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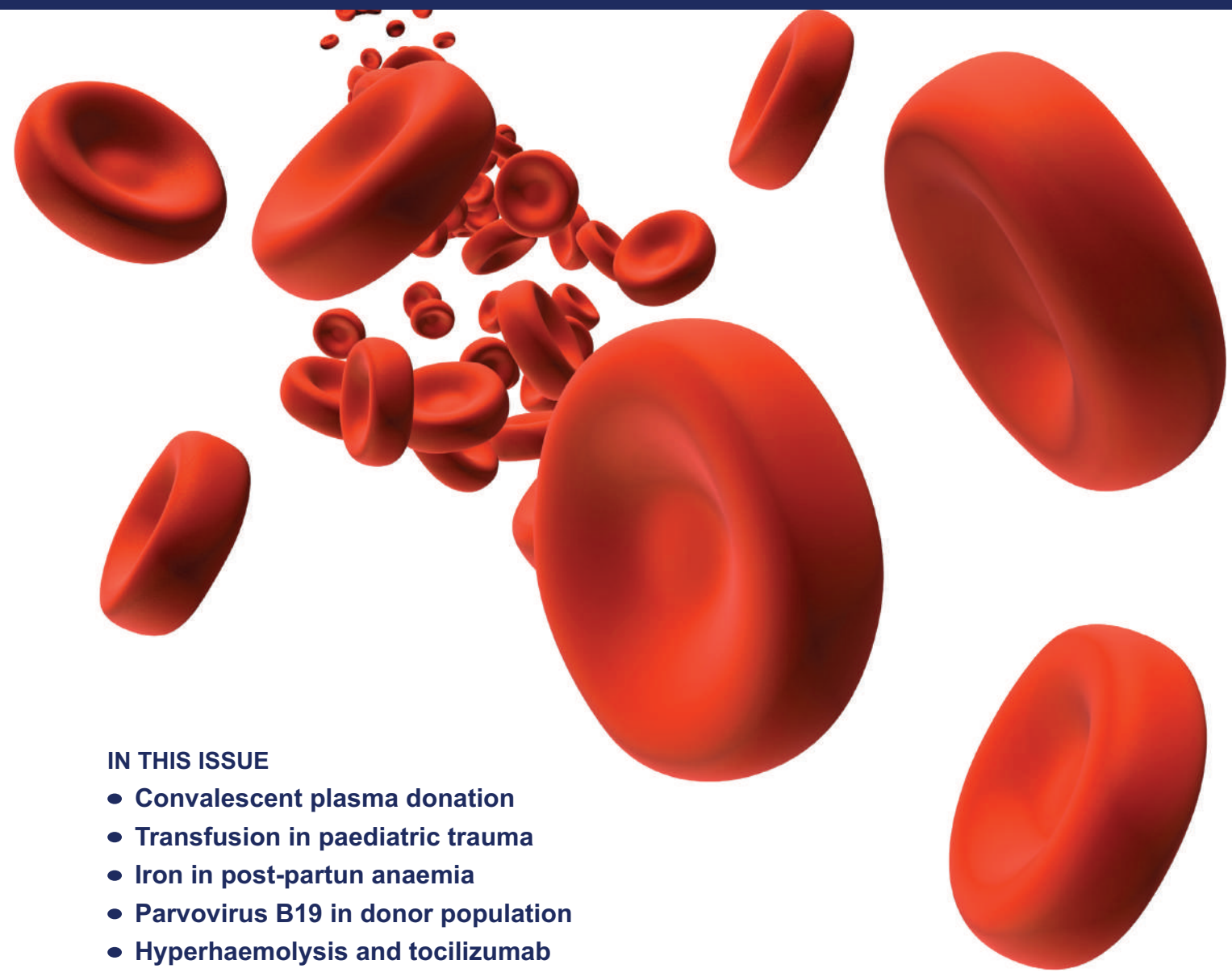

IN THIS ISSUE

- Convalescent plasma donation
- Transfusion in paediatric trauma
- Iron in post-partun anaemia
- Parvovirus B19 in donor population
- Hyperhaemolysis and tocilizumab

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Transfusion Medicine

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Transfusion Medicine will publish articles on transfusion medicine in its widest context, including blood transfusion practice (blood procurement, pharmaceutical, clinical, scientific, computing and documentary aspects), immunohaematology, immunogenetics, histocompatibility, medico-legal applications, and related molecular biology and biotechnology.
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ORIGINAL ARTICLE

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A critical contribution in a time of crisis: Examining motivations and deterrents to COVID-19 convalescent plasma donation and future donation intentions among prospective Canadian donors

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Abstract

Objectives: To understand motivations and deterrents to donate COVID-19 convalescent plasma for a clinical trial and determine whether they predict intention to donate source plasma.

Background: During the COVID-19 pandemic, Canadian Blood Services was involved in three nationally coordinated convalescent plasma clinical trials, requiring the recruitment of several thousand prospective convalescent plasma donors. Understanding the motivations and deterrents of donors in the unique context of a clinical trial and ongoing pandemic can inform recruitment for source plasma donation beyond a clinical trial.

Methods and Materials: We invited 2785 Canadians who had registered interest in donating COVID-19 convalescent plasma to participate in an online survey containing a 42-item scale on motivators of and deterrents to donation. Between April 26th and May 19th, 2021, 979 responded (35.1%). We included a final sample of 820 participants with sufficient data across all scales. Exploratory and confirmatory factor analysis determined the factor structure of the scale. Regression analysis assessed the extent to which the factors predicted intention to donate.

Results: Four factors were identified: 'helping relationally', 'deterrents to donation', 'social facilitators', and 'access to the donation centre', each with good internal consistency (α = 0.78–95). Higher scores on the helping relationally scale were associated with higher odds of intention to donate, whereas higher scores on the deterrents scale were associated with lower odds of intention to donate.

Conclusion: Participants were motivated by an interest in helping people who are ill and contributing to research committed to finding treatments in a time of crisis. Outside the crisis context, blood service operators seeking to recruit source plasma donors should emphasise its lifesaving potential and the impact of donation on the community.

KEYWORDS
blood donation, convalescent plasma, COVID-19, donation intentions, donation motivation, factor analysis, plasma donation

1 | INTRODUCTION

From 2020 to 2021, hundreds of clinical trials took place internationally to determine whether convalescent plasma from donors recovered from COVID-19 was an effective therapy for people hospitalised with COVID-19.[1,2] During the COVID-19 pandemic, Canadian Blood Services was involved in three nationally coordinated convalescent plasma trials approved by Health Canada. The primary trial was a Randomised, Open-Label Trial of **CON**valescent Plasma for Hospitalised Adults with Acute **CO**VID-19 **R**espiratory Illness (CONCOR-1),[3] a collaboration between Canadian Blood Services, Héma-Québec (the blood collection agency in Quebec), 10 research teams and 72 hospital sites in Canada, the United States, and Brazil. To source sufficient COVID-19 convalescent plasma for the clinical trial, Canadian Blood Services created, advertised, and managed a registry of prospective donors recovered from COVID-19 in Canada. Prospective donors were recruited through pamphlets and posters at clinics, social media outreach, paid recruitment (e.g., radio advertisements, social media content etc.), earned media, internal communications, and recruitment by the clinical trial investigators. Several thousand prospective donors signed up to the registry, creating a unique opportunity to expand our knowledge about the characteristics, motivations, and deterrents of prospective plasma donors within a pandemic context.

At the same time, there is increasing demand for plasma-derived therapies to treat bleeding disorders, burns, and immune deficiencies in Canada, with a resultant increase in the need for plasma donors to contribute 'source' plasma. Unlike plasma collected for transfusion (such as convalescent plasma), source plasma is pooled from multiple donors then manufactured into therapies called 'plasma protein products', through a process called fractionation. The international publicity about convalescent plasma as a potential treatment for COVID-19 raised the profile of plasma as a potential lifesaving treatment.[4] While the CONCOR-1 clinical trial found that convalescent plasma is not an effective treatment for COVID-19,[3] understanding convalescent plasma donor motivations can inform how we approach recruitment of source plasma donors during the current COVID-19 pandemic, and beyond. Thus, our research objective was to understand motivations and deterrents to donate COVID-19 convalescent plasma for a clinical trial and determine whether they predict intention to donate source plasma.

Our research objective requires attention to how the motivations and deterrents to donation differ across contexts. The context for donation—in this case a pandemic and a clinical trial—may influence who is motivated or deterred from donating plasma, potentially mobilising new populations of donors or generating insights about deterrents for particular social groups. Particularly, the context of donating blood for research can affect donor motivations and deterrents,[5] thus, we approached the survey design and analysis with a sociological lens to account for the influence of context.

The sociology of donation situates donors within wider social structures, and relatedly, interrogates concepts that have been central to analysing motivations of donors. There is a growing scholarship challenging the concept of altruism, arguing that donation is rarely simply a gift, but often an opportunity for reciprocity, personal gain, or mutual exchange,[6] embedded in the context of a community.[7,8] For example, researchers have found that appeals towards enhancing the status of an organisation, giving back to community, performing a civic duty, having blood donation tied to meaningful aspects of their social network,[7,8] or meeting the increasing need for plasma-derived treatments for recipients with a range of illnesses[9] can be more effective in recruiting donors than appeals to altruism. The pandemic, for many, was a significant life event that could impact donor motivation,[10] and differentially impacted our ability to interact socially with others (depending on one's work, caregiving responsibilities, housing, etc.), which could intern motivate or deter certain demographics. Social science research on blood donation in the context of the COVID-19 pandemic is thus required to examine how national emergencies can encourage donation as a symbol of national solidarity, while noting that the longevity of a pandemic can pose unique challenges to blood collection agencies.[11]

During the first wave of the COVID-19 pandemic in 2020, researchers in Australia and the United Kingdom (UK) distributed a survey measuring the motivations and deterrents of COVID-19 convalescent plasma donors. Masser and colleagues[12] found that awareness of COVID-19 convalescent plasma among the UK sample was low, that a stronger sense of altruism through adversity and moral civic duty were positively related to intention to donate, and that generic fears about infection were negatively related. Our study builds on the scales developed by Masser and colleagues[12] by applying them to the Canadian context, following the third wave of COVID-19 and completion of the CONCOR trial. Consequently, we sought to understand predictors of intention to donate plasma going forward, rather than for donating convalescent plasma, specifically. Our analysis extends Masser and colleagues'[12] concept of 'altruism from adversity', suggesting that beliefs centred around gratitude and reciprocity are developed in the context of social relationships, based in relations of reciprocity,[13] and is done to benefit others and oneself or one's family. This notion of *mutual* benefit[14] may be particularly salient in the context of the COVID-19 pandemic given the prevalence and threat of infection within communities worldwide, and the likelihood that people known to an individual, including family members, friends, colleagues, and neighbours, might fall ill and need convalescent plasma.[13,15,16] We also sought to understand whether social facilitators such as donating to get out of the house and see people, and encouragement from friends and family, were relevant predictors of plasma donation in the context of a pandemic. Finally, we reframe

their concept of 'logistics' to suggest that travel and convenience are socially mediated features of donation as they speak to a donor's work and caregiving responsibilities and their access to donation.[17,18]

Thus, this study aimed to: (1) determine and confirm the factor structure and internal consistency of the motivators and deterrents to becoming a COVID-19 convalescent plasma donor scale in a sample of Canadians registered to donate convalescent plasma; and (2) determine to what extent the factors predicted intention to become a regular plasma donor in the future. We see donation as existing within wider social structures such as family, education, and work, and the act of donation as involving a complex web of social actors—the donor, the recipient, practitioners.[6] Thus, our analysis considers motivations and deterrents as existing socially, where decisions are made in relation to other people and communities.

2 | MATERIALS AND METHODS

We conducted a cross-sectional survey of a convenience sample of prospective COVID-19 convalescent plasma donors who had voluntarily registered their interest to donate with Canadian Blood Services. The University of Toronto (Ref#: 40052) and Canadian Blood Services (Ref #: 2020.056) research ethics boards approved this study.

