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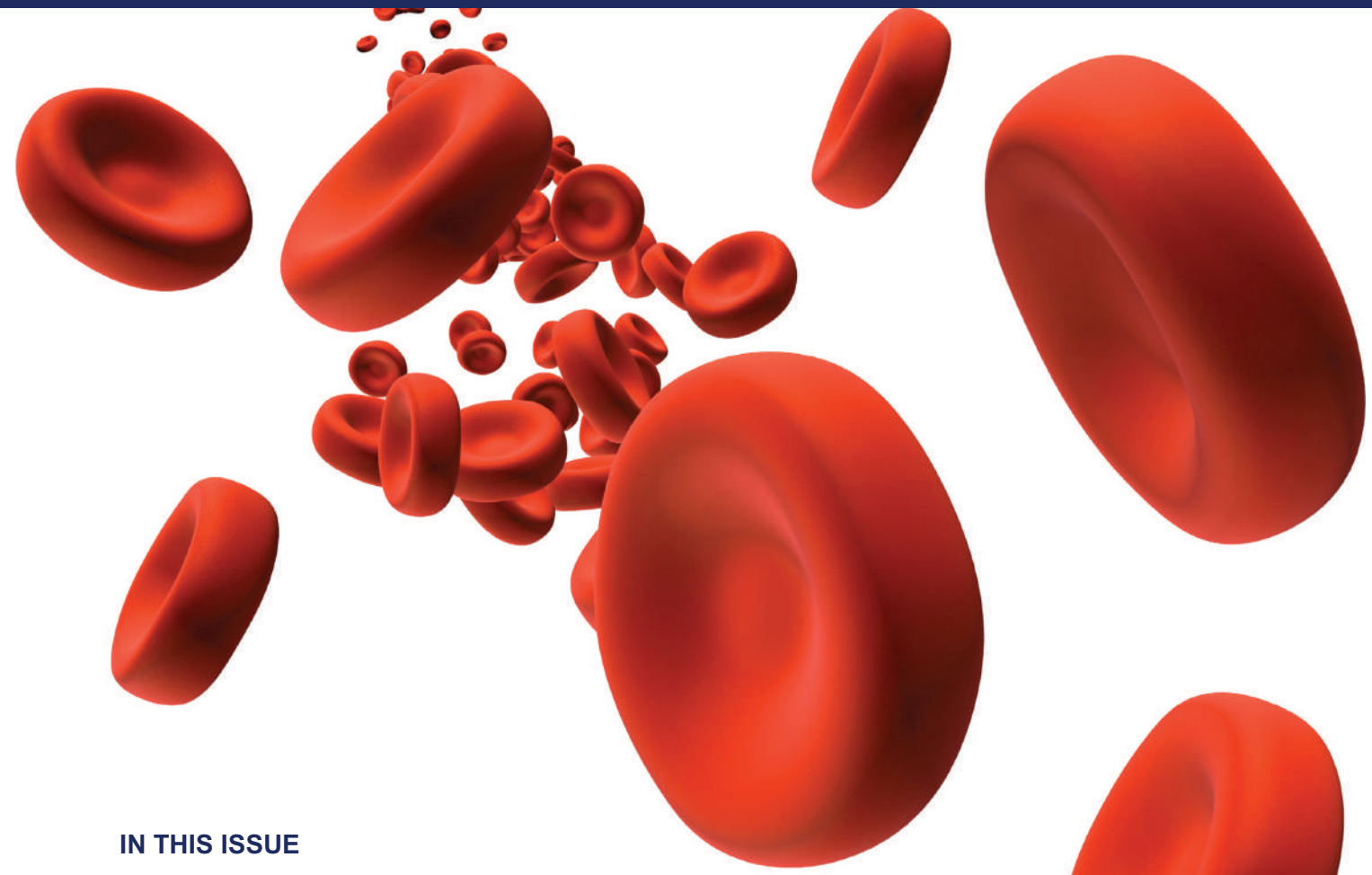

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Transfusion Medicine

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REVIEW

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Determining the strength of evidence for an association between sexual indicators and risk of acquiring HIV and sexually transmitted infections: Providing evidence for blood donation policy change

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Abstract

In 2019 the For The Assessment Of Individualised Risk (FAIR) project began a review of UK blood donor selection policy to determine if a more individualised approach to donor selection could be safely implemented. An evidence base was required to inform selection policy to move from a population to a more individual based policy, specifically what sexual behaviours/indicators should be considered as screening questions to maintain the safety of the blood supply. Eight sexual behaviours/indicators were reviewed: history of bacterial sexually transmitted infections (STIs), chemsex, number of recent partners, condom use, type of sex, sexual health service (SHS) attendance, new sexual partner and exclusivity. We conducted searches in multiple databases to identify literature looking at the association between these behaviours/indicators and HIV/STI acquisition risk. A scoring system to determine strength of evidence was devised and applied to papers that passed screening. Key studies were identified which achieved the maximum score and more in-depth reviews were conducted for these. We identified 58 studies, including 17 key studies. Strong evidence was found linking a previous bacterial STI, chemsex and increasing numbers of sexual partners to acquisition risk. Condom use, type of sex and new partners were found to have some strength of evidence for this link. SHS attendance and exclusivity had minimal evidence. We recommended that the behaviours/indicators viewed as having strong or some strength of evidence should be considered as screening questions in a more individualised approach to donor selection criteria.

KEYWORDS
blood donation, donor selection, health policy, HIV, STI, transfusion

1 | INTRODUCTION

All four UK blood services have processes in place to minimise the chance of transfusion-transmitted infections (TTIs), these include donor selection, donation testing and processing, and blood component storage.[1] In the UK all blood donations are tested for markers of bloodborne infections including HIV, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and syphilis, however, the window period of the

tests means that very recently acquired infections may not be detected.[2] Donor selection criteria therefore provide an important blood donation safety measure to reduce the chance that someone with a recently acquired infection would donate. It also provides a safety measure against bloodborne infections which are not currently part of routine tests. Until recently in the UK most donor selection criteria were based on population-based risks of acquiring a blood borne infection, for example all gay, bisexual or other men who have sex with men (GBMSM) were deferred from donating if they had had sex with another man in the preceding 3 months. This time period was based on the window period for tests conducted. Similar deferral criteria were applied to people in other groups at increased risk of HIV or STIs including people who have been paid for sex, people who had partners with a known infection and people who have had sex with someone from an area with high HIV prevalence, mainly Sub-Saharan Africa.

In 2019 the For The Assessment Of Individualised Risk (FAIR) project was set up. The aim of this work was to evaluate if it was possible to safely change the blood donation criteria to a more individualised risk-based approach. This required identifying the best questions to ask people to select lower-risk individuals to donate, some of whom had been previously deferred from blood donation, while still maintaining the safety of the blood supply. The approach to do this combined epidemiological, behavioural and psychological evidence about current and potential future donors. The FAIR project led to changes in UK blood donation criteria in 2021. This study was conducted as part of the project and contributed to the evidence base to support this change, alongside other evidence relating to these behaviours/indicators regarding recall, acceptability, practicality and more. Many other countries have since made similar changes including Canada, USA and France whereby donor selection processes no longer ask questions about sex between men.

Certain sexual behaviours, or certain indicators of sexual behaviours, are associated with an increased likelihood of acquiring HIV/STIs. Here, we build on work carried out in 2018 at Canadian Blood Services and Héma-Québec, which asked donors about the frequency of specific sexual behaviours/indicators and to what degree they would be comfortable responding to questions on these as part of their pre-donation screening. From this, we considered chemsex, number of recent partners, condom use, type of sex, new sexual partner and exclusivity to be of most relevance to a UK donor selection policy. The use of internet/social media to find partners was part of the Canadian work but following discussions with HIV/STI surveillance experts this was not deemed to be a relevant behaviour/indicator or an acceptable avenue of questioning in a UK setting. Following discussions with experts in sexual health we also included two additional behaviours/indicators (history of bacterial STI and Sexual Health Service (SHS) attendance) as they are often considered risk indicators for acquisition of HIV/STIs within UK sexual health settings. Overall, the behaviours/indicators considered to be relevant for selecting donors at lower risk of acquiring infections through sex were: chemsex, number of recent partners, history of bacterial STIs, SHS attendance, new sexual partner, condom usage, exclusivity and type of sex.

Chemsex is a term for the use of drugs before/during sexual activity to facilitate it and it has been linked to participation in sexual practices which increase acquisition risk, such as condomless sex and high numbers of partners.[3,4] While history of bacterial STIs and attending SHS do not themselves increase acquisition risk it has been suggested they are predictors of future acquisition risk; these are sometimes referred to as proxy measures or indicators of risk.[5] Condoms act as a barrier to infection during penetrative sex and so their consistent use decreases acquisition risk. Different types of sex carry varying risk of acquisition and so when referring to type of sex in this study we are referring to the variation in acquisition risk between sex acts encompassing oral, vaginal, anal and receptive versus penetrative sex.[6] While there is no evidence of gonorrhoea nor chlamydia transmission via transfusion, and transfusion-transmitted syphilis has not been identified in the UK setting since surveillance began in 1996 this review will consider them because they are STIs, which can indicate higher risk sexual practices.[7] It should be noted that currently antibody tests are used to detect syphilis infection in blood donors, meaning anyone with a history of infection is deferred.

While the association with these behaviours/indicators and HIV/STI acquisition risk is somewhat established, determining the strength of evidence will help to support the formulation of questions to blood donors for a more individualised risk assessment. Important details about the behaviours/indicators from each study were also recorded to provide a finer level of granularity in the evidence to further refine the questions to consider for the more individualised approach.

2 | MATERIALS AND METHODS

In total five literature searches were conducted in November 2019 in both Medline and EMCare using synonymous terms for HIV, STI and for specific STIs plus terms for the eight sexual behaviours/indicators; chemsex, number of recent partners, history of bacterial STIs, SHS attendance, new sexual partner, condom usage, exclusivity and type of sex (Data S1). To help ensure similarity of the epidemiology in the UK at the time inclusion criteria included literature published after January 1981 and studies conducted in Europe, North America, Australia and New Zealand. In order to align the evidence base more closely with UK blood donors, studies were excluded if their study population included: people under 17 years old, known HIV positive individuals, PrEP users or injecting drug users. Studies on incarcerated populations were also excluded as collection no longer occurs in prisons in the UK. Other exclusion criteria included studies with less than 50 participants, those with no comparison group, co-infection studies, and those where the risk was not specified, for example people labelled simply as high risk. Studies were screened and included if they assessed the association between at least one of the eight sexual behaviours/indicators and risk of HIV/STI acquisition risk and did not meet any exclusion criteria.

Three rounds of screening were conducted against the aforementioned inclusion/exclusion criteria. The first was by a literature search expert based on title and abstract followed by deduplication by this same expert. The second round was conducted by an epidemiologist

also based on title and abstract only and the third screening round was conducted by the same epidemiologist based on the full text. All studies that passed these three screening rounds were included in the analysis.

We wanted to assess the strength of evidence for the link between HIV/STI acquisition risk and each sexual behaviour/indicator based on the literature identified. To do this a scoring system was devised to, after screening, assign a score to each identified study based on the size of the study population and number of study sites (Table 1). The system devised for this was adapted from a similar system used previously by Brady et al.[8] Any study scoring the maximum of three was classified as a key study. Once all studies had a score, the sexual behaviours/indicators they found linked to acquisition risk were listed next to each study. The score of the study was then applied to the sexual behaviours/indicators listed next to them. So, if a study scored two and found evidence linking acquisition risk with both condom use and number of recent partners then these behaviours both got two points. The scores were added up by sexual behaviour/indicator to reach a final tally. Thereby if four studies which scored one point and two studies which scored three points linked chemsex to HIV/STI acquisition risk the final tally for chemsex was 10 ($4 \times 1 + 2 \times 3$).

As well as assigning scores to the behaviours/indicators in each of the identified studies any key findings relating to the sexual behaviours being investigated, which were potentially relevant to a more individualised risk assessment were recorded. This included exact definitions of the sexual behaviours, any time periods applied, and problems encountered when collecting information.

3 | RESULTS

3.1 | Number and characteristics of included studies

The result from the screening process can be seen in Figure 1. Fifty-eight studies were identified and included in subsequent analysis of which 17 were key studies (Table 2). Out of the total nine were case–controls, 24 were cohort, and 25 were cross-sectional studies with 46 of 58 focused solely on GBMSM populations (Tables 2 and 3).

TABLE 1 Scoring system for included studies.

Score	Criteria
1	Study population of 50–199
	One study location & study population of 200–999
2	Multiple study locations & study population of 200–999
	One study location & study population of 1000–4999
3 (key study)	Multiple study locations & study population of 1000–4999
	Study population of 5000+

3.2 | Strength of evidence

Overall, previous bacterial STI, chemsex, number of recent partners, condom usage and type of sex had high scores and several key studies supported their link to acquisition risk (Table 4). One study linked SHS attendance to acquisition risk and very few studies, none of which were key studies, were found linking new sexual partners to risk. No studies were found linking partner exclusivity to acquisition risk.

3.3 | Previous bacterial STI

The final score for this indicator was 49 and nine key studies supported a link between history of a bacterial STI and HIV/STI acquisition risk.[9,12–15,17–19,24] Where key studies did not use baseline diagnosis as their metric but instead asked about STIs in a retrospective time period, all but one of them either used 6 or 12 months as their time period.[12,14,17,18,24] Two of these retrospective studies looked at a history of any STIs and did not specify that the STI was bacterial.[12,18]

Two cohort studies found participants who had a bacterial STI diagnosis (particularly syphilis, gonorrhoea or chlamydia) at the start of the study had an increased risk/rate of subsequent HIV acquisition, with one showing an HIV acquisition rate over three times higher for those diagnosed with syphilis; 7.2 (95% CI: 6.0–8.4) compared with 2.0 (95% CI: 1.7–2.3) diagnoses per 100 person years.[13,14] A third cohort study taking place in GBMSM attending SHS across England looked at the odds of developing a bacterial STI following their initial clinic attendance.[15] It found those who had a bacterial STI at the start of the study had 1.43 (95% CI: 1.17–4.26) times the odds of acquiring a subsequent one.

3.4 | Chemsex

The final score for this indicator was 46 and seven key studies supported a link between chemsex and HIV/STI acquisition risk.[12,16,17,22–25]

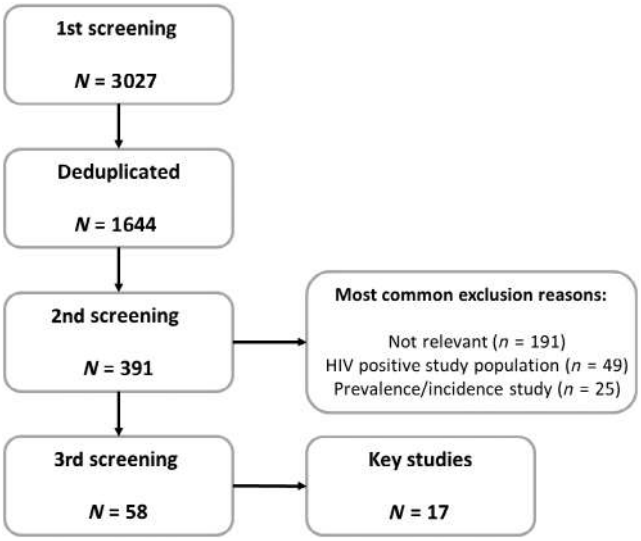

FIGURE 1 A flow chart to show the screening process for literature.

TABLE 2 Details of key studies identified.

Study	Publication year	Study type	Population size	Population description	Country	Chemsex	No. of partners	Previous bacterial STI	GUM attendance	New sex partner	Condom use	Exclusivity	Type of sex
Kassler et al.[9]	1994	Case–control	6175	GUM clinic attendees	USA			X					
Parazzini et al.[10]	1995	Case–control	1711	GUM clinic attendees	Italy						X		
Buchbinder et al.[11]	2014	Cohort	1248	MSM & trans women	USA						X		X
Ackers et al.[12]	2012	Cohort	4684	High-risk MSM	USA	X	X	X			X		X
Llata et al.[13]	2018	Cohort	14 824	MSM GUM clinic attendees	USA			X					
Desai et al.[14]	2017	Cohort	26 200	MSM GUM clinic attendees	England			X					
Desai et al.[15]	2018	Cohort	1278	MSM GUM clinic attendees	England		X	X					
Katz et al.[16]	2016	Cohort	3715	MSM	USA	X							
Koblin et al.[17]	2006	Cohort	4295	MSM	USA	X	X	X			X		X
Aghaizu et al.[18]	2016	Cross-sectional	10 364	MSM	England		X	X					
Fournet et al.[19]	2016	Cross-sectional	3053	Male sex workers	Netherlands			X					
Dickson et al.[20]	2015	Cross-sectional	3138	MSM	New Zealand		X				X		X
Dukers-Muijrers et al.[21]	2009	Cross-sectional	12 949	GUM clinic attendees	Netherlands				X				
Rudy et al.[22]	2009	Cross-sectional	6435	MSM GUM clinic attendees	USA	X							
Sewell et al.[23]	2017	Cross-sectional	1484	MSM GUM clinic attendees	UK	X							
Ferrer et al.[24]	2015	Cross-sectional	2197	MSM	Europe	X		X					
Kohli et al.[25]	2019	Cross-sectional	16 065	MSM	UK	X							

TABLE 3 Details of non-key studies identified.

Study	Publication year	Study type	Population size	Population description	Country	Chemsex	No. of partners	Previous bacterial STI	GUM attendance	New sex partner	Condom use	Exclusivity	Type of sex
Brewer et al.[26]	2006	Cross-sectional	241	MSM	USA	X	X	X					
Wagstaff et al.[27]	1999	Cohort	562	African-American males	USA			X					
Kelley et al.[28]	2015	Cohort	562	MSM	USA			X					
Pathela et al.[29]	2013	Cohort	276	MSM GUM clinic attendees	USA			X					
Turner et al.[30]	2013	Cross-sectional	326	MSM GUM clinic attendees	USA								X
Zetola et al.[31]	2009	Case–control	13 662	MSM	USA			X					
Suligoi et al.[32]	2002	Cross-sectional	776	GUM clinic attendees	Italy			X					
Vall et al.[33]	2001	Cross-sectional	1093	GUM clinic attendees	Spain			X					
Glynn et al.[34]	2017	Cohort	871	MSM GUM clinic attendees	USA								X
Cheung et al.[35]	2016	Cohort	5256	MSM GUM clinic attendees	Australia			X			X		
Kim et al.[36]	2003	Cross-sectional	564	MSM GUM clinic attendees	USA	X							
Donovan et al.[37]	2001	Case–control	374	MSM GUM clinic attendees	Australia			X			X		
Valle[38]	1988	Cohort	235	MSM	Finland			X					
Gorbach et al.[39]	2019	Cohort	512	MSM	USA	X							
Barbee et al.[40]	2017	Case–control	880	MSM GUM clinic attendees	USA			X					
Down et al.[41]	2017	Cross-sectional	545	MSM	Australia					X			
Wilkinson et al.[42]	2017	Cross-sectional	4685	MSM	Australia			X					
Ferrer et al.[43]	2016	Cohort	3544	MSM GUM clinic attendees	Spain		X	X			X		X
Lyons et al.[44]	2014	Cohort	1034	MSM	Australia		X						

TABLE 3 (Continued)

Study	Publication year	Study type	Population size	Population description	Country	Chemsex	No. of partners	Previous bacterial STI	GUM attendance	New sex partner	Condom use	Exclusivity	Type of sex
Templeton et al.[45]	2010	Cohort	1427	MSM	Australia		X						X
Menza et al.[46]	2009	Cohort	1903	MSM GUM clinic attendees	USA	X	X				X		X
Prestage et al.[47]	2009	Cross-sectional	746	MSM	Australia		X						
Forna et al.[48]	2006	Case–control	132	Black women	USA			X					
McNulty et al.[49]	1997	Cohort	528	Sexually active MSM	Australia		X						
Craib et al.[50]	1995	Case–control	375	Gay men attending healthcare facilities	Canada	X	X						
Gattari et al.[51]	1994	Cohort	67	Prostitutes attending a GUM clinic	Italy						X		
Ellerbrock et al.[52]	1992	Cohort	1082	Pregnant women	USA		X						
Prestage et al.[53]	2009	Cohort	1427	MSM	Australia	X							
Thiede et al.[54]	2009	Cross-sectional	142	MSM GUM clinic attendees	USA	X					X		X
Ellerbrock et al.[55]	2004	Cross-sectional	1324	Resident of a rural community	USA		X	X					
Calzavara et al.[56]	2003	Cross-sectional	183	MSM	Canada						X		X
Achterbergh et al.[57]	2020	Cross-sectional	4461	MSM GUM clinic attendees	Netherlands	X							
Evers et al.[58]	2019	Cross-sectional	600	MSM	Netherlands	X							
Drückler et al.[59]	2018	Cross-sectional	4925	MSM GUM clinic attendees	Netherlands	X							
Pakianathan et al.[60]	2018	Cohort	1734	MSM GUM clinic attendees	England	X							
Tomkins et al.[61]	2018	Cohort	357	MSM GUM clinic attendees	England	X							

(Continues)

TABLE 3 (Continued)

Study	Publication year	Study type	Population size	Population description	Country	Chemsex	No. of partners	Previous bacterial STI	GUM attendance	New sex partner	Condom use	Exclusivity	Type of sex
Bazan et al.[62]	2015	Cross-sectional	331	Female GUM clinic attendees	USA	X							
Ottaway et al.[63]	2017	Case–control	260	MSM GUM clinic attendees	England	X					X		X
Heiligenberg et al.[64]	2012	Cross-sectional	1861	MSM & female GUM clinic attendees	Netherlands	X							
Carey et al.[65]	2009	Case–control	444	MSM	USA	X		X			X		X
Niccolai et al.[66]	2004	Cross-sectional	411	Adolescent women	USA					X			

Some of the key studies did not specifically link drug use to sex but instead took use of drugs commonly used for chemsex, such as methamphetamine and gamma hydroxybutyrate (GHB)/gamma butyrolactone (GBL) as their risk factor.[16,22,25] Within the key studies that investigated use of specific drugs, methamphetamine was most commonly linked to HIV/STI acquisition with GHB/GHL, mephedrone and amyl nitrate use also specifically being linked.

One cross-sectional study by Sewell et al. and one cohort study by Koblin et al. looked at a range of drug use before/during sex, with the latter also including alcohol use.[17,23] They found that participants engaging in chemsex had 2.14 (95% CI: 1.83–2.50) times the odds of having had a bacterial STI and 1.58 (95% CI: 1.09–2.29) times the odds of HIV acquisition, respectively.

