groups were treated separately.

For the English data, it was also possible to examine longitudinal patterns of HT results within donors over time. Donors with at least four clear HT screening results over a period of at least 1 year were categorized as follows: 'always negative', 'always positive', 'flipped negative to positive', 'flipped positive to negative' or 'fluctuating'. The last category contains donors whose HT status changed twice or more during the period; the two 'flipped' categories comprise donors with only a single status change. The proportion of donors in each category was calculated, with breakdowns according to ABO group, sex, age and ethnicity.

RESULTS

The basic donor characteristics of the two cohorts included in the analysis are summarized in Table 1. The proportion of male donors in the Australian cohort was slightly higher than that of England; however, the distribution of ABO group and age of donors was similar in both data sets.

The proportion of donations testing HT-positive, as defined by each country, by sex and age of donor is shown in Figure 1. For both countries, the HT positivity rate was higher in female donors than male donors, declined with donor age and was higher in group O than A donors. However, the absolute proportion of donors testing positive, as tested and defined by each country, was considerably higher in the Australian cohort compared with England. For the entire cohort of donors, including group AB, the overall rate of HT positivity was 37% in Australia and 9% for England. For group O donations, these values were 51% and 14%, and for group A donations, they were 22% and 5%, respectively. Data for group B donations are shown in Figure S2; less than 0.1% of all group B donations in England were HT-positive, compared with 17% in Australia. Data showing indeterminate results for donations in England are shown in Table S2.

The influence of ethnicity on the proportion of donors testing as HT-positive is shown in Figure 2. These data were only available for England. Donations from Black, Asian or mixed ethnicity donors showed a higher rate of HT positivity than White donors. This was true for groups O and A, and for both male and female donors, but was most noticeable where the rates of HT positivity were higher, for example, group O female donors.

Monthly longitudinal data from HT testing are shown in Figure 3. Although there was variation in the proportion of donors testing positive over time, there was no obvious seasonal variation seen in either Australia or England. However, the HT positivity rate in England showed a greater degree of variation from month to month than that observed in Australia, which was more stable.

Patterns of testing results for donors from England who had four or more screening results during the period of data collection are shown in Tables 2 and 3. For group A donors, 94% tested negative and 2% tested positive on all occasions. A further 4%–5% either fluctuated or flipped. For group O donors, these values were 82%, 6% and 12%, respectively. The proportion of donors who consistently tested negative increased with increasing age of the donor, for both group O and A donors.

DISCUSSION

Screening for HT anti-A and -B has been undertaken for many years in England but was standardized across the United Kingdom in 2008

TABLE 1 Summary of basic donor characteristics.

		Number (%) of donations from this group during the period covered	
		England	**Australia**
Sex	Female	2,271,116 (51.9%)	659,705 (43.1%)
	Male	2,107,287 (48.1%)	869,674 (56.9%)
Age group	Under 20	80,665 (1.8%)	44,896 (2.9%)
	20–29	733,442 (16.8%)	309,492 (20.2%)
	30–39	844,322 (19.3%)	300,000 (19.6%)
	40–49	847,288 (19.4%)	277,904 (18.2%)
	50–59	985,371 (22.5%)	291,922 (19.1%)
	60–69	674,268 (15.4%)	232,472 (15.2%)
	70 and over	213,047 (4.9%)	72,693 (4.8%)
ABO group	A	1,614,863 (36.9%)	546,627 (35.7%)
	AB	119,153 (2.7%)	40,779 (2.7%)
	B	466,099 (10.6%)	124,537 (8.1%)
	O	2,178,288 (49.8%)	817,436 (53.4%)
Ethnic group (England only)	Asian	114,203 (2.6%)	n/a
	Black	37,312 (0.9%)	
	Mixed/multiple	62,000 (1.4%)	
	Other	18,651 (0.4%)	
	White	4,099,380 (93.6%)	
	Unknown	46,857 (1.1%)	

Abbreviation: n/a, not applicable.

following a review of UK-wide haemovigilance data. Of the reports of haemolytic transfusion reactions to minor ABO-incompatible platelets, 17 of 23 cases occurred in the 13 years from 1996 to 2008, with only 6 of 23 occurring in the subsequent 13 years from 2009 to 2021 (Dr Helen New, personal communication, NHSBT, 2024) [13]. Current testing uses a direct saline agglutination test, which principally measures IgM antibodies, and should give a negative result at a dilution of 128 or equivalent dilution by other techniques in order to be labelled as HT negative [14]. The screening test is set up using the same automated equipment that is used for routine blood grouping of donations and applied to every donation. Therefore, it is high throughput and low cost, with England testing in excess of 1.4 million donations per year. Australia adopted a similar approach to screening donations in 2018, following reports of haemolytic transfusion reactions to out-of-group platelets [15].

In this study, we report on 2–3 years of data from routine testing of HT anti-A/B in blood donors in England and Australia. Our data demonstrate the influence of donor-related variation on the likelihood of testing HT-positive for anti-A/B using the largest cohort of data published to date. We observed a higher frequency of donors testing positive in group O donors than in group A, and in females compared with males. Our data are consistent with previous smaller studies showing higher titres of anti-A and -B in group O donors compared with groups B and A [7, 8, 16, 17]. The rate of HT positivity in group B donors was considerably lower than that in Australia. We assume this is partly due to differences in the reagent red cells used, but further study would be required to elucidate this. We also observed a higher rate of positivity in females compared with males across all age groups and all ABO groups studied. Studies from as early as the 1950s suggested that females, especially those who gave birth to group A babies, have a higher incidence of anti-A haemolysins than the rest of the donor population [18, 19]. Our data suggest that policies to use only male donors to produce fresh frozen plasma as a TRALI risk reduction strategy will also reduce, but not eliminate, the risk of transfusion of HT anti-A/B.

We observed a notable decrease in the proportion of donors testing positive for HT anti-A and -B with increasing age of the donor. The levels of anti-A/B are thought to increase from birth to reach a maximum between 5 and 10 years of age [20]. Our data are consistent with a previous study of 1000 individuals, which demonstrated that the levels of anti-A/B haemolysins decline with age, particularly in females [5]. Interestingly, the latter study showed that even in females below the age of 19, who presumably were less likely to have been pregnant than older cohorts, the levels of anti-A are higher in girls than boys. We did not observe any significant trends in our data by season, although we did observe variation over time, which may in part be caused by changes in reagent red cell batches. Early reports suggested that lower levels of anti-A/B haemolysins are observed in winter [8]. However, later studies suggest that there is little influence on seasonal variation [5, 21].

Very few studies have assessed the influence of ethnicity on anti-A/B levels. We observed a difference in the likelihood of testing HT-

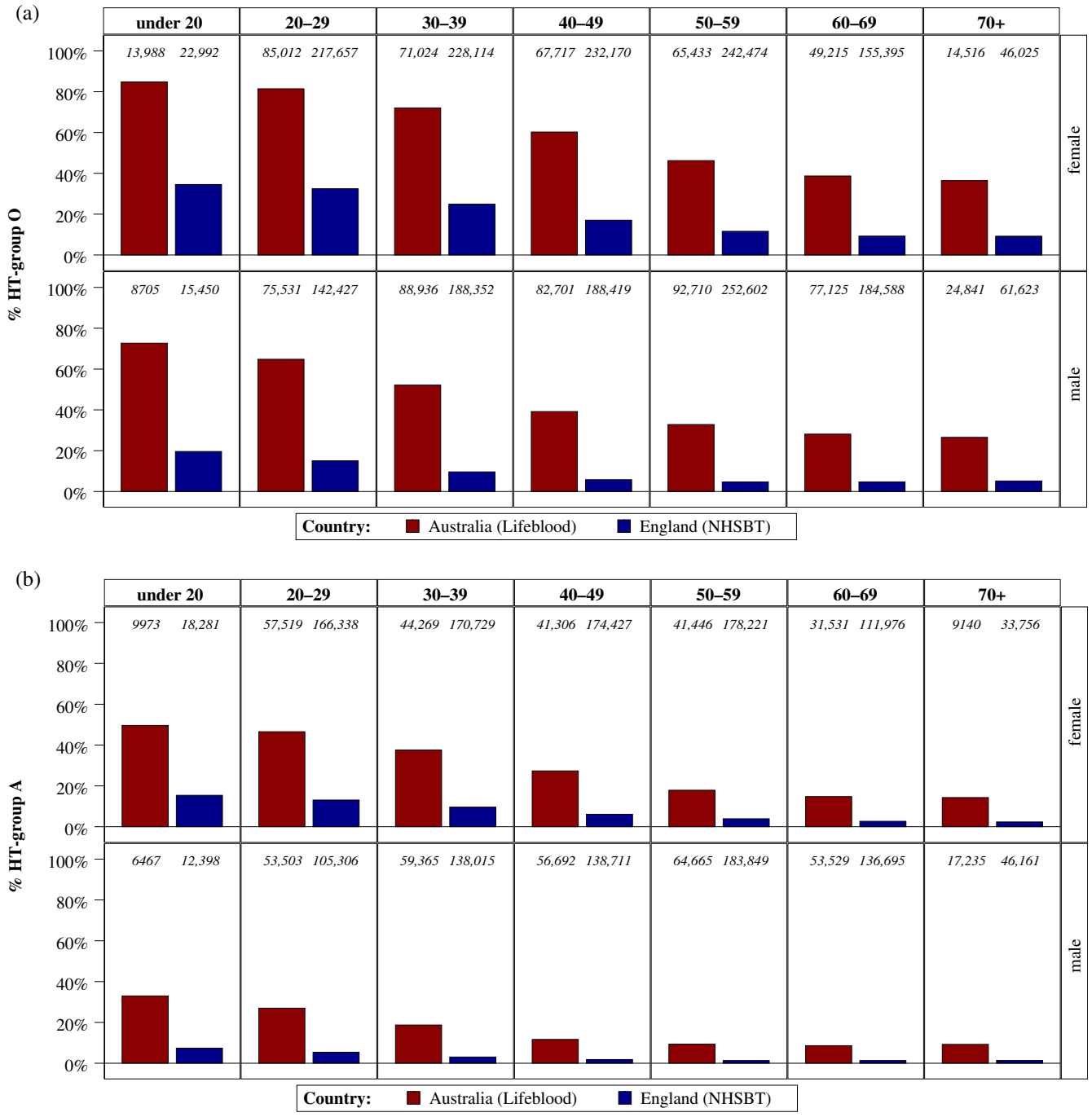

FIGURE 1 High-titre (HT) positivity rates in England and Australia by donor sex and age group (group O) (a) and (group A) (b). Number of donations tested in each subgroup shown at top of bars.

positive dependent upon ethnic background of the donor, with all other groups studied having a higher likelihood of testing positive than White donors. A previous study of 300 UK donations suggested that anti-A/B were highest in Black female donors, but this was not statistically different from the rest of the donor population [22]. In contrast, a study assessing the relative contribution of genetic factors to anti-A/B levels suggested that the levels of all ABO antibodies were higher in Black donors [23], and this has also been reported to be true for total IgG and IgM [24]. Others have postulated that this may reflect ancestral exposure to differing pathogens including parasitic infection.

We also assessed the consistency of results for a given donor over time. The majority of donors were consistently either negative or positive over the study period (3 years). However, a small subset of donors either fluctuated between positive and negative, or flipped from testing as one to the other for the rest of the study period. We assume that donors whose results fluctuated between positive and negative probably have titres of antibodies that are close to the

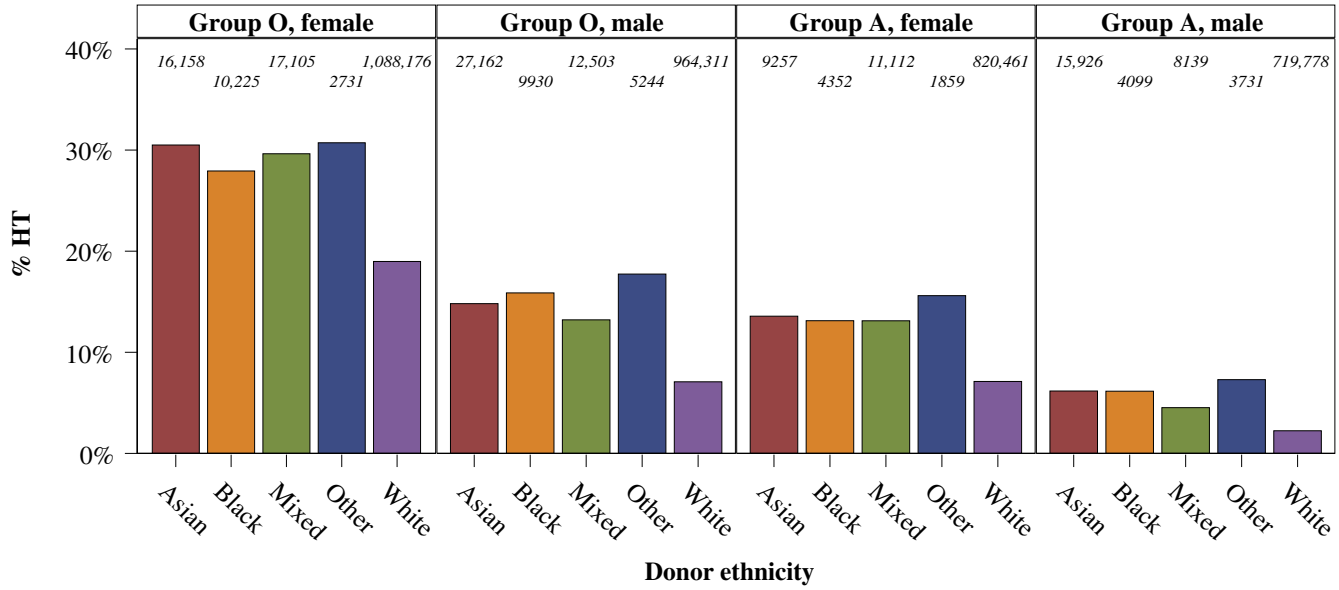

FIGURE 2 High-titre (HT) positivity rates in England by ABO group, donor sex and ethnicity. Number of donations tested in each subgroup shown at the top of bars.