Between 10 April 2020 and 2 February 2021, 4291 people provided their contact information to Canadian Blood Services' COVID-19 convalescent plasma registry via email to express interest in donating plasma to the CONCOR-1 clinical trial; 2785 registrants consented to be contacted for research purposes. Individuals were eligible to enrol if they were previously confirmed positive for COVID-19 by a laboratory test; were younger than 67 years old (at the time of the study, people over 67 were not eligible to donate apheresis products for their first donation); had fully recovered from the virus; and were symptom free for at least 28 days.

We sent a personalised email to the 2785 consenting prospective donors on 26 April 2021 through the Research Electronic Data Capture (REDCap) platform,[19,20] a gold standard, secure data management web application for building and managing online surveys and databases hosted at the University of Toronto. REDCap automatically emailed non-responders a reminder at 2 and 4 days after original contact.[21] The survey closed on 19 May 2021. Prior to proceeding with the survey, participants read the study information letter (see Appendix S1) and acknowledged their consent. The survey recruitment period occurred after the convalescent plasma clinical trials in Canada had ended recruitment, when globally, results of trials indicated that outcomes for those treated with convalescent plasma did not significantly differ from controls treated with the standard of care.[2]

3 | MEASURES

Six individuals piloted the survey to ensure that the questions were clear. Each took an average of 20 minutes to complete the questionnaire. We asked participants to provide details about their demographic characteristics including sex, age, sexual orientation, race, education level, and income level as well as their COVID-19 infection details. For the latter, participants were asked if they tested positive for COVID-19 (yes, no, unsure). If they replied 'no' or 'unsure,' they were asked if they had a close contact with someone who had tested positive for COVID-19. Individuals who reported a close contact with a confirmed positive COVID-19 infection were considered positive for the purposes of the analysis.

Revised motivators and deterrents of donating convalescent plasma scale: We adapted the scale originating in Australia,[22] and developed by Masser et al., into a 56-item scale.[12] The original scale was found to have a 12-factor structure, with good internal consistency.[12] To account for differences in national and pandemic context, and to address the primary outcome (i.e., intention to donate plasma in the future), we prioritised the scales measuring motivators and facilitators, and deterrents and barriers to donating convalescent plasma and removed the section 'Reflections on COVID-19 infection'. To better understand how donation is a social act involving friends, family and other social networks, and how donation is embedded in wider social structures,[6] we added five items addressing how other social facilitators in a pandemic might influence motivation to donate plasma. Our additional items sought to measure how participants are situated in a social life, focusing on their relationship to work and the time they have for donation,[9] their proximity and ease of access to the donation centre,[17,18] their relationship with friends and family who donate and the 'social capital' involved in donation,[7,8] knowledge and familiarity with the donation process,[23,24] and interest in supporting research through donation.[5,25] In its final form, the scale contained 42 items measured on a 7-point Likert scale, ranging from strongly disagree[1] to strongly agree.[7]

Intention to donate: Participants were asked, using a 7-point Likert scale (1—strongly disagree to 7—strongly agree), about their intention to donate and frequency of intended donation (once a week to never) for blood products, and separately, plasma, in the future. Participants were also asked if they had successfully completed a convalescent plasma donation.

Open-ended questions: Participants were asked to share what they know about convalescent plasma, how they found out about the clinical trial, and, if relevant, why they were unable to successfully complete a convalescent plasma donation.

4 | STATISTICAL ANALYSES

We summarised the sample using descriptive statistics, including mean and standard deviations for age, and frequency counts and percentages for nominal variables. This part of the analysis was undertaken using SAS (version 9). We analysed the three open-ended questions using inductive coding, refined the preliminary codes into defined categories, then calculated the category frequencies.

The first objective was undertaken using factor analysis. As the dimensionality of the scale had never been determined in its revised form, we conducted an Exploratory Factor Analysis (EFA) in Mplus

(version 7).[26] EFA was undertaken in a random split-half of the sample to validate the factor structure identified using Confirmatory Factor Analysis (CFA) in the hold out portion of the sample. A robust maximum likelihood estimator was used and a GEOMIN rotation, an oblique rotator that allows for correlations between factors.[26] This appeared to be a reasonable approach given the medium to large-sized correlations found among factors in the Masser et al, study.[12] Parallel analysis and Velicer's MAP test were used to extract the optimal number of factors.[27] We assessed model fit using a variety of fit indices including: Root Mean Square of Approximation (RMSEA, <0.06 recommended), Comparative Fit Index (CFI, >0.95 recommended), Tucker-Lewis Index (TLI, >0.95 recommended), and Standardised Root Mean Square residual (SRMR, >0.08 recommended).[28] The model Chi Square statistic is reported for completeness but not used to judge model fit due to its sensitivity to sample size.[28] Items were candidates for removal if they had a low-loading value (i.e., <0.3) or were cross-loaded (loading on multiple factors with a loading value >0.3). After the optimal number of factors was selected and adequate model fit was observed, the final solution was determined with consideration of theoretical meaningfulness and adequate factor separation. In the hold out portion of the sample, we undertook CFA to confirm the factor structure implied by the EFA. We assessed model fit using the model fit indices described above. Modification indices were requested to identify places where model fit could be improved. Changes to the model were made only if theoretically justified. Missing item level data was accounted for using robust full information maximum likelihood (MLR) for model estimation based on the assumption of Missing At Random (MAR). Most items had 2% missing or less; the maximum missing was 6.5%. Little's MCAR test was significant ($p = 0.012$), supporting the MAR assumption and the use of full information maximum likelihood for handling missing data.

Once we determined and confirmed the factor structure of the scale, we assessed internal consistency for each subscale and the overall scale using Cronbach's alpha coefficient. Compositive reliability was additionally assessed based on the standardised factor loadings from the CFA.[29] Finally, we presented item and scale level descriptive statistics which included means and variances, and subscale, means, and standard deviation in the overall sample. Individual mean imputation was used to calculate composite scores.

To address the second study objective we used multiple regression, selecting two outcomes: (1) intent to donate plasma as a regular donor going forward, and (2) intent to donate blood products as a regular donor going forward. Predictor variables included the composite scores for the four subscales. We ran the models unadjusted and adjusted for the following covariates: age (<36, 36–55, >55 years), gender (women, men), education level (≤high school, college, university, other), rural, and history of donation in the past year. Model diagnostics revealed that the distribution of the intention to donate variables was not compatible with Ordinary Least Squares regression due to a heavy right skew. Therefore, logistic regression was undertaken using a binary version of the outcome, categorising those scoring above the neutral point of the scale[4] as intending to donate and those scoring neutral or below as not intending to donate. To address missing data in the outcome and the predictor variables, Multiple Imputation (MI) was undertaken using the variables described above, plus additional demographic variables that were hypothesized to be related to missingness (i.e., income, sexual orientation, and race). Twenty datasets were imputed. Analyses were undertaken using SAS (version 9.4).

4.1 | Sample size calculations

We calculated minimum sample size to achieve the primary objective of completing an EFA and a separate CFA. The sample size for EFA is best estimated using the average loading on a factor, known as the degree of factor saturation.[30] To mirror the Masser et al. study,[12] the analysis required a medium to high factor saturation across subscales (range 0.44–0.88). This suggested a sample size of 150 would suffice.[30]

For CFA, samples sizes between 150 and 315 participants are adequate assuming the data is normally distributed and the level of missingness is low.[26] Using the most conservative estimates, a minimum sample size of 150 participants for the EFA and a separate sample of 300 participants for the CFA, resulted in a combined total sample size of at least 450.

5 | RESULTS

We emailed the survey to a total of 2785 individuals who had expressed interest in donating their convalescent plasma to a clinical trial. In total, 979 participants answered at least one question from the survey (response rate of 35.1%). We removed participants from the final analysis if they did not test positive for COVID-19 (20/979, 2.0%), and therefore would be ineligible for convalescent plasma donation, or had completely missing data on the scale (119/979, 12.2%). This resulted in a final sample of 820.

Table 1 presents the demographic characteristics of the sample. Slightly more participants identified as female (56.8%) than male (43.1%), most were heterosexual (82.9%), and there was a roughly equal spread across all age groups between 26 to 66 years (range 22%–23%), while ages <25 and 67+ represented 10.9% of the participants. Most participants who reported a self-identified race/ethnic group were White (79.2%). Over half of respondents reported having a university degree (55.6%), and another 21.9% had a college degree. For those who reported their family income, 31.3% stated they earn >$150 000 and 11.5% earned <$60 000.

Approximately a third (283/820, 34.6%) were current blood donors, indicating that they had donated blood products in the past year; 62.9% of these donations occurred within the previous 3 months of completing the survey. In the past year, most donated whole blood (90.1%), while a few participants donated plasma (12.4%) or platelets (5.7%). Of the participants who were unsure or had not donated blood products in the past year ($n = 537$), 23.1% ($n = 124$) said they tried to donate blood products but were considered ineligible. 95.7% of survey participants had not donated plasma in the past year, indicating that most participants were new or infrequent plasma donors.

TABLE 1 Demographic characteristics of the sample

Demographic characteristic	*n* (%)
Age ($n = 804$)	
<25	78 (9.7)
26–35	181 (22.5)
36–45	175 (21.7)
46–55	185 (23.0)
56–66	175 (21.7)
67+	10 (1.2)
Gender ($n = 819$)	
Male	353 (43.1)
Female	465 (56.8)
Another identity	1 (0.1)
Sexual orientation ($n = 797$)	
Asexual	60 (7.3)
Bisexual	24 (2.9)
Gay or lesbian	20 (2.4)
Heterosexual/straight	679 (82.9)
Another identity (e.g., pansexual, queer, demisexual)	14 (1.7)
Race/ethnic group ($n = 804$)	
Asian-East	17 (2.1)
Asian-South	42 (5.5)
Asian-South East	21 (2.6)
Black	8 (0.9)
Latin American	12 (1.5)
First Nations/Metis	11 (1.3)
Middle Eastern	11 (1.3)
White	648 (79.2)
Mixed heritage	22 (2.7)
Another identity	12 (1.5)
Education ($n = 812$)	
High school degree or less	168 (20.5)
College degree	175 (21.9)
University degree	455 (55.6)
Other	14 (1.7)
Family income ($n = 639$)	
$0–29 999	26 (3.3)
$30 000–59 999	65 (8.2)
$60 000–89 999	102 (12.9)
$90 000–119 999	108 (13.6)
$120 000–149 999	90 (11.4)
$150 000 or more	248 (31.3)

Most participants (23.1%) found out about the convalescent plasma clinical trial from traditional media (e.g., the news, radio), followed by internet searches (17.4%), being contacted by Canadian Blood Services (16.4%), word of mouth (16.2%), social media (7.4%), their own research motivated by an interest to help (7.0%), and referral from a healthcare provider (4.6%). When asked, 20.9% of respondents said they did not know much, or anything, about convalescent plasma. Those that discussed convalescent plasma described what it is, what it does, or how it works (40.8%), its potential for use in the treatment of COVID (14.3%), a general sense of its helpfulness (10.4%), its use in research (8.2%), or donation procedures (4.9%).

In total, 231 participants successfully donated convalescent plasma (28%), while 307 attempted to donate but were unsuccessful (37%). When asked, half of those who attempted but were unable to donate said they were ineligible (primarily due to current or past pregnancy, travel history, or insufficient weight 50.1%). The remainder cited the end of the trial (26.0%), a lack of follow up (10.5%), logistical barriers (5.5%), or experiencing adverse events while donating (5.2%).

5.1 | Exploratory factor analysis

We conducted an EFA in a random split half of the sample ($n = 410$). Parallel analysis and Velicer's MAP test indicated a model with four factors (Table 2). The first factor, 'helping relationally', explained 31.8% of the total variance and contained 10 items with factors loadings ranging from 0.86 to 0.25. The second factor, accounting for 11.9% of the total variance, we called 'donation deterrents', contained 16 items with factor loadings ranging from 0.97 to 0.24. The third factor, 'social facilitators', explained 4.9% of the variance and contained 11 items with factor loadings ranging from 0.82 to 0.17. The fourth and final factor, 'access to the donation centre', explained 3.6% of the variance and had five items with factor loadings ranging from 0.78 to 0.34. Model fit for the 4-factor model was adequate, with the RMSEA = 0.058, and SRMR = 0.04, but the CFI/TLI were below recommended cutoffs (CFI = 0.88, TLI = 0.85). There were several items with loadings below 0.3 or that were loaded on multiple factors. Four items were candidates for removal due to low loadings (Item Number: 8, 37, 42, 21). Another five items had problematic cross-loadings (Item Number: 6, 31, 5, 30, 19). To resolve the cross-loadings, we tried a simpler factor structure with 3 factors and a more complex one with five factors, and while both options resolved some cross-loadings, the 3-factor model introduced additional low-loading items and the 5-factor model generated item groupings without discernable themes. It was decided that the four-factor structure was the best model with the low-loading and cross-loaded items removed. The EFA was re-run on the final 33-item scale and the four-factor model was indicated again by parallel analysis and model fit indices were slightly better. Table 2 presents the item loadings and item level statistics for the initial and revised models of the scale.