Several studies supported a link between chemsex and other potentially high-risk behaviours, such as sex with a person who injects drugs (PWID), unprotected anal intercourse (UAI), higher numbers of sexual partners, group sex and lower condom use.[22,23,25]

3.5 | Number of recent partners

The final score for this indicator was 33 and five key studies supported a link between increased numbers of partners and increased HIV/STI acquisition risk.[12,15,17,18,20] One cohort study looked at high risk GBMSM across 47 US cities and in an adjusted regression model found that those with >10 partners in the past 6 months had 2.4 (95% CI: 1.7–3.3) times the odds of HIV acquisition compared with those with <5 partners.[12] A cross-sectional study in GBMSM in New Zealand also looked at number or partners in the past 6 months but with STI diagnosis as the outcome.[20] It found significantly increased STI diagnosis for those with 6–10, 11–20, 21–50 and >50 partners compared with those with 1, and a general trend of increasing odds with increasing partner number was seen. One cross-sectional study in GBMSM in London found increased odds of HIV acquisition up to 69.8 (95% CI: 35.5–138.2) with increasing numbers of sexual partners but this looked specifically at UAI, and so this is likely to explain the large odds ratios.[18]

3.6 | Condom use

The final score for this indicator was 28 and five key studies found that decreased condom usage was associated with increased HIV/STI acquisition risk.[10–12,17,20] Out of these only two specifically looked at condom usage not in combination with the type of sex. One was a cross-sectional study of GBMSM in New Zealand which found that, compared with those reporting high usage, those reporting low/medium condom use with casual partners or with regular partners had increased odds of reporting a bacterial STI in the past year.[20] The second was a case–control study on SHS attendees in Northern Italy, male and female, which found people reporting regular condom usage had 0.5 (95% CI: 0.4–0.5) times the odds of acquiring HIV compared with those reporting occasional or no use.[10]

TABLE 4 Results of scoring system for each sexual behaviour/indicator, number of keys studies associated with each sexual behaviour and the study populations key studies were carried out in.

Behaviour	Score	No. of key studies[a]	Study populations of key studies
Previous bacterial STI	49	9	GBMSM, SHS attendees, male sex workers
Chemsex	46	7	GBMSM
No. of recent partners	33	5	GBMSM
Condom use	28	5	GBMSM, trans women, SHS attendees
Type of sex	25	4	GBMSM, trans women
SHS attendance	3	1	SHS attendees
New sexual partner	3	0	N/A
Exclusivity	0	0	N/A

[a]Many studies identified multiple behaviours associated with risk of HIV/STI acquisition, therefore this column adds up to more than the total number of key studies.
Abbreviations: GBMSM, gay, bisexual or other men who have sex with men; SHS, sexual health service.

Most of the key studies identified combined condom usage and type of sex, for example condomless anal sex, condomless receptive sex, or condomless receptive anal sex, and compared these groups to those not partaking in these behaviours.[11,12,17] This makes it difficult to determine if the increased risk is associated with condom use, type of sex or both.

3.7 | Type of sex

The final score for this indicator was 25 and four key studies showed an association between type of sex and HIV/STI acquisition risk.[11,12,17,20] One cross-sectional study looked specifically at anal sex, regardless of insertive or receptive, and found that those reporting anal sex in the past 6 months had 2.3 (95% CI: 1.3–2.7) times the odds of reporting a bacterial STI in the past year.[20]

Other studies looked at anal sex in combination with condom usage which posed the same aforementioned issue with separating out which behaviour the risk is associated with.[11,12,17] One such study found those having receptive UAI with a partner presumed to be negative had 1.92 (95% CI: 1.38–2.68) times the odds of HIV acquisition compared with those who did not engage in UAI.[17] The other two studies found associations between HIV acquisition and condomless anal sex and between HIV acquisition and condomless receptive sex of any kind.[11,12] Overall, anal sex and specifically UAI the were found to be most associated with an increased risk although often these behaviours were not separated.

3.8 | SHS attendance

The final score for this indicator was three and one key study showed an association between HIV/STI acquisition risk and attending a SHS.[21] However, this cross-sectional study did not compare SHS attendees to non-attendees but rather took a population of attendees and looked at who opted out of HIV screening. It found that heterosexuals opting out had 1.85 (95% CI: 1.39–2.45) times the odds of having a history of STIs. Furthermore, it found that both heterosexuals and GBMSM who opted out had higher odds of having a current STI-related complaint; 1.98 (95% CI: 1.57–2.51) and 4.22 (95% CI: 2.43–7.33), respectively.

A potential reason for very little evidence being found is because this behaviour meant restricting studies to those looking at screening within a healthcare setting rather than screening done elsewhere. For instance, a study by Ferrer et al.[24] and another by Boyer et al.[67] were not included because a healthcare setting was not specified. However, they found that those who had had an HIV test or STI check in the previous year had greater odds of testing positive for HIV or STIs at the time of the study, which suggests the opposite relationship to that suggested by the Dukers-Muijrers et al.[21] study.

3.9 | New partners

The final score for this indicator was three and no key studies were identified that showed a link between having a new sexual partner and HIV/STI acquisition risk however, two articles were identified that did not meet the criteria to be classified as key studies.[41,66] One study in Australia found that few HIV infections occurred between GBMSM in long term sexual relationships and most occurred among GBMSM in new sexual relationships.[41] The second study was among adolescent women in the US and found that having had a new sexual partner in the previous 12 months was strongly associated with STI acquisition.[66]

3.10 | Exclusivity

The final score for this indicator was zero and no studies were found that linked exclusivity to HIV/STI acquisition. This is potentially because exclusivity was difficult to define or was defined by the study in terms of number of recent partners and so was categorised under

this sexual behaviour instead. Some included studies did refer to casual sexual partners which could be interpreted as a substitute for non-exclusive but was not interpreted as such in this review.

4 | DISCUSSION

Our review found very strong evidence of a link between HIV/STI acquisition risk and having had a previous bacterial STI, having engaged in chemsex, and having had an increasing number of recent partners. These were therefore strongly recommended for consideration in a more individualised risk assessment for blood donors. These recommendations and the information from this study, alongside many other evidence pieces, helped to inform the wider FAIR review that occurred in 2021.

There was some consensus across studies when assessing recent bacterial STIs with most key studies looking at either a six or 12 month period since treatment completion being associated with an increased risk of further STIs or HIV.[9,12–15,17–19,24] Since having had a bacterial STI represents an indicator of risk and not the source of risk itself then the time period used for this likely cannot be based on the commonly established period of 3 months for blood donor deferral. More research may help to determine an appropriate time period with a longer period representing a more cautious approach. With respect to chemsex, there was clear consensus that methamphetamine consumption increased risk but there was no clear consensus related to other chemsex drugs or what dosages related to acquisition risk.[12,16,17,22–25] We therefore recommended further exploration of risk association with all drugs mentioned in the studies plus any other relevant drugs. Most literature found on chemsex had a study population of exclusively GBMSM which may mean this finding is less applicable to other groups, however some research suggests chemsex is more prevalent among GBMSM possibly minimising this issue of applicability.[68] Furthermore, since the risk from chemsex comes from it's association with practices, such as condomless sex and high numbers of partners rather than chemsex itself it may be that the risk is mitigated from questions on other behaviours. We were not able to determine this from the evidence presented here. Given the strong evidence linking chemsex and acquisition risk a more cautious approach would be to include it alongside questions on other behaviours/indicators.

There was no unanimous agreement across the studies as to what number of recent partners during what time period is deemed as high risk. For blood donation purposes it may be pertinent to relate the time period applied for this to the established period of 3 months. Several studies found that acquisition risk increased with increasing number of sexual partners.[12,18,20] More research is needed to identify the best cut off for number of recent partners but, in lieu of this, a more cautious approach of a low number may be optimal.

The strength of evidence for condom usage and for type of sex being linked to HIV/STI acquisition risk was strong but with potential limitations due to multiple studies combining the two behaviours thereby making it difficult to separate the effects of just one.[11,12,17] It was suggested a question on either may be worth considering for inclusion in a more individualised risk assessment but further research would be required to untangle the risks posed by each. Furthermore, errors when using condoms and issues surrounding recall of condom use have previously been identified.[69–71] While this was not looked at in this study it would potentially cause issues for questions surrounding condom use and so require consideration. Memory recall was evaluated elsewhere in the FAIR project. Looking at type of sex in reality encompasses several different behaviours, in particular: oral, vaginal or anal sex and receptive or penetrative sex. Many of the studies identified combined these, for example into receptive anal sex, sometimes specifying this was condomless too.[11,12,17] However overall, there was a lot of agreement between studies that anal sex of various types, particularly receptive, represented the greatest risk and a question on this was also put forward for consideration in an individualised risk assessment.

There was very little evidence found to support SHS attendance being associated with HIV/STI acquisition risk.[21] Testing for HIV/STIs in other settings was included in some studies we found but did not meet the criteria for consideration here. Those attending may represent a high-risk group but they may also represent lower-risk individuals who are conscious of mitigating risk. Therefore, including a question on SHS attendance in a more individualised risk assessment was not recommended, unless further research uncovered stronger evidence presenting a clear relationship with acquisition risk.

We found no evidence showing a relationship between exclusivity and HIV/STI acquisition. It is unlikely that no relationship exists, but rather that either the risk is so low it has not been studied or studies defined exclusivity in terms of numbers of sexual partners or 'casual' partners, which are not the same as exclusivity. This seems plausible given that many studies were found which looked at number of recent partners and several which referred to casual partners as defined by the participant. Having had a casual partner may be interpreted as a substitute for non-exclusiveness, however, the opposite of a causal relationship is not necessarily an exclusive one and so conclusions about exclusivity cannot be drawn from these studies. We found very little evidence for a link between having had a new partner and acquisition. Given the nature of HIV/STI transmission and the strong evidence we identified linking number of partners with acquisition risk we believe this lack of evidence related to new partners is due to similar issues with definitions as with exclusivity. Our findings did not provide evidence for including exclusivity or new partners in a more individualised assessment however they should not be ruled out entirely given the issues with defining these terms in studies. Due consideration should be given to language understood by donors, which may differ from language used in research.

Based on our review alone there was insufficient evidence to support including a question on new sexual partners in a more individualised risk assessment.

For many of the behaviours/indicators looked at here the majority of studies relating to them relied on self-reporting, in particular: chemsex, number of recent partners, condom use and type of sex. Exact methods varied between studies but self-reporting is subject to

recall bias so, although it is unclear the direction of effect this bias would have on these, this makes the findings in these less reliable. Self-reporting is also required for blood donation screening and so reliability of recall is important when considering any of these for inclusion in a risk assessment and was specifically examined elsewhere for FAIR. While we applied exclusion criteria to limit study populations to those not excluded from donating due to other criteria it is likely many of the study populations still differ from typical donor populations. This was partly intentional as we wanted to look at populations wider than those eligible to donate prior to the 2021 rule change but nevertheless these differences may negatively impact the applicability of these studies to donor populations even after the rule change. On top of this the scoring system used here, while based on previously published work, is untested. This may produce bias in which studies are deemed to be more relevant and how evidence is weighted. However, the use of this system as a guide proved useful to draw conclusions but it is not advised that great emphasis is put on precise scores, which was avoided here. On top of this, studies involving PrEP/PEP users were excluded here which may call into question the applicability of our findings since these drugs are increasingly common among the UK population, especially GBMSM. However, currently individuals who have taken PrEP/PEP in the prior 3 months are prohibited from donating blood in the UK and, even if this were to change, the drugs are currently recommended for individuals at higher risk who would be likely be excluded for other reasons anyway. Further research into PrEP/PEP in relation to blood donation is being undertaken.

This review provided evidence for changes to blood donation policy in the UK and may be useful for other countries with similar epidemiology. It may also help to inform work outside the blood donation landscape such as in sexual health research/policy where defining high-risk groups is important. However, when considering changes to blood donation policy this review must be considered in combination with research into reliability of recall, acceptability of screening questions and practical issues around implementation. These areas as they relate to the behaviours/indicators researched here were explored in other strands of the FAIR project.

AUTHOR CONTRIBUTIONS

Conceptualization: K.L.D, S.R.B and J.F. Methodology: K.L.D, C.R. and J.F. Investigation: K.L.D. and J.F. Project administration: K.L.D, S.R.B and J.F. Writing—original draft: J.F. Writing—review & editing: K.L.D, S.R.B, C.R. and J.F.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

All data used comes from published literature, which is available to others. All literature included in our final analysis from which conclusions were drawn are included in the references.

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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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The infected blood inquiry: Impact on public perceptions of blood supply risk, safety, and donation attitudes

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Abstract

Background: The UK's Infected Blood Inquiry (IBI) highlighted a major public health scandal, with at least 30 000 people infected and more than 3000 deaths attributable to infected blood and blood products. This study investigates the impact of the IBI announcement on May 20, 2024, on public perceptions of blood supply risk, safety, and donation intentions in the UK compared to the USA.

Methods: A 2 (country: UK vs. USA) × 2 (time: pre-, post-IBI announcement) between-within-subject study was conducted with 1635 participants (888 UK, 747 USA). Pre-IBI data were collected from May 3 to 7, 2024, and post-IBI data from May 30 to June 30, 2024. Key measures were perceived infection risk from transfusion, transfusion safety, willingness to donate and encourage others. The impact was assessed using differences-in-differences (DiD) and reliable-change-indices (RCI).

Results: UK participants showed a significant but small decrease in perceived safety compared to USA participants, with 1 in 30 UK individuals perceiving a significant reduction in perceived transfusion safety. Decreases in perceived safety were associated with significant decreases in willingness to donate and encouragement of others in the whole sample and in USA participants and significant decreases in willingness to encourage others in UK participants. Older people reported a greater reduction in safety, and non-donors were more likely to be put off donating and not ask others to donate as a result of their perception that safety had been reduced.

Conclusion: Overall, perceived safety decreased marginally in the UK general population. Future research should explore the long-term impacts of the IBI.

KEYWORDS
blood safety, donor attitudes, infected blood inquiry, perceived risk

1 | INTRODUCTION

The use of infected blood and blood products, examined in the Infected Blood Inquiry (IBI), highlights one of the most severe public health scandals in the UK's history.[1,2] The IBI showed that between 1970 and the early 1990s, over 30 000 NHS patients received blood transfusions, or blood products, infected with hepatitis C or HIV. Of these, around 3000 have since tragically died, severely impacting their families and loved ones.[1,2] These infections were primarily due to the UK importing clotting factors, and other blood products from paid

donors overseas as it was unable to meet domestic demand.[1,3] These plasma products were often manufactured from large pools of donors (up to 60 000) that included donors from high-risk populations, meaning that one infected donation could contaminate an entire batch.[1,4,5] In relation to whole blood donation, the IBI saw that some donor selection measures in the UK took too long to implement (e.g., the 'AIDS leaflet'), that additional tests for hepatitis C could have been introduced sooner, and there were delays in decision making not helped by the regional nature of services at this time (page 5, vol 1).[1]

Persistent efforts by the affected individuals and advocacy groups eventually led to the establishment of an independent public statutory inquiry.[1] Led by Sir Brian Langstaff, a former High Court judge, and his team, the inquiry commenced on July 11th 2017 and was tasked with investigating the circumstances that led to the use of infected blood and blood products in the UK. Over several years, the IBI collected extensive evidence from numerous groups—including victims (the infected), families (the affected) and countless other stakeholders such as expert groups, medical professionals, and government witnesses (see timelines and groups involved here). The findings of the IBI, released in seven volumes on May 20th, 2024 (https://www.infectedbloodinquiry.org.uk/), confirmed the failure to act and the inability of successive governments to properly investigate the scandal. In response, the UK Prime Minister at the time, Rishi Sunak[6] issued a public apology—'a day of shame for the British state'—acknowledging the government's failure and promising compensation for the 'infected' and 'affected'.[7]

This research explores the short-term impact of the announcement of the IBI findings on the general public's perceptions regarding overall blood safety and donation behaviour (i.e., people's willingness to donate blood and encourage others to donate). We examine perceptions of the safety of blood as an index of people's perceptions of the overall safety of processes linked to blood transfusion and the use of other blood products. That is, people are unlikely to be aware of the subtle difference between types of blood products and whole blood versus plasma. Thus, their overall perception of the safety of blood for transfusion acts as a good general index of the safety of blood products within the general population.

People perceive risk as higher and safety as lower when the risk could potentially affect them.[8–10] Furthermore, people judge risk in terms of potential consequences (the harm that they may experience) rather than by probabilities,[8,11] and extract gist information about risk based on heuristics such as the availability heuristic.[9,12] Therefore, we hypothesise that compared to the USA, people in the UK will show reductions in their perceptions of overall blood safety and increased perceptions of infection risk from transfusion. Furthermore, we would expect that people may wish to psychologically and behaviourally distance themselves from an action perceived as harmful to others.[13] This may result in a generally reduced willingness to be a blood donor and willingness to encourage others to donate as well.

Given the historical nature of the events comprising the IBI and the literature on risk, we also explore whether these effects vary by various (socio-)demographics that are comparable across the two countries in terms of age, sex, education, and donor status. This research provides valuable insights into the short-term impacts of the IBI on public perceptions and behaviour of the overall supply of blood and blood products, underscoring the importance of maintaining transparency and accountability in public health communications and practices.

2 | MATERIALS AND METHODS

2.1 | The sample

The sample consists of 1635 adults from the general populations in the USA ($N = 747$) and the UK ($N = 888$), from which we collect data pre-IBI (between 3rd and 7th May 2024) and post-IBI (between 30th May and 30th June 2024). The data were collected through an online platform Prolific, with the survey constructed on Qualtrics, quota balanced across gender (female, male). Participants were paid around £9 ($11) p/h for each survey (payment information). Prolific has a built-in option for follow-up studies (link). The initial survey was part of a larger study surrounding perceptions of incentives in whole blood (See Supplementary 'Prolific survey questions' File for more information). Due to the high sensitivity of the IBI, especially among those who have received transfusions, and our focus on willingness to donate (which requires eligibility to donate), only non-recipients of blood were recruited for the post-IBI study.

We employ causal econometric techniques to quantify the effect of the IBI announcement on the general population, as well as on specific demographic groups (e.g., age, sex, and previous donor history). The rationale for including the USA as a comparison country is that it is likely to have received comparatively less media coverage surrounding the IBI than the UK. As a result, we would expect comparable responses across the two time periods with respect to perceptions of risk and safety of the blood supply in the USA (i.e., little variation), but negative effects on perceptions of risk and safety in the UK. Additionally, the USA is demographically and culturally similar to the UK, with a comparable blood donation system. Other European countries, though arguably similar to the UK, would have likely received more media coverage surrounding the IBI and are, thus, less suitable comparators.

2.2 | Design and timelines

2.2.1 | Design

We conducted a 2 (Country: UK, USA) by 2 (Time: pre-post) between-within-subject study. The between-subject factor was the country, with the USA as a control for change in the UK (see statistical analysis section below). The within-subject factor was the pre-post IBI data collection. The majority of participants (93.8%) answered the post-IBI survey in the first week (i.e., between 30th May and 5th June 2024) (Figure S1 in the Supplementary File).

2.3 | Measures

The following were assessed in both the pre- and post-IBI surveys:

Infection risk and transfusion safety: *Perceived infection risk* was measured by: '*What do you feel the level of infection risk is to a patient receiving blood in the UK/USA?*' (country varied by country of current residence) (from 1 = 'No risk at all to 5 "An extremely large risk"'). *Perceived transfusion safety* was assessed by: '*To what extent do you feel it is safe in the UK/USA to have a blood transfusion if you need one?*' (from 1 = 'Not at all safe' to 11 'Completely safe').

Willingness to donate and encourage others: Willingness to donate ('*I am willing to donate blood (assuming you are eligible)*' and willingness to encourage others ('*I am willing to encourage others to donate blood*') were self-reported on 1= 'Not at all' to 7 = 'Completely' scales. These measures correlate with donation behaviour while also measuring two distinctions: (i) willingness to donate is approaching (Approach) the decision to donate, and (ii) encouraging others is about thinking of the wider social decision-making of others to donate (Encourage).[14,15]

Demographics: We collected data on age, sex, education and donation history. Age was measured in years and split into three categories: (i) 'Gen Z' (18–26 years) (=1), (ii) Millennials ('27–42' years) (=2), and (iii) 'Gen X + Boomers' (>42 years) (=3). These categorisations were chosen because these generational groups are widely recognised and understood, allowing for more practical insights into groups that might be affected.[16] Sex was assessed as female (=1) and male (=0), with the option of prefer not to say, coded as missing (=.). Education was defined as either non-tertiary (=0) or tertiary (=1) educated. For blood donor history, we distinguish between those who have (i) never donated blood (=1) and those who have donated blood at least once (=2). These demographic questions were only asked in the initial pre-IBI survey (given the relatively short period between the two data collection points).

We also asked several other questions about ethnicity, income, political ideology, and region (country of residence and region/state currently residing). Given differences across countries (USA/UK), the questions differed slightly (i.e., income brackets and ethnicity are defined differently in the USA relative to the UK). As such, we focus on age, sex, education, and donor history, which are characteristics where response options are comparable across the two contexts.

2.4 | Timelines and cultural context

Generally, it has been recommended that some cultural context should be provided to aid in understanding research findings.[17] To this end, we explored the media coverage of the IBI in the UK and USA, covering the pre- and post-IBI data collection period. This provides a descriptive backdrop to the broader penetration of the IBI announcement. A web search targeted the top four news websites in the USA,[18] and the BBC in the UK. The search was conducted through the news website search function and supplemented with 'Google Site Search' through the search term 'infected blood'. The timeframe aimed to capture pre-during-post announcement of the IBI, covering April 2024–June 2024.

In addition, we utilised Google Trends data to gauge public interest in the term 'Infected Blood' across the UK and USA during the same period. Google's 'Interest' index measures '…search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. A value of 50 means that the term is half as popular. A score of 0 means there was not enough data for this term'.

This combined approach provides insights surrounding media coverage and public search behaviour, offering a clearer picture of how the IBI was represented and received by the public in the two countries.

2.5 | Statistical analysis and power calculations

Statistical analyses were conducted in Stata 18. All tests are two-tailed. Statistical significance is determined by $p < 0.05$. We explore the effects of the IBI both at the aggregate population level using regression models but also at the level of each individual in the sample using the Reliable Change Index (RCI) proposed by Jacobson and Truax.[19]

2.5.1 | Causality—difference-in-difference (DiD) analysis

To examine causality, we ran a two-period fixed effects DiD model. The DiD model allows us to infer a causal effect of the IBI announcement by comparing changes in outcomes before and after the announcement between individuals in the UK (treatment group) and the USA (control group).

The DiD model used to quantify the change in safety involved standardising both 'infection risk' (M = 0, SD = 1) and 'safety of transfusion' (M = 0, SD = 1). A two-period fixed-effects DiD model was employed with the following specification described in Equation (1):

$$y_{it} = \alpha_i + \beta_1(\text{Post\_IBI}_{it} \times \text{UK}_i) + \gamma_i + \lambda_t + \epsilon_{it}, \quad (1)$$

where y_{it} is the outcome variable (i.e., infection risk and safety of transfusion), α_i the intercept, $\beta_1(\text{Post\_IBI}_{it} \times \text{UK}_i)$ captures the difference-in-differences estimate, γ_i represents the individual (panel) fixed effects, λ_t the time-fixed effects and ϵ_{it} is the error term. Standard errors are clustered at the individual level to account for repeated observations over time. Both 'infection risk' and 'safety of transfusion' are standardised (M = 0, SD = 1).