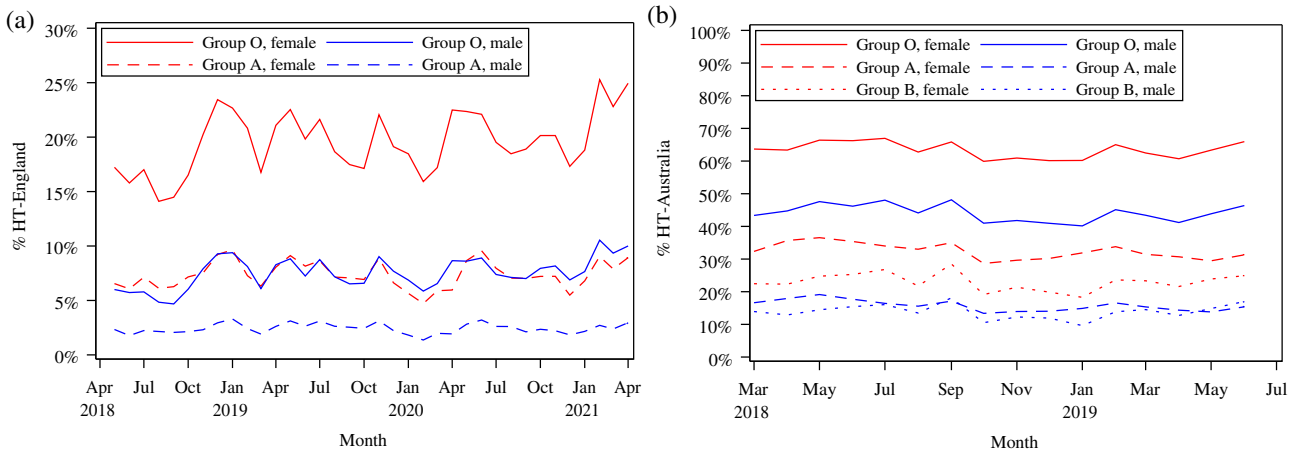

FIGURE 3 Monthly high-titre (HT) positivity rates by ABO group and donor sex in England, May 2018–April 2021 (a) and Australia, March 2018–June 2019 (b).

screening cut-off. Most concerning is the proportion of donors who switched from being negative to then testing positive thereafter—about 4% of group O donors and 1% of group A donors, who may have been missed if a policy of testing donors once only had been followed. Whilst these values appear small, they reinforce our policy of testing every donor every time. Although repeated testing of donors will enhance the likelihood of predicting a donor's HT status at a subsequent donation, this will depend on both the robustness of testing methods as well as environmental factors between donations. There is a paucity of other data on how the levels of anti-A/B vary for a given individual over time. A previous study of 56 healthy volunteers in Denmark showed IgM and IgG anti-A and anti-B titres were stable, over a period of 1 year (measured every 3 months), and suggested donors need not be tested more than once within the same year [9].

Our data suggest that genetic determinants may play a key role in influencing whether an individual has HT anti-A/B. Common and rare variants have been shown to be associated with total immunoglobulin levels in the population [25]. The relative contribution of genetic and environmental factors in determining anti-A/B titres remains to be established. A previous study of anti-A/B titres in families suggested that 20%–30% of variation is genetically determined, lower than that for total IgG and IgM levels for which this value may be as high as 50% [23].

The purpose of screening for anti-A/B in blood donations is to reduce the risk of a HTR that may occur following transfusion of ABO minor incompatible plasma or platelets. There is widespread variation in techniques used to measure anti-A/B for those blood providers who do this routinely, as well as the cut-off used and whether IgM

TABLE 2 Patterns of high-titre-positive/-negative results in group O repeat donors in England, by donor sex and age group.

Sex	Age group (at first donation)	Total repeat donors	Percentage of repeat donors with this pattern of HT results				
			Always negative (%)	Always positive (%)	Flipped − to + (%)	Flipped + to − (%)	Fluctuating (%)
Female	Under 20	2503	55.8	19.9	7.7	4.9	11.7
	20–29	21,518	60.2	18.3	6.3	4.6	10.5
	30–39	23,574	70.3	12.7	5.3	3.3	8.4
	40–49	28,139	78.4	8.1	4.4	2.1	7.0
	50–59	30,136	83.0	4.7	5.4	1.4	5.6
	60–69	19,040	86.1	3.7	3.8	1.1	5.3
	70 and over	4926	87.4	4.1	2.3	1.1	5.1
	All ages	129,836	76.0	9.3	5.0	2.4	7.3
Male	Under 20	1806	73.1	9.4	4.3	3.6	9.7
	20–29	15,170	79.7	6.3	3.0	3.0	8.1
	30–39	20,010	86.3	3.6	2.8	1.5	5.8
	40–49	23,078	90.8	1.8	2.4	0.8	4.2
	50–59	30,763	91.1	1.4	3.3	0.6	3.6
	60–69	21,600	91.7	1.6	2.0	0.7	4.0
	70 and over	6294	92.5	2.1	1.3	0.7	3.5
	All ages	118,721	88.7	2.7	2.7	1.1	4.8
Overall		248,557	82.1	6.1	3.9	1.8	6.1

Abbreviation: HT, high-titre.

TABLE 3 Patterns of high-titre-positive/-negative results in group A repeat donors in England, by donor sex and age group.

Sex	Age group (at first donation)	Total repeat donors	Percentage of repeat donors with this pattern of HT results				
			Always negative (%)	Always positive (%)	Flipped − to + (%)	Flipped + to − (%)	Fluctuating (%)
Female	Under 20	1841	79.3	5.5	4.5	3.0	7.8
	20–29	16,328	83.1	5.3	2.8	2.9	5.9
	30–39	17,535	88.1	4.0	1.9	1.7	4.3
	40–49	21,165	91.9	2.3	1.2	1.2	3.3
	50–59	22,055	94.5	1.3	1.5	0.8	2.0
	60–69	13,909	96.2	0.9	0.8	0.4	1.7
	70 and over	3659	96.9	1.0	0.5	0.5	1.2
	All ages	96,492	90.9	2.7	1.6	1.4	3.4
Male	Under 20	1456	88.6	2.3	1.5	2.1	5.6
	20–29	11,646	92.1	1.5	0.9	1.5	3.9
	30–39	15,510	95.5	0.9	0.6	0.6	2.4
	40–49	17,986	97.3	0.5	0.5	0.3	1.5
	50–59	24,012	97.7	0.3	0.5	0.3	1.2
	60–69	17,010	97.8	0.4	0.4	0.3	1.2
	70 and over	4922	98.3	0.5	0.2	0.2	0.9
	All ages	92,542	96.4	0.7	0.5	0.5	1.8
Overall		189,034	93.6	1.7	1.1	0.9	2.6

Abbreviation: HT, high-titre.

and/or IgG are measured. Defining a critical cut-off is challenging, in part because there is no definitive relationship between titre and risk of HTR [26]. The impact of the testing method on the HT rate obtained is illustrated by our data where striking differences are observed between England and Australia, despite similar testing methods. Overall, 37% of all donations tested as HT-positive in

Australia compared with 9% in England, and this disparity persists after stratification by ABO group, sex and age. It is well known that the variation in testing methods can cause variation in titres of anti-A/B measured, and this is not standardized internationally. Here the only difference in the method was the reagent red cells used: A_2B cells in England and A_1 and B cells in Australia. We postulate that this difference is due to reduced sensitivity of the method used in England as a result of lower antigen expression in A_2B cells compared with A_1 or B cells, rather than differences in our donor populations. We consider that differences in ethnicity are unlikely to explain our findings because >93% of donors in England at the time of study are White and this is not expected to be dissimilar for Australia. We cannot exclude whether differences in donor selection may affect the HT rate between England and Australia—this would require future large prospective studies to assess.

In addition, the volume and antibody levels in incompatible plasma transfusions, recipient factors such ABO zygosity [27] and complement regulatory deficiencies [28] are thought to play a role in determining the likelihood of a HTR occurring. A recent systematic review of reports of HTR to ABO-incompatible plasma or platelets transfusions has shown that whilst anti-A titres as low as 32 have been associated with case reports of HTR, this is rare [29]. Most cases were associated with anti-A group O components transfused to non-O recipients, with IgM levels of 128 or above and/or IgG of 256 or above. However, many reports do not give data on the titre of implicated antibodies, nor the measurement methods used in detail including the choice of reagent red cells. Reports of HTR associated with anti-B from either group O or group A components are far less common, with the associated titres generally exceeding 512, and fatal case reports being very rare [29].

HTRs are infrequent events, despite ABO minor incompatible plasma and platelet transfusion not being an infrequent event worldwide. There is a paucity of data relating to the frequency of HTR to minor ABO-incompatible plasma/platelet transfusion, which has been reported to be 0.01%–0.05% [30], and will depend on clinical policies for transfusion and mitigating actions taken to reduce the risk of HTR, including screening for anti-A/B. It is thought that in part the rarity of HTR may be attributable to anti-A or -B in incompatible plasma or platelet transfusions binding to A/B antigens on the recipients' endothelium, as well as dilution of plasma in the recipient [31]. For platelets, those stored in 60%–65% additive solution are likely to pose a lower risk due to the dilution of plasma. Large-scale data on titre levels in conjunction with haemovigilance data are required to fully estimate the risk reduction afforded.

In summary, our data demonstrate in a large cohort of donors from two national blood providers that there is a clear effect of age, sex and ethnicity on whether donors test as HT-positive for anti-A/B. In addition, small differences in testing methods can have a marked effect on the rate of HT positivity. This is an important consideration in modelling the risk of out-of-group plasma and platelet transfusions. The cut-off we have chosen in the United Kingdom and Australia is a pragmatic choice aimed at balancing the reducing risk of HTR on the one hand, whilst ensuring an adequate supply of donations on the other. This balance is a matter for individual blood providers to decide based on local considerations, and by monitoring the effectiveness of policies using haemovigilance data or other data.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Melanie Robbins https://orcid.org/0009-0003-2131-2281
Rebecca Cardigan https://orcid.org/0000-0001-6823-8937

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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

Mortality-associated risk factors for transfusion-associated circulatory overload

Lipika Soni[1] | Samia Saeed[2] | Christine Cserti-Gazdewich[2,3,4,5,6] | Mark J. McVey[1,7,8,9]

[1]Department of Anesthesia and Pain Medicine, Hospital for Sick Children, Toronto, Ontario, Canada

[2]Department of Laboratory Medicine & Pathobiology, University Health Network, Toronto, Ontario, Canada

[3]Blood Transfusion Laboratory (Laboratory Medicine Program), Toronto General Hospital, University Health Network, Toronto, Ontario, Canada

[4]Department of Medicine (Medical Oncology & Hematology), University Health Network, Toronto, Ontario, Canada

[5]Division of Hematology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

[6]Utilization, Efficacy, & Safety of Transfusion (QUEST) Research Program, University of Toronto Quality, Toronto, Ontario, Canada

[7]Department of Physics, Toronto Metropolitan University, Toronto, Ontario, Canada

[8]Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada

[9]Department of Physiology, University of Toronto, Toronto, Ontario, Canada

Correspondence
Mark J. McVey, Anesthesia and Pain Medicine Hospital for Sick Children, 555 University Ave, Room 5308 Black Wing, Toronto, ON M5G 1X8, Canada.
Email: mark.mcvey@utoronto.ca

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Abstract

Background and Objectives: Respiratory transfusion reactions associate strongly with morbidity and mortality, and transfusion-associated circulatory overload (TACO) is the leading cause of reaction-related deaths. Risk factors for TACO include transfusion speed and volume and cardiorenal comorbidities.

Materials and Methods: An academic health network haemovigilance database was interrogated to assess variables associating with 371 cases of TACO and involved-visit outcomes, using univariate and multivariate regression analysis.

Results: TACO reactions over 11 years were reported in 179 males and 192 females, median age (interquartile range) 65 (53–75) years. In-hospital and 28-day mortality were 17.5% and 12.9%, respectively. In univariate regression modelling, male sex, injury severity grade, product volume administered, the use of platelets and intensive care admissions were each associated with in-hospital and 28-day mortality ($p < 0.05$). However, after multivariate regression analysis, only male sex in transfusion recipients independently associated with mortality ($p < 0.05$).

Conclusion: In this cohort, male recipient sex and platelet administration were associated with TACO-involving admissions not ending in survival.

Keywords

death, ICU, mortality, platelets, sex, transfusion-associated circulatory overload

Highlights

- Males showed an elevated risk of mortality associated with transfusion-associated circulatory overload (TACO).
- Platelet transfusions showed an elevated risk of mortality associated with TACO.
- Intensive care unit admissions were associated with mortality during TACO.

INTRODUCTION

Respiratory transfusion reactions (RTRs) are associated with morbidity and mortality [1]. Discrimination between RTRs, for example, transfusion-related acute lung injury (TRALI), transfusion-associated

This work was presented in part at the ISBT Conference in Sweden 2023.

circulatory overload (TACO) or transfusion-associated dyspnoea can be important to guide management, but is challenging. RTRs also occur disproportionately in those who are critically ill, creating further diagnostic and therapeutic ambiguity [1].

Established risk factors associated with TACO include rapid and high-volume transfusions, extremes of recipient age, emergency surgery, as well as comorbid recipient conditions such as hypertension and renal or cardiorespiratory compromise [2–5]. TACO occurs commonly (in 1%–11% of transfusions) and is associated with significant in-hospital mortality (15%–28%) and is the leading cause (at 30%–40%) of transfusion related deaths [4, 5]. Considering these deadly correlates, an effort to identify risks in the cases that are most severe may assist in prognostication, prevention or targeted management. In a haemovigilance database, we analysed for the strongest associating variables in cases of TACO, focusing particularly on TACO-involving stays that ended in death.

MATERIALS AND METHODS

Study population

Research Ethics Board approval was obtained (REB#1000080295) for retrospective analysis of available variables in a multi-site hospital network real-time haemovigilance database. Included patients were non-pregnant adults (>18 years), from 1 January 2010 to 31 December, 2020. The tertiary hospitals were Princess Margaret Cancer Centre, Toronto General Hospital and Toronto Western Hospital [6].

Defining TACO reactions

The assessment of RTRs for features of TACO drew from existing definitions, as specified by the Provincial Transfusion Transmitted Injuries Surveillance System/the Public Health Agency of Canada and the International Society of Blood Transfusion revision, with an additional institutional rubric for degrees of certainty [6]. Within the database, 407 TACO reactions were catalogued over 11 years. Closer scrutiny identified 19 cases where TACO had actually been ruled out and 17 cases with massive haemorrhage (transfused ≥10 units in ≤24 h). The latter were excluded, leaving 371 TACO reactions for final analysis.