5.2 | Confirmatory factor analysis

We ran CFA in the hold out portion of the sample ($n = 410$) using the four-factor model of 33 items identified using EFA (Table 3). Initial model fit was borderline, with RMSEA = 0.063, CFI = 0.851, TLI = 0.839 and SRMR = 0.080. The modification indices showed

TABLE 2 Exploratory factor analysis

						Factors							
						Initial model				Revised model			
Item number	*N*	Item	Survey section	Mean	Variance	Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre	Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre
2	815	Through donating convalescent plasma, I could help others.	MF	6.47	1.25	**0.858**	−0.039	−0.104	−0.001	**0.886**	−0.024	−0.1	0.029
7	815	I like to help others, and donating convalescent plasma is just one way I could help.	MF	6.14	1.49	**0.822**	−0.103	0.001	0.111	**0.806**	−0.076	0.033	0.054
1	816	I was in a unique position to help by donating convalescent plasma where other people could not.	MF	6.20	1.72	**0.734**	0.023	0.067	0.01	**0.737**	−0.011	−0.073	0.009
10	817	Donating convalescent plasma could help research into COVID-19 treatments.	MF	6.23	1.38	**0.72**	−0.099	−0.035	−0.084	**0.739**	−0.099	−0.021	−0.054
4	816	Donating convalescent plasma would make me feel proud.	MF	5.71	2.11	**0.658**	0.018	0.208	−0.084	**0.647**	0.052	0.19	−0.161
11	812	Donating convalescent plasma could potentially help my family and friends if they became ill.	MF	5.67	2.26	**0.571**	0.013	0.195	−0.064	**0.582**	0.004	0.202	−0.07
12	814	Donating convalescent plasma was the morally right thing to do.	MF	5.63	2.09	**0.51**	−0.101	0.252	−0.017	**0.531**	−0.067	0.271	−0.001
6	813	Donating convalescent plasma is a story I could tell others about.	MF	4.63	2.95	**0.446**	0.042	**0.382**	0.064	-	-	-	-
8	818	There are very few people who could help through donating convalescent plasma.	MF	4.48	2.98	**0.258**	0.038	0.138	0.07	-	-	-	-
37	768	I was confident that I could complete convalescent plasma donation successfully.	AB	6.18	1.68	**0.249**	0.18	0.058	0.085	-	-	-	-
29	785	I worried that donating convalescent plasma would mean I lost valuable antibodies that I still needed.	DB	1.53	1.50	0.094	**0.972**	−0.049	0.066	0.088	**0.957**	−0.059	−0.04
35	784	I worried I would become ill again if I donated convalescent plasma.	DB	1.40	1.12	−0.025	**0.939**	0.002	−0.091	−0.027	**0.923**	0.001	−0.061
34	786	If I donated convalescent plasma again, it would set my recovery back.	DB	1.43	1.14	−0.04	**0.905**	−0.002	−0.067	−0.042	**0.895**	−0.003	−0.047

TABLE 2 (Continued)

Item number	*N*	Item	Survey section	Mean	Variance	Factors							
						Initial model				Revised model			
						Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre	Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre
27	781	I would have felt like a guinea pig if I donated convalescent plasma.	DB	1.39	1.10	−0.037	**0.861**	−0.001	−0.025	−0.056	**0.861**	−0.006	−0.006
36	782	I worried that I might inadvertently infect others with COVID-19 through donating.	DB	1.38	1.11	−0.003	**0.82**	0.068	0.007	−0.009	**0.815**	0.069	0.013
28	784	My friends and family would not have wanted me to donate convalescent plasma.	DB	1.46	1.35	−0.004	**0.816**	−0.006	0.023	−0.015	**0.792**	−0.004	0.013
33	780	I needed more time to recover from COVID-19 before I could donate.	DB	1.50	1.41	−0.074	**0.792**	−0.052	0.041	−0.085	**0.787**	−0.052	0.035
22	785	I was worried about getting re-infected if I donated convalescent plasma.	DB	1.53	1.63	0.033	**0.784**	−0.011	0.034	0.026	**0.787**	−0.015	0.03
40	766	Donating convalescent plasma took too much of a toll on my body.	AB	1.70	1.50	0.062	**0.644**	0.06	0.087	0.087	**0.641**	0.047	0.175
31	784	Logistically, it was just too difficult for me to donate convalescent plasma because of caregiving responsibilities.	DB	1.45	1.30	0.058	**0.63**	0.005	**0.308**	-	-	-	-
23	781	I did not really feel well enough to donate convalescent plasma.	DB	1.61	1.62	−0.131	**0.618**	0.054	−0.081	−0.144	**0.648**	0.051	−0.006
32	783	Others who were fitter than me could donate convalescent plasma.	DB	1.77	2.07	0.016	**0.605**	0.062	0.101	0.005	**0.61**	0.049	0.095
26	784	I did not think that convalescent plasma would be an effective therapy for COVID-19.	DB	1.77	1.74	−0.095	**0.57**	−0.057	0.118	−0.119	**0.585**	−0.065	0.062
25	784	I did not want to be around other people in the donor centre.	DB	1.75	1.96	−0.115	**0.532**	0.102	0.127	−0.124	**0.551**	0.098	0.101
38	768	I have been asked to donate convalescent plasma too often.	AB	1.84	1.90	0.021	**0.403**	0.136	0.079	0.039	**0.394**	0.123	0.177
42	769	I would have liked to know if I had anti-bodies before I made the donation.	AB	3.96	5.14	0.138	**0.243**	0.08	0.075	-	-	-	-

(Continues)

TABLE 2 (Continued)

Item number	*N*	Item	Survey section	Mean	Variance	Factors							
						Initial model				Revised model			
						Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre	Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre
15	811	Donating convalescent plasma could help me get back some sense of control over my life.	SM	2.98	3.03	−0.119	−0.086	**0.819**	0.025	−0.108	−0.05	**0.823**	0.028
16	813	Donating convalescent plasma would be a way to repay being saved.	MF	3.31	3.54	0.054	0.027	**0.732**	−0.028	0.064	0.015	**0.737**	−0.059
13	816	I have felt a little 'down' since recovery and donating convalescent plasma was something I could do to pull myself back up.	MF	3.17	3.28	−0.037	0.02	**0.726**	0.003	−0.025	0.016	**0.722**	0.004
17	801	Donating convalescent plasma was a way for me to get out of the house and see other people.	SM	2.47	2.71	−0.044	0.1	**0.543**	0.042	−0.048	0.133	**0.505**	0.02
14	815	Donating convalescent plasma was part of my civic duty.	MF	4.35	3.46	0.231	−0.139	**0.538**	0.098	0.25	−0.097	**0.552**	0.086
5	815	Donating convalescent plasma would make others feel more positively about me.	MF	4.11	2.55	**0.322**	0.112	**0.506**	0.036	-	-	-	-
9	817	I would have felt guilty if I did not sign up to donate convalescent plasma.	MF	3.56	3.38	0.232	0.045	**0.488**	−0.023	0.252	0.094	**0.476**	−0.002
20	800	Friends/family/people around me were encouraging me to donate.	SM	2.80	3.16	−0.051	0.068	**0.482**	−0.014	−0.043	0.097	**0.445**	−0.022
3	814	If convalescent plasma were available when I had COVID-19, then it could have helped me.	MF	3.83	3.44	0.111	0.065	**0.315**	−0.091	0.114	0.064	**0.317**	−0.072
18	802	I was not working or in school, so I had time to donate convalescent plasma.	SM	2.47	3.64	−0.186	0.085	**0.301**	−0.006	−0.172	0.105	**0.286**	−0.003
21	799	I'm a regular donor already so it made sense for me to donate convalescent plasma	SM	3.22	4.92	0.064	0.081	**0.165**	0.032	-	-	-	-

TABLE 2 (Continued)

						Factors							
						Initial model				Revised model			
Item number	*N*	Item	Survey section	Mean	Variance	Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre	Helping relationally	Donation deterrents	Social facilitators	Access to the donation centre
41	769	It was difficult for me to get to a centre to donate convalescent plasma.	AB	1.99	2.43	−0.012	0.049	−0.012	**0.779**	−0.012	0.011	−0.003	**0.96**
24	783	I did not want to travel to the donor centre to donate convalescent plasma.	DB	1.83	2.23	−0.139	0.249	−0.007	**0.664**	−0.201	0.301	−0.007	**0.516**
30	782	Logistically, it was just too difficult for me to donate convalescent plasma because of transportation challenges	DB	1.60	1.80	0.035	**0.413**	0.021	**0.632**	-	-	-	-
39	770	It was not easy for me to donate convalescent plasma given my other commitments.	AB	2.29	2.80	0.058	0.279	0.025	**0.411**	0.029	0.266	0.012	**0.468**
19	800	The donor centre was very close to me, so it was easy for me to donate	SM	3.07	3.31	0.128	0.126	**0.32**	**0.343**	-	-	-	-

Note: Initial Model fit indices: Chi-square test of model fit 1748.853 ($p < 0.001$); RMSEA = 0.058, CFI = 0.878, TLI = 0.850, SRMR = 0.038. Revised Model fit indices: Chi-Square test of model fit 919.662 ($p < 0.001$); RMSEA = 0.056, CFI = 0.918, TLI = 0.892, SRMR = 0.033.

Abbreviations: DB, deterrents and barriers to donating; AB, ability to donate convalescent plasma; SM, social motivations for donating; MF, motivators to, and facilitators of, donating convalescent plasma.

Bolding indicates the items loading on to each factor.

TABLE 3 Standardised factor loadings derived from confirmatory factor analysis

		Loadings	
Item number	**Item**	**Estimate**	**Standard error**
Factor 1: Helping relationally			
7	I like to help others, and donating convalescent plasma is just one way I could help.	0.801	0.038
11	Donating convalescent plasma could potentially help my family and friends if they became ill.	0.631	0.041
10	Donating convalescent plasma could help research into COVID-19 treatments.	0.805	0.038
4	Donating convalescent plasma would make me feel proud.	0.585	0.046
2	Through donating convalescent plasma, I could help others. (a)	0.819	0.045
12	Donating convalescent plasma was the morally right thing to do. (d)	0.483	0.063
1	I was in a unique position to help by donating convalescent plasma where other people could not. (a)	0.638	0.061
Factor 2: Donation deterrents			
8	I worried that donating convalescent plasma would mean I lost valuable antibodies that I still needed.	0.785	0.048
14	I worried I would become ill again if I donated convalescent plasma. (b)	0.879	0.037
13	If I donated convalescent plasma again, it would set my recovery back. (b)	0.852	0.045
6	I would have felt like a guinea pig if I donated convalescent plasma.	0.752	0.07
15	I worried that I might inadvertently infect others with COVID-19 through donating.	0.842	0.05
7	My friends and family would not have wanted me to donate convalescent plasma.	0.698	0.072
12	I needed more time to recover from COVID-19 before I could donate.	0.813	0.042
1	I was worried about getting re-infected if I donated convalescent plasma.	0.739	0.055
40	Donating convalescent plasma took too much of a toll on my body.	0.695	0.048
2	I did not really feel well enough to donate convalescent plasma.	0.79	0.037
11	Others who were fitter than me could donate convalescent plasma.	0.635	0.054
5	I did not think that convalescent plasma would be an effective therapy for COVID-19.	0.617	0.056
4	I did not want to be around other people in the donor centre. (c)	0.641	0.05
38	I have been asked to donate convalescent plasma too often.	0.537	0.064
Factor 3: Social facilitators			
15	Donating convalescent plasma could help me get back some sense of control over my life.	0.839	0.031
16	Donating convalescent plasma would be a way to repay being saved.	0.729	0.037
13	I have felt a little 'down' since recovery and donating convalescent plasma was something I could do to pull myself back up.	0.673	0.039
17	Donating convalescent plasma was a way for me to get out of the house and see other people.	0.507	0.051
14	Donating convalescent plasma was part of my civic duty. (d)	0.423	0.058
20	Friends/family/people around me were encouraging me to donate.	0.341	0.057
3	If convalescent plasma were available when I had COVID-19, then it could have helped me.	0.335	0.053
9	I would have felt guilty if I did not sign up to donate convalescent plasma.	0.406	0.055
18	I was not working or in school, so I had time to donate convalescent plasma.	0.235	0.058
Factor 4: Access to the donation centre			
41	It was difficult for me to get to a centre to donate convalescent plasma.	0.773	0.05
39	It was not easy for me to donate convalescent plasma given my other commitments.	0.605	0.062
3	I did not want to travel to the donor centre to donate convalescent plasma. (c)	0.808	0.04

Note: Items with matching letters were modelled to have correlated residual variances. Model fit: Chi-Square Test of model fit: 1090.267 ($p < 0.001$); RMSEA = 0.055; CFI = 0.889, TLI = 0.878, SRMR = 0.077.