2.5.2 | Reliable Change Index (RCI) analyses

To examine significant changes at the individual level, we construct an RCI for each individual's infection risk and safety.[19–23] The RCI represents the raw change score (i.e., post-IBI – pre-IBI) divided by

the index of random error resulting from unreliability. If the absolute value of this RCI exceeds 1.96, this represents a significant change for that individual. The RCI sign gives the direction of the change. However, current evidence suggests that a threshold of 1.645, reflecting 90% confidence that reliable change has occurred, should be adopted as the original threshold is overly stringent.[23] Therefore, we adopt this threshold in our analysis. The formula for the RCI is described in Equation (2):

$$RC = \frac{\overline{X}_{Post\ IBI} - \overline{X}_{Pre\ IBI}}{S_{Diff}}, \quad (2)$$

where $\overline{X}_{Post\ IBI}$ (mean of variable post-IBI), $\overline{X}_{Pre\ IBI}$ (mean of variable pre-IBI), s_1 (standard deviation of variable pre-IBI), and $S_{Diff} = \sqrt{2(S_E)^2}$. $S_E = s_1\sqrt{1 - r_{xx}}$, with r_{xx} representing the test-retest reliability of the variable (measured by Pearson's correlation between Pre-IBI and Post-IBI) (see Jacobson and Truax[19] for more details).

2.5.3 | Impact of reliable change on negative changes in approach and encourage

We assess the impact of significant changes in infection risk and safety on negative changes in willingness to donate blood and encourage others to donate. We employ several logistic models, a class of binary responses (see Wooldridge[24]) of the following form (Equation (3)):

$$P(\triangle y_i = 1 | \triangle x_i) = F(\beta_0 + \beta_1 RCI_{infection\ risk_i} + \beta_2 RCI_{safety_i} + X_i\beta + \epsilon_i), \quad (3)$$

where $\triangle y_i$ is the difference in the outcome variable between pre- and post-IBI for each individual, turned into a 'negative' binary response (i.e., takes on a value of 1 if a decreased change willingness to donate or encourage others to donate is observed. β_0 is the intercept. $\beta_1 RCI_{infection\ risk}$ and $\beta_2 RCI_{safety}$ capture the reliable change in infection risk and safety for each individual, respectively. $X_i\beta$ represents a vector of additional controls (age, sex, education, and prior donation status), and ϵ_i is the error term. F is a function that takes on values strictly within zero and one, such that $0 < F(q) < 1$, for all real numbers q. The logistic function $F(q) = \frac{e^q}{1+e^q}$ is the cumulative distribution function for the standard logistic distribution. The logistic model is estimated using maximum likelihood estimation (see Wooldridge[24] for more details). Standard errors are clustered at the individual level to account for repeated observations over time. Coefficients are described in terms of Odds Ratios (OR).

2.5.4 | Power analysis

Based on effect sizes reported by Merz et al.[25] to achieve a power of 0.80 with alpha of 0.05 for a 2 (between) by 2 (within) design to detect an interaction with a small effect size (Cohen's $D = 0.105$) requires 855 in USA (pre and post) and 855 in the UK (pre and post).[26]

3 | RESULTS

3.1 | Field quasi-experiment

Sample summary statistics: The pre-IBI sample comprises 2060 observations ($N = 1032$ USA, $N = 1028$ UK) (Table S1 Supplementary File). Of these 2060 observations, 175 (17.96%) in the USA and 107 (10.41%) in the UK stated they were prior blood recipients. For reasons described above, these recipients were excluded from the post-IBI study. As a result, 1778 participants (857 USA, 921 UK), were invited to participate in the post-IBI study. Of these, 747 responded in the USA (87.16% response rate), and 888 (96.41% response rate) in the UK. Overall, these are good response rates, with a typical rule of thumb being that <5% attrition leads to little bias and >20% poses serious threats to validity.[27] Furthermore, comparing the pre- and post-IBI demographics, we see that younger people, particularly in the USA, were more likely to 'drop out' of the study ($p < 0.01$). There were no other differences in demography (i.e., sex, education and prior donor status) (Table S2 Supplementary File). Summary statistics for the main variables are in Table S3 in the Supplementary File.

Perceptions of risk and safety: The two measures are significantly negatively correlated, showing that an increased perception of risk is associated with a lower perception of safety (pre-IBI: $r = -0.51$, $p < 0.01$, post-IBI: $r = -0.52$, $p < 0.01$) (Tables S4–S6, Supplementary File).

Figure 1 presents the results for perceived (i) infection risk and (ii) safety of transfusion across country (UK/USA) and pre- and post-IBI. Significance is determined by several ordinary least squares regressions (controlling for age, sex, education, prior donor status and region/states residing in), clustered at the individual level to account for repeated observations over time (Tables S7–S10 Supplementary File). For perceived infection risk, there was a significant ($p < 0.01$) decrease over time in the USA but no significant difference in the UK ($p = 0.97$).

For perceived safety of transfusion, there was no significant difference pre- and post- in the USA ($p = 0.58$), but a small but statistically significant decrease in the UK ($p < 0.01$). The decline in the UK was 1.83%, which is a small change. Furthermore, for both counties, we see that perceived infection risk is on the lower end of the scale, and perceived safety is on the higher end of the scale—reflecting low levels of 'concern' in the blood supply for both countries. Also, pooling across pre- and post-IBI, the perceived safety of the blood supply is higher in the UK than in the USA ($p < 0.01$) (Table S3 in the Supplementary File).

Table 1 shows the DiD results, with the average treatment effect on the treated (ATET) being a significant increase in infection risk ($p < 0.05$) and a significant decrease in safety ($p < 0.05$). For perceived infection risk, this is due to the decrease in perceived infection risk in the USA sample, not an increase in the UK (as would have been expected). Regarding the magnitude of the effect on perceived safety, those in the UK perceived the blood supply to be 0.11 standard deviations less safe than those in the USA post-IBI, which is a small effect.[26,28]

These results show a small but significant decline in perceived safety in the UK sample. We observe no significant change in the level

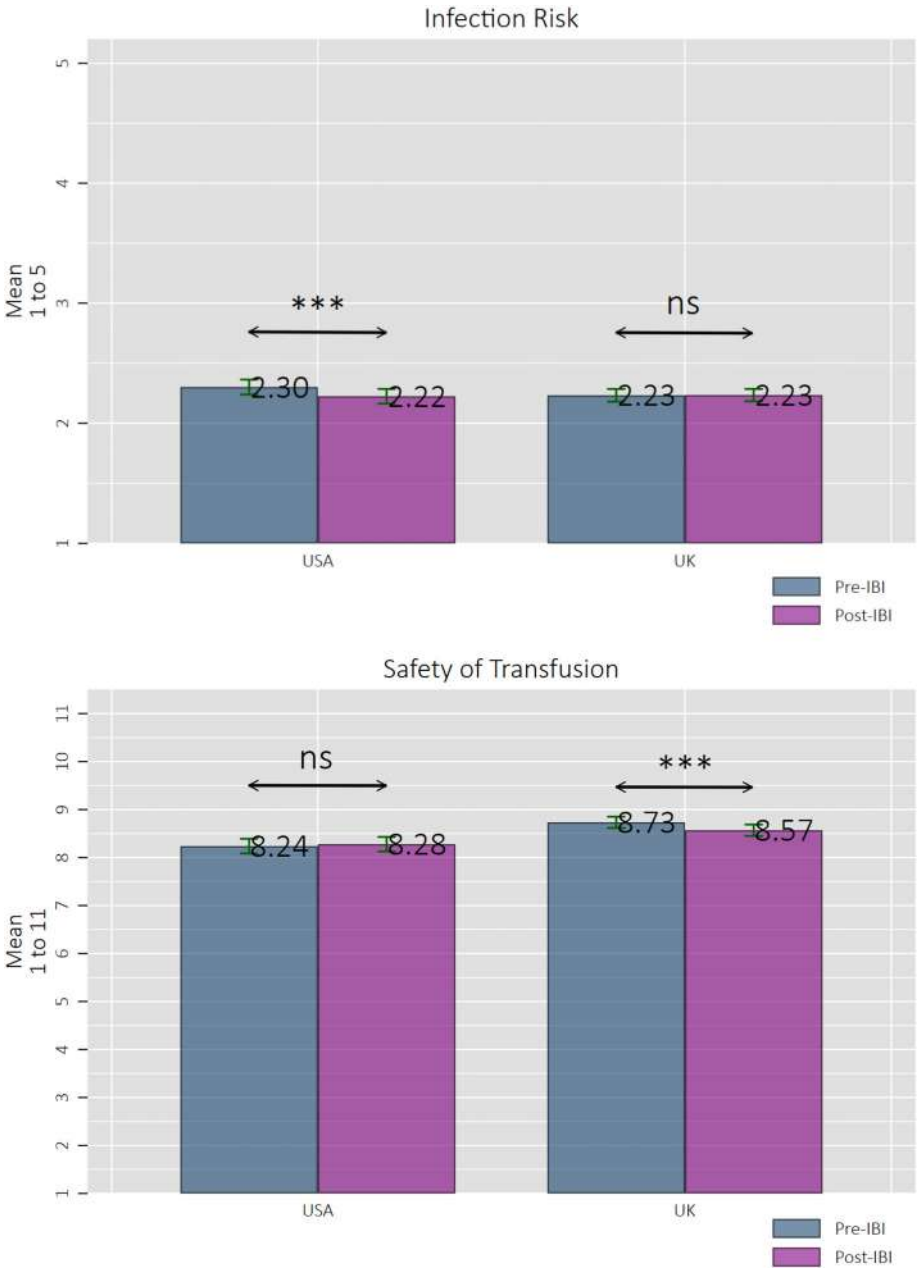


FIGURE 1 Perception of infection risk and transfusion safety. Perceived infection risk ('What do you feel the level of infection risk is to a patient receiving blood in the UK/USA?') (country varied by country of current residence) (from 1 = 'No risk at all to 5 "An extremely large risk"'. Perceived transfusion safety ('To what extent do you feel it is safe in the UK/USA to have a blood transfusion if you need one?') (from 1 = 'Not at all safe' to 11 'Completely safe'). Confidence intervals (CIs) are 95%. ***$p < 0.01$; **$p < 0.05$; *$p < 0.1$.

of perceived infection risk in UK participants. These results also do not vary across the responses of the 'early' completers (i.e., first week) and 'late' completers (after the first week).

3.2 | Individual analysis (RCI)

Figure 2 shows the reliable change (RCI estimates) from pre- to post-IBI in infection risk and safety across the two countries (USA/UK) represented as Waffle plots. These represent the number of people who change (positively, negatively) per hundred and if this change is statistically significant for that individual. Looking at those who show a statistically significant change, we observe a significant increase in perceived risk for 4.1% of the UK sample and 3.5% of the USA sample (Figure 2). Overall, there were no significant differences between the two countries for this measure. For the UK sample, 3.3% had a significant drop in perceived safety and 4.4% in the USA sample—a difference that is not statistically significant (Figure 2). However, when looking at the overall distribution of the measure, we see that the UK sample is significantly different to the USA sample, primarily driven by the higher number of participants who had a drop in perceived safety overall (significant and non-significant decreases) (Table S11 Supplementary File).

3.3 | Impact of changes in perceived risk and safety

Table 2 shows the logistic regression results, expressed as odds ratios (OR), across the UK (columns 1–2), USA (columns 3–4) and for

TABLE 1 Two-period fixed effects diff-in-diff models.

Variables	(1) Infection risk	(2) Safety
ATET	**0.099****	**−0.107****
	(0.048)	(0.047)
Constant	0.021*	0.017
	(0.012)	(0.012)
Observations	3261	3261
# Observations	3261	3261
# Clusters	1635	1635

Note: Dependent variables are standardised ($M = 0$, SD $= 1$).
ATET = Average Treatment Effect on the Treated, estimating the diff-in-diff with the UK and the treatment group and the USA as the control. A positive ATET indicates an increase in the dependent variable due to the treatment, while a negative ATET indicates a decrease. Cluster robust standard errors in parenthesis to account for repeated observations over time.
***$p < 0.01$; **$p < 0.05$; *$p < 0.1$.

the total sample (columns 5–6). There were no significant effects on infection risk. The results show that a significant decrease in perceived transfusion safety, relative to no change, is associated with a significant decrease in willingness to donate in the USA (OR = 3.396, $p < 0.01$), and for the total sample (OR = 2.336, $p < 0.01$), but not in the UK (OR = 1.594, $p = 0.31$). For encouraging others to donate, a significant decrease in perceived safety is associated with a significant decrease in encouraging others in the UK (OR = 2.697, $p < 0.05$), USA (OR = 2.072, $p < 0.05$), and across the total sample (OR = 2.396, $p < 0.01$). Positive changes in perceptions of safety show no differences in reduced approach and encouraging others. Supplementary Tables S12 and S13 provide a robustness check using the simple change score and the sample restricted to one-week post-IBI.

These results show that significant deviations in perceived transfusion safety are associated with decreased willingness to donate and encourage others to donate in the USA and the total sample. For the UK, we only see a significant association for encouraging others.

3.4 | Exploratory analysis across age, sex and donor status

We explored the differences in increased perceptions of risk (↑Δ Risk), decreased perceptions of safety (↓ΔSafety), decreased perceptions of approach (↓Δ Approach) and encouraging others (↓Δ Encourage) across age, sex, education and previous donor history. The results, summarised in Table 3, are derived from several logistic regressions. Below, we discuss the significant findings; non-significant results are not reported (see Table S14, Supplementary file for regressions restricted to first-week post-IBI).

3.4.1 | Age

Older participants: Millennials (OR = 0.435, $p < 0.05$) and Gen X + Boomers (OR = 0.412, $p < 0.05$) relative to Gen Z in the USA have a lower likelihood of having an increased change in their perception of infection risk. For the UK, Millennials (OR = 2.248, $p < 0.05$) and Gen X + Boomers (OR = 2.417, $p < 0.01$) relative to Gen Z are associated with a significantly higher likelihood of having decreased changes in the perception of safety. The latter results in the UK highlight that older people might be more affected by the announcement of the IBI report as they perceive themselves more at risk, in line with previous literature showing that younger people generally perceive themselves as less vulnerable to health risks.[29–31] An alternative account is that they are psychologically closer to the inquiry, given the time when infected blood was around and their age, making them more aware of the historical context.[32,33]

3.4.2 | Sex

Women in the UK had a significantly higher increase in perception of infection risk (OR = 1.642, $p < 0.01$). These results are in line with previous literature showing that women are generally more risk-averse than men,[34–39] are more likely to perceive the same events as riskier than men[36] and are more likely to require blood transfusions.[40–45]

3.4.3 | Education

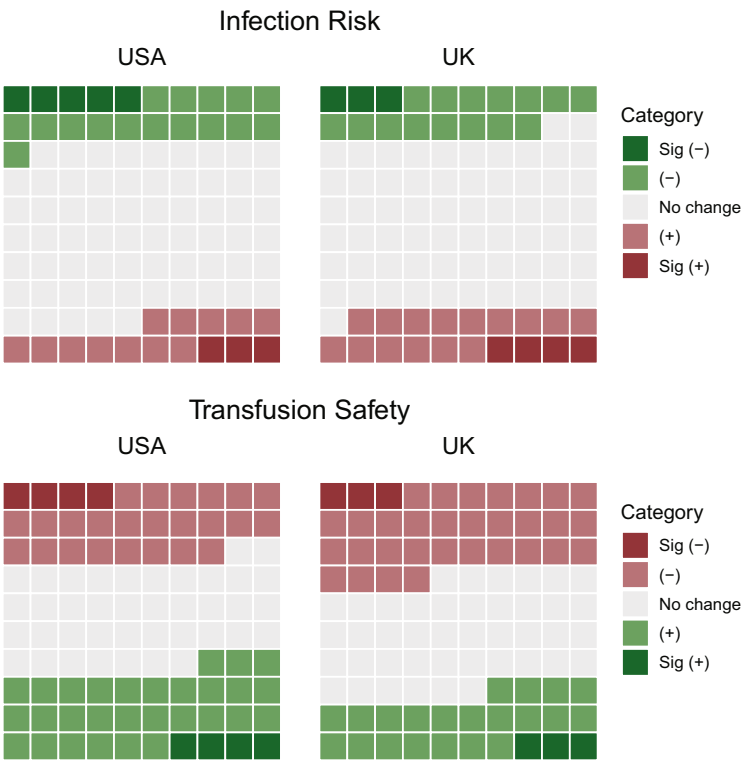
Education was generally not significantly associated with any of the outcome measures, except for reduced encourage in the USA. This may highlight that more educated people in the USA are more likely to follow the news.[46]

3.4.4 | Donor history

Blood donors in the UK are associated with a lower likelihood of having a decrease in approach (OR = 0.659, $p < 0.05$) and encourage (OR = 0.665, $p < 0.01$). These results are in line with the idea that blood donors are less affected by the announcement of the IBI than non-donors, perhaps due to the continued belief that they are benefitting the well-being of others,[47,48] and having higher trust in the NHS and NHSBT.[17]

3.5 | Cultural context (UK and US media coverage of the IBI)

Figure 3 (Panel A) shows the timelines of data collection and (Panel B) media coverage across the UK (BBC) and the USA (Fox News,



(a) Waffle plots of RCI

	USA	UK	Total	p-value
N(%)	747 (45.7%)	888 (54.3%)	1,635 (100.0%)	
Infection Risk				
Sig. (-)	36 (4.8%)	30 (3.4%)	66 (4.0%)	0.268
(-)	122 (16.3%)	133 (15.0%)	255 (15.6%)	
No change	471 (63.1%)	555 (62.5%)	1,026 (62.8%)	
(+)	92 (12.3%)	134 (15.1%)	226 (13.8%)	
Sig. (+)	**26 (3.5%)**	**36 (4.1%)**	62 (3.8%)	
Safety				
Sig. (-)	**33 (4.4%)**	**29 (3.3%)**	62 (3.8%)	**<0.001*** **
(-)	178 (23.8%)	278 (31.3%)	456 (27.9%)	
No change	285 (38.2%)	361 (40.7%)	646 (39.5%)	
(+)	218 (29.2%)	189 (21.3%)	407 (24.9%)	
Sig. (+)	33 (4.4%)	31 (3.5%)	64 (3.9%)	

(b) Summary statistics and significance of RCI

FIGURE 2 Reliable change indices (RCI) for risk and safety. (A) Waffle plots show relative percentages for RCI values of infection risk and safety. Each square represents a percentage (there are 100 squares in each figure). Note that the legend for infection risk is red for increases and green for decreases, while for safety it is red for decreases and green for increases; (B) Summary statistics of the RCI measures, with Chi-squared tests (for proportions). ***$p < 0.01$; **$p < 0.05$; *$p < 0.1$.

MSNBC, CNN and NYT). Media surrounding the IBI was substantial in the UK, and minimal in the USA. In the UK, there was moderate activity in the months leading up to the announcement, with 15 articles published in April 2024, rising to 66 in May and a substantial drop-off in June with only three articles. Around the time of the IBI announcement, the nature of these articles varied addressing (i) *the cover-up* ('Infected blood inquiry finds scandal "was not an accident"'); (ii) *Personal impact stories* of both victims and families ('Infected blood: "They put my whole family at risk")'; (iii) *Compensation and justice* ('Infected blood scandal: Sunak promises "comprehensive" blood compensation'); (iv) *Government and political reactions* ('Rishi Sunak: "Unequivocal apology" for victims of infected blood scandal'); and (v) *Regional and institutional failures* ("Welsh minister apology for infected blood 'tragedy'). Of the 84 articles in April, May, and June 2024, 60 were written between the two data collection points (08/05–29/05), representing a significant proportion of the total media surrounding the topic (>70%).

Data from Google Trends surrounding the search term for 'Infected Blood' (Figure 3, Panel C) shows that the UK saw significantly higher relative rates of search activity than the USA, particularly around the time of the IBI announcement (20th May 2024). In fact, there was more than five times the relative interest for the term

TABLE 2 Logistic regressions (in odds ratios) for positive and negative changes across pre- and post-IBI.

	UK		USA		Total	
Variables	**↓ Δ Approach**	**↓ Δ Encourage**	**↓ Δ Approach**	**↓ Δ Encourage**	**↓ Δ Approach**	**↓ Δ Encourage**
Infection risk: *Baseline: No change*						
Sig. (−)	0.675	1.118	0.728	0.903	0.706	0.962
	(0.350)	(0.497)	(0.352)	(0.415)	(0.243)	(0.298)
(−)	0.787	1.022	0.832	0.851	0.810	0.933
	(0.199)	(0.237)	(0.241)	(0.227)	(0.152)	(0.162)
(+)	0.825	0.656*	1.260	0.854	1.014	0.710*
	(0.208)	(0.153)	(0.374)	(0.265)	(0.187)	(0.131)
Sig. (+)	0.591	0.424*	1.671	1.089	0.956	0.654
	(0.286)	(0.190)	(0.825)	(0.526)	(0.308)	(0.205)
Transfusion safety: *Baseline: No change*						
Sig. (−)	1.594	**2.697****	**3.396*****	**2.072****	**2.336*****	**2.389*****
	(0.730)	(1.135)	(1.363)	(0.754)	(0.692)	(0.655)
(−)	1.277	1.282	1.553*	1.531*	**1.381****	**1.373****
	(0.250)	(0.231)	(0.382)	(0.358)	(0.209)	(0.195)
(+)	1.278	0.889	0.869	1.166	1.039	0.984
	(0.294)	(0.193)	(0.220)	(0.278)	(0.176)	(0.155)
Sig. (+)	0.964	0.382*	1.413	0.712	1.156	0.534
	(0.472)	(0.214)	(0.673)	(0.390)	(0.386)	(0.209)
Constant	1.597	0.459	0.642	0.273*	0.890	0.270
	(1.088)	(0.368)	(0.469)	(0.213)	(0.588)	(0.217)
Region/State controls	✓	✓	✓	✓	✓	✓
Observations	880	880	705	714	1589	1598
Pseudo R^2	0.0422	0.0404	0.0648	0.0533	0.0407	0.0390
Log Likelihood	−458.6	−510.9	−364.2	−386.7	−834.1	−906.5
Degrees of Freedom	28	28	53	54	66	67
Chi^2	38.80	42.40	54.55	47.12	69.97	72.79
Prob < chi^2	0.0842	0.0397	0.415	0.735	0.346	0.293

Note: Logistic regressions (represented by odds ratios, OR) for decreased changes in approach (↓ Δ Approach) and encouraging others (↓ Δ Encourage) by country (UK, USA). Independent variables represent RCI values for (i) Infection Risk, and (ii) Transfusion Safety. Additional controls include age, sex, education, prior donor status and region/states residing in), clustered at the individual level to account for repeated observations over time. Cluster robust standard errors in parenthesis.