TACO risk factors

To assess for TACO risk factors associated with in-hospital or 28-day mortality, the following parameters were analysed: age (years), sex, received-red blood cells (RBCs) (yes(Y)/no(N), volume in mL, speed mL/min), −platelet (Y/N), −plasma (Y/N), total number of units of all blood products transfused, total volume transfused (mL) and speed mL/min of blood products transfused, pre-transfusion haemoglobin (Hb; g/L), post-transfusion Hb (g/L), change in Hb from pre- to post-transfusion (Hb delta), TACO reaction severity (graded based on severity: [1] minor [required no treatment or only agents that nursing can provide from automatic orders], [2] moderate [required physician review with or without unplanned treatment], [3] severe [escalation in care/ disposition change now needing major supplemental oxygen] and [4] life-threatening/fatal [requirement for lifesaving care such as intubation] and also TACO-severity stratified into grade groupings [as either high grade (grades 3 + 4) or low grade (grades 1 + 2)]), new intensive care unit (ICU) admission, hospital length of stay, new symptoms (chills, rigours, dyspnea, wheezing, abnormal chest X-ray, fever [temperature >38°C]), requirement for oxygen supplementation or new diuretic use post-transfusion, change in post-transfusion systolic blood pressure (i.e., ≥20% change from pre-transfusion), change in post-transfusion heart rate (i.e., ≥20% change from pre-transfusion) and post-translation respiratory rate (i.e., tachypnea respiratory rate >30 breaths per minute). Platelet units examined in this study were plasma-containing platelets (i.e., no platelet-additive solution [PAS]). Where there was uncertainty on a contributing non-cardiogenic insult, concomitantly suspected TRALI was also noted if it applied.

Statistical analysis

Analyses were conducted using SPSS v24.0 software (IBM Corporation, Chicago, IL) and R open-source statistical software (version 1.3.1073; RStudio, PBC, http://www.r-project.org). Data were assessed for normal distribution using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed continuous variables were summarized by calculating the mean or median, standard deviation and range. Nominal/categorical variables were represented as frequency and percentages and analysed with chi-square testing, which when statistically significant ($p < 0.05$) were reported with odds ratios (ORs) and 95% confidence intervals (CIs). The chi-square test was performed on 369 cases out of 371 cases as the mortality outcome was missing for two cases. Risk factors were additionally analysed using univariate and multivariate Cox-regression models to determine independent associations with risk factors and TACO mortality (Cox regressions were carried out on only 364 TACO cases due to incomplete outcomes data in seven cases). To estimate the survival function with statistically significant risk factors in multivariate Cox regression analysis Kaplan–Meier curves were plotted and the differences were assessed by using the log-rank test.

RESULTS

TACO epidemiology

The incidence of TACO in the haemovigilance database was 371/696,563 components or 5 per 10,000 (95% CI: 4–6/10 k), or by time, one event every 11 days (95% CI: once every 9–12 days). Of the included 371 TACO occurrences (median [interquartile range (IQR)] age: 65 [53–75] years), 179 were in males and 192 in females. TACO cases were stratified as possible ($n = 193$, 52%), probable ($n = 76$, 21%), most

likely ($n = 80$, 22%) and definite ($n = 22$, 6%). In terms of stratifying TACO by severity, these were either: life-threatening ($n = 31$, 8%), severe ($n = 83$, 22%), moderate ($n = 204$, 55%) or mild reactions ($n = 53$, 14%). TACO reactions involved RBCs ($n = 274$, 74%), platelets ($n = 121$, 33%) and/or plasma ($n = 28$, 8%). Fever was reported in 34% of cases. The median (IQR) length of stay was 19 (6–39) days and in-hospital and 28-day mortality was 17.5% and 12.9%, respectively.

Factors associating with in-hospital and 28 day mortality included recipient age, recipient sex, grade (TACO-severity), transfusion of platelets and ICU transfer ($p < 0.05$; Table 1). To address more complex cases, we reviewed those where concomitant TRALI could not be ruled out. There were 29 such events (TACO + TRALI) that were also associated with mortality ($p < 0.05$; Table 1). These suspected overlap cases involved platelets 34% of the time. All other risk factors were not significantly associated with mortality ($p > 0.05$). The odds of survival were 1.97 times greater in patients with no platelet transfusions compared to those who received platelets (OR [survival] = 1.97; 95% CI: 1.1–3.4). In-hospital mortality was significantly different if platelets were involved in the reaction, Chi-square = 3.96, ($p = 0.05$). The odds of survival were 3.5 times greater in patients who did not require ICU admission (OR [survival] = 3.5; 95% CI: 1.9–6.6). The odds of survival was lower in males (OR [survival] = 0.55; 95% CI: 0.3–1.0).

Using univariate regression modelling, male recipient sex, grade (TACO-severity), component implicated (platelets), as well as transfer to ICU, were found to be associated with both in-hospital and 28-day mortality ($p < 0.05$; Table 2).

To further address potential confounding, multivariate regression analysis was undertaken and showed that only male sex persisted as an independent factor associated with in-patient mortality (hazard ratio [HR] = 0.52; 95% CI: 0.3–0.9) and 28-day mortality (HR = 0.46; 95% CI: 0.02–0.9) ($p < 0.05$; Figure 1).

DISCUSSION

In this Canadian urban-academic haemovigilance database, we identified factors in TACO cases that were associated with mortality. Male sex recipients, platelet administration, higher grades of TACO-severity, concurrent suspicions of TRALI (TACO + TRALI) and transfer for ICU care were associated with non-survival. Unexpectedly, only recipient male sex was found to be independently associated with 28-day and in-hospital mortality.

Although previously established risk factors for TACO have included the transfusion of plasma and elevated circulating fluid status

TABLE 1 TACO risk factors associated with in-hospital and 28-day mortality.

	In-hospital mortality			28-day mortality		
Parameter	Survivors ($n = 303$)	Non-survivors ($n = 66$)	p value	Survivors ($n = 321$)	Non-survivors ($n = 48$)	p value
Age (years) median (IQR)	65.9 (53.9–76.0)	59.4 (50.1–68.7)	0.02	65.5 (53.7–75.9)	59.2 (53.7–69.0)	0.05
Sex (male/female)	139/164	40/26	0.03	149/172	30/18	0.04
TACO grade (high grade/low grade)	83/220	32/34	<0.001	90/231	25/23	<0.001
Events involving platelet transfusion *n* (%)	90 (29.7)	30 (45.4)	0.01	98 (30.5)	22 (45.8)	0.04
TACO + TRALI diagnosis *n* (%)	19 (6.3)	10 (15.1)	0.02	21 (6.5)	8 (16.7)	0.02
Transfer to ICU required *n* (%)	38 (12.5)	21 (35.6)	<0.001	44 (13.7)	15 (31.2)	<0.001

Note: TACO-severity grade = high grade: (severe to life-threatening)/low grade: (mild–moderate). $p < 0.05$ was considered statistically significant.
Abbreviations: ICU, Intensive Care Unit; IQR, interquartile range; *n* (%), total no of cases per category (*n*) and the percentage of those cases per category (%); SD, standard deviation; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

TABLE 2 Cox univariate regression analysis assessing the relationship of TACO risk factors and mortality.

	In-hospital mortality		28-day mortality	
Parameter	HR (95% CI)	p value	HR (95% CI)	p value
Sex	0.5 (0.3–0.9)	0.01	0.5 (0.3–0.9)	0.02
High grade/low grade	1.8 (1.1–2.9)	0.02	2.1 (1.2–3.7)	0.01
Platelets transfusion involved	1.6 (1–2.6)	0.05	1.7 (0.95–3.0)	0.07
New ICU admission	1.9 (1.1–3.2)	0.02	2.0 (1.1–3.7)	0.03

Note: Severity grade = high grade: (severe to life-threatening)/ low grade: (mild–moderate); $p < 0.05$ was considered statistically significant.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; TACO, transfusion-associated circulatory overload.

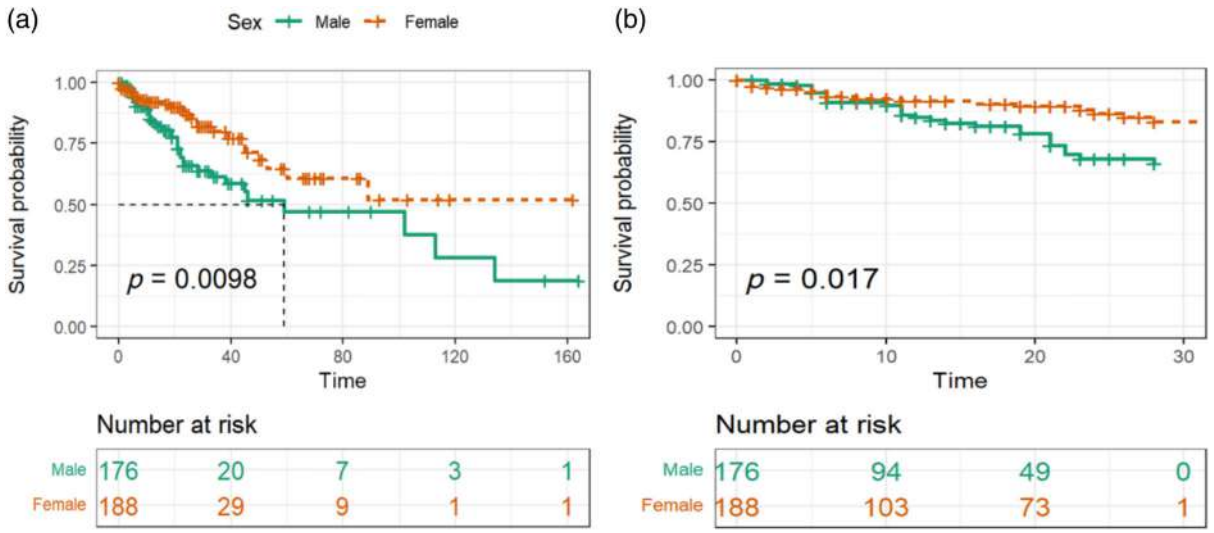

FIGURE 1 Male recipient sex associated with increased mortality. Data are depicted as Kaplan–Meier curves (log-rank tests) showing the differences in survival probability between male (green lines) and female (orange lines) for (a) in-hospital and (b) 28-day mortality in transfusion-associated circulatory overload (TACO) cases where the *x* axis represents time in days and the *y* axis is the survival probability. $p < 0.05$ indicates statistical significance.

or cardiorenal compromise [2–5], the mechanisms and modes of linkage to mortality remain incompletely understood. To validate and potentially find additional factors related to TACO, we probed for risk factors associated with the most severe cases, particularly those with the most objective and concerning outcome of death. Our findings challenge two adult population studies, which conversely showed an association between female recipient sex and TACO, although whether this association was maintained in TACO-affected admissions that ended in death was not examined [2, 7]. Other lung injuries such as acute respiratory distress syndrome or RTRs such as TRALI have shown more severe presentations in male recipients [7, 8].

Here, we also show an association with platelet transfusions and mortality for our admissions affected by TACO. Platelet count depreciations in lung injury states (e.g. coronavirus) have associated with death [9], and although platelet transfusions have an established patho-mechanistic link in TRALI [1, 10–12], they have not yet been causally implicated in TACO [1]. Our findings suggest either that platelets are a confounder (as an indicator of underlying illness severities already destined for death) or that they may likewise contribute collateral injury and severity to TACO itself. Indeed, inflammatory mechanisms have already been implicated in reports on the frequency of fever in TACO, as in others on TRALI where platelets have mediated injury [1, 10–12].

Our findings are limited by the fact of their retrospective and observational nature. We therefore acknowledge potential confounders that were neither measured nor controlled. The available haemovigilance database did not record sufficient or analysable details on circulatory fluid status or the number and severity of comorbidities such as renal or cardiac disease status. Lastly, we studied platelets suspended in plasma. Plasma is a colloid and could potentially create a greater risk of TACO then platelets suspended in PAS. As many blood-banking systems are beginning to utilize PAS platelets, it will be interesting to see if this association with TACO persists, despite lower amounts of plasma. This analysis is therefore hypothesis-generating, and future prospective (mechanistic and larger epidemiologic) studies are warranted to check these findings.

Despite these limitations, this collection of 371 TACO cases identifies unexpected signals of concern (in recipient male sex and in platelet-product-involving events) for the most severe admission outcomes.

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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.

ORCID

Christine Cserti-Gazdewich https://orcid.org/0000-0002-5297-6406

Mark J. McVey https://orcid.org/0000-0002-0918-7030

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SHORT REPORT

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Transfusion-related acute lung injury induced by human leucocyte antigen-II antibodies: Analysis of antibody typing and source

Zou Yu[1] | Zheng Mao[1] | Liao Xiuyun[2] | Jiang Tianhua[1]

[1]Deyang People's Hospital, Deyang, Sichuan, China

[2]Deyang Central Blood Station, Deyang, Sichuan, China

Correspondence
Jiang Tianhua, No. 173, North Taishan Road, Jingyang District, Sichuan, Deyang, China.
Email: 1501951397@qq.com

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Abstract

Background and Objectives: To explore transfusion-related acute lung injury (TRALI) induced by human leucocyte antigen (HLA)-II antibodies, and to analyse antibody typing and source.

Materials and Methods: We retrospectively analysed the clinical symptoms and signs of two leukaemia patients with suspected TRALI from the same female donor. HLA phenotyping was performed on the two patients, the platelet donor, her husband and her two children. The HLA and human neutrophil antigen antibodies in the donor's plasma were identified.

Results: The clinical manifestations of two leukaemia patients were those of TRALI, and we treated them with timely ventilator support. A high titre of HLA-II antibodies was in the plasma of the platelet donor. The antibodies were directed at HLA-DRB3*03:01, HLA-DRB1*09:01, HLA-DRB1*12:02, HLA-DRB3*01:01 and HLA-DRB1*12:01:01G, which were specific to the HLA antigens of the two patients. High-resolution HLA genotyping suggested that the donor's HLA-II antibodies were derived from immune stimulation by the husband's antigens during pregnancy.