TABLE 4 Intent to donate convalescent plasma and blood products models

	Intent to donate convalescent plasma								Intent to donate blood products							
	Model 1				Model 2				Model 1				Model 2			
Effect	Odds ratio	95% Confidence limits		*p* Value	Odds ratio	95% Confidence limits		*p* Value	Odds ratio	95% Confidence limits		*p* Value	Odds ratio	95% Confidence limits		*p* Value
Helping relationally	1.03	1.01	1.06	0.017	1.03	1.00	1.06	0.0627	1.05	1.02	1.09	0.0004	1.05	1.01	1.08	0.0042
Donation deterrents	0.98	0.96	1.00	0.015	0.98	0.96	0.99	0.0074	0.98	0.96	1.00	0.0389	0.98	0.96	1.00	0.019
Social facilitators	1.01	0.99	1.03	0.347	1.01	0.99	1.03	0.2772	1.01	0.99	1.03	0.3844	1.01	0.99	1.03	0.3803
Access to donation centre	1.00	0.95	1.05	0.912	1.00	0.95	1.05	0.9875	1.01	0.95	1.06	0.82	1.01	0.96	1.07	0.6896
Age 18–35 (vs. age 36–55)					1.17	0.81	1.69	0.3912					1.42	0.93	2.17	0.1078
Age > 55 (vs. age 36–55)					0.72	0.48	1.08	0.1093					0.71	0.46	1.11	0.1343
Woman (vs. man)					1.09	0.79	1.51	0.5806					1.13	0.78	1.62	0.5179
High school or less (vs. university)					1.15	0.54	2.44	0.7176					1.46	0.64	3.32	0.3679
College (vs. university)					1.16	0.78	1.71	0.4694					1.02	0.66	1.60	0.9148
other (vs. university)					0.79	0.52	1.19	0.254					1.14	0.69	1.90	0.611
Rural (vs. urban)					0.91	0.48	1.74	0.7758					1.00	0.50	2.01	0.9998
Donated in the past year					1.88	1.36	2.59	0.0001					4.72	2.92	7.65	<0.0001

that correlating the residual variances of several pairs of items would improve model fit. The three pairs of items with high modification index values were sequentially placed in the survey and spoke to a similar concept (e.g., 'I worried I would become ill again if I donated convalescent plasma' and 'If I donated convalescent plasma again, it would set my recovery back'); thus, modelling a correlation between the residual errors seemed reasonable. A fourth pair of items was not sequential, but similarly worded, speaking to types of duty (e.g., 'Donating convalescent plasma was the morally right thing to do' and 'Donating convalescent plasma was part of my civic duty'). We reasoned those concepts of moral and civic duty may have been understood similarly for many participants and that modelling a correlation between residual variances was justified. After adding the correlations, model fit was deemed adequate with two out of the four indices meeting recommended cutoffs (RMSEA = 0.055, CFI = 0.89, TLI = 0.88 and SRMR = 0.077). According to Kenny, if the RMSEA for the null model is <0.158, incremental fit indices (i.e., CFI/TLI) are not informative because of a mathematical fact that the null version of a model with an RMSEA of 0.05 and TLI of 0.90 must have had a RMSEA of 0.158.[31] As the null model had an RMSEA of exactly 0.158, very little improvement in the CFI/TLI would be possible. With this knowledge, we opted to avoid adding more ad hoc correlated errors and accepted the model with no further changes (Table 3).

5.3 | Internal consistency

Cronbach's alpha indicated good internal consistency for the overall scale ($\alpha = 0.84$) and each subscale (helping $\alpha = 0.88$; donation deterrents $\alpha = 0.95$; social facilitators $\alpha = 0.78$; access $\alpha = 0.78$). Similar results were found when calculating composite reliability, although the coefficient for the overall scale was higher ($\Sigma = 0.96$) and each subscale was slightly lower (helping $\Sigma = 0.86$; donation deterrents $\Sigma = 0.94$; social facilitators $\Sigma = 0.76$; access $\Sigma = 0.78$).

5.4 | Scale descriptives

The highest average item scores were found for the helping relationally subscale; scores for the donation deterrents subscale were lowest, and scores for the other social facilitators subscale were closest to neutral. The mean total scores for the subscales based on the 33-item scale were as follows: helping = 41.8 (SD = 7.1), donation deterrents = 21.9 (SD = 13.0), other social facilitators = 28.6 (SD = 9.9) and access = 6.0 (3.9).

5.5 | Prediction of intent to donate

Approximately two-thirds of study participants (67.0%) agreed with the statement that they would consider donating *plasma* as a regular donor going forward ($n = 501$), with mean score of 5.4 (SD = 1.7) out of 7. This proportion was slightly higher for participants agreeing with the statement that they would consider donating *blood products* as a regular donor going forward ($n = 630$, 77.0%), with a mean score of 5.7 (SD = 1.6) out of 7.

Intention to donate plasma was associated with higher scores on the helping relationally scale (Odds Ratio [OR] = 1.03; 95% CI = 1.01–1.06), and lower scores on the donation deterrents scale (OR = 0.98, 95% CI = 0.96–1). Neither of the social facilitators or access subscales were found to be independently associated with intent to donate convalescent plasma. A similar pattern of results was found when using intent to donate blood products as the outcome (Table 4). When adjusting for covariates, the deterrents scale remained significantly associated with intent to donate both convalescent plasma and blood products; however, helping relationally only remained a significant predictor of intent to donate blood products.

6 | DISCUSSION

With less than 5% of survey registrants being current plasma donors, the context of the pandemic and the clinical trial presented an opportunity for these registrants to become plasma donors. Understanding the motivations, deterrents, and intentions to donate from this group could provide insight into how to recruit future source plasma donors.

Our analysis revealed that motivators and deterrents of donating convalescent plasma could be grouped to represent four factors: 'helping relationally', 'deterrents to donation', 'social facilitators', and 'access to the donation centre'. Furthermore, some factors predicted intention to donate plasma in the future, while others did not. Importantly, 'helping relationally' was found to be a significant motivator of intention to donate plasma again. This subscale contained items relating to wanting to donate to help people who are ill with COVID-19 and to help their family and friends, indicating that helping is meaningful in relation to people they know, and to people who are ill. The motivation to help also extended to supporting a broader research community devoted to finding treatments. Furthermore, helping because it is morally right, or to feel proud, suggests that helping via donation makes the participant feel good about themselves. These reasons, that help is about relationships with others and about feeling positive about oneself, support the view that altruism is constructed relationally. Our analysis supports previous literature suggesting that donation is a social exchange,[8,13–16] particularly in a pandemic context where a person's family, friends and community could benefit from a treatment for COVID-19. In this study, helping was about a contribution to the community, which produced a sense that the donor was doing the right thing and generating a sense of pride.

These findings suggest that donating plasma can be more than a unidirectional act of giving, but also a critical contribution to one's community in a time of crisis. Blood collection was one of the few permitted activities during lockdowns, with proper safety precautions in place.[32] Our findings suggest that in a context where there are many restrictions on peoples' ability to offer help, donating convalescent plasma was one way they felt they could do their part. Furthermore, giving was connected to an interest in helping family members

that could become ill and benefit from treatment—a bidirectional relationship that signals the importance of community and social networks.[8] The act of supporting research on COVID-19 treatments also suggests an interest in contributing to finding a solution that could impact the whole community, indicating a level of reciprocity.[25] Our findings about helping others relationally are relevant in the sourcing of plasma to produce plasma protein products, such as immune globulin. While the clinical trial for convalescent plasma has closed, potential donors could be made aware of other lifesaving treatments produced with plasma protein products, and the impacts of those treatments for people in their communities.

Our findings concur with Masser and colleagues,[12] in that motivations were countered by fears about donating and the donation process, collectively understood as donation deterrents. The deterrents we measured indicated that participants were hesitant to donate during a pandemic and concerned about risks to their own health. Participants worried that they could become reinfected, or that donating convalescent plasma would set their recovery back. There was also a relational component to these concerns, as they involved the possibility of infecting others with COVID-19 through donation, or that others who are physically fitter were better candidates for donation. These findings resonate with the literature on donating convalescent plasma in the context of an epidemic,[33–35] suggesting that clinical trial perspectives are influenced by the contexts surrounding the relevant virus, and deserve further exploration.

'Access to the donation centre' did not predict intention to donate. While this could indicate that prospective donors were motivated to help others in a time of crisis despite any barriers to access, it may be more indicative of a study sample that did not face significant issues around travel or competing commitments. Most survey respondents reported high socio-economic status, including university-level education and high-income levels, and were predominantly white and heterosexual. As a convenience sample who volunteered to donate convalescent plasma and participate in research, the sample may represent those most able to engage with Canadian Blood Services. Further research should examine whether access to donation centres is significant for source plasma donors who are asked to consider donating on an ongoing basis.

Furthermore, the items termed 'social facilitators in a pandemic' did not predict intention to donate. Many of these motivations were specific to the COVID-19 context, such as getting back a sense of control, repaying being saved, getting out of the house, and feeling better after recovering from COVID-19. Since the nature of the COVID-19 context and 'crisis' differed across waves of infection, these items may not have fully captured all relevant social factors and contextual features across the entire pandemic period. Thus, these social facilitators to donation are likely highly context-specific, and it is understandable that they would not predict an interest in continuing donation outside of the specific crisis context.

Despite common rhetoric during the pandemic that 'we are all in this together,' we now understand that experiences of the pandemic and its impacts were highly stratified depending on social location, which has differentially affected working conditions and employment, caregiving responsibilities, housing, and health. Thus, further research is required to investigate the nature of motivators and deterrents, including issues of access related to distance, travel, cost, and competing commitments, across a more diverse sample and across various social locations.

This research contribution should be considered in light of the following limitations. To gather data in a timely way, we employed a convenience sampling method and had a low-response rate (35.1%). However, the analysis was adequately powered, and the results reflect the motivations and deterrents of those most motivated to engage with Canadian Blood Services and related activities, which is a meaningful sample even if compromised by selection bias. The study was also likely limited by recall bias, given that participants were asked to reflect on motivations and deterrents at the time that they signed up to the registry, which could have been up to 3 months to 1 year prior to survey administration. While the factor structure was validated internally using the random split sample approach, external validation of the scale will be needed to provide more robust evidence regarding dimensionality. Several items were found to cross-load and others had very low-loading values. It is possible that selecting a model with more factors would have resulted in less items being removed. However, as this was not a replication study, and given the important contextual differences, we sought to develop an instrument that could account for important aspects of the pandemic context, including social factors, to predict intentions to donate plasma going forward. Thus, we decided to select a model with high interpretability, rather than preserving all the original items. While the added social facilitator items when treated as a composite scale did not predict intent to donate, future research should try to determine whether these facilitators interact with measures of social position to produce more or less intention in different social groups. Finally, this clinical trial and the global pandemic were unprecedented and required a quick response from researchers wanting to measure its effects. Thus, we did not test the added items for face validity but relied on the scholarly literature in this area and theory on donation studies.