***$p < 0.01$; **$p < 0.05$; *$p < 0.1$.

in the UK (Index = 100, 20th May 2024) than in the USA (Index = 18, 22nd May 2024). This data further supports the argument that the USA saw relatively little media coverage on the issue.

4 | DISCUSSION

Despite the significant implications of the IBI findings, the UK participants in our sample continue to see the safety of its blood supply as very high. In fact, UK blood is perceived as safer by UK participants than American blood is perceived by US participants. Following the IBI announcement, during June, there was a significant but very small (1.83%) decline in the perceived safety of the UK blood supply by people in the UK, but no change in perceived transfusion infection risk. Thus, while there was a statistically significant decline in perceived safety, overall, the UK blood supply remains seen as very safe. While more people in the UK (34.6%) than in the US (28.4%) showed a decrease in perceived safety when we consider the number of people who showed a significant decline in perceived safety, it is small: 3.3% in the UK and 4.4% in the USA.

This relatively small impact is likely a result of several factors. First, it indicates that the public may feel that the inquiry was comprehensive, open and fair. Indeed, Sir Brian Langstaff, instrumental in putting the report together, received a standing ovation after announcing its release.[49] Moreover, the speech in the House of Commons reaffirmed the government's commitment to enacting legislation to compensate those affected by the scandal with mutual support across the parties.[50,51] Second, it is clear that UK blood services have changed

TABLE 3 Logistic regressions (in odds ratios) for exploratory demographics analysis.

	↑ Δ Risk		↓ Δ Safety		↓ Δ Approach		↓ Δ Encourage	
Variables	**USA**	**UK**	**USA**	**UK**	**USA**	**UK**	**USA**	**UK**
Age								
Baseline: Gen Z								
Millennials	**0.435****	0.745	0.997	**2.248*****	0.628	0.689	0.877	0.886
	(0.159)	(0.231)	(0.346)	(0.706)	(0.225)	(0.196)	(0.319)	(0.237)
Gen X + Boomers	**0.412****	0.950	1.063	**2.417*****	0.814	0.619*	1.189	0.801
	(0.150)	(0.295)	(0.372)	(0.769)	(0.288)	(0.180)	(0.426)	(0.216)
Sex								
Baseline: Males								
Female	0.861	**1.642*****	0.966	1.237	0.760	1.045	0.927	0.767*
	(0.186)	(0.295)	(0.171)	(0.179)	(0.141)	(0.171)	(0.168)	(0.116)
Education								
Baseline: Non-tertiary								
Tertiary	0.798	1.115	1.108	1.041	0.821	1.068	**1.600****	1.243
	(0.181)	(0.214)	(0.215)	(0.161)	(0.165)	(0.187)	(0.322)	(0.199)
Donor history								
Baseline: Non-donors								
Donor	1.196	0.780	0.872	0.812	0.890	**0.659****	1.069	**0.665****
	(0.269)	(0.144)	(0.154)	(0.122)	(0.170)	(0.116)	(0.200)	(0.106)
Constant	0.175	0.152***	0.171**	0.282***	0.794	0.734	0.207**	0.685
	(0.196)	(0.064)	(0.140)	(0.109)	(0.549)	(0.261)	(0.150)	(0.234)
Region/State controls	✓	✓	✓	✓	✓	✓	✓	✓
Observations	681	880	717	880	709	880	718	880
Pseudo R^2	0.0580	0.0248	0.0345	0.0236	0.0370	0.0341	0.0387	0.0188
Log Likelihood	−291.3	−417	−414.3	−554.5	−376.1	−462.6	−393.8	−522.4
Degrees of Freedom	36	16	42	16	42	16	43	16
Chi^2	35.41	21.95	27.47	24.48	27.67	29.63	32.79	18.81
Prob < chi^2	0.496	0.145	0.959	0.0795	0.957	0.0200	0.871	0.279

Note: Logistic regressions (represented by odds ratios, OR) for increased changes in risk (↑ Δ Risk), decreased changes in safety (↓ Δ Safety), decreased changes in approach (↓ Δ Approach) and encouraging others (↓ Δ Encourage). Key demographics of interest are age (Gen Z, Millennials, Gen X + Boomers), sex (male, female), education (non-tertiary, tertiary), and prior donor status (non-donor, donor). Additional controls include regions/states residing in. Standard errors are clustered at the individual level to account for repeated observations over time. Cluster robust standard errors in parenthesis.
***$p < 0.01$; **$p < 0.05$; *$p < 0.1$.

their practices extensively since the 1970–90s, and blood in the UK today is very safe.[1,52,53] Third, it is also possible that this minimal impact in the general population sample is a function of the large drop-off in media coverage observed in June 2024, which may have been a result of other major political events pulling focus away from the IBI, such as the announcement of a UK general election (22nd May 2024), and the continued developments of the Post Office Horizon scandal.[54]

In terms of behavioural impact, we observe that those showing a significant decline in perceived safety are less willing to donate blood or encourage others to donate in the full sample and the USA. However, in the UK, we only observe a significant effect in encouraging others. Thus, it may be that in the UK, while people may feel that they would not be put off donating, they would not want to take responsibility for encouraging others to donate. These results are consistent with previous research, showing the positive relationship between the perception of safety and willingness to donate.[25,55] However, the relatively weaker response in the UK suggests that while perceptions of the safety of the blood supply might have been slightly shaken, they do not drastically alter the general public's overall willingness to donate blood, potentially due to the aforementioned factors.

While there are clear overall effects, there are also important demographic variations. Women are more likely to feel that the infection risk has risen post-IBI reporting, older people feel that safety has reduced, and non-donors are more likely to be put off donating and asking others to donate.

These findings clearly demonstrate that the IBI announcement had minimal impact on the UK general public, aside from a slight

FIGURE 3 Data Collection Timelines and Media Coverage Across UK and USA. (A) 'Pre-IBI' data collection (03/05–07/05), 'Post-IBI' data collection (30/05–30/06). Post-IBI data collection was longer as participants needed additional time to complete the follow-up survey. (B) The number of articles were observed through the following search terms on Google (www.google.com) between 01/04 and 30/06: 'site:www.bbc.com "infected blood"', 'site:www.msnbc.com "infected blood"', 'site:www.foxnews.com "infected blood"', and 'site:www.cnn.com "infected blood"'. (C) Google Trends search data for the UK/USA for the term 'Infected Blood'. The *y-axis* refers to Google's 'Interest' index, described as: 'Numbers represent search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. A value of 50 means that the term is half as popular. A score of 0 means there was not enough data for this term'. The graph shows maximal interest in the UK around the IBI announcement (20th May 2024), with a sharp drop-off afterwards. There is relatively low interest across the USA, with a small spike a few days after the IBI announcement. The data to produce these graphs can be accessed from the following Google Trends link.

(a) Days of data collection and articles across UK and USA by month

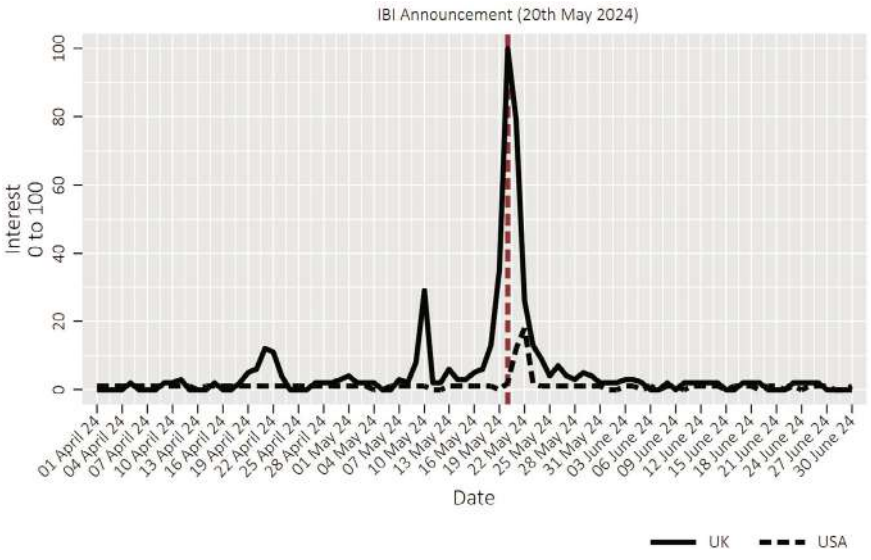
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
April 2024	1 *0 | 0*	2 *0 | 0*	3 *0 | 0*	4 *0 | 0*	5 *0 | 0*	6 *0 | 0*	7 *0 | 0*
	8 *0 | 0*	9 *0 | 0*	10 *0 | 0*	11 *0 | 0*	12 *0 | 0*	13 *0 | 0*	14 *3 | 0*
	15 *0 | 0*	16 *0 | 0*	17 *0 | 0*	18 1 | 0	19 *0 | 0*	20 *1 | 0*	21 *0 | 0*
	22 *8 | 0*	23 *0 | 0*	24 *1 | 0*	25 0 | 0	26 *0 | 1*	27 *0 | 0*	28 *0 | 0*
May 2024	29 *0 | 0*	30 *1 | 0*	1 *1 | 0*	2 0 | 0	3 *0 | 0*	4 *0 | 0*	5 *2 | 0*
	6 *0 | 0*	7 *2 | 0*	8 *0 | 0*	9 *2 | 0*	10 *0 | 0*	11 *0 | 0*	12 *0 | 0*
	13 *2 | 0*	14 *2 | 0*	15 *0 | 0*	16 *2 | 0*	17 *1 | 0*	18 *2 | 0*	19 *7 | 0*
	20 *21 | 2*	21 *13 | 2*	22 *1 | 1*	23 *2 | 0*	24 *2 | 0*	25 *1 | 0*	26 *2 | 0*
June 2024	27 *0 | 0*	28 *0 | 0*	29 *0 | 0*	30 *1 | 0*	31 *0 | 0*	1 *0 | 0*	2 *0 | 0*
	3 *0 | 0*	4 *0 | 0*	5 *1 | 0*	6 *0 | 0*	7 *0 | 0*	8 *0 | 0*	9 *0 | 0*
	10 *0 | 0*	11 *0 | 0*	12 *0 | 0*	13 *0 | 0*	14 *0 | 0*	15 *0 | 0*	16 *0 | 0*
	17 *1 | 0*	18 *1 | 0*	19 *0 | 0*	20 *0 | 0*	21 *0 | 0*	22 *0 | 0*	23 *0 | 0*
	24 *0 | 0*	25 *0 | 0*	26 *0 | 0*	27 *0 | 0*	28 *0 | 0*	30 *0 | 0*	

Pre-IBI data collection
Report announcement
Post-IBI data collection

(b) Total articles across UK and USA by month

	UK (BBC)	USA (Fox News)
April 2024	15	1
May 2024	66	5
June 2024	3	0

(c) Google Trends Searches for 'Infected Blood'



decrease in perceived safety. Consequently, NHSBT can be reassured that the overall psychological and behavioural effects of the IBI inquiry on the general population are minimal. However, it is important to acknowledge that blood recipients, particularly those requiring multiple transfusions over their lifetime, have experienced and continue to experience significant impacts. The work reported here is not intended to undermine or diminish the concerns and experiences of this specific group. Indeed, the work reported here focused solely on the general public who had not received a transfusion. Future research needs to be undertaken to explore the impact of the IBI on blood recipients, especially those requiring multiple transfusions.

4.1 | Limitations and future directions

There may be some selection bias (i.e., attrition), but this is unlikely given that the follow-up response rates are all about 85%.[27] However, it must be noted that the US sample is slightly underpowered; and we also acknowledge that the study only evaluates the 'short-term' impacts of the IBI announcement and that longer-term evaluation and studies exploring the impact on current blood recipients and victims are needed. More objective data from NHSBT surrounding the number of registrations and successful donations would better determine the direct impacts on the organisation. Finally, while we examined perceptions of overall blood safety for transfusion, future work should consider differentiating between blood, blood products and plasma.

This work provides an initial evaluation surrounding the impact of the IBI. We aim to follow up with participants from this sample over the coming years to explore longer-term impacts. We also plan to use the same questions to explore the impact of the IBI on recipient populations, particularly as the implications of the IBI are realised over the coming years (i.e., as compensation is provided to victims and their families).

5 | CONCLUSIONS

The general public in the UK perceives the current blood supply as extremely safe, and the IBI announcement had a minimal impact on this perception. Compared to the UK, blood safety perceptions are lower in the USA. Moreover, significant reductions in safety perceptions are associated with a lower willingness to donate blood. However, in the UK, even those who perceive a reduction in safety do not show a significantly lower willingness to donate. Future research should explore long-term impacts, continue to monitor public perceptions as compensation schemes are rolled out, and examine opinions and perceptions of blood recipients.

AUTHOR CONTRIBUTIONS

Richard Mills, Eamonn Ferguson, Barbara Masser, and Eva-Maria Merz set up the survey, and Richard Mills and Eamonn Ferguson analysed the data and wrote the manuscript. Robert Smith researched the media impact surrounding the IBI. Eva-Maria Merz, Mark Croucher, Barbara Masser, Robert Smith and Susan R. Brailsford provided feedback on the analysis and comments on several iterations of the draft.

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[Correction added on 13 December 2024, after first online publication: Paragraphs 2 and 3 of Section 2.5.1, first sentence of Section 2.5.2, and Figure 2 as well as its caption were corrected].

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

DATA AVAILABILITY STATEMENT

Data and analysis files will be made freely available on the Open Science Framework.

ETHICS STATEMENT

This research was reviewed and approved by the Ethics Review Board in the School of Psychology, University of Nottingham (F1351: 30/05/2022; F1366: 06/07/2022; F1411: 03/02/2023; F1422: 22/02/2023).

PARTICIPANT CONSENT STATEMENT

All participants were over 18 years old and provided full informed consent.

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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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Evaluating utility of routine ferritin testing in blood donors: A hospital-based blood donor centre experience

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Abstract

Background and Objectives: Iron deficiency (ID) poses a prevalent concern among blood donors, especially impacting young donors, premenopausal females and frequent donors. In alignment with recommendations to address ID, routine ferritin testing was implemented in a hospital-based donor centre.

Materials and Methods: Data set, encompassing 26 164 ferritin values from 16 464 blood donors over 33 months, were analysed retrospectively. Ferritin levels were assessed concerning donor characteristics such as sex, age, ethnicity and donation frequency.

Results: Ferritin testing revealed age, sex and ethnicity variations, emphasising the heightened risk of ID in young females meeting all donation criteria under 23 year of age who demonstrated the lowest mean baseline ferritin (41% [CI: 34%–48%] < 26 ng/mL; 20% [CI: 14%–25%] < 15 ng/mL). Postmenopausal females exhibited ferritin levels similar to similarly aged males. Irrespective of sex, donors showcased mean ferritin recovery within 6 months. Analysis of ferritin recovery post-donation showed a five-fold increase in risk (compared with first visit) of ID when donors return at a 2-month interval. 'Regular' donors (≥10 visits) approach a median steady ferritin level (∼30–35 ng/mL) by the sixth visit.

Conclusion: As reliance on regular blood donors increases, donation policies must strike a balance between blood centre resources and the risks posed to both regular and at-risk donors. Frequent blood donation led to donors attaining a mean steady state ferritin level above the threshold for ID. At-risk groups, particularly premenopausal females, were several times more likely to experience ID after donation but demonstrated recovery rates similar to their group's baseline levels. This valuable information informed the development of new donor deferral policies.

KEYWORDS
blood donations, donor safety, ferritin testing

This work was performed at the Department of Pathology & Laboratory Medicine, Children's Hospital Los Angeles, Los Angeles, CA.

1 | INTRODUCTION

Iron deficiency (ID) and iron deficiency anaemia (IDA) pose significant concerns in blood donors, particularly in at-risk groups such as young donors, premenopausal females, frequent donors and those with haemoglobin (Hb) values near the minimum eligibility threshold.[1] The Association for Advancement of Blood and Biotherapies (AABB) recommends proactive measures by blood collection establishments to monitor, limit, or prevent iron deficiency in donors. These measures include providing comprehensive educational materials to donors, implementing specific interventions such as donor iron supplementation, adjusting inter-donation intervals or annual donation frequency and conducting donor ferritin testing-based interventions. Additionally, post-implementation monitoring of these interventions is advised.[2]

Ferritin emerges as a superior predictor of total body iron stores compared with Hb, with decreasing ferritin levels serving as a sensitive and early indicator of iron store depletion in blood donors.[3] Donor ferritin testing, coupled with iron supplementation, has demonstrated efficacy in enhancing the recovery of Hb and iron stores, thereby reducing the incidence of pre-donation anaemia and donation deferral.[4,5] Monitoring ferritin levels and providing iron supplementation or iron status information proves effective in preventing iron deficiency in donors with continued donations.[6] Aligning with AABB recommendations, the hospital-based blood donor centre (BDC) at Children's Hospital Los Angeles, Los Angeles, CA (CHLA), initiated routine ferritin testing for all donors and implemented a ferritin-based deferral policy starting in October 2018.

However, routine donor ferritin testing poses logistical and operational challenges, consuming significant BDC resources. Meeting regulatory requirements, efficiently collecting and performing ferritin testing, communicating results with donors and implementing a ferritin-based deferral policy are among the operational challenges. Amidst the COVID-19 pandemic, with the goal of streamlining donor centre operations and enhancing efficiencies, CHLA BDC reassessed its ferritin testing strategy. This manuscript shares the experience of a hospital-based BDC in utilising routine donor ferritin testing, presents post-implementation data, and outlines the rationale for discontinuing ferritin testing.

2 | MATERIALS AND METHODS

This retrospective study at the CHLA BDC spanned 1 October 2018 to 31 July 2021, coinciding with a start and cessation of routine ferritin testing. Institutional Review Board approval was secured for privacy compliance. All successful donors meeting all donation criteria including Hb criteria were included (Hb >12.5 g/dL for females and 13.0 g/dL for males), with serum ferritin testing performed on each one of them on the specimen collected during donation. The serum ferritin testing was performed by Creative Testing Solutions (Tempe, AZ) using the Beckman Coulter (Brea, CA) AU Clinical Chemistry Analysers which utilises a latex agglutination methodology. Five single-time donors were excluded from data analyses due to having missing/aberrant recorded ages. The highest recordable ferritin level on our instruments was capped at 451 ng/mL and was used as such in the analysis.

Beginning in October 2018, CHLA BDC implemented routine ferritin testing for all allogenic and autologous whole-blood donors. Ferritin result based interventions were specifically targeted at young donors (17–22 years of age, male and female) and premenopausal adult female donors (23–50 years of age). Depending on ferritin levels, the inter-donation interval for these donors was extended. A 'low' ferritin level (13–25 ng/mL) resulted in a temporary deferral for 4 months, while a 'very low' ferritin level (≤12 ng/mL) led to a 12-month temporary deferral. Educational material on treating iron deficiency and specific instructions on using over-the-counter iron supplements were provided to these donors; no iron supplementation was offered by the CHLA BDC.

Following the discontinuation of ferritin testing in July 2021, specific interventions were introduced to limit or prevent iron deficiency in all allogenic and autologous whole-blood donors. Enhanced donor education materials and communications were provided to all donors, with a particular emphasis on iron deficiency prevention, especially for at-risk premenopausal females and frequent donors. The inter-donation interval for all young donors (17–22 years of age, male and female) was extended to 12 months (temporary deferral). Other donors were advised to limit whole blood donations to 2 times per year and platelet donations to 10 times per year with no deferral.

Data for this study was collected from the ElDorado Donor Blood Management System (Haemonetics Corp, Boston, MA). Descriptive statistics were used to represent the baseline population. Data analysis was performed using Microsoft Excel (Redmond, WA). Donor characteristics were described as means, percentages, ratios and ratios of percentages. A significance level of $p < 0.05$ was applied.

3 | RESULTS

3.1 | Demographics

Over the 2 years and 10 months study period (1 October 2018 to 31 July 2021), a total of 16 464 individual blood donors had 26 163 successful visits for whole blood donation at CHLA BDC. Ferritin testing was successfully performed on specimens collected at each visit. Females comprised 57% ($n = 9409$) of donors seen at CHLA-BDC during the study period. Detailed donor demographics for each visit by age and sex are presented in Table 1.

3.2 | Ferritin levels

Ferritin cutoffs of <26 ng/mL ('low') and ≤12 ng/mL ('very low') were utilised to categorise donors at higher risk of IDA. Data was further categorised based on these cutoffs (Table 2). Distinctions were made between 'First time' and 'Repeat' donors to account for changes in

TABLE 1 Donor demographics by age and sex.

Donor demographics	Male	Female
Ethnicity (% total donors, % 1-time donors, % repeat donors)		
African American	1.3%, 1.0%, 0.3%	1.2%, 0.9%, 0.3%
Asian	4.2%, 3.1%, 1.1%	5.1%, 3.6%, 1.5%
Asian Pacific Island	0.5%, 0.4%, 0.1%	0.6%, 0.4%, 0.2%
Caucasian	19.1%, 13.2%, 5.9%	24.6%, 17.0%, 7.6%
Hispanic	14.8%, 11.5%, 3.3%	21.8%, 16.9%, 4.9%
Native American	0.1%, 0.1%, 0.1%	0.1%, 0.1%, 0.0%
Other/not stated	2.9%, 2.1%, 0.7%	3.8%, 2.8%, 0.9%
Age groups, all donors		
17–22 year	4.4%	5.4%
23–50 year	28.9%	40.6%
≥51 year	9.5%	11.1%
Age groups, repeat donors only[a]		
17–22 year	11.3% ($n = 728$)	13.0% ($n = 886$)
23–50 year	27.4% ($n = 4758$)	28.4% ($n = 6691$)
≥51 year	32.1% ($n = 1569$)	28.5% ($n = 1832$)
Median inter-donation interval for repeat donors only,[a] months (interquartile range)		
17–22 year	6.1 (3.9–8.6)	5.3 (3.8–9.4)
23–50 year	4.9 (3.2–8.7)	6.2 (3.7–10.1)
≥51 year	5.4 (3.3–9.2)	6.2 (3.6–10.4)
Median haemoglobin at donation, g/dL (IQR)		
17–22 year	15.4 (14.8–16.0)	13.7 (13.1–14.3)
23–50 year	15.1 (14.5–15.8)	13.8 (13.2–14.4)
≥51 year	14.7 (14.1–15.3)	13.7 (13.2–14.4)
Median ferritin at donation, ng/mL (IQR)		
17–22 year	84 (56–130)	29 (18–51)
23–50 year	129 (77–208)	39 (23–66)
≥51 year	108 (58–192)	67 (38–113)

Abbreviation: IQR, interquartile range.
[a]During the study period.

TABLE 2 Ferritin levels and donor categorisation.