Conclusions: This study described two cases of TRALI caused by HLA-II antibodies from the same female donor. Appropriate management of blood donors with a history of multiple pregnancies is crucial.

Keywords

adverse effects, HLA class II antibodies, transfusion-related acute lung injury (TRALI)

Highlights

- We report two cases of transfusion-related acute lung injury (TRALI) caused by human leucocyte antigen-II antibodies from the same donor.
- The donor's antibodies were derived from the immune stimulation of pregnancy.
- Management of blood donors with a history of multiple pregnancies is crucial.

Zou Yu and Zheng Mao contributed equally to this work.

INTRODUCTION

Transfusion-related acute lung injury (TRALI) is a syndrome characterized by acute non-cardiac pulmonary oedema and hypoxaemia during or within 6 h following a blood transfusion [1]. Restriction of plasma products to those from male donors limits exposure to the effects of alloantibodies from (multi)parous women, thereby reducing the incidence of TRALI [2, 3]. We report two cases of TRALI mediated by human leucocyte antigen (HLA)-II antibodies from the same female platelet donor.

CASE PRESENTATION

Patient A was a 47-year-old man with acute leukaemia. During chemotherapy, he received more than 20 blood transfusions. After receiving 150 mL of apheresis platelets, he suddenly developed tachypnoea and a sense of laryngeal contraction. The heart rate rose to 121/min, with a blood pressure of 190/106 mmHg, SpO_2 of 82% and a body temperature of 36.6. On physical examination, the patient had unstable breathing, pallor, no rash and a few wet rales in both lungs. Dyspnoea worsened gradually with decreased blood oxygen saturation, which fluctuated between 82% and 84%. Wheezing and more severe wet rales developed. The platelet transfusion was stopped immediately. An electrocardiogram (ECG) was monitored and oxygen was given via face mask at 5 L/min. The patient's tachypnoea, throat tightness and respiratory symptoms improved.

Patient B was a 70-year-old woman with acute leukaemia. She received 20 transfusions of red blood cells and platelets with no adverse reactions. After positive blood cultures, she received continuous oxygen inhalation and anti-infection treatment during hospitalization. She was slowly transfused about 100 mL of apheresis platelets and suddenly developed dyspnoea with wheezing. The heart rate fluctuated between 122 and 167 beats/min, respirations from 26 to 32/min, blood pressure was 167/102 mmHg, SpO_2 was 92% (on oxygen inhalation) and body temperature was 36.5. She was tachypnoeic and pale, had no rash, but a few wet rales in both lungs. The platelet transfusion was suspended. The patient was transferred to the Intensive Care Unit under oxygen inhalation. She was given oxygen via a face mask at a rate of 5 L/min, then changed to high-flow oxygen by nasal tube at a rate of 35 L/min, with her oxygen concentration being 40%. An arterial cannula was inserted. Thereafter, both lungs had significant wheezing and wet rales on auscultation. The next day, the patient's respiratory symptoms significantly improved, with a slow respiratory rhythm and some dry and wet rales in both lungs. The symptoms of tightness and dyspnoea gradually disappeared within a week, and computed tomography scan indicated that the bilateral lung infiltrates had significantly decreased.

Donor investigations

The platelets administered to both patients with suspected TRALI were from the same female donor. She was 28 years old with a G3P2 pregnancy record and no history of other diseases. This double platelet donation was her first, and she had never received any blood transfusion. The time interval between this platelet donation and the last pregnancy was 3 years.

MATERIALS AND METHODS

Ethics statement

This study was approved by the Ethics Committee of the Deyang People's Hospital (approval number: LWH-OP-006-A04-V2.0).

Donor HLA–human neutrophil antigen (HNA) antibodies, testing and typing

Assessing the presence of donor leucocyte antibodies and compatibility testing is a critical part of the TRALI investigative process [4]. Donor HLA–HNA antibody testing and antigen typing were performed by the HLA Reference Laboratory of the Institute of Blood Transfusion, Chinese Academy of Medical Sciences. The Luminex flow liquid chip method was used with the LABScreen reagent of ONE lambda (Canoga Park, CA, USA). If HLA or HNA antibodies were detected, a virtual cross-match was done using the antibody specificities detected and the patient's HLA genotype. An mean fluorescent intensity (MFI) of more than 9000 was considered a positive reaction.

HLA high-resolution genotyping test

HLA and HNA genotyping were performed on the recipients' samples. HLA high-resolution genotyping was performed by the Institute of Blood Transfusion via the next-generation sequencing (NGS), second-generation sequencing typing, method (AllType™ NGS 11-Loci reagent from ONE lambda, USA, Lot-Ngs015).

RESULTS

Donor HLA–HNA antibodies testing and typing

Platelet antibody (human platelet antigen and HLA) screening results of the two patients were negative. The donor's plasma had no HLA-I or HNA antibody but was strongly positive for several HLA-II antibodies. After half a year, the donor's antibodies were re-examined, and showed no significant change in the intensity of HLA-II antibodies. Table 1 shows five HLA antibodies that were cognate matches for HLA antigens in the two patients (see Table 2).

HLA high-resolution genotyping

HLA genotyping performed on the two patients revealed HLA antigens corresponding to the donor HLA antibodies. HLA genotyping of

TABLE 1 Five HLA antibodies that were cognate matches for HLA antigens in the two patients.

Allele specificity	Mean fluorescent intensity (MFI)
DRB1*12:02	25,576.45
DRB1*12:01	22,765.26
DRB3*03:01	17,609.14
DRB1*09:01	13,747.45
DRB3*01:01	11,614.42

Abbreviation: HLA, human leucocyte antigen.

the donor's husband and children indicates that the HLA-II antibodies were likely derived from immune stimulation during pregnancy with the two children (see Table 2).

Total white blood cells, neutrophils, BNP, procalcitonin and inflammatory factors

The percentage of neutrophils in patient A was 63.1% before TRALI occurred, and was 90.6% afterwards. The total number of white blood cells, the absolute value and the percentage of neutrophils in patient B were 2.78×10^9/L, 1.85×10^9/L and 66.5% before TRALI occurred, and became 8.99×10^9/L, 6.45×10^9/L and 71.7% during TRALI, respectively.

The brain natriuretic peptide (BNP) value of patient A was 11.2 pg/mL before the platelet transfusion and was 70.8 pg/mL after the transfusion. The BNP value of patient B was 620.1 pg/mL pre-transfusion, which increased to 780.2 pg/mL during the onset of pulmonary symptoms. In patient A, only interleukin (IL)-6 level went up and the remaining IL levels did not change appreciatively. In patient B, IL-10 and IL-17 levels went up, but IL-6 level went down (see Table 3).

Unfortunately, no imaging was performed immediately after the transfusion, during the onset of TRALI.

DISCUSSION

These two leukaemia patients had acute episodes of hypoxaemia and non-cardiac pulmonary oedema during transfusion, diagnosed as TRALI. This is seen as acute respiratory distress during or within 6 h after transfusion, and may be accompanied by fever and chills, tachycardia, and hypoxaemia, with an oxygenation index ≤300 mmHg or blood oxygen saturation <90% [5]. Both patients received supplementary oxygen, but had an estimated oxygenation index (PaO_2/FiO_2) below 300 mmHg, which is consistent with the presence of acute lung injury.

TRALI is thought to be the result of two factors [6, 7]. The first hit is the underlying condition of the patient (e.g., a proinflammatory condition), and the 'second hit' is the transfusion. Both patients had leukaemia, and patient B had both leukaemia and bacteraemia. Patients with leukaemia undergoing induction therapy have been

TABLE 2 HLA high-resolution genotyping of the two patients, the platelet donor, her husband and her two children.

Sample	A	B	C	DRB345	DRB1	DQA1	DQB1	DPA1	DPB1
Blood donor	A*02:03	B*13:01	C*03:04	DRB5*02:02	DRB1*16:02	DQA1*01:02	DQB1*05:02	DPA1*02:02	DPB1*02:01
	A*11:01	B*55:02	C*04:03	DRB5*02:03	DRB1*16:02	DQA1*01:02	DQB1*05:02	DPA1*02:02	DPB1*02:02
Donor's husband	A*11:01	B*15:02	C*08:01	DRB3*03:01	DRB1*12:02	DQA1*01:02	DQB1*05:02	DPA1*02:01	DPB1*05:01
	A*24:02	B*51:02	C*14:02	DRB5*01:01	DRB1*15:01	DQA1*01:02	DQB1*06:01	DPA1*04:01	DPB1*296:01
Child A	A*11:01	B*13:01	C*03:04	DRB3*03:01	DRB1*12:02	DQA1*01:02	DQB1*05:02	DPA1*02:01	DPB1*02:02
	A*24:02	B*51:02	C*14:02	DRB5*02:03	DRB1*16:02	DQA1*01:02	DQB1*05:02	DPA1*02:02	DPB1*05:01
Child B	A*02:03	B*15:02	C*04:03	DRB5*01:01	DRB1*15:01	DQA1*01:02	DQB1*05:02	DPA1*02:02	DPB1*02:02
	A*11:01	B*55:02	C*08:01	DRB5*02:02	DRB1*16:02	DQA1*01:02	DQB1*06:01	DPA1*04:01	DPB1*296:01
Patient A	A*11:01	B*46:01	C*01:02	DRB3*03:01	DRB1*09:01	DQA1*01:02	DQB1*03:03	DPA1*01:03	DPB1*05:01
	A*24:02	B*52:01	C*07:02	DRB4*01:03	DRB1*12:02	DQA1*03:02	DQB1*05:02	DPA1*02:01	DPB1*21:01
Patient B	A*02:01	B*39:01	C*01:02	DRB3*01:01	DRB1*04:04	DQA1*03:01	DQB1*03:02	DPA1*02:02	DPB1*02:01
	A*02:07	B*46:01	C*07:02	DRB4*01:03	DRB1*12:01:01G	DQA1*05:08	DQB1*03:02	DPA1*02:02	DPB1*05:01

Note: The significance of underlining the text: the donor has the HLA-II antibodies against the patient's genotype. The donor's antibody were likely derived from the immune stimulation during pregnancy with the two children, which came from their father's HLA gene.
Abbreviation: HLA, human leucocyte antigen.

TABLE 3 Routine blood, BNP, PCT and inflammatory factor tests for patients.

	Patient A		Patient B		
Items	Pre-transfusion	Post-transfusion	Pre-transfusion	Transfusion	Post-transfusion
WBC	0.65	0.64	2.78	8.99	2.37
NEUT#	0.41	0.58	1.85	6.45	1.88
NEUT%	63.1	90.6	66.5	71.7	79.3
RBC	2.16	2.05	2.15	2.38	1.77
Hb	63	60	66	73	55
PLT	1	5	17	53	24
BNP (pg/mL)	11.2	70.8	620.1	780.2	144.1
PCT (ng/mL)	0.23	14.01	0.61	0.68	0.83
IL-2 (pg/mL)	0.37	0.35	0.35	0.69	0.35
IL-6 (pg/mL)	1.43	2.75	387.83	137.05	1.33
IL-10 (pg/mL)	1.91	1.98	5.34	129.3	1.84
IL-17 (pg/mL)	1.56	1.58	1.56	11.9	1.94

Abbreviations: BNP, brain natriuretic peptide; Hb, haemoglobin; IL, interleukin; NEUT#, absolute neutrophil count; NEUT%, neutrophil percentage; PCT, procalcitonin; PLT, platelet; RBC, red blood cells; WBC, white blood cells.

shown to be at increased risk of TRALI [8]. Unfortunately, pulmonary radiographic examinations were not performed in either patient during the transfusion reactions. But further testing of the patients and donor revealed HLA-II antibodies that had specificities for the patients' HLA antigens. A large infusion of HLA-II antibody (MFI > 1500) is a TRALI risk factor [9]. In this study, BNP increased in both patients during TRALI. However, the BNP level of patient A was lower than 300 pg/mL, and the BNP level of patient B did not increase 1.5-fold before and after the transfusion. Previous studies reported that transfusion-associated circulatory overload (TACO) can be ruled out when BNP < 300 pg/mL or N-Terminal ProBNP (NT-proBNP) < 2000 pg/mL, whereas high NT-proBNP post-transfusion/pre-transfusion ratio >1.5 may suggest TACO [10, 11]. Therefore, TACO can be excluded in these two cases based on the BNP value. Combined with the clinical manifestations, laboratory findings and diagnostic results, the diagnosis of TRALI was confirmed. According to the newly revised guidelines for the diagnosis of TRALI in 2019, patients are divided into type I and type II, depending on whether they have risk factors for acute respiratory distress syndrome (ARDS) before transfusion [1]. Patient A had no risk factors for ARDS before transfusion, and thus was classified as TRALI type I. In contrast, patient B had a risk factor for ARDS before transfusion (reduced left ventricular function), showed deteriorating respiratory status after transfusion and was classified as TRALI type II. Cytokines or secreted factors have increasingly been utilized to validate risk factors for TRALI [12]. IL-6 and IL-10 changed significantly in two patients with TRALI at onset, so cytokine concentrations are related to the pathogenesis of TRALI.

The prevention strategies against TRALI include screening blood donors and blood preparation treatment [12]. Washing, leucoreduction and/or storing platelets in platelet-additive solution (PAS) can reduce the risk of TRALI. Most HNA and HLA antibodies occur in female multiparous blood donors [13]. The number of pregnancies correlates positively with the incidence of HLA antibodies [14]. In our study, the female blood donor had had three pregnancies and two children. Three years after the last pregnancy, the HLA-II antibodies were still strongly positive, and the antibody titre did not decrease after half a year. Therefore, the plasma-rich products of female donors with a history of multiple pregnancies are high-risk factors for TRALI [15].

Finally, we suggest preparing apheresis platelet concentrates containing less plasma and more additive solution, which can decrease the concentrations of the donor antibodies. In addition, we can screen all platelets for HLA antibodies like some blood centres in other countries, which is easier with apheresis platelets rather than whole blood. This measure can be used as a way to reduce TRALI risk.

In conclusion, this is the first study in China to report two cases of TRALI caused by HLA-II antibodies from the same donor. These cases highlight the management of female multiparous blood donors. A prevention strategy and a haemovigilance system corresponding to China's national conditions should be established to improve clinical transfusion safety.