We investigated motivations and deterrents to donating convalescent plasma to better understand this unique donor population and determine if their motivations and deterrents were possible predictors of future intention to donate plasma outside of the context of a clinical trial. We applied a sociological lens to our analysis to consider how motivations and deterrents are situated in the social context, and how social relations inform motivations and deterrents. Participants in this study appeared to be motivated by an interest in helping others because they wanted to be a part of the solution to the pandemic, and they were in a unique position to help. Beyond the crisis context, these results suggest that blood service operators seeking to recruit source plasma donors should emphasise its lifesaving potential, particularly for people living with conditions for which plasma-derived medicines are indicated, its impact on their community, and the feeling of pride that one can gain from donation. Furthermore, in the context of a pandemic, blood services can mitigate deterrents by emphasising the extensive safety precautions that have been put in place at all blood donation centres across jurisdictions.

AUTHOR CONTRIBUTIONS

Conceptualization: Kelly Holloway, Jennie Haw, Quinn Grundy; *Methodology*: Kelly Holloway, Jennie Haw, Sarah Brennenstuhl, Quinn Grundy; *Formal analysis*: Kelly Holloway, Larkin Davenport Huyer, Sarah Brennenstuhl, Quinn Grundy, Dana Hart; *Investigation*: Kelly Holloway, Chantal Campbell, Ridwaanah Ali, Quinn Grundy; *Data curation*: Chantal Campbell, Sarah Brennenstuhl; *Writing—original draft*: Kelly Holloway; *Writing—review and editing*: Kelly Holloway, Chantal Campbell, Ridwaanah Ali, Larkin Davenport Huyer, Sarah Brennenstuhl, Jennie Haw, Quinn Grundy, Dana Hart; *Visualisation*: Chantal Campbell, Larkin Davenport Huyer, Sarah Brennenstuhl, Dana Hart; *Supervision*: Kelly Holloway, Quinn Grundy; *Project administration*: Chantal Campbell, Ridwaanah Ali; *Funding acquisition*: Kelly Holloway, Quinn Grundy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The full anonymous data set is available from the authors upon reasonable request.

ETHICS STATEMENT

This study was approved by the University of Toronto (Ref#: 40052) and the Canadian Blood Services (Ref #: 2020.056).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLES

Mapping anticipated advantages and disadvantages of implementation of extensive donor genotyping: A focus group approach

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Abstract

Background and objectives

Current genotyping techniques allow typing of all relevant red cell, human leukocyte and platelet antigens in a single analysis. Even genetic markers related to donor health can be added. Implementation of this technology will affect various stakeholders within the transfusion chain. This study aims to systematically map the anticipated advantages and disadvantages of a national rollout of blood group genotyping of donors.

Materials and methods

Two focus-group sessions were held with a wide representation of stakeholders, including representatives of donor and patient organisations. A dedicated software tool was used to collect the reflections of participants on genotyping for blood group antigens and extensive matching.

Results

From 162 statements collected, 59 statements (36%) were labelled as 'hopes' and 77 (48%) as 'fears'. Twenty-six (16%) statements remained unlabelled. The statements were divided in 18 categories under seven main themes: patient health, genotyping, privacy issues and ethical aspects, donor management, inventory management and logistics, hospital and transfusion laboratory and general aspects. The discussion on the propositions was analysed and summarised.

Conclusion

Stakeholders believe that a genotyped donor pool can result in a reduction of alloimmunization and higher availability of typed blood products. There are concerns regarding logistics, costs, consent for extended typing, data sharing, privacy issues and donor management. These concerns need to be carefully addressed before further implementation.

KEYWORDS

Blood donor, non-blood donors, transfusion

1 | INTRODUCTION

The demand for plasma products is constantly increasing all over the world and the need will rise in the future due to the significant increase of the need of patients with coagulopathy, immunological and metabolic diseases, as well as new treatments with plasma-derived medicines (http//apps.who.int/medicinedocs/en/d/Js21936 en/pdf, 2015).[1,2] About 9.3 million litres of recovered plasma are discarded in the world every year (http//apps.who.int/medicinedocs/en/d/Js21936 en/pdf, 2015).[2] In 2010, over 33 million litres of plasma were fractionated by 78 fractionators.[1] Countries without a domestic fractionation plant can perform contract plasma fractionation with fractionators abroad to decrease the plasma wastage and improve the access of patients to plasma-derived medicines (http//apps.who.int/medicinedocs/en/d/Js21936 en/pdf, 2015).[1,2]

The Iranian Blood Transfusion Organisation (IBTO) is a national non-profit, centralised organisation, which was established in 1974.

phase have been shown to transmit infections to recipients of red cells, platelets and plasma-derived blood products.[1] B19V is a small non-enveloped DNA virus, with three known genotypes that infect humans.[2] In immunocompetent individuals, B19V infections are largely asymptomatic although by targeting of erythroid progenitor cells in the bone marrow, B19V creates a temporary reduction in reticulocytes as well as in circulating lymphocytes, neutrophils and platelets.[3] More severe infection outcomes such as prolonged anaemia or transient aplastic crisis may therefore occur in those with pre-existing haematological diseases, such as sickle cell anaemia[4] or autoimmune haemolytic anaemia.[5] Infections acquired during early pregnancy (<18 weeks) may lead to hydrops fetalis.[6]

The intense viraemia that occurs during acute infections has led to documented instances of transfusion transmitted B19V infections, first described in the 1990s.[1] B19V may be transmitted by all blood components (red cells, platelets, fresh frozen plasma, cryoprecipitate) and also through pooled plasma products (reviewed in reference 7). The latter have a high probability of infectivity, given the large pool sizes and individual plasma donations with extremely high viral loads associated with primary infections up to 10^{14} DNA copies /ml[8,9];. These may contaminate an entire manufacturing pool. B19V infectivity is also relatively resistant to inactivation by heat, detergents or commercial pathogen inactivation methods such as Intercept (Cerus) during the fractionation process used to manufacture immunoglobulins and other products from plasma.[10,11] NAT screening to eliminate highly viraemic donations has therefore been widely adopted to reduce the possible risk of B19V transmission by plasma-derived products.[12–14] The European Pharmacopoeia accordingly specifies a requirement that plasma pools used for manufacturing, typically comprising between 6000 and 24 000 individual donations, should contain B19V DNA loads of less than 10 000 international units (IU)/ml.[15,16] This cut-off was determined based on calculations of residual infectivity following virus inactivation. It is mandatory to discard all final manufacturers' plasma pools exceeding these levels of B19V DNA.

Development of effective strategy for B19V screening of plasma destined for fractionation in the UK has become a priority. The use of UK-sourced plasma was discontinued in 1998 in response to concerns over the spread of variant Creutzfeldt Jakob Disease (vCJD). However, the absence of diagnosed cases of vCJD cases in the UK since 2016 after mandatory changes introduced in animal industry led to a comprehensive review of the evidence of the safety of UK plasma for the manufacture of immunoglobulins over 20 years later.[17] It concluded that it would be safe to use UK-sourced plasma providing robust safety standards and other risk mitigation measures remained in place.

However, re-starting plasma product manufacturing from UK-sourced plasma requires consideration of how plasma might be efficiently tested for B19V. A crucial decision is whether to implement testing of component plasma units to identify and exclude highly viraemic donations only (>10^6 IU ml^{-1}) that would contaminate final manufacturing pools over the regulatory threshold. To investigate this, we have evaluated a previously established RT-PCR assay for high-throughput quantitative detection of B19V DNA,[18] and generated baseline data on the incidence of B19V viraemia and associated viral loads in blood donors in England between 2017 and 2021. B19V variants in positive samples were genomically characterised to determine infecting genotypes and any potential epidemiological linkage between infected donors.

The time points were selected to further investigate potential changes in infection frequencies of B19V during the COVID pandemic; elsewhere, there is evidence that incidences of clinically reported cases of both have declined substantially during the prolonged periods of lockdown designed to interrupt the transmission of SARS-CoV-2.[19,20] We have explored the operational implications of introducing B19V screening if it was to be introduced in England for donor follow-up and potential lookback investigations.

2 | METHODS

2.1 | Quantitative B19V PCR

A previously described method for B19V DNA and HAV RNA detection by PCR was used.[18] Analytical sensitivities of the PCRs were determined for all three B19V genotypes by assaying serial dilutions of each WHO International Standard in 50 ng μL^{-1} DNA carrier (Table S1; Supporting Information). Probit analysis was used to determine the 95% limit of detection (LOD) for the assays using SPSS version 26.

International standards for the three B19V genotypes were obtained from the National Institute of Biological Standards and Control (NIBSC, London, UK; code 09/110).

2.2 | B19V testing

A volume of 200 μm of pools comprising 96 plasma samples were initially screened in replicate following nucleic acid extraction using the Quick-DNA/RNA Viral Kit (Zymo Research, Cambridge Bioscience, UK). One fifth of the eluate (representing 40 μl of original sample) was used in the PCR. Pools showing positive reactivity (Ct values <40) in one or both replicates were re-tested. Pools showing positivity in 3/4 or 4/4 combined replicates were assigned as positive; those showing reactivity in 1/4 replicates were assigned as negative. Those positive in 2/4 replicates were retested in replicate in a third PCR. Those showing reactivity in 3/6 or 4/6 of replicates were assigned as positive. Those negative on the third PCR were scored as negative (2/6 reactive overall).

Selected pools showing a range of viral loads were split into their eight component minipools of 12 plasma samples and nucleic acid was extracted from these minipools. Upon identification of one or more positive minipools of 12, the 12 individual samples within each were identified with individual sample PCR.

2.3 | B19V sequencing

B19V DNA from nine positive samples were amplified by nested primers using primers spanning the VP2 region and sequenced via

sanger sequencing (Table S1, Supporting Information). Sequence data were read between positions 3876 and 4953 (positions numbered relative to the AY386330 reference sequence) and compared with available B19V complete genome sequences in this region (sequences listed in Table S2, Supporting Information). Phylogenetic analysis of B19V nucleotide sequences was performed by using the program MEGA6.[21]

2.4 | B19V serology testing

Subsets of donor samples were assayed for B19V IgG ($n = 192$) and IgM ($n = 16$) antibodies using the Serion ELISA for parvovirus B19 IgG/IgM following the manufacturer's instructions (Wurzburg, Germany). Testing was extended to assay IgG and IgM antibodies in the 10 individual samples identified B19V DNA positive by screening. Samples were assigned as positive, indeterminate, or negative based on the manufacturer's criteria.

3 | SUBJECTS STUDIED

3.1 | Plasma samples and controls

Three groups of anonymised plasma samples were obtained from NHS Blood and Transplant (NHSBT):

a. Twenty nine thousand five hundred and ninety two archive donations collected in September 2017 in England in the pre-pandemic period.
b. Three thousand three hundred and sixty samples from plasma donors in 2020 enrolled in the SARS-CoV-2 convalescent antibody programme.
c. One thousand eight hundred residual NAT minipools each containing 24 samples (total 43 200 individual donations) collected betweenJanuary and February 2021 for HBV/HIV/HCV and HEV RNA screening by Roche Nucleic Acid Testing (NAT).

Although the sources of the 76 065 samples at the three points varied, this did not affect the representativeness of donors of blood and plasma over these periods as they were collected from a large number of geographically dispersed donor centres in England, and comparable in age ranges and gender.

3.2 | Ethical statement

Signed consent was obtained from each donor at the time of donation. This included consent to NHSBT to use their data for the purposes of clinical audit to assess and improve our services as well as to increase our knowledge of the donor population.

3.3 | Survey

The potential gain from the introduction of pre-testing of donations before manufacturers' pooling was evaluated against current practice in Europe. In the absence of published data on testing policies as regards to screening methods, assay sensitivities, viral load thresholds and actions taken in the event of positive donations being detected, we performed a survey of current screening practice in European Blood Establishments in September 2020.