	Male	Female
Ferritin levels		
≤12 ng/mL	224	1256
13–25 ng/mL	941	3021
≥26–450 ng/mL	10 457	9914
≥451 ng/mL	318	32
Median ferritin at first donation for all donors,[a] ng/mL (IQR)		
17–22 year	87 (58–132), $n = 728$	30 (18–51), $n = 886$
23–50 year	137 (84–220), $n = 4758$	42 (24–70), $n = 6691$
≥51 year	117 (64–201), $n = 1569$	71 (41–118), $n = 1832$
Median ferritin for donors who visited only once,[a] ng/mL (IQR)		
17–22 year	89 (59–132), $n = 646$	30 (17–52), $n = 771$
23–50 year	146 (90–232), $n = 3454$	42 (24–71), $n = 4793$
≥51 year	129 (73–225), $n = 1065$	78 (44–123), $n = 1309$
Median ferritin at first visit for donors with at least three visits,[a] ng/mL (IQR)		
17–22 year	68 (47–134), $n = 31$	38 (28–53), $n = 28$
23–50 year	105 (61–183), $n = 673$	44 (27–70), $n = 782$
≥51 year	84 (44–162), $n = 308$	51 (33–88), $n = 248$
Median ferritin at last visit for donors with at least three visits,[a] ng/mL (IQR)		
17–22 year	46 (20–72), $n = 31$	19 (16–33), $n = 28$
23–50 year	49 (28–87), $n = 673$	26 (16–42), $n = 782$
≥51 year	49 (28–79), $n = 308$	35 (21–54), $n = 248$
Median decrease in ferritin between first and second donation for donors with two visits,[a] ng/mL (IQR)		
17–22 year	18 (4–40), $n = 82$	13 (1–19), $n = 115$
23–50 year	29 (4–60), $n = 1304$	11 (0–27), $n = 1898$
≥51 year	20 (0–49), $n = 504$	14 (1–35), $n = 523$
Median ferritin at first donation by ethnicity, ng/mL (IQR)		
African American	123 (77–212), $n = 209$	41 (24–83), $n = 199$
Asian	183 (103–312), $n = 688$	56 (32–103), $n = 839$
Asian Pacific Island	220 (133–347), $n = 82$	78 (34–120), $n = 97$
Caucasian	116 (70–185), $n = 3152$	46 (27–78), $n = 4053$
Hispanic	127 (76–203), $n = 2429$	40 (23–70), $n = 3586$
Native American	103 (72–196), $n = 24$	57 (28–81), $n = 16$
Other/not stated	132 (80–218), $n = 471$	44 (24–72), $n = 619$

Abbreviation: IQR, interquartile range.
[a]During the study period.

donor behaviour during the COVID-19 pandemic, with an increase in visits from 'Repeat' donors and a decrease in visits from donors <23 years old. Blood donation visits per year remained relatively stable at CHLA BDC during this time (Figure 1).

3.3 | Age, sex and ethnicity

Young donors (defined as 17–22 years old) trended toward lower median ferritin levels compared with donor's ≥23 years old (Figure 2 and Tables 1 and 2). Male donors exhibited equivalent to statistically higher median ferritin levels across all age groups and every visit and donation interval. Borderline inadequate haemoglobin levels in females (12.5–13.0 g/dL) at a donation showed a relative risk of a ferritin <26 ng/mL of 1.54 (1.20–1.97) at a return donation within

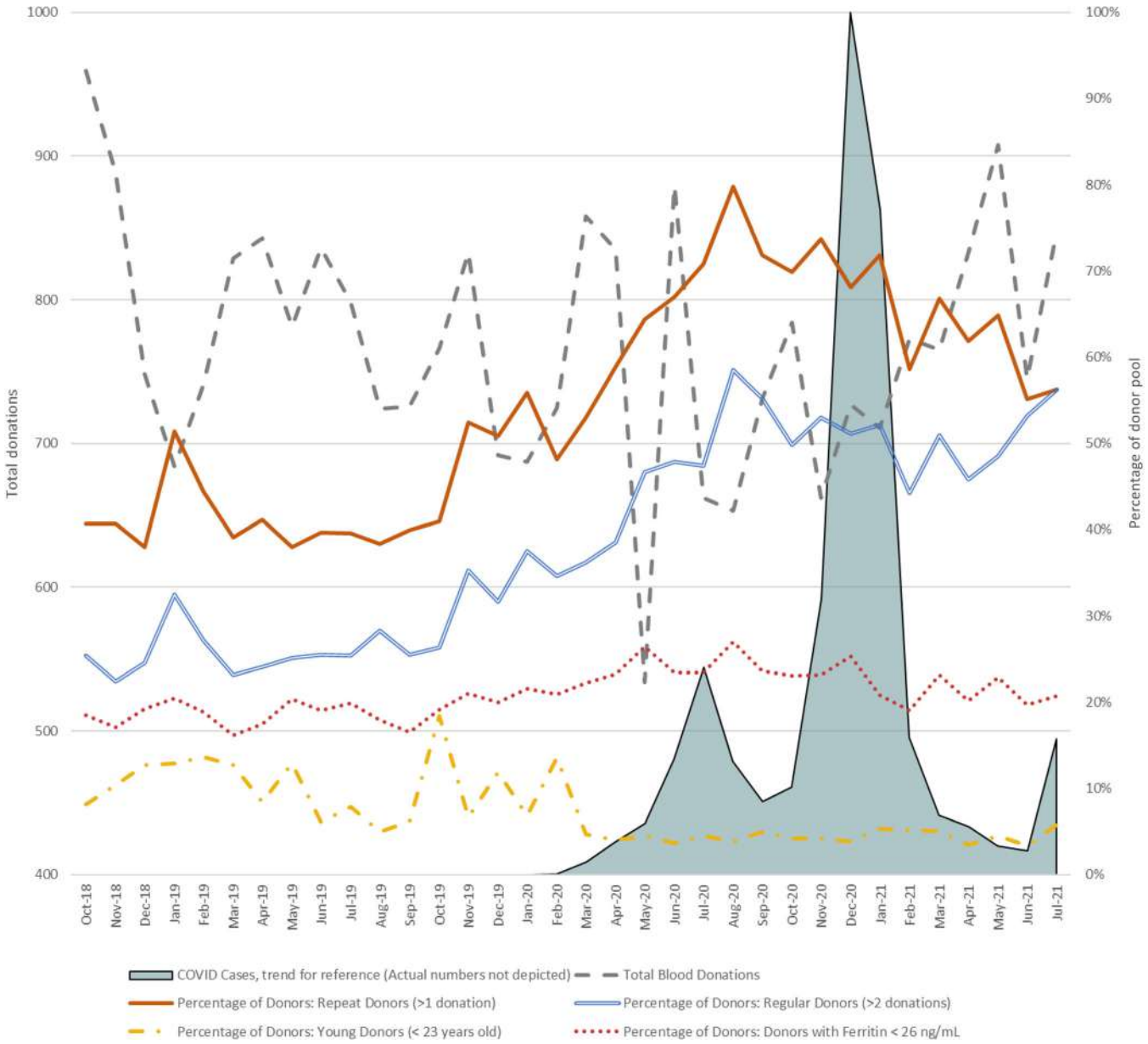

FIGURE 1 Blood donation trends during COVID-19: Trend of Children's Hospital Los Angeles, Los Angeles, CA (CHLA) blood donor centre (BDC) donation volumes and donor population during the COVID-19 pandemic, with California COVID-19 case volume data from the CDC.

6 months. Caucasian, Hispanic and Asian donors constituted the majority of whole blood donation visits as shown in Table 2.

3.4 | Donors with one visit only: Baseline ferritin data

A total of 12 038 donors (57% female) donated only once during the study period, providing baseline ferritin data. Median ferritin levels varied by sex and age (Figure 2). Young donors (17–22 years) exhibited the lowest median ferritin levels, with females showing lower levels than males. The difference between male and female ferritin levels persisted in donor's aged ≥23–50 years. However, the gap between male and female ferritin levels began to close around age 51, with overlapping baseline ferritin levels observed in their 60s.

Figure 3 illustrates the prevalence of the risk of iron deficiency in donors with only one visit. The majority of male donors (96.9% ± 0.5%, $n = 5166$) had ferritin levels ≥26 ng/mL. Approximately 60% of young female donors (17–22 years), 70% of premenopausal female donors (≥23–50 years) and 90% of postmenopausal females (≥51 years) had ferritin levels ≥26 ng/mL.

3.5 | Ferritin recovery

A total of 2356 donors (63% female) donated twice during the study period. Ferritin recovery post-donation was assessed by comparing

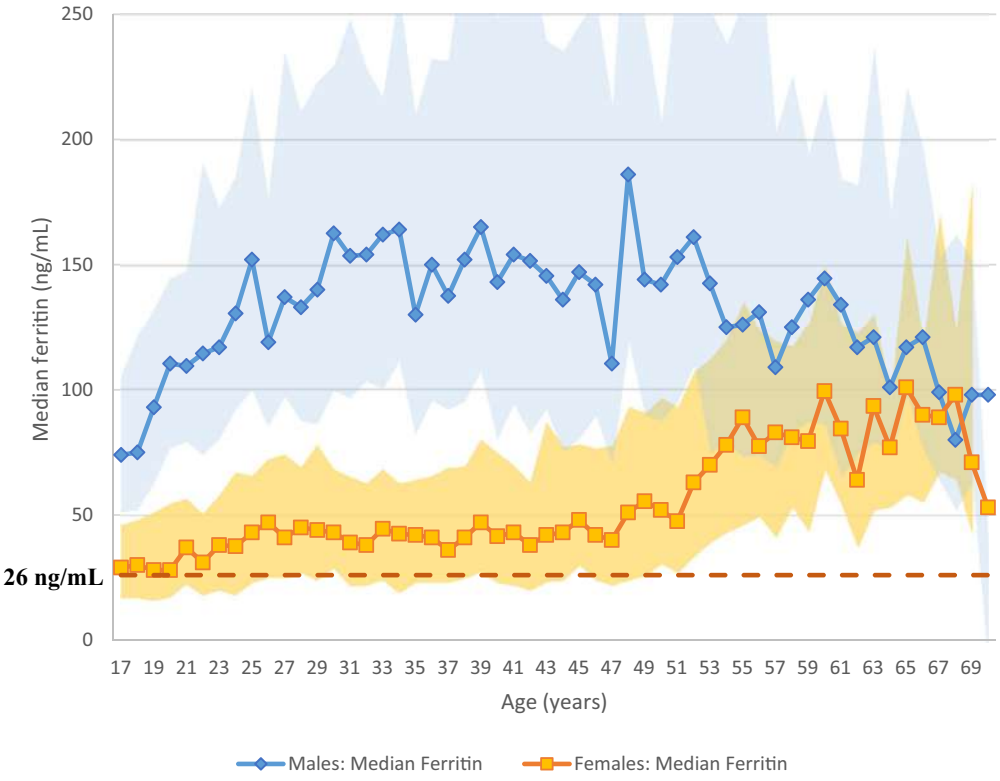

FIGURE 2 Ferritin levels for donors with one visit: Median ferritin levels by sex and age for donors with one visit, with background shadow indicating IQR. IQR, interquartile range.

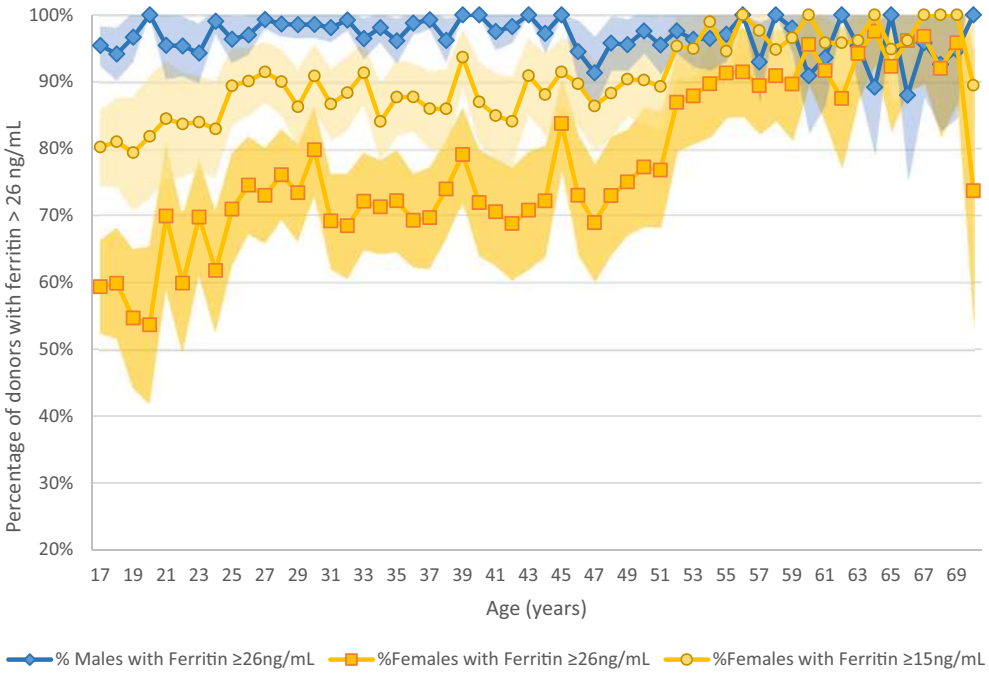

FIGURE 3 Iron deficiency risk in donors with one visit: Percentage of donors with one visit demonstrating ferritin levels ≥26 and ≥15 ng/mL for females and ≥26 ng/mL for males against age, with background shadow indicating the 95% confidence interval.

ferritin levels at the first and second visit (Table 2). Donors returning at a 2-month interval were approximately five-fold more likely to be in the lower ferritin group (<26 ng/mL) compared with donors on their first visit (Figure 4). As the donation interval increased, ferritin levels recovered and the risk of iron deficiency decreased. At a donation interval of ≥6 months, the likelihood of donors belonging to the lower ferritin group diminished to approximately one-fold risk compared with the baseline at the first visit.

3.6 | 'Regular' donors: ≥10 Visits

Eighty-nine donors (21% females) visited CHLA-BDC at least 10 times each during the study period (total 1045 successful visits). These 'regular' donors were further categorised into 'new regular' donors (started donation during the study period) and 'repeat regular' donors (had at least one previous donation at CHLA BDC before the study period). Figure 5 shows the median ferritin levels for both

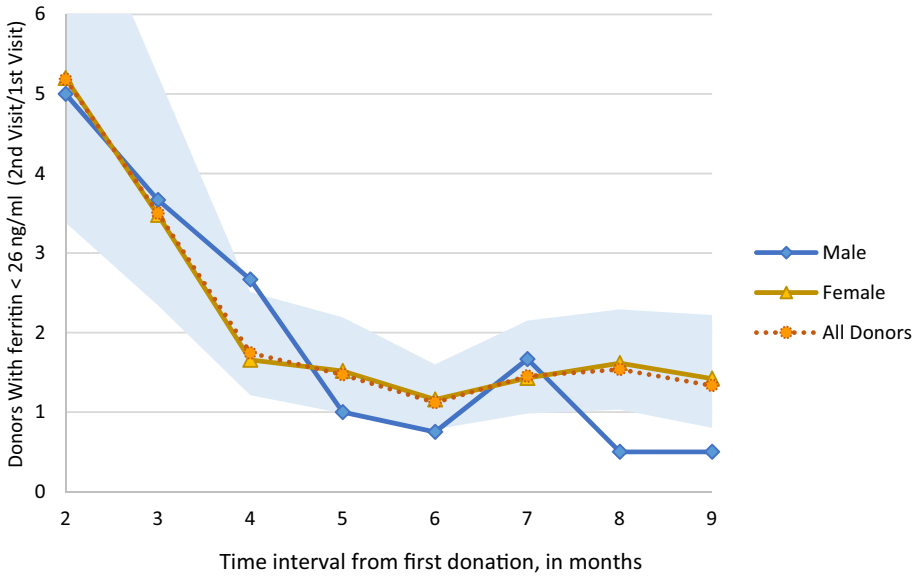

FIGURE 4 Ferritin recovery post-donation: Fold increase in proportion of donors with ferritin <26 ng/mL on their second donation over time, with background shadow showing the 95% confidence interval.

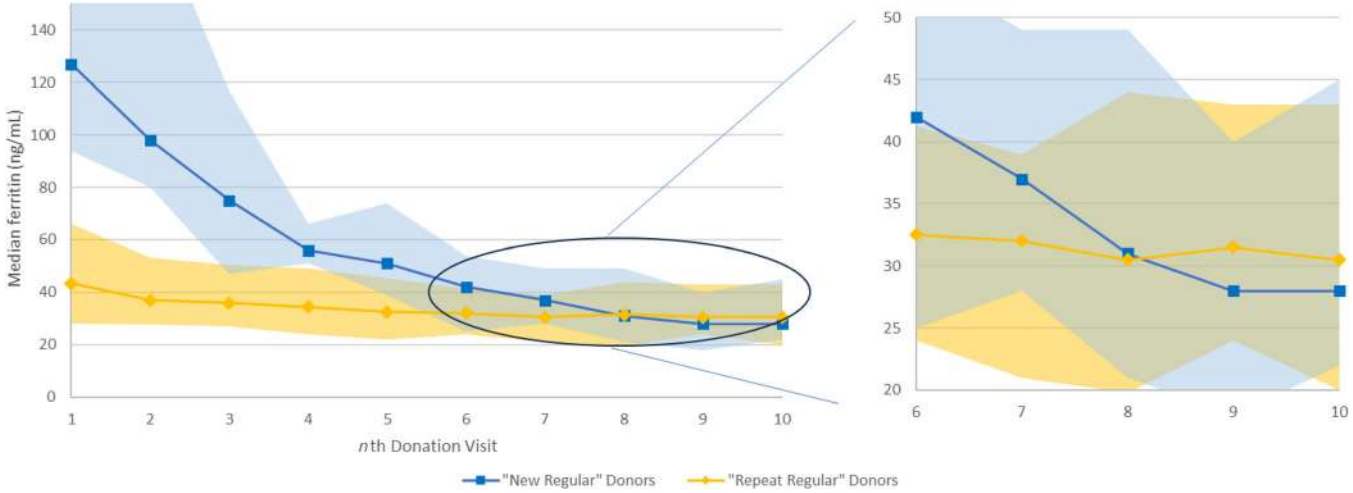

FIGURE 5 Ferritin levels for 'regular' donors: Median ferritin levels at the *n*th donation for 'new regular' and 'repeat regular' donors, with background shadow representing the IQR. A zoom-in as new regular donors approach the ferritin levels of repeat regular donors is shown. IQR, interquartile range.

groups up to 10 visits. 'New regular' donors had higher median baseline ferritin levels at their first visits during the study period compared with 'repeat regular' donors. The gap narrows, and a steady median ferritin level of ~35 ng/mL is attained by both groups around the approximately the sixth visit, with minimal further decrease in mean ferritin levels for subsequent visits (up to visit 10).

4 | DISCUSSION

Blood donor centres plays a crucial role in collecting, testing and distributing blood products to hospitals, ensuring a safe and sufficient blood supply for medical treatments and emergencies. Blood centres also have to mitigate risks such as iron depletion in donors and must achieve these goals with finite resources while preventing critical blood shortages.[7,8]

The COVID-19 pandemic significantly impacted BDC, donations decreased due to lockdowns, resources were limited and change in donor demographics were seen. A notable drop in total blood units collected, particularly from young and single-time donors, occurred at the start of the pandemic, with a sustained decrease in young donors throughout the study.[9] Despite the loss of young donors, the blood supply showed recovery due to an increase in repeat donors. A mild increase in the percentage of donors with low ferritin was observed, emphasising the importance of assessing iron deficiency risk in the changing donor landscape.

We observed that donors of Asian and Asian Pacific Islander ethnicity appeared to have higher median ferritin levels in our donor pool

(Table 2). However, the interquartile ranges (IQRs) were broader and overlapped with those of other ethnicities. The variation in ferritin levels within populations might be attributed to environmental factors.[10–16]

Sex differences in ferritin levels are pronounced, with young females identified as a high-risk category.[10,17–20] The risk was notably skewed, with the youngest females at the highest risk.[20] While premenopausal females as a larger category are generally at risk, any restrictions would constrain nearly half the donor pool; hence, we focus on the highest risk young females. Considering the decreased number of young donors due to COVID-19, their higher likelihood of being single-time donors, and the specific vulnerability of young females, a maximum donation limit of once per year was set for donors under 23 years of age. We included young males as well out of an abundance of caution and concern for the potential detrimental effects of iron deficiency in youth.[21–23]

As repeat donors became a larger fraction of the blood supply, concerns about donor iron recovery post-donation intensified.[24] Ferritin recovery was similar between sexes, with a rapid recovery before tapering toward baseline levels around 6 months (Figure 4).[4,25,26] A recommended donation limit of two times per year was established based on this data. Regular donors contributing extensively to the blood supply exhibited a steady state balance in ferritin levels after a few donations, showing stability despite the initial downwards trend observed in other studies (Figure 5).[21,27] If this vital yet at-risk group were to continue contributing, we needed to know if iron inevitably spiral ever downward or reached a steady state.[27] Fortunately, a major strength of our data comes from collected ferritin levels at every visit for our donors over a 33-month duration allowing us to readily track the ferritin levels in our regular donors.

In conclusion, our facility's extensive and long-duration ferritin testing supports, refines and expands on AABB concerns for at-risk groups.[21] Our data supports considerable baseline differences in ferritin status according to sex and age, with both sexes recovering similarly toward their baseline levels after donation.[4,25,26] Females are a particular at-risk group with young females starting with the lowest baseline ferritin levels.[10,17–20] Females with borderline low Hb at donation are at increased risk of low ferritin levels. Finally, regular donors will reach a steady state balance rather than continue to decrease in ferritin after a few donations.[27] Considering these findings, and the need to conserve our limited staffing, which was stretched thin managing the logistics of collecting and reporting ferritin results to donors, our donor centre decided to discontinue routine donor ferritin testing. While ferritin testing at every donation may provide high sensitivity for iron deficiency,[28] it may not always be practical or feasible for blood centres.[7,8] We have used these findings to tailor our donation policies that we have shared here balance blood centre resources while supporting a continued safe blood donation process for donors.

AUTHOR CONTRIBUTIONS

P.P. performed the research and wrote the first draft of the manuscript; H.H. and S.C. collected and analysed the data and reviewed and edited the manuscript; G.M. performed and supervised the research and reviewed and edited the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest relevant to the manuscript submitted to Transfusion Medicine.

DATA AVAILABILITY STATEMENT

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

PATIENT CONSENT STATEMENT

Patient consent was not required, as this study involved a retrospective analysis of anonymized blood donor data without any identifiable patient information.

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ORIGINAL ARTICLE

TRANSFUSION MEDICINE WILEY

Resuscitation of adult shocked trauma patients using major haemorrhage protocol guided by viscoelastic haemostatic assays versus formulaic approach

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Abstract

Background: The resuscitation of trauma patients with critical bleeding may follow a formulaic approach using high ratios of blood components or a viscoelastic haemostatic assay (VHA) guided approach. The aim of this study was to compare the two strategies for resuscitation of shocked trauma patients.