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Z.Y. and Z.M. performed literature search, reviewed the institutional case studies and wrote the manuscript; L.X. tested laboratory tests related to donor specimens; J.T. supervised the study, and reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in CNKI at https://www.cnki.net/, reference number 10.13303/j.cjbt.issn.1004-549x.2023.10.007.

ORCID

Jiang Tianhua https://orcid.org/0009-0007-3174-4845

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SHORT REPORT

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Urban arbovirus exposure in blood donations from an endemic area of Brazil

Rhayany Redon de Sant'Anna[1,2] | **Priscila Conrado Guerra Nunes**[1] | **Flavia Barreto dos Santos**[1]

[1]Laboratório das Interações Vírus-Hospedeiros, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro, Brazil

[2]Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti, Hemorio, Rio de Janeiro, Brazil

Correspondence
Flavia Barreto dos Santos and Priscila Conrado Guerra Nunes, Laboratório das Interações Vírus-Hospedeiros, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz (Fiocruz), Rio de Janeiro 21040-900, Brazil.
Email: flaviab@ioc.fiocruz.br and priscila.nunes87@gmail.com

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Abstract

Background and Objectives: In Brazil, urban arboviruses, such as dengue virus (DENV), Zika virus (ZIKV) and chikungunya virus (CHIKV), constitute a major public health problem, and due to their endemicity and asymptomatic cases, they pose a potential threat to blood donations. Rio de Janeiro (RJ), Brazil, has been impacted by extensive DENV epidemics over the last 30 years and, after 2015, by CHIKV and ZIKV.

Materials and Methods: Urban arboviruses DENV, ZIKV and CHIKV were investigated in blood donations ($n = 778$) at the State Institute of Hematology, HEMORIO (RJ) from 2019 to 2022 by serological and molecular methods.

Results: An overall arbovirus exposure was observed in 26.1% of the blood donations. Anti-DENV IgM was detected in 4.0% of samples and two donations were DENV NS1 positive. Positive anti-CHIKV IgM was observed in 4.7% of the donations. Co-detection of anti-CHIKV IgM and anti-DENV IgM was observed in 1.0% of donors, and CHIKV prevalence was 21.3%. All blood donations tested were negative for the DENV, ZIKV and CHIKV RNA.

Conclusion: IgM seroprevalence to the arboviruses analyzed here is an indicator of recent infection in asymptomatic donors, showing that the population of blood donors can be a vehicle for new infections, especially during epidemic periods.

Keywords

arboviruses, blood donation, chikungunya, dengue, Zika, Rio de Janeiro, Brazil

Highlights

- Given the high occurrence of asymptomatic arbovirus cases and the fact that viraemia precedes the onset of symptoms, an increased risk of transmission via blood transfusion during outbreaks may occur, especially during epidemics.
- Although there was no detection of the arbovirus RNA in the blood donations analysed, the serological investigation demonstrated that donors were recently exposed to dengue virus and chikungunya virus (CHIKV).
- The high seroprevalence of anti-CHIKV immunoglobulin G antibodies demonstrates that the donor population in Rio de Janeiro was significantly exposed to this urban arbovirus.

Priscila Conrado Guerra Nunes and Flavia Barreto dos Santos contributed equally to the work.

INTRODUCTION

The epidemics caused by the flaviviruses dengue virus (*Orthoflavivirus denguei*, DENV), Zika virus (*Orthoflavivirus zikaense*, ZIKV) and alphavirus chikungunya (*Alphavirus chikungunya*, CHIKV) constitute a serious public health problem in Brazil, with overlapping epidemiology and transmission cycle in urban environments closely related to the *Aedes aegypti*. The high percentage of DENV and ZIKV asymptomatic cases (60%–87%) [1], and up to 28% of CHIKV [2], may result in an increased risk of transmission via blood transfusion during outbreaks [3].

Although the arboviruses' transmission is mainly vectorial and the risk of transmission via blood transfusion or blood components is low, this still constitutes a major concern for transfusion safety [4]. Previous studies have already reported the presence of the main arboviruses in blood donors around the world and in Brazil [5–7], and although rare, clinically significant infections have been documented in cases of transfusion transmission of DENV [8] and ZIKV [9] from asymptomatic blood donors, and outcomes may be unfavourable for recipients [10].

Here, we aimed to investigate the prevalence of main arboviruses of medical importance in Brazil (DENV, ZIKV, CHIKV) in volunteer blood donors assisted at the Arthur de Siqueira Cavalcanti State Institute of Hematology (HEMORIO) at Rio de Janeiro (RJ). The state of RJ, located in the southeast region of the country, has been extensively affected by epidemics of urban arboviruses. From 2019 to 2022, a total of 88,488 cases of dengue, 3639 cases of Zika and 108,183 cases of chikungunya were notified in RJ, and in this period, HEMORIO received 317,067 blood donations.

MATERIALS AND METHODS

Ethical statement and study design

This study was approved by the Research Ethics Committees of HEMORIO (CAAE: 45084221.8.3001.5267) and FIOCRUZ (CAAE: 45084221.8.0000.5248) that waived the informed consent form. This cross-sectional analytical study included samples of plasma from 783 blood donors (0.25%) of the total of 317,067 collected at HEMORIO. The samples were randomly aliquoted during the first semesters, the period of highest arbovirus transmission, from 2019 to 2022. Of the 783 donors, 5 were excluded because they did not reside in the state of RJ and/or did not have complete information in the database, totalling 778 samples. Samples from 2019 to 2021 ($n = 578$) were subjected only to serological tests due to the inadequate storage conditions for molecular detection. Samples collected in the first semester of 2022 ($n = 200$) were investigated by serological and molecular methods. All laboratory diagnoses for the investigation of DENV, ZIKV and CHIKV were carried out at the Virus-Host Interactions Laboratory, LIVH/Oswaldo Cruz Institute, FIOCRUZ.

Arboviruses serological investigation

Serological diagnosis of dengue was performed for the detection of specific IgM antibodies using the commercial Anti-Dengue Type 1-4 IgM Kit (Euroimmun, Lubeck, Germany) and NS1 antigen capture using PLATELIA™ Dengue NS1 Ag Kit (Biorad Laboratories). Serological diagnosis of chikungunya was performed by IgM using the Anti-CHIKV ELISA IgM Kit (Euroimmun, Lubeck, Germany) and for detection of specific anti-CHIKV IgG, the Anti-CHIKV ELISA IgG Kit (Euroimmun, Lubeck, Germany), according to the manufacturer's instructions. Due to the extensive serological cross-reactivity of commercially available ZIKV kits with dengue, the diagnosis of ZIKV was based solely on molecular detection.

Arboviruses molecular investigation

Viral RNA was extracted using the commercial Bio Gene DNA/RNA Kit (Bioclin Quibasa, Brazil), as described by the manufacturer. To enable processing, extraction was initially carried out in a pool of five samples. Forty pools were prepared, each made up of 100 µL of each sample and subjected to RNA extraction. In the event of a positive result, pooled samples were extracted individually to determine the infected donor. For the molecular detection and typing of DENV, quantitative reverse transcription polymerase chain reaction (RT-qPCR) was used according to the protocol described by Santiago et al. [11], for CHIKV, the protocol described by Lanciotti et al. [12] was used, and for ZIKV, the protocol described by Lanciotti et al. [13] was used.

Maps design

The maps were created using the IBGE (Instituto Brasileiro de Geografia e Estatística) database available at https://www.ibge.gov.br/geociencias/informacoes-sobre-posicionamento-geodesico/sirgas/16257-centro-de-analise-ibge.html and using the QGIS software version 3.34.

Statistical analysis

Statistical analysis on dengue and chikungunya prevalence was performed using the chi-square test with the GraphPad Prism software, version 10.0.2, and p value ≤0.05 was considered significant. As we only have one NS1-positive case, this was excluded from the chi-square analysis.

RESULTS

Demographic profile of blood donors

In 2019, the blood donations analysed ($n = 201$) were collected from January to July, in 2020 ($n = 191$) from January to June, in 2021 ($n = 186$) from January to April and in 2022 ($n = 200$), January to April, periods of higher arbovirus circulation. Of all, 53.9% (419 of 778) were female and 46.1% (359 of 778) were male, with age ranging

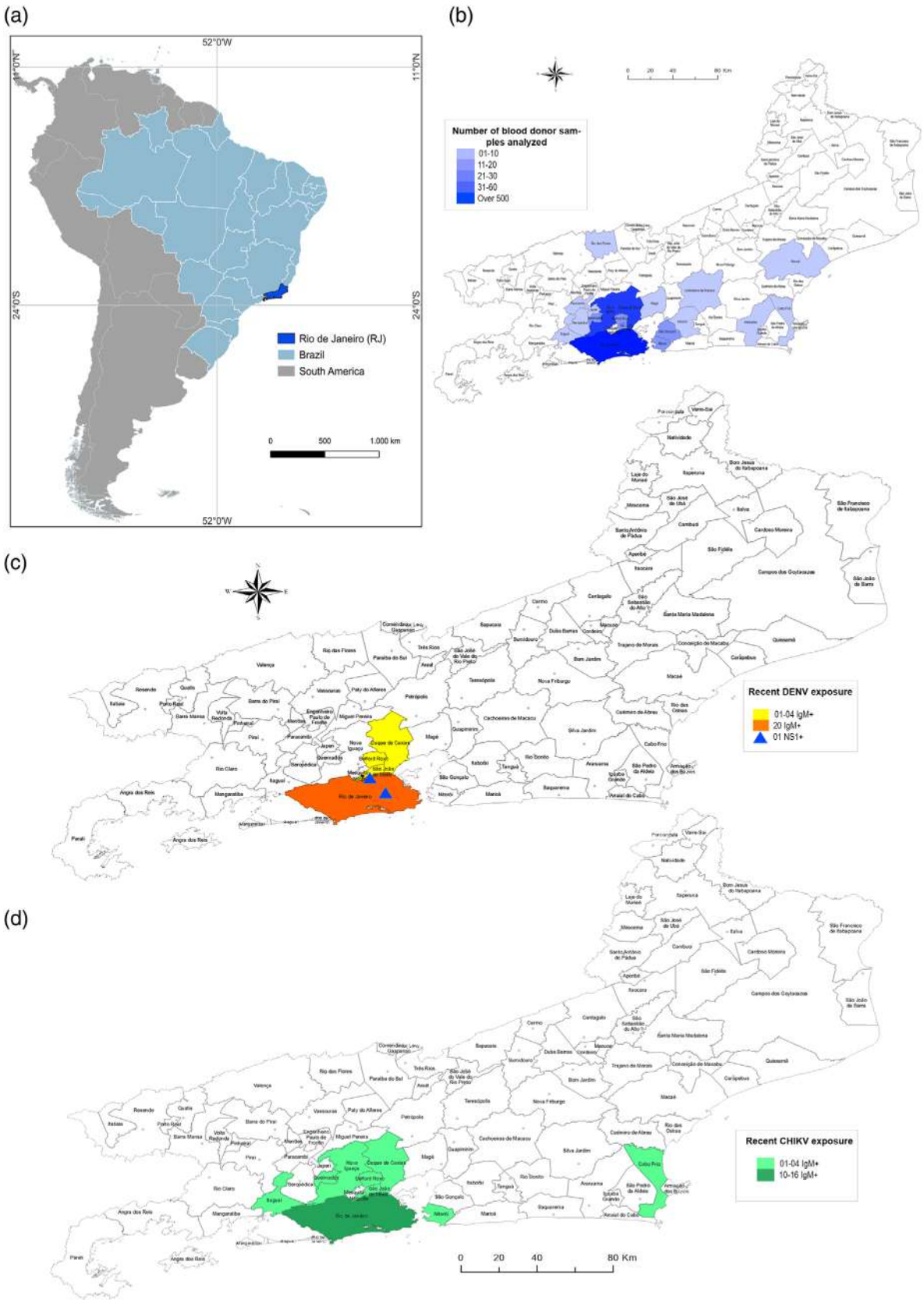

FIGURE 1 Investigation of urban arboviruses in blood donations in the state of Rio de Janeiro (RJ), Brazil, 2019–2022. (a) Localization of the state of RJ, Brazil. (b) Distribution of the total samples from blood donors analysed, according to municipality of residence. (c) Distribution of asymptomatic donors with indicative recent exposure to dengue represented by a positive anti-dengue virus (DENV) IgM and/or dengue NS1 and (d) to chikungunya represented by a positive anti-chikungunya virus (CHIKV) IgM.

from 17 to 72 years old. The highest percentage of donors analysed was in the 20–39 age group (62.5%). A total of 4.7% (37 of 778) of the donors presented a positive serological diagnosis for viral hepatitis (B and C), Chagas disease, HIV, HTLV or syphilis. The state of RJ located in the south-east region of Brazil (Figure 1a) has 92 municipalities. Herein, donors analysed were representative of 21 of those, and 70.0% (545 of 778) were mainly from the municipality of RJ, followed by Duque de Caxias (7.4%; 58 of 778) and Nova Iguaçú (4.1%; 32 of 778), as observed in Figure 1b.

Investigation of recent exposure and prevalence of urban arboviruses in blood donors

All samples were subjected to serological assays to determine recent DENV and CHIKV exposure by detecting anti-DENV and anti-CHIKV IgM antibodies and presence of dengue NS1 antigen. Anti-DENV IgM-positive results were observed in 4.0% (31 of 778) of the samples, with the highest number of positive donations from 2022 (Table 1). A DENV NS1-positive antigen detection was confirmed in two asymptomatic donors (0.3%; 2 of 778) from 2019, who had a negative anti-DENV IgM result. Likewise, anti-CHIKV IgM antibodies were observed in 4.7% (37 of 778) of the blood donations and 35 presented inconclusive results. A higher positivity was observed in donations received during 2020 (8.9%; 17 of 192) (Table 1). In eight donors, the co-detection of anti-CHIKV IgM and anti-DENV IgM antibodies (1.0%; 8 of 778) was reported: six females and two males from the municipalities of RJ ($n = 2$), Belford Roxo ($n = 3$), Duque de Caxias ($n = 1$), Nilópolis ($n = 1$) and São João de Meriti ($n = 1$) (Figure 1c,d).