4 | RESULTS

4.1 | Sensitivity and reproducibility of the B19V PCR

The analytical sensitivity of the B19V DNA assay was determined using dilution series of the WHO International Standards (Table S3, Supporting Information). From these, the 95% LODs were calculated by Probit analysis for the three B19V genotypes (Table 1). They ranged from 29 IU ml^{-1} in VP2 for B19V genotype 2 to 365 IU ml^{-1} for B19V genotype 1 using NS1 primers (Table 2).

Multiple testing of the B19V genotype 1 standard produced Ct values with relatively low variability between values on replicate testing (Table 2). For example, a mean Ct value of 28.16 and standard deviation (SD) of ±0.23 was recorded for 5000 IU (1.25×10^5 IU ml^{-1}) dilution of the genotype 1 standard using the NS1 primers and 27.36 (SD ± 0.48) for VP2. Inter-assay variability was comparable for other dilutions (Table 2).

TABLE 1 Sensitivity and reproducibility of B19V PCR—lower limits of detection

Virus	Region	IU	IU mL^{-1}[a]
B19V			
Genotype 1	NS1	14.6	365
	VP2	7.0	175
Genotype 2	NS1	1.3	38
	VP2	1.2	29
Genotype 3	NS1	4.2	105
	VP2	2.7	67

[a]Based on extraction of 200 µl of sample, elution into 50 µl of which 10 µl was amplified by PCR.

TABLE 2 Sensitivity and reproducibility of B19V PCR—assay Ct value and inter-sample variability

IU	N[a]	NS1[b]	VP2
5000	13	28.16 (0.23)	27.36 (0.48)
500	29	32.34 (1.23)	31.20 (0.97)
50	29	35.57 (1.79)	34.84 (1.89)
5	26	38.29 (1.14)	37.48 (1.12)

[a]N: number of replicates tested.
[b]Ct value: mean (± SD).

4.2 | Screening of blood donations

We screened 76 065 plasma samples in pools of 96 for B19V DNA; 29 505 from 2017, 3360 in 2020 and 43 200 in 2021. On initial screening of the 793 pools, a total of 80 positive pools were identified (Table 3; Table S4, Supporting Information). Viral loads obtained by NS1 and VP2 PCRs closely correlated (Figure 1A) and spanned a wide range from <100 to

TABLE 3 Detection frequencies of B19V DNA and HAV RNA in study samples—viraemia frequencies

Virus	Period	Donations	PCR Positive	Frequency	Total > 10^5 IU m^{-1}	Frequency	Sero-positivity
B19V	All	76 065	80	0.11%	2	0.003%	–
	2017	29 505	79	0.27%	2	0.007%	143/192
	2020	3360	1	0.030%	0	–	–
	2021	43 200	0	–	0	–	–

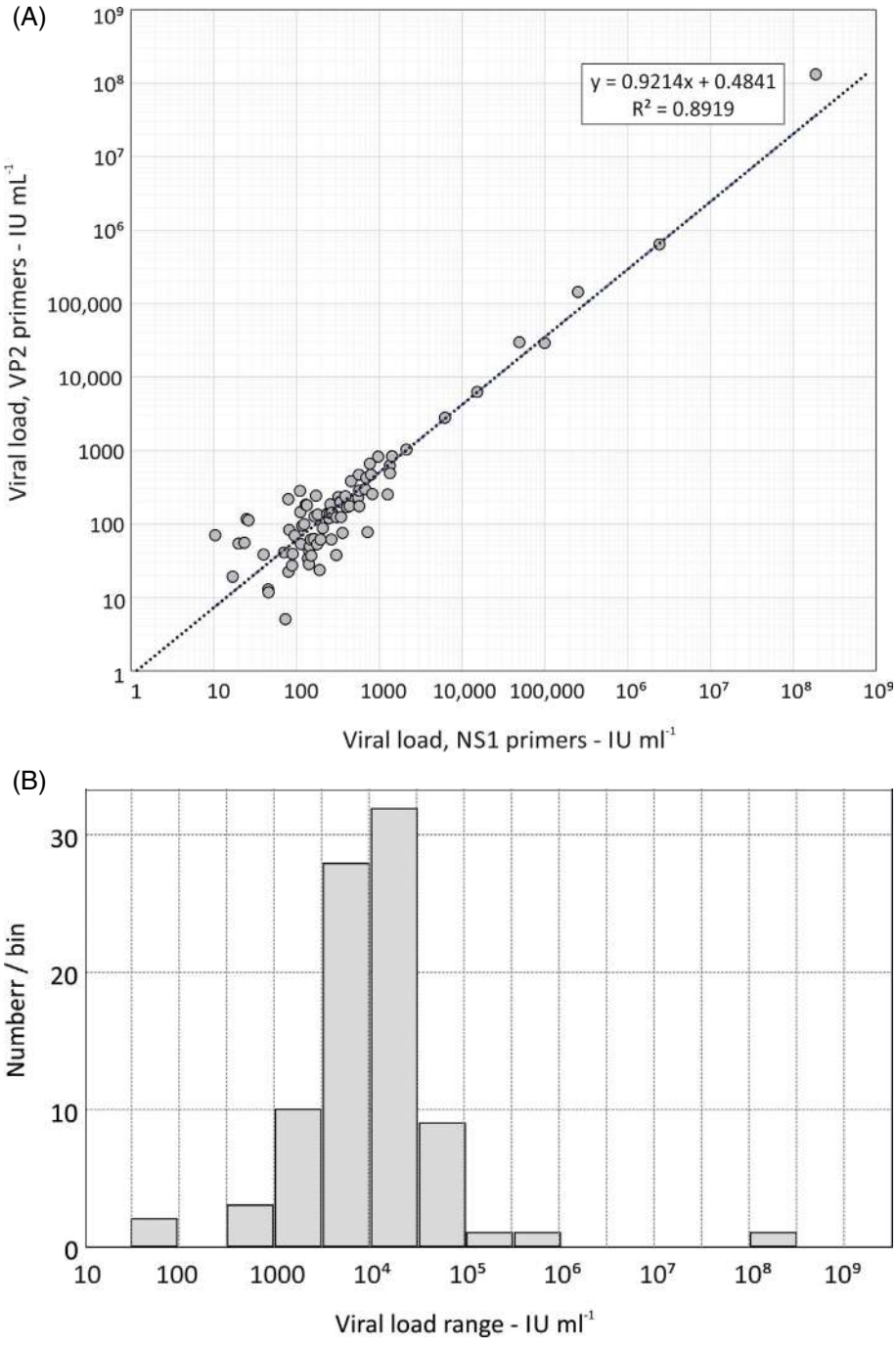

FIGURE 1 (A) Correlation between viral load quantitation in study samples in NS1 and VP2 B19V PCR assays. A regression line of log transformed viral loads in the two assays is shown as a dotted line; the formula for the regression line and correlation coefficient, R^2, are shown in the box. (B) Distribution of viral loads of study samples quantified by NS1 PCR. All viral loads of the B19V positive samples identified on screening were based on values calculated from individual testing or from pooled testing, expressed in IU ml^{-1} by reference to co-tested calibrated run controls of B19V genotype 1

TABLE 4 Detection frequencies of B19V DNA and HAV RNA in study samples—testing of component donations

Pool ID	Pools of 12[a]	Single[a]	Individual donation	NS1 VL[b]	VP2 VL[b]	B19V IgG[c]	B19V IgM[c]
A001	1	1	A001/A10	9.28×10^2	2.07×10^2	Pos (2.1)	Pos (3.2)
B081	1	1	B081/C3	1.25×10^4	2.97×10^4	Pos (2.8)	Neg (0.4)
B110	1	1	B110/C12	1.59×10^c	2.79×10^c	Pos (2.7)	Neg (0.5)
B112	1	1	B112/C2	nd	3.86×10^2	Pos (2.7)	Neg (0.2)
B122	1	2	B122/F2	1.96×10^b	6.60×10^b	Pos (2.6)	Neg (0.3)
			B122/F11	2.52×10^4	2.90×10^4	Pos (2.6)	Pos (1.8)
B219	1	1	B219/D11	4.77×10^7	1.32×10^8	Neg (0.1)	Neg (0.2)
B256	1	2	B256/G5	6.39×10^4	1.44×10^5	Pos (2.6)	Pos (3.2)
			B256/G12	3.89×10^3	6.27×10^3	Pos (2.6)	Neg (0.6)
B280	1	1	B280/E5	6.15×10^5	6.37×10^5	Pos (1.5)	Pos (3.4)

[a]Number of positive sub-pools on splitting.
[b]Units in IU ml^{-1}; shaded by viral loads.
[c]Net ODs after subtraction of substrate blank; shaded by reactivity; OD ranges for result assignments: IgG assay: positive (grey and black filled cells): >0.42; indeterminate: <0.42, >0.29; Negative: <0.29 (unfilled cells); IgM assay: positive: >0.41 (grey and black filled cells); indeterminate: <0.41, >0.29 (unfilled cells); Negative: <0.29 (unfilled cells).

>10^8 IU ml^{-1} (Figure 1B). Two samples containing high levels of B19V DNA (1.32×10^8 IU ml^{-1} and 6.37×10^5 IU mL^{-1} in the VP2-based PCR) were identified from donations collected in 2017 (1:14752). Apart from a single PCR-positive sample from 2020, all other B19 positive samples were also collected in 2017 (79:29505; 0.3%) (Table 3). The remaining sample with low-level B19V DNA was identified in convalescent plasma donor in 2020 (1:3360; 0.03%).

A selection of positive pools of 96 samples over a range of viral loads were split to individual samples of minipools and tested (Table 4); from these, 6 out of 8 minipools yielded single positive sample and the remaining two minipools yielded two. Viral loads in the samples were comparable to those calculated from pooled testing taking the dilution factor into account. Comparison of VP2 sequences from nine of the resolved single donation samples was performed to investigate potential epidemiological linkage between infected donors and rule out contamination as a cause of the observed positive test results. VP2 sequences from nine of the resolved single donation samples were all of genotype 1, but with little apparent linkage between strains infecting different donors (Figure S1, Supporting Information).

High rates of past exposure to B19V were apparent on testing a selection of individual samples from 2017 for B19V IgG antibodies by ELISA (Tables 3 and 4). The overall seropositivity was 74.5% (143/192 samples positive), with a further three showing equivocal reactivity. Individual positive samples identified through splitting pools were assayed for IgG and IgM anti-B19V antibodies by ELISA (Table 4). All seven samples with viral loads <10^5 IU ml^{-1} were seropositive for IgG and either negative or weakly reactive for IgM (2 negative, 2 indeterminate, 3 positive). This contrasts with 15/16 IgM negative, 1/16 IgM indeterminate in 16 randomly selected PCR negative donor samples (data not shown). Contrastingly, the sample with the highest viral load (1.3×10^8 IU ml^{-1}) was seronegative for IgG and IgM, while two samples with viral loads >10^5 IU ml^{-1} were IgG positive and strongly IgM positive, in all three cases consistent with proximity to seroconversion.

4.3 | Survey results

A total of 12 blood establishments providing plasma for fractionation, all members of the European Blood Alliance (EBA), responded to our donor survey. Testing methods (i.e. from individual [ID] NAT to pooling of up to 512 donations, commercial platforms or in-house methods) and policies for the initiation of clinical follow up of viraemic donors and blood component recipients varied greatly between centres (Table 5). Only one blood establishment provided plasma for fractionation without additional B19V testing. The fractionator performed B19V testing for five blood establishments in minipools, but without results being provided back to the blood establishment or blood donors in four cases. One blood establishment receiving results informed their donors of B19V results. Of the remaining six establishments, five undertake B19V testing of their own donations and one sends their samples to another country. A range of commercial (Roche, Grifols) and in-house assays were used. Pool sizes for screening were typically 96. Of these six, only one country informs the donors of their B19V result. None of the respondents of the survey indicated that their blood establishments informed recipients of transfused blood components of their exposure to B19V.