Methods: This was a registry-based cohort study including shocked trauma patients from two trauma centres–one practising a formulaic approach, with VHA unavailable during trauma resuscitation and the other practicing a VHA-guided resuscitation strategy. The primary outcome was the total units of blood components transfused in 24 h after adjusting for differences in baseline characteristics and time to death.

Results: Between 01 Jan 2020 and 31 Dec 2022, 152 eligible patients were categorised to the formulaic group and 40 to the VHA group. Prehospital times were longer in the formulaic group (2.0 vs. 1.4 h), and more patients in the VHA group (38% vs. 17%) were transfused prehospital blood components. Formulaic resuscitation was associated with significantly more blood components transfused (adjusted incidence rate ratio 1.5; 95%CI: 1.4–1.7, $p < 0.001$). Using a formulaic approach, patients were administered more red blood cells, plasma and platelets, but fewer cryoprecipitate. There was no significant association of the formulaic approach with in-hospital mortality (adjusted odds ratio 2.4; 95%CI: 0.7–8.0, $p = 0.17$).

Conclusions: Given the cost and potential adverse effects of blood component transfusions, VHA-guided transfusion strategies present an attractive option, particularly among centres managing high volumes of shocked patients. Further trials, enrolling the population most likely to benefit from precision transfusion strategies, are indicated.

KEYWORDS
blood, emergency medicine, transfusion, viscoelastic haemostatic assay, wounds and injuries

1 | INTRODUCTION

Trauma is a leading cause of death for young adults worldwide.[1] Despite ongoing medical and public health improvements, the incidence of trauma is increasing and with it, death due to trauma.[2] Approximately 40% of trauma deaths result from haemorrhage, and most frequently within the first 24 hours after injury.[3] Clinical practice guidelines recommend the activation of major haemorrhage protocols (MHP) for initial management of hypovolaemic status and haemostatic dysfunction.

Providing appropriate transfusion therapy while simultaneously diagnosing and controlling life-threatening bleeding and prioritising treatment of other potentially life-threatening conditions is challenging.[4] MHPs are designed to provide standardised delivery of blood components and synthetic agents directed at haemostasis. Formulaic transfusion regimes recommend high volumes of fresh frozen plasma (FFP), platelets and, in some cases, cryoprecipitate or fibrinogen concentrate to trauma patients being transfused with red blood cells (RBCs) to mitigate the hazards of crystalloid resuscitation and isolated red cell transfusion. Once critical bleeding is controlled, ongoing resuscitation is guided by standard laboratory tests, including those of coagulation function.

An alternative strategy is the use of point of care Viscoelastic Haemostatic Assays (VHA). VHA offers the potential for earlier diagnosis of trauma induced coagulopathy and ongoing monitoring of transfusion requirements based on coagulation abnormalities. This is a functional, dynamic and repeatable set of parameters designed to assess clot formation, timing, strength, and dissolution. The use of VHA has been associated with mortality benefits in medical and surgical care.[5,6] In adult trauma patients presenting with signs of haemorrhagic shock, VHA augmented protocols, when compared with conventional coagulation tests augmented protocols, have not been proven to be superior.[7,8] Limitations of trials were that only a small proportion of patients had coagulation dysfunction and were managed with MHPs. The population that may benefit from VHA guided resuscitation therefore remains undefined.

In the setting of uncertainty of superiority of one strategy over another, there is variability in practice among different trauma services. In Australia, two comparable level I trauma centres use different MHPs- one initiating formulaic transfusion of blood components, and the other guiding resuscitation using VHA. Thus, the aim of this study was to compare units of blood components transfused and hospital outcomes among patients presenting with hypovolaemic shock after trauma. The primary hypothesis was that VHA guided resuscitation of hypovolaemic shocked adult major trauma patients would be associated with lower volumes of blood component transfusion and lower mortality.

2 | METHODS

2.1 | Design

This was a registry-based retrospective cohort study.

2.2 | Setting

The Gold Coast University Hospital (GCUH) incorporates a level 1 trauma centre. Annually, there are approximately 1500 trauma team activations, including 200 'Trauma Responds', which is the highest level of acuity. The resuscitation of shocked patients is guided by a MHP, that includes VHAs performed using rotational thromboelastometry (ROTEM).[9] The trauma registry includes all patients with injury severity score (ISS) >12. The Alfred Hospital in Melbourne is an adult tertiary referral hospital in the state of Victoria, Australia, and incorporates a level 1 trauma centre.

The Alfred receives in excess of 5000 trauma patient presentations per year, of which 1500 are classified as major trauma. All major trauma patients are received by a trauma team. The resuscitation of shocked patients is guided by a MHP, that does not include VHAs. The MHP recommends transfusion of 4 units of RBC, 2 units of FFP and one adult dose of pooled platelets, till critical bleeding is controlled. Cryoprecipitate is recommended when fibrinogen levels are less that 1.0 g/L. The trauma registry includes all patients with ISS > 12, all trauma intensive care unit (ICU) admissions, all trauma hospital transfers and all deaths after injury.

2.3 | Inclusion and exclusion criteria

Adult (age ≥ 18 years) patients after injury presenting directly from the scene of incident to the emergency department and with an initial systolic blood pressure of ≤90 mmHg were eligible for inclusion. Hence, patients transferred after initial resuscitation at other centres were excluded. Patients who developed hypotension in the emergency department after an initial systolic blood pressure of >90 mmHg were not included. Patients deemed to be dead on arrival to hospital were not included.

2.4 | Data sources

Patients were identified from the trauma registries of the two centres. Demographic and clinical characteristics of patients were extracted from the trauma registries. Both registries utilise trained data collectors and personnel who are certified in injury severity coding. Details of transfused blood components were extracted using explicit chart review, with pre-specified definitions for each variable.

2.5 | Outcomes

The primary outcome variable was the total units of blood components transfused. The total was the sum of RBCs, FFP, platelets and cryoprecipitate, and also fibrinogen concentrate, with a dose of 1 g counted as one unit. Secondary outcomes were the units of each component and death at hospital discharge.

2.6 | Statistical analysis

An intention-to-treat analysis was performed. In the hospital practicing formulaic transfusion (The Alfred), VHA was not available for use during trauma resuscitation during the study period. Among patients managed at the centre practicing VHA-guided resuscitation (GCUH), patients who did not have VHA performed were retained in the VHA group.

Normally distributed continuous variables were presented using mean (standard deviation [SD]), ordinal or skewed data were presented using median (interquartile range [IQR]), and categorical data presented using count (percentages). The association between exposure variables and the counts of units of blood components in 24 h was assessed using a Poisson regression model and presented using adjusted incidence-rate ratios (IRR) with 95% confidence intervals (95%CI). Person-hours were incorporated into the model as an offset to account for variations in exposure due to deaths within 24 h. For the outcome of hospital mortality, logistic regression analysis was used and the results reported using adjusted OR (aOR) with corresponding 95%CIs. A p-value <0.05 was considered statistically significant. All analyses were performed using Stata version 18.0 (College Station, TX, USA).

The study was approved by The Alfred Hospital Human Research and Ethics Committee (Project ID 336/23) under the National Mutual Acceptance scheme. The requirement to seek informed consent from patients or person responsible was waived.

3 | RESULTS

During the study period between 01 Jan 2020 and 31 Dec 2022, there were 152 eligible patients who were categorised to the formulaic group and 40 that were categorised to the VHA group. There were 3 patients managed at GCUH who were not investigated with VHA. Baseline characteristics of patients are presented in Table 1. There were differences with regards to pre-hospital time with longer times for formulaic group, while more patients in the VHA group were managed with pre-hospital blood components. On presentation to hospital, lactate levels in the VHA group were higher. There were no significant differences among all other variables.

In the VHA group, fibrinogen concentrate was administered to 20 patients, and no patients in the formulaic group were managed with fibrinogen concentrate. Outcomes, adjusted for differences in baseline characteristics, are listed in Table 2. After adjustment for prehospital time, pre-hospital blood component transfusion, hospital lactate levels and early deaths, in the first 24 h, patients in the formulaic group were administered 16.9 (95%CI: 16.2–17.7) units of blood components, compared with 11.4 (10.4–12.4) units in the VHA group (adjusted IRR 1.3; 95%CI: 1.4–1.6). The formulaic group received significantly more units of RBCs (IRR 1.2; 95%CI: 1.1–1.5), FFP (IRR 5.4; 95%CI: 3.8–7.7), platelets (IRR 6.5; 95%IC: 4.7–9.0), and fewer units of cryoprecipitate (IRR 0.6; 95%CI: 0.5–0.7). At hospital discharge, there were 34 (22.4%) deaths in the formulaic group and 4 (10.0%) in the VHA group with no significant association of MHP strategy and mortality (aOR 2.3; 95%CI: 0.74–7.11).

Details of each regression model are presented in Tables S1–6. There were 115 (75.7%) patients in the formulaic group and 28 (70.0%) patients in the VHA group who were admitted to intensive care units ($p = 0.47$). There were no differences between the total length of stays in hospital (formulaic median 11.1; IQR: 3.9–24.8 versus VHA 15.7; IQR 6.6–26.7; $p = 0.08$).

4 | DISCUSSION

The use of a VHA-guided resuscitation strategy for shocked trauma patients was associated with lower units of blood components transfused, with no difference in hospital mortality. Using a VHA-guided approach, fewer units of RBCs, plasma and platelets were administered to patients, but more cryoprecipitate and fibrinogen concentrate were administered. These results suggest that a more efficient and targeted transfusion strategy can be achieved using a VHA-guided resuscitation approach.

During development of Australia's critical bleeding guidelines, data from randomised controlled trials that had included trauma patients concluded the mortality rate in critically bleeding VHA groups to be 24%, compared with 30% when not using VHA (RR 0.75; 95% CI: 0.48–1.17; $p = 0.20$).[10] However, pooled results from observational studies had suggested that VHA-guided transfusion protocols were associated with a significantly lower mortality rate than transfusion protocols that are guided by standard laboratory tests (17% vs. 19%; RR 0.75; 95%CI 0.62–0.92; $p = 0.004$). This mortality benefit could not be confirmed by our study. In the setting of trauma, the single randomised controlled trial did not report a reduction in red cell volumes.[7] However, consistent with our study, in the meta-analysis of cohort studies performed as part of development of the critical bleeding guidelines and more recent investigations, a significant association of lower transfusion volumes with VHA guided resuscitation was observed.[10–12]

VHAs provide detailed overview of coagulation and therefore enable a more precise strategy against trauma induced coagulopathy.[13] The outcomes of patients after VHA-guided therapy, as with any investigation, are reliant on correct interpretation and requires individualised and targeted therapy of coagulopathy. Such strategies are more difficult to implement and requires additional resources, when compared with formulaic transfusion.[14] Thus, the investment to a VHA platform requires more than just installation of a device, but a hospital wide change in guidelines for management of the critically bleeding patient that needs to be followed from trauma reception in the emergency department through to the operating room or angiography suite and intensive care until critical bleeding is controlled.[15] Success of implementation of such guidelines should serve as examples for other centres to follow should a change in transfusion strategy be considered.[16,17]

TABLE 1 Baseline characteristics of included patients.

	Formulaic group ($n = 152$)	VHA group ($n = 40$)	p-value
Age (years)	53.6 (SD 20.4)	50.5 (SD 20.0)	0.39
Sex			0.46
Male	109 (71.7%)	31 (77.5%)	
Female	43 (28.3%)	9 (22.5%)	
Mechanism of injury			0.16
Motor vehicle crash	43 (8.3%)	12 (30.0%)	
Motorcycle crash	19 (12.5%)	11 (27.5%)	
Pedestrian	16 (10.5%)	4 (10.0%)	
Pedal cyclist	8 (5.3%)	3 (7.5%)	
High fall	15 (9.9%)	1 (2.5%)	
Low fall	15 (9.9%)	5 (12.5%)	
Assault	17 (11.2%)	3 (7.5%)	
Other	19 (12.5%)	1 (2.5%)	
Pre-hospital time (hours)*	2.0 (1.4–3.0)	1.4 (1.1–2.1)	0.001
Pre-hospital blood component transfusion	26 (17.1%)	15 (37.5%)	0.005
Initial FAST scan			0.29
Positive	42 (27.6%)	16 (40.0%)	
Negative	90 (59.2%)	21 (52.5%)	
Unavailable or equivocal	20 (13.2%)	3 (7.5%)	
Initial systolic blood pressure (mmHg)	73.2 (SD 16.3)	74.4 (SD 14.0)	0.65
Initial heart rate (beats/min)	98.6 (SD 29.7)	100.9 (SD 30.7)	0.67
Initial Glasgow Coma Scale			0.16
0–8	64 (42.1%)	11 (27.5%)	
9–12	6 (4.0%)	3 (7.5%)	
13–15	82 (54.0%)	26 (65.0%)	
Initial INR			0.26
<1.3	98 (69.0%)	32 (86.5%)	
1.4-15	24 (16.9%)	3 (8.1%)	
1.5	20 (14.1%)	2 (5.4%)	
Initial fibrinogen level (g/L)			0.08
<1.0	5 (3.6%)	2 (6.3%)	
1.0–2.0	23 (16.3%)	11 (34.4%)	
>2.0	113 (80.1%)	19 (59.4%)	
Initial lactate level (mmol/L)			<0.001
≤2.0	56 (39.2%)	3 (7.5%)	
2.1–4.0	43 (30.1%)	19 (47.5%)	
>4.0	44 (30.8%)	18 (45.0%)	
Injury severity score			0.17
0–12	12 (7.9%)	0	
13–25	65 (42.8%)	17 (42.5%)	
26–45	53 (34.9%)	19 (47.5%)	
>45	22 (14.5%)	4 (10.0%)	
Abbreviated injury score (Head) >2	43 (28.3%)	14 (35.0%)	0.44

Abbreviations: SD, standard deviation; VHA, viscoelastic haemostatic assay.
*Time from injury to hospital arrival.

TABLE 2 Adjusted outcomes associated with major haemorrhage protocol strategy.

Outcomes	Formulaic group ($n = 152$)	VHA group ($n = 40$)[c]	Measure of association (adjusted)	*p*-value
Total blood components (units)*	17.3 (16.6–18.0)	11.4 (10.4–12.4)	1.5 (1.4–1.7)[a]	<0.001
Red blood cell (units)*	5.8 (5.4–6.2)	4.7 (4.0–5.3)	1.2 (1.1–1.5)[a]	0.008
Plasma (units)*	3.9 (3.5–4.2)	0.7 (0.5–1.0)	5.4 (3.8–7.7)[a]	<0.001
Platelets (units)*	5.3 (4.9–5.7)	0.8 (0.6–1.1)	6.5 (4.7–9.0)[a]	<0.001
Cryoprecipitate (whole blood units)*	1.9 (1.7–2.2)	3.3 (2.8–3.9)	0.6 (0.5–0.7)[a]	<0.001
Fibrinogen concentrate (units or grams)*	0	1.4 (1.0–1.7)	-	-
Mortality at hospital discharge (%)	20.0 (13.9–26.1)	10.7 (1.3–20.1)	2.4 (0.7–8.0)[b]	0.17

Abbreviation: VHA, viscoelastic haemostatic assay.
*Adjusted for pre-hospital time, pre-hospital transfusion units, lactate levels and early deaths.
[a]Adjusted Incidence rate ratios (95%CI).
[b]Adjusted odds ratio (95%CI).
[c]Reference group for measures of association. Blood components are those transfused in hospital (does not include prehospital transfusion).

Despite the challenges, a reduction in blood component transfusion is an attractive outcome and current guidelines support the use of VHA-guided MHP to be an acceptable strategy for resuscitation of critically bleeding patients. The volume of blood components transfused has been repeatedly associated with adverse outcomes.[18] Therefore, strategies to reduce transfusion volumes by enabling earlier haemostasis are targets for ongoing research. Strategies currently being evaluated include effective dosing of tranexamic acid, fibrinogen concentrates, prothrombin complex concentrates, and whole blood, while concurrently achieving surgical or angiographic control of haemorrhage.

This study is limited in being an observational study where categorisation of the two groups, while geographically separated, was not random. Although there were no obvious differences in most baseline characteristics, and we performed statistical adjustment for observed differences, it is possible that unmeasured confounders existed. The use of systolic blood pressure as a single measure of haemorrhagic shock provides a crude selection of such patients, and it is possible to further refine the group using other measures of tissue perfusion such as point of care lactate levels.[19] During the study period, both centres were participating in the PATCH-Trauma trial and the effect of tranexamic acid, if any, was expected to be equally distributed.[20] We did not collect data on crystalloid and colloid volumes. While these were recommended to be used sparingly during resuscitation at the two centres, crystalloid and colloid volumes have been previously associated with patient outcomes and were a potentially unmeasured confounder. Finally, despite including all eligible patients over a 3-year period, the sample size was relatively low. Unequal group sizes may have also affected the precision of estimates. While the models were adequately powered for the event rates, repeating the analysis with larger samples may provide more convincing evidence for the outcomes. While the equivalent mortality rates provide some reassurance, more patient-centred outcomes such as multi-organ failure, renal replacement therapy and rates of potential adverse effects of trauma care require assessment to ensure safety of the resuscitation strategies and should be included as part of future trials.

5 | CONCLUSIONS

A VHA-guided strategy for resuscitation of shocked trauma patients was associated with lower units of blood component transfusion, with no differences in mortality at hospital discharge. Given the importance of reduction in blood component volumes as an outcome measure, a VHA-guided transfusion strategy presents an attractive option, particularly among centres receiving high numbers of shocked trauma patients. Further trials, enrolling the population most likely to benefit from precision transfusion strategies is indicated.

AUTHOR CONTRIBUTIONS

Conception or design of the work: B. M. and J. W. *Data collection*: E. W., C. T., S. C. and C. K. *Data analysis and interpretation*: B. M. *Drafting the article*: B. M. *Critical revision of the article*: E. W., D. C., S. H. and J. W. *Final approval of the version to be published*: All authors.

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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 (BM). The data are not publicly available due to ethical considerations given the relatively small sample size.

PATIENT CONSENT STATEMENT

The requirement to seek informed consent from patients or person responsible was waived by the ethics committee.

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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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Validation of pathogen reduced plasmas from maxi-pools combined with fast thawing

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Abstract

Objectives: Fast thawing for emergency situations and reduction of plasma wastage.

Background: Evaluation of plasma units, pooled and pathogen reduced (PR) in "maxi-pools" with amotosalen and UVA light, and fast thawing.

Methods/Materials: Per replicate, 10 WB-derived leukocyte depleted plasma units were frozen within 24 h at ≤ −25°C and stored for 7 days. After thawing, a maxi-pool was constituted from the 10 units. After splitting into 4 sub-pools of 650 mL, the sub-pools were PR treated then split into 3 units resulting in 12 PR plasma units at 200 mL. Hundred and twenty PR plasma units were produced in total. The units were frozen at ≤ −25°C for 1 week, then thawed either in a fast plasma thawer for 5 min or in other control devices (17 to 23 min). FVIII:C, Fibrinogen, albumin, IgG, protein S and VWF were measured in plasma units, maxi-pools and plasmas after PR treatment and thawing.

Results: There was a statistically significant ($p < 0.001$) but still clinically acceptable (over the recommended levels of ≥0.5 IU/mL and ≥2 g/L) reduction of FVIII:C and Fibrinogen after PR with 69% and 87% recovery, respectively. Other proteins were not significantly affected by the processes.

Conclusion: Pooling 10 plasma units before the PR treatment standardises volume and protein content of plasma units. Besides the economic value of generating 12 products for transfusion, this procedure combined with a thawing time of about 5 min is of value in emergency situations and may reduce plasma wastage.

KEYWORDS
fast thawing, maxi-pools, pathogen reduced, plasma

1 | INTRODUCTION

Many authors agree that early and timely plasma transfusion reduces mortality of trauma patients. High fresh frozen plasma to red blood cells (FFP:RBC) and platelets to red blood cells (PLT:RBC) ratios are associated with a survival benefit.[1] Transfusion packs containing 4 units of erythrocytes, 4 units of plasma and 1 platelet unit have been adopted in our institution for trauma patient care. This practice had a detrimental effect on the outdating of plasma. In year 2005, 14% of plasmas for transfusion were outdated, and that figure raised to 25% in 2018. The plasma needed for the transfusion packs is thawed as soon as the order comes in, and in our institution the ward can return the unused units back to the blood bank. If there is no need for thawed plasma within 7 days after thawing, the plasmas are discarded. Also, if there is not enough documentation on how plasmas were stored at the ward department, or operating room, the plasmas

are registered as outdated and discarded if not transfused. There is also a tendency in an acute situation to thaw extra plasma at the blood bank to be able to deliver the transfusion packs in a timely manner. These observations led to an interest in developing a "just in time" plasma supply methodology not involving previously thawed plasma. Devices using radio wave[2] are becoming available and make it possible to rapidly thaw plasma in a dry environment without the additional preparation time of making a water bath available. This has also triggered a need to standardise the volume of plasma units to the lowest acceptable volume, that is, 200 mL, making the time thawing will take more predictable and shorter. This volume standardisation coupled with fast thawing allowed to decrease outdating of plasmas to 12%.

Clinicians also expressed a wish to have more standardised products with regards not only to volume but also content. In Sweden there is pooled solvent detergent (SD)-treated plasma available (Octaplas, Stockholm, Sweden). However, it is registered as a medicine, and there is a separate legal framework for medicines and rules for procurement processes which are outside of blood banking. PR plasma made from pools smaller than 12 units is considered as a blood component,[3] not a medicine. Pooled plasma is shown to be more homogeneous in contents of coagulation factors and other proteins[4] as well as giving less transfusion reactions.[5] The clinicians were looking for a product that could be used for patients reacting with allergic reactions against plasma. Also standardised volume for plasmapheresis was an advantage.

In our institution we have used a pathogen reduction (PR) technology, INTERCEPT® Blood System (Cerus Europe B.V., Amersfoort, The Netherlands) for platelets since 2007. The decision was taken after a fatal case of bacterial contamination. It was felt appropriate to introduce the same technology to a pooled product for plasma. We developed a 10-unit plasma pooling technique allowing to optimise the use of pathogen inactivation (PI) processing sets and delivering 200 mL end products for transfusion.

The objective of our study was to assess, based on plasma quality parameters tested in-vitro, a preparation procedure based on pools of 10 previously frozen plasma units subsequently split into volumes compatible with the process for PI treatment and thawed post-frozen storage with a fast thawer (Conroy, Upplands Väsby, Sweden, CS201).