For dengue, the highest frequency of positive donors was in the age group between 20 and 39 years old, corroborating the higher frequency of donations in this age group. For chikungunya, two donors between 17 and 19 years of age showed indication of recent CHIKV infection by the detection of specific anti-CHIKV IgM antibodies; however, as observed for dengue, the highest frequency of positive donors was between 20 and 39 years of age.

TABLE 1 Investigation of recent exposure and prevalence of urban arboviruses in samples from asymptomatic blood donors ($n = 778$) received at HEMORIO.

	Anti-DENV IgM detection		Anti-CHIKV IgM detection		Anti-CHIKV IgG detection	
Year	Positive/ prevalence (*n*, %)	Inconclusive/ prevalence (*n*, %)	Positive/ prevalence (*n*, %)	Inconclusive/ prevalence (*n*, %)	Positive/ prevalence (*n*, %)	Inconclusive/ prevalence (*n*, %)
2019 ($n = 201$)	7 (3.5)	8 (4.0)	8 (4.0)	10 (4.9)	20 (10.0)	1 (0.5)
2020 ($n = 191$)	10 (5.2)	7 (3.7)	17 (8.9)	6 (3.1)	53 (27.7)	10 (5.2)
2021 ($n = 186$)	3 (1.6)	4 (2.1)	3 (1.6)	9 (4.8)	38 (20.4)	0
2022 ($n = 200$)	11 (5.5)	17 (8.5)	8 (4.0)	10 (5.0)	55 (27.5)	0
Total	31/778 (4.0)	36/778 (4.6)	36/778 (4.7)	35/778 (4.5)	166/778 (21.3)	11/778 (1.3)

Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus.

TABLE 2 Distribution of asymptomatic donors with some indication of exposure to DENV and/or CHIKV ($n = 203$) by type of infection (recent or previous) by year.

	Blood donors with indication of exposure to DENV and/or CHIKV ($n = 203$)			
	Indication of recent DENV infection (*n*, %)		Indication of recent CHIKV infection (*n*, %)	Indication of previous CHIKV exposure (*n*, %)
Year	Anti-DENV IgM	DENV NS1	Anti-CHIKV IgM	Anti-CHIKV IgG
2019 ($n = 33$)	7 (21.2)	2 (6.0)	8 (24.2)	19 (57.6)
2020 ($n = 63$)	10 (15.9)	0	17 (27.0)	51 (81.6)
2021 ($n = 41$)	3 (7.3)	0	3 (7.3)	37 (90.2)
2022 ($n = 66$)	11 (16.7)	0	8 (12.1)	54 (81.8)
Total ($n = 203$)	31/203 (15.3)	2/203 (0.01)	36/203 (17.7)	161/203 (79.3)
p value*			0.0643	

Abbreviations: CHIKV, chikungunya virus; DENV, dengue virus.
*p value was calculated using the chi-square test. $p \leq 0.05$ is statistically significant.

Here, 21.3% (166 of 778) of asymptomatic blood donors presented specific anti-CHIKV IgG antibodies, indicating previous exposure to the virus. Depending on the year analysed, the prevalence ranged from 10.0% to 27.7%, with the highest percentage observed in 2020 (Table 1).

Overall, 26.1% (203 of 778) of blood donors analysed from 2019 to 2022 showed some indication of recent exposure to DENV and/or CHIKV. Regardless of the year, it was observed that 79.3% (161 of 203) of the donors were previously exposed to CHIKV, characterized by the presence of specific anti-CHIKV IgG antibodies, with a high prevalence in 2021 (90.2%; 37 of 41; $p = 0.0643$) (Table 2).

Molecular detection of viral RNA was performed by RT-qPCR in all 200 blood donations from 2022, and all samples tested were negative for the DENV, ZIKV and CHIKV RNA.

DISCUSSION

Although the risk of transmission of infectious agents by transfusion of whole blood or blood components is relatively low, the emergence of some pathogens, including arboviruses, has become a relevant threat to transfusion safety in the last 20 years [4, 14], given the high occurrence of asymptomatic cases in DENV and ZIKV infections, and the fact that viraemia precedes the onset of symptoms. To date, there are no recent studies that characterize the incidence rates, seroprevalence and actual percentage of donors positive for arboviruses of medical importance, and how pathogenic the use of blood products with viraemia in recipients may be. Some data include viral RNA investigation, demonstrating percentages in asymptomatic donors: 5% for DENV, 1% for CHIKV and 2% for ZIKV. Despite a limited number of samples tested in this study, the results found show a total seroprevalence of 4% for anti-DENV IgM and 4.7% for anti-CHIKV IgM [15].

The detection rate of IgM anti-DENV in 2021 was the lowest (1.6%). In 2019, the state of RJ reported 50,595 probable cases of dengue, with the capital region, where HEMORIO resides, leading the number of cases (22,046) and with a risk of a new epidemic in the following year, 2020. However, due to the emergence of SARS-CoV-2, which resulted in the under-reporting of cases of urban arboviruses, and the precariousness of laboratory diagnosis faced with a new demand, cases in 2020 decreased significantly—8496 cases were reported. In 2021, there was a low incidence in the state, which may corroborate the low seropositivity in the same year of the study. In 2022, however, the state of RJ reported 23,120 dengue cases.

The highest seropositivity for anti-CHIKV IgM-positive donations (8.9%) was in 2020, despite a greater number of chikungunya cases having been reported in 2019, when the state notified more than 99,000 cases. The higher percentage of symptomatic cases in CHIKV infections may be a limiting factor for candidates to donate or even for inability during the pre-donation screening, if the disease is recent. However, the high seroprevalence of anti-CHIKV IgG demonstrates that the donor population in RJ was significantly exposed to this urban arbovirus. The last major CHIKV epidemic in RJ and Brazil was in 2018, so a higher seroprevalence was expected, especially in the following year, 2019. In this study, the year with the highest detection of anti-CHIKV IgG in donors was 2020 (27.7%).

Despite some limitations, such as low number of samples analysed and limited molecular analysis of some samples due to storage conditions, this study shows the importance of investigating arboviruses in blood banks throughout endemic areas such as of Brazil and other Latin American countries for the safety of transfusions. Blood banks have used different strategies to identify them, such as the use of new serological markers and the implementation of nucleic acid tests (NATs) for ZIKV. However, NAT screening has limitations, such as low concentrations of genetic material, resulting in undetectable viruses in a window period when the donor can be potentially infectious [14]. Therefore, the use of serological methods may be a reliable approach, such as DENV NS1 investigation, a protein involved in viral replication and suggestive of an active infection.

Although there was no detection of viral RNA from the three urban arboviruses analysed here, the serological investigation demonstrated the donors' exposure during the period. Moreover, despite the number of samples analysed, the seroprevalence of IgM is an indicator of recent infection in asymptomatic donors, showing that the population of blood donors can be a vehicle for new infections.

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F.B.d.S. and P.C.G.N. designed the research study; R.R.d.S. performed the research, and collected and analysed the data; R.R.d.S., F.B.d.S. and P.C.G.N. wrote the paper.

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.

ORCID

Flavia Barreto dos Santos https://orcid.org/0000-0002-1309-5366

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REPORT

Vox Sanguinis ISBT International Society of Blood Transfusion

Generating pathways to domestically sourced plasma-derived medicinal products: Report from a workshop by the International Plasma and Fractionation Association and the Working Party on Global Blood Safety of the International Society of Blood Transfusion

Albert Farrugia[1,2] | Robert Perry[1] | Françoise Rossi[1] | Leni von Bonsdorff[1] | Glynis Bowie[3] | Jean-Claude Faber[4] | Jeh-Han Omarjee[5] | Jay Epstein[4] | Jenny White[6]

[1]International Plasma and Fractionation Association, Amsterdam, The Netherlands

[2]Faculty of Medicine and Health Sciences, The University of Western Australia (M509), Perth, Australia

[3]Western Province Blood Transfusion Service (WPBTS), Cape Town, South Africa

[4]Global Blood Safety Working Party, International Society for Blood Transfusion, Amsterdam, The Netherlands

[5]Microbiological Sciences, National Bioproducts Institute, Durban, South Africa

[6]International Society for Blood Transfusion, Amsterdam, The Netherlands

Correspondence
Albert Farrugia, Faculty of Medicine and Health Sciences, The University of Western Australia, Perth, Australia.
Email: albert.farrugia@uwa.edu.au

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Abstract

Plasma-derived medicinal products (PDMPs) are recognized internationally as essential medicines required to treat various acute and chronic conditions including congenital deficiencies of plasma proteins in haemophilia and primary immune deficiency. Global provision of these medicines is dominated by a small number of commercial companies, influencing the price and availability of the products. Achieving a level of strategic independence from this dominance is now seen as a public health priority in many countries. During the Regional Congress of the International Society for Blood Transfusion (ISBT) in Cape Town, South Africa, in November 2023, around 50 delegates from 24 countries participated in a workshop (WS) organized jointly by the International Plasma and Fractionation Association (IPFA) and the ISBT Working Party on Global Blood Safety on pathways towards provision of PDMPs from domestic plasma independent of commercial purchase in the open market. The WS was structured around three themes, each addressed by a separate group:

A. Quality/safety requirements for plasma for fractionation (PfF)
B. Stepwise access for safe plasma proteins

No part of this manuscript was constructed with the use of artificial intelligence.

C. Approaching contract fractionation

A synthesis of conclusions from these groups included the following:

1. The need to acquire support from government authorities for a national plasma policy, recognizing the difficulties posed by unstable political and bureaucratic environments.
2. The value of embedding plasma and PDMPs within a patient blood management (PBM) paradigm to promote optimal clinical use of PDMPs.
3. Training of blood/plasma collection personnel in the relevant principles of Good Manufacturing Practice (GMP), coupled with regulatory oversight of plasma product production in the engaged jurisdictions.
4. Appreciation that limited access to contract fractionation may necessitate a stepwise approach, which may include small-scale preparation of versions of essential plasma proteins as an intermediate phase towards the manufacture of industrial-scale PDMPs from domestic plasma.

Highlights

- The development of healthcare includes access to plasma-derived medicinal products (PDMPs) as essential therapies for a number of medical conditions.
- Strategic independence from the vagaries of the commercial market necessitates the generation of a supply of high-quality plasma from domestic donors.
- A number of models exist for the use of this plasma, depending on the state of the health system, but all of them conferring control of the supply of PDMPs on the public health service.

INTRODUCTION

The provision of plasma-derived medicinal products (PDMPs) in the global market is dominated by the activities of an increasingly concentrated and small number of commercial companies that extract their products, predominantly, from a population of paid plasma donors, mainly from the United States. This generates challenges for countries seeking to protect their national health systems from disruptions in the supply of these essential medicines, as the vagaries of the free market, underpinned by the core need of securing a return on investment for the commercial sector, adopt supply policies that may not be convergent with the needs of public health. The establishment of publicly owned blood services affords an opportunity to address and alleviate this problem, through the generation of plasma recovered from whole blood donations, ensuring, from current therapeutic principles of blood component therapy, the availability of a regular supply of raw material for fractionation. As the collection of blood approaches a level of sufficiency with clinical red cell needs, this supply of recovered plasma may be augmented with plasma collected specifically for fractionation through plasmapheresis from the same publicly managed, voluntary, non-remunerated donor pool. Recent findings indicate that this source can provide a more resilient supply compared to paid donor collection.

The growing recognition of the vulnerability in the provision of essential PDMPs increased during and after the COVID-19 epidemic when the supply of the key product, immunoglobulin (Ig), from the United States was straitened and prices increased significantly [1]. This has stimulated a number of processes, including the 2020 Emergency Support Instrument for COVID convalescent plasma (CCP) [2] and the SUPPLY project in Europe [3], aimed at increasing the collection and fractionation of publicly owned plasma. While projects such as SUPPLY are building on a foundation of established public provision, now embedded within healthcare systems and overseen by expert competent regulatory authorities, these prerequisites are either lacking or still nascent in many low- and middle-income countries (LMICs).

The convening of the Regional International Society for Blood Transfusion (ISBT) Congress in Cape Town, South Africa, in November 2023 afforded an opportunity to hold a workshop (WS) on 'Plasma Fractionation and Stepwise Access to PDMPs' to discuss these issues, aiming to develop a group of recommendations for the stakeholders involved. The main objective of the WS was to synthesize a strategy for generating pathways for the provision of PDMPs sourced from publicly collected domestic plasma, with particular emphasis on the needs of LMICs. The wide representation from African blood services lent itself to the formation of champions advocating for the strategy in their respective countries as an additional objective.

WS structure

WS participants were registered participants of the ISBT congress who had the opportunity to indicate their wish to participate prior to

TABLE 1 Country of origin of the WS participants.

WS group	A	B	C
	Cameroon	China	Canada
	Egypt	Congo	Congo
	France	Indonesia	Indonesia
	Indonesia	Kenya	Japan
	Germany	Luxembourg	Kenya
	South Africa	Netherlands	Namibia
	Turkey	Norway	Netherlands
	United Kingdom	Pakistan	South Africa
	United States	Taiwan	Switzerland
	Zimbabwe	South Africa	Uganda
		Switzerland	United Kingdom
		United States	United States

Abbreviation: WS, workshop.

the congress or to join without prior notification. They participated in their own personal capacity, irrespective of their country of origin or organizational affiliation. A total of 50 participants self-allocated into the three WS groups:

A. Quality/safety requirements for plasma for fractionation (PfF)
B. Stepwise access for safe plasma proteins
C. Approaching contract fractionation.

Each group was moderated by a representative of the ISBT Working Party on Global Blood Safety, and group outcomes were reported by a member of IPFA.

The geographical distribution of the participants in each group is shown in Table 1. Thirteen participants were from Africa, which was the continent with the highest proportion of participants.

The professional backgrounds of those present in the WS are summarized in Table 2. Thirty-five participants were from LMICs and 15 were from high-income countries (HICs).

What follows is a review of the outcomes of the WS, followed by a discussion around the issues identified, within the context of global developments in the provision of therapies derived from human blood and plasma.

GROUP A: QUALITY/SAFETY REQUIREMENTS FOR PfF

The group addressed management systems and basic quality/safety requirements for plasma as essential prerequisites for generation of PfF.

The countries participating in this group were surveyed in order to understand the current status of quality systems in their respective jurisdictions (Table 3).