TABLE 5 Survey results of B19V and HAV screening practice in Europe

Country	Estonia	Belgium Croix-Rouge	Belgium Rode Kruis	Portugal	Italy	Switzerland	Finland	France	Germany	Austria	Netherlands	Slovenia
Plasma provided for fractionation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is plasma tested for B19V?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Who does B19V testing?	Fractionator	Fractionator	Fractionator	Fractionator	Fractionator	Referring Laboratories	In-house	In-house	In-house	Other	In-house	
What assay is used for B19V?	Not known	Not known	Not known	Not known	Not known	Commercial	Grifols	Grifols	Roche DPX		In-house	
Confirmatory testing for B19V?						No	No	No	No	No	No	
Pool size for HBV/HCV/HIV NAT?	ID	8	6	ID	ID	ID	ID	ID	96	96	6	ID
Pool size used for B19V testing	Not known	Not known	Not known	96	<512	ID NAT	16	96	96		480/96	
Do you inform donors of B19V result?	No[a]	No[a]	No[a]	Yes	No	Yes (letter)	No	No	No		No	
How long you exclude donor with B19?							None	None	2 months		2 weeks[b]	

[a]We do not receive parvovirus B19 results back from fractionator.
[b]Only if reported symptoms.

5 | DISCUSSION

Detection and quantitation of viraemia by PCR in blood donors provides one metric of the incidence of B19V infections in the survey population. The PCR assay for B19V DNA detection evaluated here showed a robust performance with the sensitivities and reproducibility as expected.[18] The information obtained in the study is vital for the rational planning of the introduction of B19V screening of UK-sourced plasma for manufacturing of medicines. In particular, knowledge of the current and likely future frequencies and viral loads of B19V viraemia are required to guide the choice of effective pool sizes for screening to ensure that final manufacturing pools are not contaminated with B19V leading to their discard.

The current study demonstrated a frequency of high-level B19V viraemia at 1:14 752 in donations collected in 2017 that was comparable to those reported elsewhere in similar screening formats.[22–24] For example, Kooistra et al.[22] reported viral loads of 10^{10} IU ml^{-1} in approximately 1:30 000 donations, >10^{9} IU ml^{-1} in 1:23 600 donations and > 10^{6} IU ml^{-1} in 1:16000 donations in an investigation of 6.5 million blood donations in the Netherlands between 2003 and 2009. B19V infections typically show a 3–4-year incidence cycle[23,25] with highest rates of B19V infection in 2013 and a lower peak in 2017.[25] However, rates of B19V DNA detection varied between countries, with Dutch blood donors showing more frequent peaks of high level viraemia in 2013, 2015, 2017 and 2019,[24] while B19V-associated cases of erythema infectiosum in Belarus peaked in only in 2006 and 2015/2016.[26] In B19V epidemic years more than 1 per 5000 donations have been shown to be viraemic, while only low levels of B19V DNA is evident in other times.[23–25] No B19V DNA was detected in blood donations collected in 2021 in this study and only one low-level positive in 2020. This virtual disappearance of B19V viraemia was much more marked than previously reported changes associated with the 2 or 4 yearly incidence cycle of B19V infections. As previously proposed,[24] implementation of infection control measures to prevent respiratory virus transmission during the COVID-19 pandemic may have had a major effect on B19V transmission too during periods of lockdown.

There was considerable variability of testing strategies for B19V in blood donations destined for fractionation by developed nations; for example NAT on minipools of varying sizes is employed by Germany and Austria, Belgium and the USA.[27] Furthermore, there are examples of alternative testing strategies to pooled NAT; for example, the Netherlands perform IgG testing on individual samples and thus deems plasma safe to use if B19V IgG positive for at least 6 months.[22] Japan performs a haemagglutination assay on individual donations for B19V antigen, with the possible imminent implementation of chemiluminescent enzyme immunoassay on pooled plasma.[28] In contrast, many developed countries do not currently test individual blood donations for B19V DNA, including China, Korea and Australia,[29] where they consider the risk of transfusion-transmitted B19V tolerable, as most transfusion-transmissions of B19V only manifest with mild or no clinical symptoms, and can be readily managed.

Of particular relevance for plasma product manufacturing and the regulations concerning acceptable viral loads in manufacturing pools, we report detection of two donors with high B19V viral loads measured by the VP2 PCR of 1.32×10^8 and 6.37×10^5 IU ml^{-1}. Assuming that manufacturers pool size is at least 6000 donations, B19V screening requires donations with B19V loads over 10^8 IU ml^{-1} to be excluded to avoid contamination of manufacturing pools above the 10^4 IU ml^{-1} threshold specified by the European Pharmacopoeia. In practice, we recommend that B19V screening of plasma prior to supply to manufacturers should identify donations containing B19V DNA loads above 10^6 IU ml^{-1}. This translates to a potential annual rate of around 68 from 2 million donations collected per year in England. This cut-off would provide a 2-log safety margin for screening and hence be capable of reliably detecting such donations while accommodating a parallel requirement not to detect low level of B19V viraemia seen in the much larger number of donations (0.3% in 2017), as their inclusion in manufacturing pools poses no transmission risk.[30,31] B19V DNA can indeed remain detectable in the blood of immunocompetent individuals at lower levels (<10^5 IU ml^{-1}) for months or even years after acute infection; based on one study up to 1% of blood donations contained low levels of B19V DNA[32] and as low as 0.006% in another.[22] B19V DNA is also known to remain detectable life-long in various tissues of immunocompetent adults after infection. These low levels of B19V DNA detected 6 months after the acute infection are considered to be non-infectious DNA remnants.[33] Furthermore, low-level viraemia usually coexists with parvovirus B19V IgG antibodies which will likely further neutralise any potential infectivity of the virus making inclusion of these units in manufacturing even less likely to lead to transmission. Since these donations contain neutralising B19V IgG antibodies· Their removal from fractionation might actually be disadvantageous as it would diminish B19V antibody levels in plasma pools and other plasma-derived products.

Based on our survey results, the proposed testing for B19V DNA in pools of 96 is compatible with plasma screening programmes established elsewhere in Europe. The Red Cross in Germany excluded donations with B19V DNA higher than 10^5 IU ml^{-1} whereas donations containing 2000 IU ml^{-1} of B19V DNA were excluded in Finland. In the Netherlands, the cut-off has been set to around 10^6 IU ml^{-1}. Irrespective of where such testing would be done (in-house, external laboratory or fractionator) and in contrast to some blood establishments in Europe, NHSBT has taken a view that positive results should be reported back to the blood donors and where these results relate to donations of whole blood, appropriate lookback investigations of recipients of blood components should be carried out. Although B19V infections are mostly asymptomatic, they can have severe consequences for an individual's health. Identification of donors with HAV infections or high level B19V viraemia will allow follow-up of potential vulnerable contacts, including immunocompromised individuals, pregnant women and those with underlying haematological disease. However, it is important to note that follow up of donors for mandatory markers also vary significantly across Europe, and by following up donors with high-level positive results, we generally aim to align ourselves to countries with similar epidemiological and public health surveillance systems.

In conclusion, our study provides the first systematic investigation of B19V viraemia frequencies and viral loads in English blood donors, and of the seropositivity for B19V that indicates the proportion susceptible to infection. These are relevant data that will help guide policy for operational screening and strategies for avoiding contaminated manufacturing for medicines pools. The ability to resolve positive pools to the level of individual positive samples enables notification and follow-up of both the infected donors and recipients of blood components produced from the donation. However, the likely retrospective nature of B19V screening may mean that results cannot be provided in time to prevent transfusion of viraemic units. Information on donor infection frequencies nevertheless could further contribute to public health surveillance.

AUTHOR CONTRIBUTIONS

HH conceived of the study and obtained funding and agreement from NHSBT for the project. SW, JR and DN performed the laboratroy work and analysis of the results. SW wrote the Methods section and part of the Results section. PS and HH performed further data analysis and co-wrote and finalised the manuscript.

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CONFLICT OF INTEREST

The authors have no competing interests.

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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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A physiology-based trigger score to guide perioperative transfusion of allogeneic red blood cells: A multicentre randomised controlled trial

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Abstract

Background: Restrictive blood transfusion is recommended by major guidelines for perioperative management, but requires objective assessment at 7–10 g/dl haemoglobin (Hb). A scoring system that considers the physiological needs of the heart may simply the practice and reduce transfusion.

Methods: Patients (14–65 years of age) undergoing non-cardiac surgery were randomised at a 1:1 ratio to a control group versus a Perioperative Transfusion Trigger Score (POTTS) group. POTTS (maximum of 10) was calculated as 6 plus the following: adrenaline infusion rate (0 for no infusion, 1 for ≤0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 2 for higher rate), FiO_2 to keep SpO_2 at ≥95% (0 for ≤35%, 1 for 36%–50%, and 2 for higher), core temperature (0 for <38°C, 1 for 38–40°C, and 2 for higher), and angina history (0 for no, 1 for exertional, and 2 for resting). Transfusion is indicated when actual Hb is lower than the calculated POTTS in individual patients. Transfusion in the control group was based on the 2012 American Association for Blood Banks (AABB) guideline. The primary outcome was the proportion of the patients requiring transfusion of allogeneic red blood cells (RBCs) during the perioperative period (until discharge from hospital), as assessed in the intention-to-treat (ITT) population (all randomised subjects).

Result: A total of 864 patients (mean age 44.4 years, 244 men and 620 women) were enrolled from December 2017 to January 2021 (433 in the control and 431 in the POTTS group). Baseline Hb was 9.2 ± 1.8 and 9.2 ± 1.7 g/dl in the control and POTTS

This study was registered at http://www.chictr.org.cn (#ChiCTR-INR-17014085).

groups, respectively. In the ITT analysis, the proportion of the patients receiving allogeneic RBCs was 43.9% (190/433) in the control group versus 36.9% (159/431) in the POTTS group ($p = 0.036$). Lower rate of allogeneic RBCs transfusion in the POTTS group was also evident in the per-protocol analysis (42.8% vs. 35.5%, $p = 0.030$). Transfusion volume was 4.0 (2.0, 6.0) and 3.5 (2.0, 5.5) units (200 ml/unit) in the control and POTTS groups, respectively ($p = 0.25$). The rate of severe postoperative complications (Clavien-Dindo grade IIIa and higher) was 3.9% in the control group versus 1.2% in the POTTS group ($p = 0.010$).

Conclusion: Transfusion of allogeneic RBCs based on the POTTS was safe and reduced the transfusion requirement in patients undergoing non-cardiac surgery.

KEYWORDS

blood transfusion, perioperative transfusion trigger score, restrictive blood transfusion

1 | INTRODUCTION

Restrictive blood transfusion is the golden standard for perioperative management in patients undergoing non-cardiac surgery. It has been recommended by a variety of professional societies and organisations, including American Society of Anesthesiologists (ASA), American Association of Blood Banks (AABB), Association of Anesthesiologists of the United Kingdom and Ireland (AAGBI), blood transfusion therapy of Miller's Anaesthesia, and Chinese Association of Anesthesiology. Haemoglobin (Hb) considered to be appropriate in initiating blood transfusion is either 6 or 7 g/dl.[1–5] In patients with Hb at a level between 7 and 10 g/dl, however, the decision requires subjective judgement based on a variety of factors, including cardiorespiratory fitness, metabolic rate, and the presence of active bleeding.

A scoring system that considers the physiological needs of the heart (referred to as the Perioperative Transfusion Trigger Score; POTTS) has been proposed in a previous study.[6] The POTTS is based on real-time assessment of the following four variables: adrenaline infusion rate to maintain adequate cardiac output (0 for no infusion, 1 for ≤0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 2 for higher rate), inspired oxygen concentration to maintain pulse oxygen saturation (SpO_2) at ≥95% (0 for ≤35%, 1 for 36%–50%, and 2 for higher), core body temperature (0 for <38°C, 1 for 38–40°C, and 2 for higher), and history of angina (0 for no, 1 for exertional, and 2 for resting). The POTTS score is calculated as 6 plus all subscores in the four variables. Red blood cells (RBCs) transfusion is indicated when the actual Hb value is less than the POTTS score.

2 | METHODS

2.1 | Patients

This multicentre, parallel-group randomised controlled trial was conducted at the Third Affiliated Hospital of Guangxi Medical University, Affiliated Hospital of Youjiang Medical University for Nationalities and Hospital of Guangxi Zhuang Autonomous Region during a period from December 2017 to January 2021 (http://www.chictr.org.cn; ChiCTR-INR-17014085). Trial protocol was approved by the Ethics Committees of all three participating centres. All participants provided written informed consent.