2 | MATERIALS AND METHODS

2.1 | Plasma preparation

Whole blood units of 450 mL ± 10% were collected in blood packs (Macopharma, Tourcoing, France) containing CPD anticoagulant solution from 100 donors having given their consent for use of donated blood products for research. There was no Institutional Review Board approval required due to the study being related to a Quality Improvement project. Such projects do not require ethical approval because they are designed to improve processes and practices within existing standards of care. Plasma from study was not used for transfusion of patients. Blood donors have given their consent for such projects. The plasma was leukocyte-depleted by filtration after separation from the red blood cells and the buffy-coat using the filter from the blood pack system (In-line Miniplas plasmafilter, Macopharma), quick frozen (Lundair, Helsingborg, Sweden) within 24 h and stored at ≤ −25°C and stored for 7 days. After thawing in a warm air operated device (Sahara Sarstedt, Nümbrecht, Germany), 10 groups of 10 A, B or AB units were weight-selected to constitute maxi-pools. The process is described in Figure 1. Maxi-pools were obtained by sterile docking (TSCD, Terumo BCT, Tokyo, Japan) 2 × 5 plasma units to two double transfer packs (DONOpack, LMB, Schwaig, Germany) of 1,5 L capacity, themselves connected to a 3 L transfer pack (Macopharma). The total plasma volume obtained was above 2,6 L and was split after homogenization into 4 sub-pools of approximately 650 mL retained in the 4 transfer packs of the 2 DONOpack units. Pooling was performed manually with careful mixing of the bags at each step, to obtain a homogeneous content in the pools before splitting.

2.2 | Pathogen inactivation

Each sub-pool of 650 mL plasma was sterile connected to an INTERCEPT plasma processing set for mixing with 15 mL of an amotosalen 6 mM solution and subsequent exposure to 3 J/cm^2 of ultaviolet light (UVA) in an INT 100 Illuminator (Cerus, Amersfoort, The Netherlands). After reduction of the amotosalen concentration below 2 µM by adsorption to an in-line compound adsorption device (CAD), 3 units of at least 200 mL PI-treated plasma were obtained and quick frozen (Lundair) within 4 h from thawing. The 4-sub pools of each maxi-pool were treated in the same manner to obtain 12 PI-treated fresh frozen plasma units (PI-PFC).

2.3 | Plasma thawing

The 12 PI-PFC from each maxi-pool were stored frozen at ≤ −25°C for 1 week and the units used for laboratory testing were either thawed in a CS201 (Conroy, Upplands Väsby, Sweden), one unit at a time, radio-wave operated plasma thawer for approximately 5 min or in a water tempering system (Plasmatherm, Barkey Corporation, Woburn, MA, USA), 4 units at a time, or a warm air based device (Sahara, Sarstedt, Nümbrecht, Germany), 3 units at a time, for approximately 20 min to serve as control.

2.4 | Plasma laboratory testing

Factor VIII (FVIII:C), Fibrinogen, von Willebrand Factor (VWF), protein S, albumin and IgG were measured in thawed plasma units, maxi-pools and PI-PFC units after PI treatment and thawing. Fibrinogen was also measured in the fresh plasma units before the initial freezing.

FVIII:C, Fibrinogen, VWF and protein S were assayed using chronometric methods on a STA-R Max coagulometer (Diagnostica Stago,

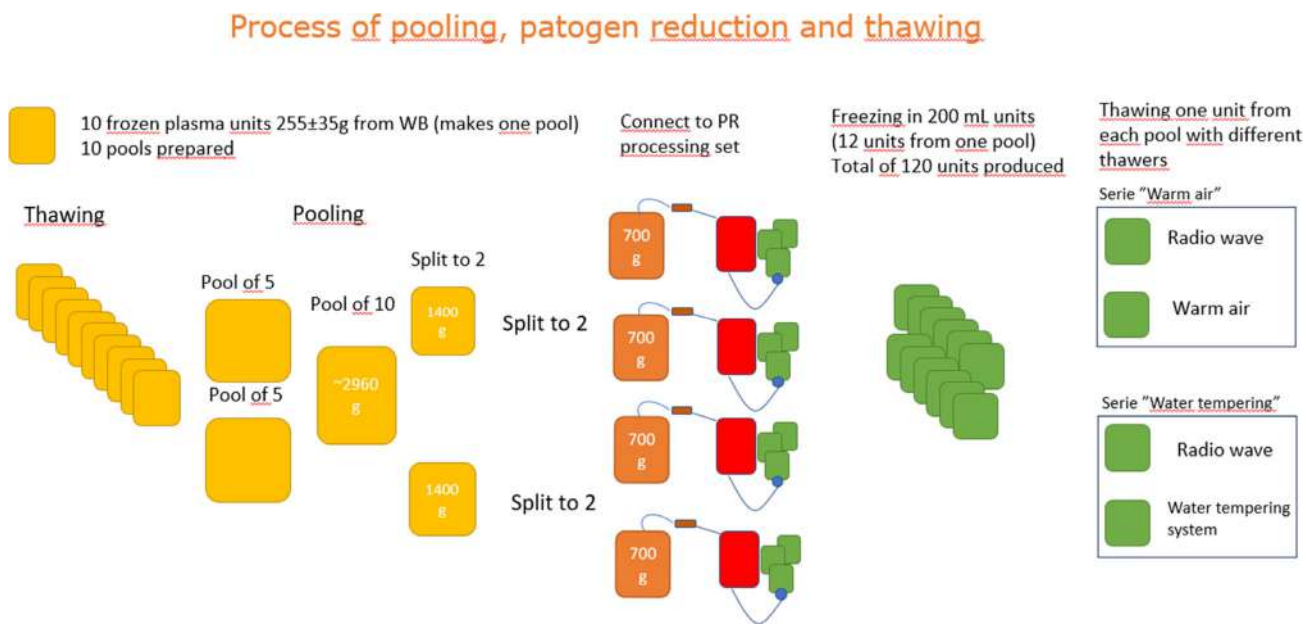

FIGURE 1 Flow chart for the preparation of PR plasma units. Where applicable, weights are indicated in grams (g). PR, pathogen reduced.

Asnières-sur-Seine France). Albumin and IgG were measured on a biochemical analyser cobas® pro, Roche. FVIII:C and Fibrinogen were selected because they are listed in the EDQM guidelines.[3] FVIII: is also known as a labile factor, time and temperature dependent. VWF is an important contributor to primary haemostasis. protein S is an anticoagulant protein. Albumin and IgG are essential constituents of plasma. FVIII:C, Fibrinogen, protein S and VWF were shown to be affected to different degrees by PR processes.[6,7]

2.5 | Statistical analysis

If the individual plasmas were compared with the pools, a two-sample Student's *t*-test comparison of means with different variance was performed. In other situations, paired t-test for comparison of the means was used.

3 | RESULTS

3.1 | Assessment of plasma quality

The measurements of plasma quality parameters at the different stages of preparation are shown in Figure 2.

The requirements according to the Guide to the preparation, use and quality assurance of blood components (EDQM), 21st edition 2023[3] for plasma, fresh frozen, PR are that it should contain for FVIII: on average, not less than 50 IU per 100 mL (i.e. 0.5 kIU/L) and for Fibrinogen ≥60% of the potency of the freshly collected plasma units.

FVIII:C content in frozen, thawed plasma was 1.1 kIU/L compared to 0.73 kIU/L in twice frozen, PR-treated and thawed plasmas, which is 69% of the original activity ($p < 0.05$). Pools had a higher mean FVIII:C activity than the individual units, but this was not statistically significant. The fibrinogen content in frozen, thawed, PR-treated-frozen–thawed units was 2.2 g/L, which is 88% of the fresh units (2.7 g/L) ($p < 0.05$).

Comparison of quality parameters after thawing with different techniques is shown in Table 1. Fibrinogen was 2% higher when thawing in warm air compared to radio wave thawing, which is statistically but not clinically significant difference, since fibrinogen levels are still 87% of those with fresh blood. There were no significant differences in VWF, albumin or IgG concentrations when comparing the once frozen units with twice frozen and PR-treated units. One marker, protein S was slightly lower on average when thawed with radio wave than with water tempering system (6%, $p < 0.05$). However, the testing method has variability in test results with CV 10%. The thawing tests were made on different dates, so the inter-methodological variability in testing method may play role in observation.

As expected, pools were more homogeneous than individual plasmas, which is shown in the results by lower standard deviation and coefficient of variation with all the markers tested (Figure 2).

3.2 | Assessment of plasma thawing

A time of around 30 min was observed for thawing frozen plasmas separated from whole blood when using a warm air thawer. After standardisation to 200 mL bags, after PRT, the thawing time decreased to about 20 min to 14–23°C. Water tempering system provides a thawing time of about 15 min for 200 mL standardised volume plasma units with a final temperature of 31–36°C after thawing. Radio wave technology thaws 200 mL plasmas within 5 min to 17–27°C.

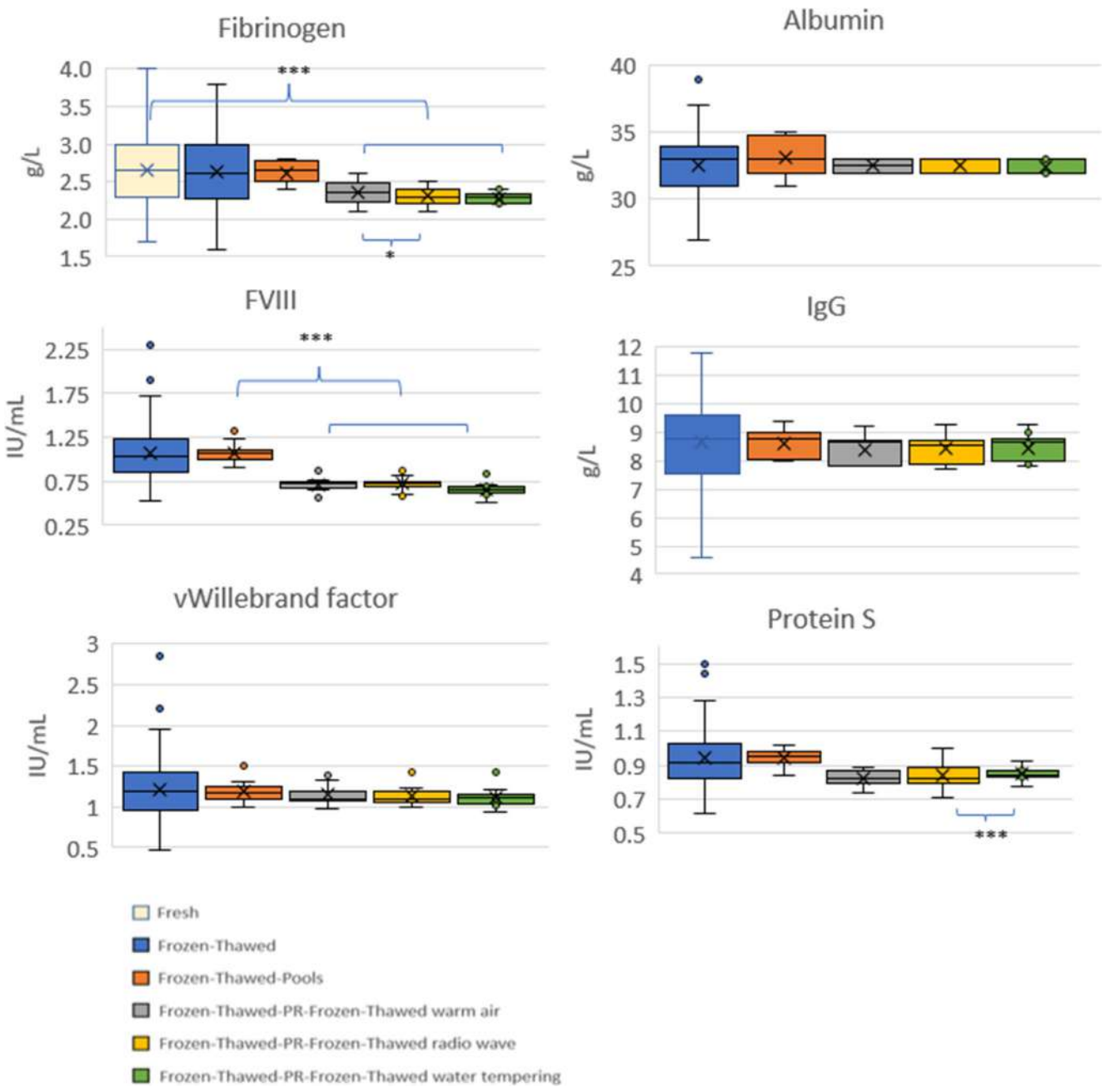

FIGURE 2 Boxplots of assays for Fibrinogen, FVIII, VWF, Albumin, IgG and protein S at the different phases of the process from the first freezing to thawing in different devices. When there are statistically significant differences between one and another phase of the process, it is shown with braces {where $^{*}p < 0.05$, $^{***}p < 0.001$. The bracket [refers to all thawers as a group that is, the final thawing procedure. Minimum ⊥, first quartile □, median____, mean X, third quartile □ and maximum values T.

4 | DISCUSSION

The validation of PR plasmas from maxi-pools combined with fast thawing showed that products meeting the European Guidelines and more standardised in volume and content can be obtained. Ang et al. have observed that the percentage decrease in FVIII:C is the highest among labile clotting factors, occurring naturally and independently of freezing and thawing procedures, with the greatest decrease within the first 24 h after plasma production.[8] In our study there was a statistically significant but still clinically acceptable (over the recommended levels of ≥0.5 IU/mL kIU/L and ≥2 g/L) reduction of FVIII:C and fibrinogen after PR with 69% and 87% recovery, respectively. These are satisfactory results considering that the plasma has been frozen and thawed twice before the final thawing just before planned transfusion other proteins were not significantly affected by the processes. The reduction of FVIII:C concentration in PR plasma is acknowledged in the guidelines with a minimum level of 0.5 IU/mL instead of 0.7 IU/mL for untreated plasma. Such reduction has been

TABLE 1 Results of the assays at the last thawing phase of the process in two series of thawing experiments.

	Plasma units from pools after A-UVA PR, 7-day ≤− 25°C storage and thawing—results per type of thawer ($N = 10$)			
Parameter	**Radio wave in warm air series**	**Warm air**	**Radio wave in Water tempering series**	**Water tempering system**
Factor VIII:C (kIU/L)	0.73 ± 0.08 [0.59;0.88]	0.72 ± 0.08 [0.56;0.88]	0.71 ± 0.05 [0.61;0.79]	0.66 ± 0.08 [0.52;0.83]
Fibrinogen (g/L)	2.31 ± 0.13 [2.1;2.5]	2.35 ± 0.16* [2.1;2.6]	2.32 ± 0.10 [2.2;2.4]	2.28 ± 0.08 [2.2;2.4]
VWF (IU/mL)	1.13 ± 0.13 [1.09;1.42]	1.15 ± 0.12 [0.9;1.38]	1.13 ± 0.08 [1.01;1.23]	1.11 ± 0.13 [0.94;1.43]
Albumin (g/L)	32.7 ± 0.5 [32.0;33.0]	32.6 ± 0.5 [32.0;33.0]	32.5 ± 0.5 [32.0;33.0]	32.4 ± 0.5 [32.0;33.0]
IgG (g/L)	8.41 ± 0.53 [7.70;9.20]	8.40 ± 0.52 [7.80;9.20]	8.42 ± 0.55 [7.70;9.30]	8.47 ± 0.51 [7.80;9.30]
Protein S (IU/mL)	0.88 ± 0.09 [0.71;1.00]	0.83 ± 0.05 [0.74;0.89]	0.81 ± 0.04 [0.74;0.88]	0.85 ± 0.04** [0.78;0.93]

Note: Mean ± SD [min;max].
Abbreviation: n.t, not tested.
*$p < 0.05$ when compared with radio wave.**$p < 0.01$ when compared with radio wave.

observed in other studies[6,9] including comparisons with SD plasma.[7] Studies showed that despite a diminished FVIII activity in PR plasma, the thrombin generation capacity was shown to be conserved equally well in plasma photochemically treated with amotosalen and UVA as in non-treated plasma,[6,7,9] demonstrating no significant effect of this technique on the global hemostatic properties of plasma requiring adequate functionality of FVIII:C and other factors. Clinical trials and hemovigilance programs suggest the observed loss of potency is of little clinical significance for the PR technique used.[10]

The main goal to assess the plasma freezing and thawing procedures was to decrease outdating of plasma. As previously mentioned, plasma outdates raised to 25% in 2018 mostly related to the return of the unused units back to the blood bank.

Just standardising the volume to 200 mL decreased outdating of plasmas to 12% in 2022, since it was more predictable how long-time thawing would take. The use of a novel radio-wave operated device allowed to consistently reduce the thawing time to 5 min. Reaching a final temperature of 17–27°C with radio wave is close to the temperature reached with warm air of 14–23°C our clinicians are used to. Warming to a higher temperature of 31–36°C with a water tempering technique is not perceived as a benefit. As a comment, after this study we have also changed our freezing process. Plasma bags are frozen on flat bed instead of vertical freezing leading to more uniform frozen units, which reach end temperature faster.

The second driver for changing the plasma procedure was to address the clinicians wish to have more standardised products with regards to content and volume. Pooled plasma is shown to be more homogeneous in contents of coagulation factors and other proteins as well as giving less transfusion reactions. The standardisation of volume and plasma protein content was observed in other studies in which mini-pools of 5 plasmas were constituted before proceeding with the PR treatment using amotosalen and UVA light.[9,11] The pooling effect allows as well to limit the number of units not meeting guidelines as seen in these studies and our protocol which was using a large pool size of 10 units before treatment. One-year quality control data showed no values below the EDQM required thresholds.

The plasma content, such as coagulation factors or other proteins, has been used as a surrogate marker for plasma quality. Frozen plasma can vary between units depending on the source of plasma as well as separation, freezing and thawing processes, so studies usually compare the quality of plasma at different stages with freshly donated plasma. Due to the in-vitro nature of the study, there are limits with extrapolation of the use of maxi-pool derived PR plasmas in clinical practice. The standardised volume and content can be considered as an aid to the clinicians for adequate dosing, but the potential benefits to the patients were not evaluated through a randomised clinical trial. Hemovigilance data are recorded with a passive system in our institution. Fast thawing directly impacted the level of discards but the time to availability of transfusion packs was not measured. We did not conduct a cost-effectiveness evaluation of the change of practice.

In our institution we have used PR technology for platelets since 2007. The decision was taken after a fatal case of bacterial contamination. It was natural to introduce the same technology to a pooled product for plasma.

5 | CONCLUSION

Pooling of plasmas results in standardised volume and content of plasma for transfusion compared with the individual plasmas. Freezing the initial plasma shortly after component separation keeps the quality of plasma on the same level as it would be for fresh plasma. Freezing allows to plan the further steps of the process according to the needs for products and access to staff performing the manual pooling procedures. The pooling phase of the process and the second freezing step maintain the quality of plasma, especially when throughput time is planned to be short. The introduction of PR technology for pooled plasma was straight forward since the equipment and method were already in use for platelets.

Fibrinogen and FVIII levels were acceptably maintained in the final products and fulfilled the requirements with good margins. Other proteins such as IgG, albumin or VWF were well maintained and the concentrations were not significantly different from the ones in once frozen units.

The standard volume of 200 mL allows together with new freezer techniques and future thawing devices to optimise the procedure and achieve optimal plasma supply for acute situations in a timely manner.

AUTHOR CONTRIBUTIONS

MKA has contributed to study design, data collection, analysis and interpretation of result, and manuscript preparation. FK has contributed to study conception and design. HL has contributed to data collection and analysis, and manuscript preparation.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

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CASE STUDY

TRANSFUSION MEDICINE WILEY

Pitfalls of reasoning in hospital-based transfusion medicine

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Abstract

Introduction: Hospital-based transfusion involves hundreds of daily medical decisions. Medical decision-making under uncertainty is susceptible to cognitive biases which can lead to systematic errors of reasoning and suboptimal patient care. Here we review common cognitive biases that may be relevant for transfusion practice.

Materials and Methods: Biases were selected based on categorical diversity, evidence from healthcare contexts, and relevance for transfusion medicine. For each bias, we provide background psychology literature, representative clinical examples, considerations for transfusion medicine, and strategies for mitigation.

Results: We report seven cognitive biases relating to memory (availability heuristic, limited memory), interpretation (framing effects, anchoring bias), and incentives (search satisficing, sunk cost fallacy, feedback sanction).

Conclusion: Pitfalls of reasoning due to cognitive biases are prominent in medical decision making and relevant for hospital transfusion medicine. An awareness of these phenomena might stimulate further research, encourage corrective measures, and motivate nudge-based interventions to improve transfusion practice.

KEYWORDS
cognitive biases, heuristics, medical decision-making, nudges, transfusion medicine

1 | INTRODUCTION

Every blood transfusion begins with a decision. The decision may be reflexive or reflect the culmination of several complex individual judgements about the appropriateness (e.g., consent and indication), safety (e.g., patient and product factors), and efficacy of transfusion (e.g., applying available evidence to a specific patient).[1] Yet clinical judgements can be fallible due to biases of reasoning that may arise in judgement under uncertainty.[2] In the hospital setting, this might lead to erroneous transfusion practice, inappropriate diagnostic testing and ineffective transfusion policy. Likewise, an awareness of cognitive biases may inform root-cause analyses of transfusion decisions and suggest behaviorally informed countermeasures (also known as 'nudges') to improve practice (Table 1).

A multitude of cognitive phenomena have been described in psychological sciences. Herein we discuss seven common pitfalls of reasoning, give examples of known applications in healthcare, and discuss potential relevance for hospital-based transfusion (Table 2).[3] The biases are chosen to represent a diversity of phenomena relating to biases of memory (availability heuristic, limited memory), interpretation (framing effects, anchoring bias) and incentives (search satisficing, sunk cost fallacy, feedback sanction).

2 | COGNITIVE BIASES IN HOSPITAL TRANSFUSION MEDICINE

2.1 | Availability heuristic

In human memory, recent occurrences are easier to recall than distant ones.[4] Due to being more readily retrieved, recent memories relatively

TABLE 1 Glossary of Standard Terminology from Behavioural Sciences.

Concept	Definition
Cognitive psychology	The branch of psychology devoted to the study of how people think and how it impacts behaviour
Behavioural economics	The study of psychological factors involved in decision-making under constraints of limited information and cognitive capacity
Cognitive bias	Systematic and predictable patterns of decision-making which deviate from norms of rational thinking
Choice architecture	The practice of designing decision-making environments with the goal of systematically influencing choices
Nudge theory	The field of behavioural psychology which uses choice architecture to influence behaviour

dominate cognition and disproportionately affect judgement in unrelated circumstances, termed availability bias.[5] For example, when seeing a new patient with diarrhoea and abdominal pain, a physician who recently encountered a memorable case of cholangitis might be biased away from a correct diagnosis of myocardial infarction and toward an incorrect diagnosis of acute hepatitis.[6] Similarly, radiologists more intensely scrutinise particular regions of medical images reminiscent of recently encountered abnormalities, leading to higher rates of false positive findings.[7] Availability bias is further compelling because it provides an opportunity to redeem prior mistakes and re-experience previously encountered praise or satisfaction.