Challenges identified by the group included transportation of plasma and maintenance of the cold chain, with the initial cooling of blood to 2–4°C, which is identified as particularly difficult in LMIC environments. This has been identified as a particular issue for countries seeking to ferry blood collected remotely to processing centres for the generation of recovered PfF. The maintenance of equipment at that temperature was also considered to be an area that demanded attention.

TABLE 2 Professional background of participants.

Background	Number
Blood transfusion services	36
Plasma fractionation organizations	3
Regulatory agencies	2
Public health governance bodies	5
Diagnostics providers	4

Support by the government for contract fractionation was unclear in several instances, but such support was identified in some countries where the contract for fractionation is owned by the blood service.

It was clear that training is a key element in progression to an adequate level of quality and readiness for plasma collection. Advocacy for this progression, including support for converting donors of whole blood to plasma donors, was also identified as a priority in countries where this was considered appropriate within the overall context of blood and component provision.

GROUP B: STEPWISE ACCESS TO SAFE PLASMA PROTEINS—HOW TO GET STARTED SMALL SCALE AND PROGRESS

This group included delegates from developed and developing countries, from a wide background, including blood banks and fractionation agencies.

In developing a path towards the provision of domestically sourced plasma proteins, the assessment of the particular situation faced by a specific country/region is a key preliminary step. Within such an assessment, several components should be considered.

An analysis of which clinical needs can be addressed by plasma products is essential. In most LMICs, the treatment of rare chronic plasma protein deficiencies, such as haemophilia and primary immune deficiency, assumes a secondary level of importance compared to the needs of acute care and emergency medicine, explaining why albumin is the primary plasma product in these therapeutic landscapes (e.g., Indonesia [4], China [5]). The status of the blood/plasma collection system in the context of generating plasma of fractionation of sufficient quality is also crucial. Basic infrastructural needs, particularly the establishment and maintenance of a cold chain, need to be met. The ability to separate plasma from whole blood donations and, progressively, from apheresis collections needs to be assessed. Standards for safety and quality need to be established through, for example, the Good Practice Guidelines of the European Union [6] and the Pharmaceutical Inspectors Convention Scheme (PICS) Guide for Good Manufacturing Practice (GMP) [7]. These may lay the basis for a

TABLE 3 Status of plasma fractionation in participating jurisdictions.

Survey question/issue	Response
Presence of contract fractionation of plasma in the country	Yes: Four No: Five (includes countries which do supply plasma for fractionation but not under contract)
Intention to establish fractionation in the country	Yes • Five countries had a 2–3-year plan • Two countries within ≥3 years • Four countries within 5 years No: four countries
Audits for quality systems/ GMP	No audits: One Government auditors: Five Independent auditors: Four
Plasma collection	Recovered plasma from WB donations: Seven Apheresis plasma: Six Plans to collect PfF: One
Compliance with standards	Internal audits: Five External authorities: Seven Assessed by the American Association of Blood Banks (AABB) [29]: One
Standards applicable	WHO GMP [30]: Four PICS Guide for GMP [7]: Three European Union [31]: Six Food and Drug Administration [32]: Two European Department for Quality of Medicines Guide [6]: Six African Society for Blood Transfusion: Two Local standards: Two *Note:* The majority of countries were aware of the European Good Practices Guidelines
Technologies used	Automated/semi-automated for collection/separation: Eight Closed systems: Seven No answer: Two
Selection criteria for donors of PfF	Additional requirements for PfF in addition to those of whole blood: Six
Testing	Nucleic acid testing • Mini-pool: Two • Individual: Seven

Abbreviations: GMP, Good Manufacturing Practice; PfF, plasma for fractionation; PICS, Pharmaceutical Inspectors Convention Scheme.

quality system for plasma generation, which can evolve into full GMP such as required by fractionation companies and regulatory agencies.

Because this progression of blood/plasma establishments to a full GMP status will require time and investment, consideration may be given to whether a satisfactory intermediate phase, generating therapies requiring a lower level of investment, can be generated within a local environment with less stringent requirements. Intermediate products generated from mini-pools of plasma, such as have been described [8], may act as a bridge towards full-scale, pharmaceutically manufactured plasma derivatives.

TABLE 4 Rates of whole blood conversion to components.

Country	Whole blood donations converted to components (%)
Indonesia	80
Japan	100
Namibia	100
South Africa	100
Uganda	60

The next step, which is ideally performed in parallel with this intermediate development, should be the generation of sufficient volumes of plasma of sufficient quality to attract the attention and interest of fractionators providing services through contract plasma fractionation. The required volume should clearly be based on the clinical needs assessment as noted above, keeping in mind that the required PDMP mix, as well as the plasma volumes required, will change over time. Any contracts put in place should recognize this projected evolution and incorporate measures that can optimize outcomes for the contractee as well as the contractor. For example, a surplus of Ig generated through fractionating plasma, where albumin continues to be the plasma procurement driver, may be commercialized to the benefit of both parties as long as measures are in place to ensure that the contractee is not disadvantaged, as the required product mix evolves and shifts according to the exigencies and evolution of the health system. Hence, CONTROL by the owners of the plasma is essential, and such ownership needs to be retained by the public health authorities.

In addition, it should be recognized that spare fractionation capacity for the execution of such contract arrangements is limited globally, and hence progression to the next step, namely the generation of a domestic/regional capacity, is highly desirable as the ultimate goal for a system attempting a degree of strategic independence in the supply of plasma products. The commissioning of such a capacity should be part of a long-term plan, including considerations such as evolving clinical need, the provision of alternative therapies, and so on. Overall, the generation of a capacity to access plasma protein therapies from a domestic source needs to be based on a national plasma programme and underpinned by a national plan from the government, synthesized through a political consensus to ensure long-term stability and viability.

GROUP C: APPROACHING CONTRACT PLASMA FRACTIONATION

This group also had a wide representation from both developed and developing countries. Initial soundings regarding the movement to component therapy, as an essential prelude to generating PfF, revealed the rates shown in Table 4.

The overarching challenge in meeting the goal of establishing and maintaining component therapy was identified as acquiring resources

for equipment, infrastructural support for the collection centres and training. Addressing the mindset of senior government officials who are in positions that can influence this progression was also considered as fundamental. The constant turnover of key personnel in the Ministries of Health, directly or indirectly influenced by political factors, was also considered to be a significant impediment to the establishment and maintenance of a stable policy for the public blood sector. Coupled to this is the difficulty in establishing regulatory appreciation of the blood and plasma systems, even in countries with an established regulatory provision. Particular difficulties are experienced by countries as a result of geographical realities, as exemplified by Indonesia, the world's largest archipelago, with blood centres scattered across hundreds of islands. On the basis of this assessment of these current challenges, this group proposed the following recommendations to the participants:

1. Promotion of a positive relationship between users and suppliers of plasma products as a route to acquiring buy-in from clinicians for a PfF programme.
2. Promotion of a blood component policy as an embedded foundation of a patient blood management (PBM) programme.
3. Improvement of GMPs as a contributor to the minimization of waste of plasma, allowing the demonstration of the economic benefit of investing in such practices.
4. Education on the particular needs for PfF generation in the Ministries of Health and other state authorities, through an appropriately targeted lobbying effort.
5. Assessment and identification of clinical demand according to national needs and public health priorities, both current and future.
6. Improvement of the capacity of the blood system to deliver on the basis of a national plasma policy.
7. Training of staff at blood establishments on the production and control of PfF and to set up appropriate procedures for this.

It was agreed that the generation of a surplus of quality plasma through a component strategy was a pivotal goal, coupled with an alliance with Key Opinion Leaders (KOLs) for moving this forward. In addition to promoting contract plasma fractionation under a national policy as a public health goal, its economic benefits over commercial procurement of PDMPs can be emphasized. The recognition of the importance of plasma within key government and public areas of decision-making needs to be enhanced to raise plasma to the same status as blood donation. A negative image of plasma donation, which sometimes is projected through activities of the paid donor sector, needs to be countered, emphasizing that this activity is also carried out by voluntary unpaid donors.

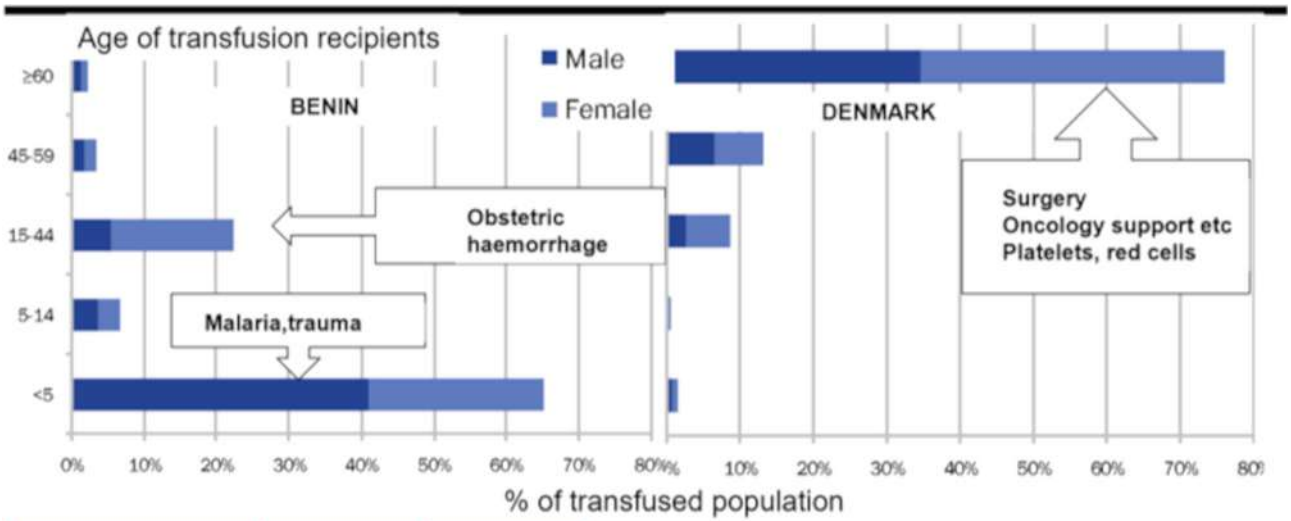
Synthesis of the groups' outcomes

The wide spread of competences, together with the perspectives gained from countries of different economic capacities, contributed to the following key insights:

1. Participants from HICs shared their experience of the effect of the recent COVID-19 pandemic on the supply of PDMPs, whereby commercial provision of critical products such as Ig was curtailed and substantial price increases were experienced [9]. This accentuated the need to acquire strategic independence in the provision of PDMPs through control of the whole supply chain.
2. The large volumes of recovered plasma wasted in Africa, subsequently reported by Moftah [10], demonstrates that adequate conformance to quality systems and standards would generate a substantial flow of plasma suitable for fractionation to PDMPs, which is possible by going through an intermediate stage of small-scale blood bank manufacture.
3. Such small-scale provision was reported to the WS by Egypt and Senegal for the provisions of pathogen-reduced cryoprecipitate [10], and other ventures may be possible if adequate technology can match patient needs.
4. A partnership between public and private agencies may be possible in generating a domestic fractionation capacity, as was reported by Indonesia [11].
5. Participants from LMICs emphasized the difficulties in maintaining engagement with government institutions due to the high turnover of bureaucrats in key positions. This was appreciated by participants from HICs who shared their experience in maintaining and embedding links with these important stakeholders.
6. Regional cooperation between blood services and a regionally located fractionator, such as is under way in Africa through the 'Plasma from Africa for Africans' programme [12], can provide a model whereby domestically sourced PDMPs can be provided and also used to generate a revenue flow for improvements in the public blood collection system [13].

DISCUSSION

In approaching the development of a stepwise approach to the provision of PDMPs, it is appropriate to start with an assessment of clinical needs in the country of interest. In this context, it is important to note that the primary role of a national blood system is to ensure adequate and evidence-based provision of blood components for transfusion in mainstream medical and surgical practice. In HICs, transfusion practice has evolved to the stage where these needs are met by components produced from whole blood and, in some instances, apheresis donations. The material and quality infrastructure that maintains this system is at a high level, and it generates a substantial volume of plasma as a by-product of the process. In many countries, the need for PfF has catalysed the conversion of whole blood to components, in tandem with the evolution of their medical services to a stage when most transfusions were needed for correction of normovolaemic rather than hypovolemic anaemia, and platelets became an established modality for oncological support. Concurrently, the need for PDMPs in these countries, dominated by the demand for Ig, has spurred the collection of PfF by plasmapheresis, an activity previously mostly limited to the paid-donor commercial sector.



	Benin	Denmark
Population	9099922	5580413
GDP/cap (PPP) $	1481	37151
Transfusions/10^3 population	6.1	9.6

FIGURE 1 Demographic and clinical use in the transfused populations of Benin (low- and middle-income country) and Denmark (high-income country). In Benin, the transfused population is much younger than in Denmark, and most blood is transfused for acute, rather than chronic, indications. From WHO 2011. GDP, gross domestic product.

As the use of albumin as a general treatment for acute blood loss has waned, the use of PDMPs in HICs has evolved, primarily, into the treatment of a number of rare, chronic disorders, which are less represented in the usage profile of LMICs (4, 5). In LMICs, the clinical demands for blood-derived therapies differ, and much of the blood collected is transfused for different clinical indications than in HICs. An analysis of the clinical use of blood in two contrasting economies, namely Denmark and Benin, demonstrates this difference [14] (Figure 1). In many LMICs, transfusion support is mostly allocated to acute conditions, involving hypovolemic loss of whole blood. As an example, in sub-Saharan Africa, red cell transfusion for trauma and malaria, a condition that is associated with hypovolemia as well as anaemia [15], forms the basis of most of transfusion support. This suggests that whole blood may be a more appropriate modality than plasma-depleted red cells for these indications. This is borne out by the results of the Transfusion and Treatment of African Children trail (TRACT), which found better outcomes for anaemic children when they were transfused with whole blood compared to packed red blood cells [16].

It is important to recognize these different clinical needs when developing a policy for generating capacity to access PDMPs. As healthcare systems in LMICs improve, it may be expected that the clinical usage profile alluded to above will approach more closely that of HICs. This shift would include an expansion in diagnostic capacity for rare diseases, currently at a level that underestimates significantly the prevalence of rare congenital protein deficiencies in LMICs [17], and would require the inclusion of rare, chronic disorders in the national ambit of therapeutic provision. Convergent with the shift of red cell needs from hypovolemic to normovolaemic anaemia, this will create conditions for the generation of a surplus of plasma, which may be considered for fractionation.

Following this first step, that is, ensuring sufficiency of safe blood for transfusion, the second step of generating a supply of PfF presents clear challenges in assuring sufficient quality according to the norms for this raw material. The introduction of these norms, several of which were identified by the WS, can also stimulate an enhancement in the overall manufacturing environment of blood collection centres, resulting in a positive feedback loop in all the quality system requirements of their operations [18]. The generation of plasma to a standard that may satisfy a contract fractionator [19] may require considerable time and investment, and an intermediate stage in the provision of essential therapies, if justified by an assessment of clinical needs, could involve the blood-bank-based production of some products such as pathogen-reduced cryoprecipitate [20]. It is important that such endeavours do not deflect from the main goal of approaching sufficiency in domestic plasma that can be fractionated into a number of PDMPs, as pharmaceutical production under the more sophisticated methods and strictly enforced GMPs of the fractionation companies is inherently superior to such small-scale product preparation. Any such technologies that affect the residual plasma after removal of these fractions, so that it cannot be utilized to prepare more than one product, should also be avoided in long-term usage.

TABLE 5 Domestic fractionation plants closed over past decades.

Country	Year began	Year closed	Reason for closing
Hungary	1970s	1990s	Govt. plant closed in 1990s; costly investment needed to maintain cGMP (current Good Manufacturing Practices); plasma supply issue
Denmark	1980s	1998 and 2003	Novo Nordisk sold its plant which was in financial distress and closed in 1998; SSI closed its plant in 2003 due to the need for costly cGMP investments to continue to compete, lack of plasma and strategic focus on vaccine production
Finland	1960s	2005	Costly investment needed to meet new cGMP; sales hampered by low prices (albumin)
Scotland	1970s	2006	Costly investment needed to meet cGMP; mad cow disease
Thailand	1984	2007	Costly investment needed to meet cGMP; new plant built by Korean commercial partner
Switzerland/Spain	1950s	2002	Costly investment needed to meet cGMP and to renew registrations in many countries for multiple products; strategic decision to focus on vaccines

Note: From Robert (IPPC 2022) [25].

The WS recognized the need to ensure buy-in from national authorities, including key political and administrative figures, in the implementation of a national plasma policy. Arguments that can be used to acquire such support include the potential economic benefits of generating a supply of domestically sourced PDMPs in lieu of importation from the open market. This would contribute to protecting the public health system from fluctuations in supply caused by discontinued commercial provision as PDMPs are shifted across geographies for commercial advantage [21]. Security of supply is also enhanced through the sourcing of plasma from voluntary donors, which has been shown to lead to a supply that is more resilient to disruptive events than paid donors [22]. Income from surplus products/fractions from a national fractionation programme can also be used to offset the costs of improving other aspects of the transfusion system [13].

Following the step of generating a stable and growing supply of quality plasma for contract fractionation, consideration may be given to the commissioning of a plasma fractionation plant in the country of interest. The WS noted that the spare capacity of the current global manufacturers for accepting plasma for contract manufacture is limited. Another consideration driving this step towards domestic manufacture is the potential of contract manufacturers perceiving that such an activity may not be to their commercial benefit, as contract-manufactured products might be able to displace some of their own market of more highly priced products (19). This may shrink access to contract fractionation in the future. These factors support consideration of a domestic or regional plant, which may be a not-for-profit project as in Thailand [23, 24] or a commercial project as in Indonesia [11]. The commitment required for this final step in getting access to PDMPs is considerably higher than in the earlier steps, and many projects initiated over the past years have not come to fruition. Several domestic plants have closed, and the reasons posed illustrate many of the issues identified by this WS [25] (Table 5) involving the need to commit to investing in continuous quality management.

Against this historical reality is the concentration of fractionation plants in Europe and the United States, with the presence of only one plant in the whole of the African continent [26] and another under construction [27]. In addition, key government figures in Africa, such as the Ethiopian Food and Drug Authority, have concurred that there is a need to produce PDMPs in that country [28]. Establishment of plasma fractionation plants, controlled by public authorities and open to commercial investment, may be the next step in the journey of countries aspiring to achieve a strategic independence for these essential medicines.

In conclusion, this WS afforded an opportunity for participants drawn from a range of countries and blood service activities to exchange experiences and gain insights aimed at establishing pathways for generating domestically sourced PDMPs. In particular, participants from LMICs were afforded an opportunity to draw on each other's experience and that of HICs to acquire tools for the advocacy and establishment of such pathways. The outcomes of the WS were synthesized in the following recommendations:

1. The need to acquire support from government authorities for a national plasma policy, recognizing the difficulties posed by unstable political and bureaucratic environments.
2. The value of embedding plasma and PDMPs within a PBM paradigm to promote optimal clinical use of PDMPs.
3. Training of blood/plasma collection personnel in the relevant principles of GMP, coupled with regulatory oversight of plasma product production in the engaged jurisdictions.
4. Appreciation that limited access to contract fractionation may necessitate a stepwise approach, which may include small-scale preparation of versions of essential plasma proteins as an intermediate phase towards the manufacture of industrial-scale PDMPs from domestic plasma.

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

ORCID

Albert Farrugia https://orcid.org/0000-0003-0804-7463

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Vox Sanguinis ISBT International Society of Blood Transfusion

LETTER TO THE EDITOR

Immunoglobulin solutions for patients with primary immunodeficiency. Comments on Burnouf et al.'s 'Stepwise options for preparing therapeutic plasma proteins from domestic plasma in low- and middle-income countries'

As the global organization representing patients with primary immune deficiency (PID), the International Patient Organization for Primary Immunodeficiencies (IPOPI) would like to express its views on the immunoglobulin preparation referred to in 'Stepwise options for preparing therapeutic plasma proteins from domestic plasma in low- and middle-income countries' in the February 2024 issue of *Vox Sanguinis* [1]. IPOPI commends any effort that can increase access to treatment for patients in low- and middle-income countries (LMIC), particularly patients suffering from PID. IPOPI notes that this preparation has been validated clinically in patients with immune thrombocytopaenia, an indication that addresses the aspects of immunoglobulin function, which are detached from those involved in PID. Clinical trials of this preparation in PID patients are therefore necessary. However, prior to its use in patients who require life-long treatment with immunoglobulin, further validation of the manufacturing method's capacity to eliminate viruses is also required. The publication cited by Burnouf et al. indicates that no such validation was performed for non-enveloped viruses [2]. IPOPI concurs with global authorities, which require the inclusion of two orthogonally distinct steps in the manufacture of plasma products [3]. IPOPI notes the authors' intention to pool several batches of the preparation to ensure conformance to the requirement that immunoglobulin products need to be derived from a plasma pool, which is sufficiently large to ensure an adequate spectrum of antibodies [4]. These manipulations, together with the actual production of the preparation, require adherence to Good Manufacturing Practices if the product is to have sufficient quality and safety. The introduction of these practices will enhance the capacity of LMIC to generate a flow of quality plasma for contract fractionation, thereby allowing the leapfrogging of the 'small-scale' preparations step in the authors' proposed approach to the next step of form of contract fractionation. IPOPI notes that this is already underway in a number of LMIC, including Iran [5] and Egypt [6].

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CONFLICT OF INTEREST STATEMENT

The authors represent the International Patient Organization for Primary Immunodeficiencies (IPOPI).

DATA AVAILABILITY STATEMENT

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

Martine Pergent[1]
Johan Prevot[1]
Leire Solis[1]
Albert Farrugia[2,3]

[1]*The International Patient Organisation for Primary Immunodeficiencies (IPOPI), Brussels, Belgium*
[2]*Network of Experts, IPOPI, Brussels, Belgium*
[3]*Faculty of Medicine and Health Sciences, The University of Western Australia (M509), Perth, Australia*

Correspondence
Albert Farrugia, Faculty of Medicine and Health Sciences, The University of Western Australia (M509), 35 Stirling Highway, 6009 Perth, Australia.
Email: albert.farrugia@uwa.edu.au

ORCID

Albert Farrugia https://orcid.org/0000-0003-0804-7463

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LETTER TO THE EDITOR

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Response to comments from the International Patient Organization for Primary Immunodeficiencies on 'Stepwise options for preparing therapeutic plasma proteins from domestic plasma in low- and middle-income countries'

We appreciate the dedication of the International Patient Organization for Primary Immunodeficiencies (IPOPI) to improving treatment access for patients with primary immunodeficiency (PID) globally. Nevertheless, we take issue with their view that local, small-scale preparation of immune globulins should not be part of a stepwise approach toward the provision of plasma-derived medicinal products (PDMPs) due to the limitations of the existing technology. Instead, we contend that single-step virally inactivated products prepared from plasma mini-pools under good manufacturing practices (GMPs) in blood establishments are reasonably safe and effective for use in settings without alternative means to mitigate patients' suffering. Furthermore, we argue that the preparation of these products promotes rather than inhibits advancement towards the production of quality-assured plasma suitable for contract fractionation.

CLINICAL VALIDATION IN PID PATIENTS

We agree with IPOPI that the immunoglobulin G (IgG) preparations discussed in our paper, which were validated for the treatment of paediatric immune thrombocytopenia [1], need further study in PID patients. We are pleased to inform, based on personal communications, that a successful clinical study of prophylaxis in patients with PID was conducted in Assiut University Hospital in the south of Egypt and that a manuscript reporting the data is in preparation.

VIRAL SAFETY AND MANUFACTURING VALIDATION

IPOPI emphasizes the need for orthogonal two-step virus elimination, including steps to remove non-enveloped viruses. We accept that the absence of validated steps to remove non-enveloped viruses is a significant limitation of currently available methods for local production of IgG. However, we assert that stepwise introduction of pathogen reduction against enveloped viruses using well-established technologies is a major safety advancement that enables an intermediate approach to essential care of patients with various inherited and acquired disorders. Importantly, safety against the major transfusion transmissible viruses can be enhanced through additional use of nucleic acid testing of donations for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and potentially, based on risk assessment, for hepatitis A virus (HAV) and Human Parvovirus B19 (B19V). Testing to assure that sufficient antibody titres against HAV and B19V are present in the plasma mini-pool can provide an added margin of viral safety of the resultant IgG. The possibility of implementing nanofiltration, a robust step of virus removal [2], in the local preparation of IgG is a technological challenge that might be overcome at some point.

POOL SIZE AND ANTIBODY SPECTRUM

Assuring an adequate spectrum of antibodies in mini-pool IgG preparations is a valid concern. However, it remains to be proven that large pools are needed to provide the necessary antibody spectrum to protect patients. Actually, small pools of IgG made from domestic plasma may contain a suitable repertoire of antibodies against local pathogens, and is preferable to lack of therapy, or treatment with counterfeit products [3], until low- and middle-income countries (LMICs) develop the capacity for larger-scale plasma processing. Still, by pooling several batches of purified immunoglobulins in preparation of each final product, the antibody diversity achieved from the processing of approximately 120 initial plasma units should ensure a broader and more consistent protective effect.

BYPASSING LOCAL PRODUCTION ON THE PATHWAY TO CONTRACT FRACTIONATION

We agree with IPOPI that the goal for optimizing the care of patients with PID is to move as quickly as possible toward contract fractionation. However, like others [4], we believe that the intermediate step of small-pool production of plasma protein products is a feasible and proactive step towards achieving this, while

offering a more immediate benefit to patients. The validity of the approach was demonstrated in Egypt, where the mini-pool solvent–detergent treatment of cryoprecipitate has been clinically evaluated [5] and has been in place for more than a decade. Similarly, the local preparation of pathogen-reduced IgG has been developed [6] and clinically studied [1]. This stepwise approach contributed to raising government awareness about the need to improve patients' treatment and the overall plasma fractionation infrastructure including the establishment of GMP in plasma preparation.

In conclusion, the stepwise approach including local, small-pool preparation of intermediary pathogen-reduced plasma protein products that is recognized by World Health Organization (WHO) [7] is a pragmatic and realistic pathway for LMICs to improve access to reasonably safe plasma protein therapies while working towards availability and affordability of PDMPs. To expect that solutions that work in high-income countries will work the same way in LMICs only delays the implementation of strategies that can be effective in LMICs. The stepwise approach described in our paper [8] will enable patients' treatment that is now lacking, while at the same time laying the groundwork for future advancements in the preparation of quality plasma and plasma fractionation capabilities. As local GMP preparation of these small-pool products expands, the volume of quality-assured plasma potentially suitable for fractionation increases. The authors are committed to strengthening international collaborations with technology suppliers and other relevant organizations to refine and implement this stepwise approach safely and effectively to ensure that patients in LMICs receive the quality care they need and deserve while progress is made towards assuring access to essential PDMPs as standard of care.

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CONFLICT OF INTEREST STATEMENT

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Thierry Burnouf[1,2]
Jay Epstein[3]
Jean-Claude Faber[4]
W. Martin Smid[5]

[1]*Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan*
[2]*International PhD Program in Biomedical Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan*
[3]*McLean, Virginia, USA*
[4]*Association Luxembourgeoise des Hémophiles, Luxembourg City, Luxembourg*
[5]*Sanquin Consulting Services, Amsterdam and Academic Institute IDTM, Groningen, The Netherlands*

Correspondence
Thierry Burnouf, Graduate Institute of Biomedical Materials and Tissue Engineering, College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan.
Email: thburnouf@gmail.com

ORCID

Thierry Burnouf https://orcid.org/0000-0002-0507-9243
W. Martin Smid https://orcid.org/0000-0001-8487-0043

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EVENTS

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

27–29 September 2024	ESPGI 2024—Platelet and Granulocyte Immunobiology. https://sanquinacademy.nl/en/offers/espgi-2024/
10–12 October 2024	Omani Society of Haematology Conference 2024. https://www.omanishc.com/
23–26 October 2024	Brazilian Congress of Haematology, Hemotherapy and Cell Therapy (Hemo 2024). https://www.hemo.org.br/2024/index.ingles.php
14–15 November 2024	BlooDHIT Conference 2024. https://bloodhit.com/
21–23 November 2024	TRANSCON 2024. https://www.transcon2024.in/
14–15 January 2025	EDQM Blood Conference: Innovation in Blood Establishment Processes. https://www.edqm.eu/en/edqm-blood-conference