Prescribers of blood products often make clinical predictions which might be subject to availability bias. Such predictions can be influenced by arbitrary occurrences because although some transfusion events occur in clusters (e.g. reactions to a particular lot of intravenous immunoglobulin), many do not (e.g. the presence of a Bombay antibody underlying a panreactive panel). A clinician who recently attended a talk on thrombotic thrombocytopenia purpura (TTP) and subsequently encountered a patient with acute thrombocytopenia might prematurely initiate plasma exchange and miss a diagnosis of Heparin-Induced Thrombocytopenia. Similarly, a recent case of paroxysmal cold hemoglobinuria might lead to hypervigilance and unnecessary evaluations for the rare Donath-Landsteiner phenomenon in patients with nuisance cold antibodies. Availability bias might be mitigated by thoughtful standard operating procedures and conscious reflection to decouple quick intuitions from considered judgements.[8]

2.2 | Limited memory

Healthcare professionals are inundated with information, yet cognitive bandwidth is finite and only a limited amount of data can used for active decision-making.[9] Average human working memory can only hold about seven pieces of information at a time (although experts can memorise more information by organising data into larger categorical 'chunks').[10] In clinical medicine, this means content beyond seven items might actually worsen decision-making if important information is incorrectly prioritised or arbitrarily forgotten. A common demonstration of limited memory is the Digit Span cognitive test, where participants are asked to memorise and recall digit sequences of increasing lengths, with most people being able to recall about 7 digits at a time.[11] This capacity diminishes further when participants are asked to recall the digits backwards (requiring an additional processing step) or during periods of fatigue (common among on-call physicians).[12] The bias is particularly relevant for clinical scenarios involving exchange of multi-part information with stressful backdrops.

Clinical communication and peer education are fundamental competencies for the clinical lead for transfusion and involve trade-offs of human memory.[13] A well-intentioned message might fail to achieve its intended effect if overly verbose or densely complex. Instead, facts about limited memory might be incorporated into the design of an electronic order set by focussing on the seven most vital aspects of transfusion.[14] Thoughtful parsimony might be especially crucial in scenarios of low cognitive bandwidth and rapid decision-making, such as in crafting a transfusion protocol for massive haemorrhage scenarios (e.g. 'the 7 T's of Massive Hemorrhage Protocol are Trigger, Team, Tranexamic acid, Testing, Targets, Temperature, Termination'), where guideline adherence has historically been poor.[15] Memory limitations might also inform the formulation of transfusion guidelines, hospital bulletins, email newsletters, and committee-meeting updates.[16] In situations where more than seven items must be conveyed, splitting information into category chunks may improve implementation and retention.[17]

2.3 | Framing effects

Even well-established messages might lack efficacy if framed naively in relation to principles of psychological framing. For instance, when comparing trade-offs, losses have greater psychological weight than equal-sized gains (e.g. losing $50 feels worse than finding $50 feels good), also known as loss aversion.[18] Consequently, people tend toward risk avoidance even when it might violate strict theories of rational decision-making and entail net losses.[19] Physicians and patients alike demonstrate a stronger preference for a treatment framed as associated with a 90% chance of survival (framed as a gain) than a 10% chance of mortality (framed as a loss).[20] The bias also affects insurance purchases, vaccination uptake and palliative care decisions.[21–23] This finding has been replicated in a population of potential blood donors: when presented with identical information about the risks of blood transfusion framed as either a gain or a loss, participants who received the loss frame showed higher stress and lower confidence in transfusion.[24] An additional framing attribute involves expressing comparisons in relative or absolute terms; for example, results of a clinical trial reported as relative effect sizes are seen as more impactful than absolute effect sizes.[25]

Hospital transfusion services frequently encounter scenarios where framing might impact clinical behaviour. For example, when developing an end-of-year transfusion committee report to provide

TABLE 2 Common Sources of Biased Reasoning in Hospital-Based Transfusion Medicine.

	Pattern	Example	Mitigation	Example
Biases of memory				
Availability heuristic	Tendency to make decisions with easily recalled information	'After attending a TTP conference, a doctor suspects several thrombocytopenic patients of having TTP'	Use systematic approaches and schema for medical judgements	'A diagnostic approach to low platelets should always consider production, consumption and sequestration issues'
Limited memory	Human working memory can only hold 4–7 items at a time	'Massive haemorrhage protocol has the following 25 components'	Use seven or fewer items or information chunks for clinical protocols	'The 7 T's of MHP: Trigger, Team, Tranexamic acid, Testing, Targets, Temperature, Termination'
Biases of interpretation				
Anchoring bias	Overemphasis on reference points in decision-making	'Give 1-unit PRBC for each 1 g/dL below 7'	Reset anchors and create decision rules	'Why give two when one will do' campaign
Framing effects	Tendency to evaluate trade-offs by how they are presented	'66% of all your transfusions are appropriate'	Choose purposeful framing when creating messages	'1 out of 3 of all your transfusions are inappropriate'
Biases of incentives				
Search satisficing	Prematurely settling for the first explanation which explains a set of facts	Reactivity to D+ and C+ cells fits the pattern of anti-D and anti-C antibodies	Create and follow standard operating procedures for common problems	'SOP to test for anti-G in patients of childbearing potential and anti-C + anti-D reactivity'
Sunk cost fallacy	Investing further to redeem losses incurred by past investments	'We have already transfused this patient 50 units, we shouldn't stop now'	Predefined checkpoints to re-evaluate decisions at regular intervals	'We will reassess the indication and futility of transfusion after every 20 units'
Feedback sanction	Emphasising direct benefits and neglecting distributed costs	'Giving RBC to a stable iron deficient patient improves anaemia quicker than intravenous iron'	Perform audit/feedback for outcomes if moral hazard is suspected	'Track and report alloimmunization rates after emergency department transfusions'

feedback to clinicians, a behaviorally savvy transfusion clinical lead might reframe '66% of transfusions were appropriate' as '1 out of 3 transfusions were inappropriate'. The latter incorporates loss framing and absolute numbers to increase the psychological impact of the message. Framing might similarly affect discussions of trade-offs for transfusion consent (with understatement of risks), resource allocation (weighing benefits and harms), and acceptance of novel technologies in transfusion.[26] Caution must be exercised when choosing a frame to ensure the downstream outcome does not violate principles of medical ethics or shared decision-making.[27]

2.4 | Anchoring bias

Information received earlier, even when irrelevant, can affect later judgements through cognitive anchoring. Underlying mechanisms of anchoring are complex and may result due to assimilation of new knowledge biased by the presence of existing knowledge.[28] Anchoring has been experimentally demonstrated whereby an existing judgement unduly influences independent future decisions. In one study, participants were assigned a randomly generated dollar amount between $5 and $500; when later asked to make a donation to a charitable cause, those who previously received a higher random value tended to commit greater amounts to charity.[29] Anchoring is also present in 'low ball' negotiation tactics, judicial sentencing and voter choice.[30–32] A common application in medical judgement is in the use of numeric laboratory thresholds (e.g. transfusion at haemoglobin below 8.0 g/dL) which are ubiquitous in transfusion guidelines and may be susceptible to anchoring biases.[33–35]

Transfusion practice can be diminished or enhanced by anchoring effects. Reflexive adherence to laboratory thresholds of transfusion is common, contradicts principles of patient-centered care and results in harm when used indiscriminately.[36,37] Conversely, anchoring can be leveraged to improve transfusion—for example, the 'why give two when one will do' campaign provided a new anchor ('one will do') to clinicians and achieved impressive reductions in two-unit transfusions.[38] Anchoring might also be relevant in various other circumstances, such as false indications for blood products (e.g., plasma for asymptomatically elevated INR), detection of transfusion reactions (e.g., 101 degree Fahrenheit for febrile reactions), and evaluation of novel therapies (e.g., prior solicitations by industry representatives).[39] Faulty reasoning due to anchoring bias might be counteracted by recognising existing anchors contributing to poor transfusion and devising thoughtful new anchors to improve practice.[36,40]

2.5 | Search satisficing

While some decisions are straightforward, others require analysis of complex factors under pressure and lead to pitfalls of hasteful reasoning.

Search satisficing (also known as premature diagnostic closure) is a heuristic whereby an individual ends their search for a solution when they come upon an emotionally satisfying rather than optimal explanation.[41] Satisficing results from trade-offs between the cost of collecting and processing information and perceived marginal benefits in decision-making, sometimes leading to informational avoidance.[42,43] The bias has a heritable component, manifests in financial investment and influences voting decisions.[44] The adage 'when the diagnosis is made, the thinking stops' encapsulates this concept.[45] Satisficing is a prevalent cause of diagnostic error in clinical pathology and manifests irrespective of years of job experience.[46] It is accentuated with an increasing number of choices and restrictive time constraints.[47]

Search satisficing is common in hospital settings where time is scarce and options abound. For example, a transfusion investigation which shows positive reactivity with reagent cells expressing D and C antigens in a pregnant patient might be signed out as an anti-D and anti-C antibody, whereas an anti-G antibody should be excluded to ensure a deserving patient receives RhD-immunoglobulin prophylaxis. A different clinical scenario might involve patients with liver disease where an elevated INR is explained away as coagulopathy of liver disease, overlooking treatable Vitamin K deficiency. Search satisficing might also impact investigations of transfusion reactions and root-cause analyses for incompatibly errors. Satisficing behaviours might be attenuated by the use of diagnostic checklists and schematic algorithms for commonly encountered problems.[48]

2.6 | Sunk cost fallacy

Poor results sometimes counterintuitively reinforce behaviour and lead to protracted misadventures. Incurred losses, also known as Sunk Costs, can discourage change because people tend to prefer the status quo and demonstrate a strong aversion to regret.[49] A classic illustration occurs in gambling behaviour where unlucky individuals often continue to invest despite diminishing chances of a favourable outcome. This is incongruous with rational choice theories, which state that decision-makers should consider immediate payoffs and ignore irretrievable sunk costs. In general, Sunk costs arise in situations where the starting point of decision utility is negative due to losses incurred in the past.[50] This pattern of behaviour is also observed in psychology studies of substance use, overeating, drug-pricing and the aviation industry (e.g. overinvestment in costly supersonic jets or the 'Concorde Fallacy').[51] In the medical context, sunk cost reasoning can lead to diagnostic cascades and futile therapies.[52] Moreover, sunk cost behaviour can be appealing because it often aligns with virtues of consistency, conscientiousness and perseverance which are highly valued in healthcare providers.

Transfusion involves constant trade-offs between patient benefit and maintaining a sufficient supply of a limited commodity. Due to high stakes, transfusion therapy can sometimes invoke strong beliefs about the efficacy of treatment. For instance, having already administered over 50 units of blood components, a strong-willed intensivist might continue to request blood products for a young moribund patient in pursuit of a miraculous recovery. Similarly, a hepatologist might committedly persist with daily plasma and red cell transfusions for a patient with cirrhosis and recent gastrointestinal bleeding, treating presumed coagulopathy and overlooking an underlying hemolytic anaemia.[53,54] Sunk cost fallacy might similarly perpetuate futile change campaigns, faulty hiring decisions and frivolous research projects lacking meaningful returns. The allure of sunk costs might be obviated by the use of precommitment strategies such as transfusion futility protocols to stop and re-evaluate proceedings, similar to predetermined termination rules used for cardiac arrests.[55]

2.7 | Feedback sanction

The benefits or losses of complex healthcare decision are seldom apparent at the point of decision. For some clinical judgements such as transfusing patients in severe heart failure, the trade-offs are known, albeit complicated.[56] For others, however, the benefits may be accrued by one party, while the harms might distribute across multiple parties and be partially invisible to the decision-maker, resulting in a phenomenon known as feedback sanction.[57] Feedback sanction arises in systems where individual agents, acting toward differing interests with asymmetric information, cause systems to deviate from the best possible outcome.[58,59] A common scenario is of a naive physician who prescribes broad-spectrum antibiotics to all patients with excellent short-term results and causes greater harm due to complications of antimicrobial-resistant infections.[60] Feedback sanction is widespread in clinical medicine because communication is imperfect and short-term priorities can differ.

Hospital transfusion services have a unique vantage for the functioning of a hospital and frequently encounter feedback sanction. For instance, two physicians simultaneously and separately caring for two exsanguinating patients might understandably want all necessary blood products for their own patient. However, the clinical lead for transfusion is privy to both, with the concurrent responsibility of protecting hospital inventory to provide effective and equitable care to all patients. Similarly, while an emergency physician might enthusiastically transfuse a young female patient seen for microcytic anaemia with the reward of rapid haemoglobin normalisation (where intravenous iron might have sufficed), they may never come to diagnose or manage subsequent alloimmunization and complicated pregnancies. At a system-level, countries where blood is provided to hospitals free of charge might struggle with incentives for hospital administrators to engage in stewardship of blood products. A counteractive for feedback sanction is to align incentives by retrospectively relaying the complete set of consequences to all decision-makers.[61]

3 | DISCUSSION

Cognitive biases arise from normal psychology, can be resistant to retraining, and may cause systematic errors of reasoning in hospital medicine. We provide seven examples of prevalent biases drawing upon commonly encountered situations in transfusion medicine, and provide potential strategies for mitigation. However, behavioural

psychology is vast area of study and our approach has some notable limitations. First, many other cognitive biases exist that may be highly relevant for transfusion medicine and warrant study in this context.[62] Second, we have primarily focused on hospital-based practice—applications for blood operators are plentiful (e.g. encouraging blood donation) and deserve further exploration. Third, biases represent one important source of deviation from ideal medical practice; noise or random error, is a another significant contributor to decision variability with distinct mitigation strategies such as 'noise audits'.[63] Fourth, the effect size of biases on behaviour can vary substantially across individuals and contexts, manifesting more strongly in conditions of relative cognitive scarcity such as fatigue, sleep deprivation, high decision-density, attentional interruptions and inexperience, suggesting some strategies for personalised interventions.[64,65] Fifth, although cognitive biases generally cannot be extinguished, awareness of these patterns might lead to better alignment among healthcare goals, intervening incentives and patient outcomes.

Behavioural insights can also be cautiously applied in designing effective 'nudge' interventions to enrich existing frameworks of implementation science for improving transfusion practice.[66] Nudge theory is the branch of psychology aimed at harnessing behavioural insights to modify choice architecture (environmental features of decisions) and influence behaviour without altering underlying incentives.[36] Potential examples of nudges in transfusion include using loss framing to discourage inappropriate transfusion, embedding anchors within electronic order sets to increase guideline adherence, devising memorable educational strategies that comport to memory limitations, and debiasing interventions to reduce inequities in healthcare.[67–69] Applied carefully and creatively, insights from psychology have the potential to illuminate how we think and advise how we might do better in transfusion medicine.

4 | CONCLUSION

Pitfalls of reasoning are prominent in medical decision making and commonly encountered in hospital transfusion medicine. An awareness of these biases and mitigation strategies might encourage further scholarship, promote reflective practice, enhance implementation strategies, enrich transfusion curricula and improve transfusion outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed to first draft. All authors contributed to manuscript preparation, critical revisions, and final decision to submit.

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DATA AVAILABILITY STATEMENT

This work did not involve the generation or analysis of original data, and no datasets were generated or analysed. Readers interested in accessing the original sources cited in this review are encouraged to refer to the references provided.

PATIENT CONSENT STATEMENT

No patient was involved, and no consent was required in the collection and interpretation of data for this manuscript.

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TRANSFUSION MEDICINE WILEY

LETTER TO THE EDITOR

What is best practice for the prevention of anti-D alloimmunisation in D-negative recipients receiving solid organ transplants from D-positive donors

Dear Editor,

A 33-year-old Caucasian woman was referred at 32^{+5} weeks of gestation after the finding of severe fetal intracranial haemorrhage (ICH) at routine ultrasound. The woman had two previous uneventful pregnancies (singleton and twins). Fetal ultrasound and magnetic resonance imaging confirmed multiple ICHs especially located in the left hemisphere, wide areas of periventricular leukomalacia, obstructive hydrocephalus and macrocrania. Fetal-neonatal alloimmune thrombocytopenia (FNAIT) was investigated. Maternal blood group was A RhD positive, paternal O RhD positive. The maternal sample was screened for platelet-reactive antibodies using solid phase technology for the detection of IgG anti-HLA class I and anti-HPA antibodies (SPRCA Capture P Ready Screen, Immucor, Italy) with and without chloroquine treatment to remove HLA antigen interference. The results were positive and negative respectively. No antibodies attached to maternal platelets were found (Capture-P, Immucor, Italy). ELISA and Luminex based platforms were used to identify the specificity of the detected antibodies (Pak-Lx Luminex and ELISA Pak plus, Immucor, Italy and Luminex MoAb, Lagitre, Italy). The assays only recognised the presence of anti-HLA A02 and anti-HLA B51 at high titre, greater than 8000 and 20 000 MFI (average fluorescence intensity) respectively, in association with different cross-reactions. Cross-match testing (Capture-P, Immucor, Italy) using maternal serum against paternal platelets tested reactive with both chloroquine-untreated and treated platelets. Additional cross-match testing was performed using platelets. Additional cross-match testing was performed using maternal serum against 14 random donor platelet samples. Eight donors were compatible and six were not. Two non-compatible donors were HLA class I A*02 and A*02 B*51 respectively. The remaining four non-compatible donors were not typed for HLA I antigen. All compatible donors were typed for the main HPA antigens but comparison of the typings did not allow to quickly exclude HPA 4b, 6b, 7b, 8b, 9b, and 11b antigen immunisation. A male newborn was delivered by caesarean section at 36 weeks of gestation after spontaneous onset of labour. At birth, platelet count was $4x10^3/\mu l$ with normal white and red blood cell count. An urgent transfusion with a platelet blood component not tested with maternal serum increased platelets to $116 \times 10^3/\mu l$; intravenous immunoglobulins were also infused. Another two transfusions were administered on days 4 and 13 due to a drop in the number of platelets ($28 \times 10^3/\mu l$ and $48 \times 10^3/\mu l$ respectively): the platelet pools were obtained from cross-match between maternal serum and sample platelets of random donors. Normal values were reached on day 17.

The newborn blood group was 0 Rh D positive. Capture-P Ready Screen aimed to detect anti-platelet antibodies was non-reactive. Cross-match testing using newborn blood was performed twice. At birth, the neonatal sample was cross-matched against paternal and maternal platelet samples: results were positive and negative, respectively. After 14 days, cross-matching against paternal platelets was repeated with and without chloroquine treatment; both resulted non-reactive.

Results of parental and neonatal HLA I and HPA genotyping performed using polymerase chain reaction (PCR) with sequence-specific oligonucleotides (PCR-SSO) and HPA BeadChip (Immucor, Italy), are shown in Table 1. The mismatches identified prompted further testing in the mother. Cross-match testing against 6 HPA-9b antigen negative donors resulted in two non-compatible and four compatible donors. The same two non-compatible donors were all compatible when The same two non-compatible donors were all compatible when cross-matching was performed with chloroquine. Cross-match testing against two donors expressing the HPA9b antigen was reactive with and without chloroquine. Cross-match testing against paternal and neonatal platelets with and without chloroquine was equally reactive. Cross-match testing was performed between maternal serum and 107 different donors in order to have available and compatible blood components available for any neonatal transfusions.

FNAIT is a cause of severe thrombocytopenia and ICH in both the fetus and newborn.[1] FNAIT-related ICH is estimated to occur in at least 10:100 000 neonates. It mainly occurs in the third trimester of pregnancy and is associated with severe neurological sequelae and mortality. In most cases, FNAIT is caused by an alloimmune response against human platelet antigens (HPAs). In the Caucasian population HPA-1a antigen accounts for up to 80% cases,[2] followed by HPA-5b (8–15% of cases) and to a lesser extent HPA-3a/5a/15b.[3] More rarely, FNAIT is associated with low-frequency human platelet antigens (LFHPAs) or to HLA class I antigens, especially when related to locus A and B and with a highly expressed titre.[4] Among LFHPAs, HPA-9b is emerging as a significative trigger for FNAIT.[5] Almost two-thirds of apparent cases of FNAIT are not resolved by laboratory confirmation of maternal immunisation against HPA antigens. When other causes of thrombocytopenia are not identified, a possible explanation may be involvement of HLA antibodies or limitations of laboratory studies.

In the current case, parental ABO compatibility excluded ABO-mediated thrombocytopenia. The detection of maternal HLA class I antibodies, identified as HLA A02 and HLA B51 antibodies, and paternal HLA I genotype (HLA A*02; B*35*51), were consistent with the clinical suspicion of FNAIT. However, an additional factor was likely to be involved, presumably related to the HPA system: genotyping showed a parental mismatch in the HPA 9 locus (mother HPA- 9a/a, father HPA 9a/b) and neonatal inheritance of the HPA-9b antigen from the father. Search for HPA antibodies (Pak-Lx Luminex and ELISA Pak plus) was inconclusive because no reactivity was detected against the glycoproteins GPIIb/IIIa, GPIa/IIa, GPIb/IX and GPIV. This can be explained by the limitations of the GP assay used which was not able to recognise the rare specificity HPA-9b. Moreover, it was not possible to find readily available source platelets from local donors carrying the target antigen because only a limited number of them had been typed for HPA and the expected frequency of HPA 4b, 6b, 7b, 8b, 9b, 11b in the population is extremely low (<1%).[3] Cross-match testing between maternal serum and both paternal and neonatal platelets was reactive after chloroquine treatment. This finding was supported by cross-match performed against HPA9b positive donors. This allowed to attribute the FNAIT to the presence of the paternally inherited HPA9b antigen on the son's platelets. It was not possible to identify any antibody specificity in neonatal serum (Capture—P Ready Screening method) presumably due to the extremely low platelet count as a result of the adhesion of the maternal alloantibodies to the neonatal platelets with consequent uptake and elimination.

Since the first report of a HPA-9b related FNAIT in 1995,[6] a total of 15 cases have been reported[5,7,8] and increasing evidence suggests that its prevalence in the population and among fathers of unresolved cases of FNAIT might be greater than previously reported.[6,9] The severity of thrombocytopenia and clinical presentation in our case is consistent with the argument that HPA-9b might be more immunogenic than others HPAs.[5] Our case supports the need to investigate alloimmunisation to HPA-9b and other rare specificities when routine screening for the most common antigens is negative or inconsistent with the laboratory and clinical findings.[3,5] We experienced diagnostic limitations mainly due to the fact that the Ag panel used (Pak-Lx Luminex Immunocor and Elisa Pak Plus Immunocor) does not identify HPA-9b. Difficulties with the detection of antibodies against HPA-9b antibodies have been described by some authors who urged further studies to fully understand the issue.[5,7] Nonetheless, even if FNAIT was strongly suspected both on clinical grounds and after the finding of anti-HLA I antibodies, the mother could not be offered intrauterine therapy of proven efficacy to begin at that gestational age.[1,9]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not openly available due to sensitivity reasons and are available from the corresponding author upon reasonable request.

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