Patients (14–65 years of age) undergoing non-cardiac surgery (either emergency or elective) were eligible. Exclusion criteria included: (1) ASA grade of V or VI; (2) permanent residence at ≥2500 metres above the sea level; (3) severe haematological disorders (hemolytic anaemia, thalassemia, iron-deficiency anaemia, megaloblastic anaemia, and aplastic anaemia); (4) burn surgery; (5) any other reason deemed not appropriate for this trial by the investigator (e.g., language barrier, psychiatric disorders, unable to physically attend the scheduled follow-up).

2.2 | Randomisation, concealment and blinding

Written informed consent was obtained prior to surgery in patients at risk of Hb <10 g/dl during surgery, but randomisation (1:1 ratio) was performed only when the actual Hb decreased to <10 g/dl during surgery. The random sequence was generated using a centralised service (www.medresman.org.cn). Allogeneic RBCs transfusion in the control group was conducted based on the 2012 American Association of Blood Banks (AABB) Guideline. Briefly, transfusion was not recommended if Hb was >10 g/dl, always recommended at <7 g/dl, and decided based on the discretion of the attending physicians at 7–10 g/dl. Transfusion in the POTTS group was based on the POTTS score, calculated as 6 plus the following: adrenaline infusion rate (0 for no infusion, 1 for ≤0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 2 for higher rate), FiO_2 to keep $SpO_2 \geq 95\%$ (0 for ≤35%, 1 for 36%–50%, and 2 for higher), core temperature (0 for <38°C, 1 for 38–40°C, and 2 for higher), and angina history (0 for no, 1 for exertional, and 2 for resting).[6] Transfusion is indicated when actual Hb is lower than the calculated POTTS score in individual patients. The anaesthesiologists and surgeons in the trial were aware of the group assignment. Patients,

research staff who conducted the follow-up, as well as the statisticians were blinded to group allocation.

2.3 | Anaesthesia and surgery

Anaesthesia protocol (types of anaesthetic drugs, doses, methods of anaesthetic management, as well as ICU treatment) were based on the standard policy at each participating centre. All participating centres adopted limited fluid resuscitation.[7] Crystalloid solution was mainly sodium lactate Ringer's injection. Fluid expansion was conducted using hydroxyethyl starch 130/0.4 and 0.9% saline. The use of coagulation components (e.g., plasma, platelets, cryoprecipitate) was based on the AABB Guideline in both groups.[8,9] Intraoperative blood salvage transfusion was conducted for clean surgeries (e.g., orthopaedic, neurosurgical procedures, and bleeding from ruptured ectopic pregnancy) in patients with >400 ml expected bleeding using an autologous-P3000 blood recovery machine (Beijing Jingjing, Beijing, China). Recovered blood was heparinised at 200 U per 100 ml blood, centrifuged and washed prior to infusion.[10] Transfusion of allogeneic RBCs was always conducted after intraoperative blood salvage transfusion.

2.4 | Outcome assessment

The primary outcome was the proportion of patients receiving allogeneic RBCs transfusion, as assessed using an intention-to-treat principle. Secondary outcomes included: (1) transfusion volume; (2) transfusion-related complication; (3) severe surgery-related complications during hospital stay (Clavien-Dindo classification grade IIIa or higher)[11–13]; (4) Hb level upon discharge. The last follow-up was conducted at 12 weeks after the surgery.

2.5 | Sample size

Sample size calculation was based on the following assumptions: (1) transfusion of allogeneic RBCs in 45.5% in the control group, and

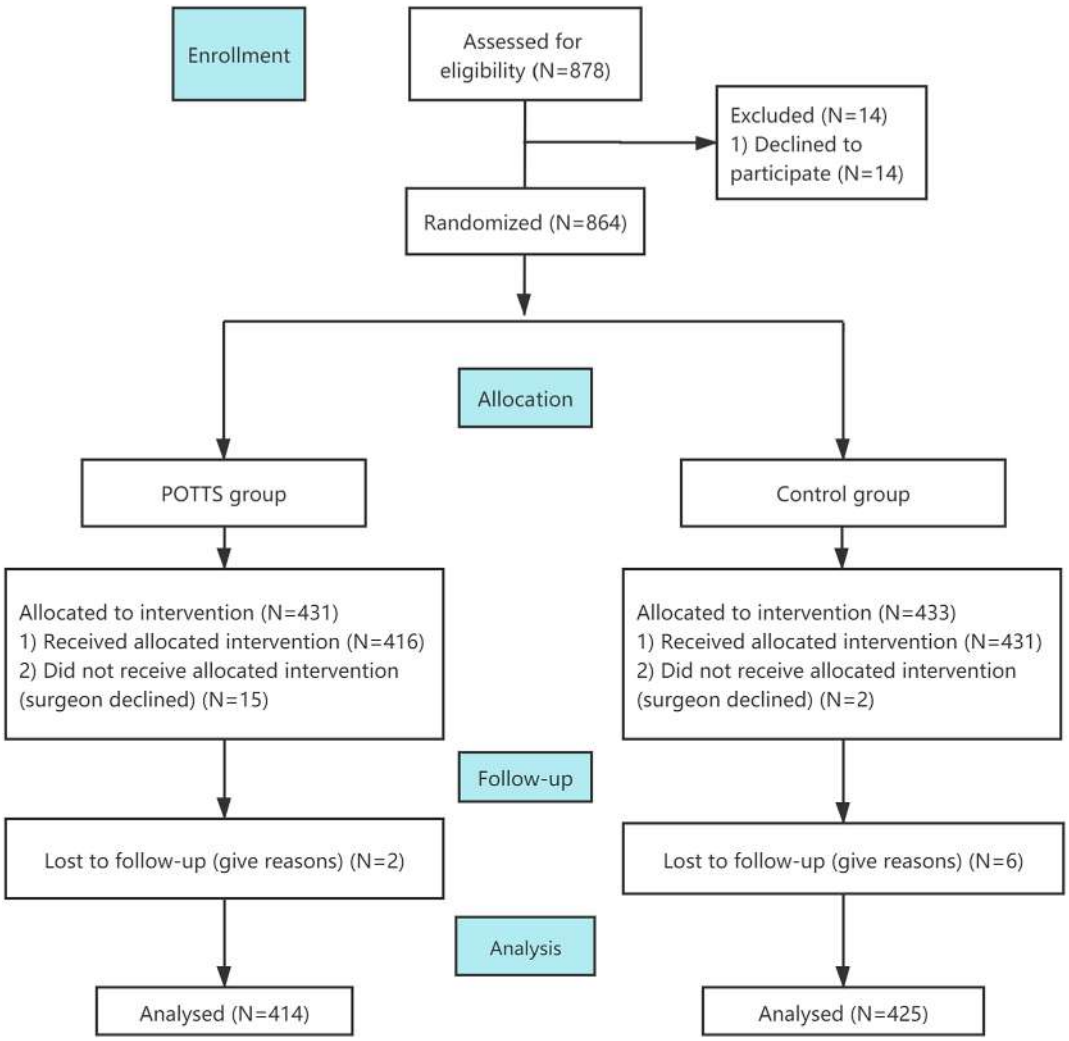

FIGURE 1 Flow diagram of the study

in 30.5% of the patients in the POTTS group (based on our pilot study); (2) single-side α of 0.025, power of 0.8, and a superiority margin of −0.10. The calculation yielded 390 patients in each group. Considering an estimated 20% dropout rate, 488 patients in each group are needed in each group.

2.6 | Statistical analysis

All statistical analyses were conducted using SPSS22.0 (IBM, Armonk, NY, USA). Normally distributed continuous variables are presented as mean ± standard deviation and analysed using Student's *t*-test. Non-normally distributed continuous variables are presented as median (interquartile range) and analysed using the Mann–Whitney test. Categorical variables are presented as proportions and analysed using the chi-square test. Statistically significant differences were defined as $p < 0.05$ (two-sided). The primary endpoint was assessed in the intention-to-treat (ITT) population (all randomised subjects) as well as in the per-protocol population (those who actually received the intended intervention).

3 | RESULTS

3.1 | Demographic and baseline characteristics

Patient flow through the trial is shown in Figure 1. Briefly, a total of 878 patients were screened from 28 December 2017 to 8 January 2021 and 864 patients were randomised. Demographics and baseline characteristics were generally comparable in the two groups (Table 1). The protocol was violated in 17 patients (2 and 15 patients in the control and POTTS groups, respectively) at the discretion of attending surgeons in surgical ward. Eight patients were lost to the follow-up (6 and 2 in the control and POTTS groups, respectively). The analysis included all randomised patients ($n = 864$).

TABLE 1 Demographic information and baseline characteristics

	POTTS ($n = 431$)	Restrictive transfusion ($n = 433$)
Male sex, *n* (%)	115 (26.7%)	129 (29.8%)
Age (y), mean ± standard deviation	44.6 ± 11.3	44.2 ± 10.9
Body mass index (kg/m^2), mean ± standard deviation	22.4 ± 3.0	22.3 ± 3.2
Preoperative Hb (g/dl), mean ± standard deviation	9.2 ± 1.7	9.2 ± 1.8
ASA class, *n* (%)		
I	68 (15.8%)	77 (17.8%)
II	290 (67.3%)	261 (60.3%)
III	63 (14.6%)	81 (18.7%)
IV	10 (2.3%)	14 (3.2%)
Co-morbidity, *n* (%)	84 (19.5%)	90 (20.8%)
Hypertension	36 (8.4%)	37 (8.5%)
Diabetes	22 (5.1%)	19 (4.4%)
Anaemia	14 (3.2%)	9 (2.1%)
Chronic hepatitis	10 (2.3%)	9 (2.1%)
Hepatic cirrhosis	2 (0.5%)	4 (0.9%)
Heart disease	16 (3.7%)	12 (2.8%)
NYHA classification, *n* (%)		
I	15 (3.5%)	9 (2.1%)
II	1(0.2%)	3 (0.7%)
III	0 (0%)	0 (0%)
IV	0 (0%)	0 (0%)

Abbreviations: ASA, American Society of Anesthesiologists; Hb, haemoglobin; NYHA, New York Heart Association; POTTS, Perioperative Transfusion Trigger Score.

3.2 | Surgery and anaesthesia

The two groups were comparable in surgery type (elective vs. emergency), specialty, malignant tumour surgery, anaesthesia method, and surgery time (Table 2).

3.3 | Intraoperative blood salvage transfusion

Blood loss, the proportion and volume of intraoperative blood salvage transfusion were similar between the two groups (Table 3).

3.4 | Allogeneic RBCs transfusion

In the ITT analysis, the rate of perioperative allogenic RBCs transfusion was 43.9% (190/433) in the control group versus 36.9% (159/431) in the POTTS group ($p = 0.036$; Table 4). Lower rate of allogeneic RBCs transfusion in the POTTS group was also evident in the per-protocol analysis (42.8% vs. 35.5%, $p = 0.030$). The POTTS group also had lower use of coagulation components (14.6% vs. 23.1%, $p = 0.001$), mainly plasma (14.4% vs. 22.6%, $p = 0.002$) and cryoprecipitate (1.6% vs. 3.9%, $p = 0.040$).

3.5 | Secondary outcomes

The rate of postoperative complications did not differ between the two groups (33 events in 21 patients in the control group versus 27 events in 24 patients in the POTTS group; Table 5). The complications included transient ischemic attack, pneumonia, hemopneumothorax requiring closed drainage, pleural effusion, deep vein thrombosis, hypertensive crisis, acute exacerbation of chronic bronchitis, respiratory failure requiring mechanical ventilation with tracheal intubation, anastomotic stoma and stricture

TABLE 2 Surgical information and anaesthesia methods

	POTTS ($n = 431$)	Restrictive transfusion ($n = 433$)	p
Type of surgery, *n* (%)			0.17
Elective	381 (88.4%)	369 (85.2%)	
Emergency	50 (11.6%)	64 (14.8%)	
Surgery time (min), median (IQR)	130 (80, 205)	130 (80, 220)	0.67
Surgical specialty, *n* (%)			0.30
Gynaecology	209 (48.5%)	201 (46.4%)	
Orthopaedics	75 (17.4%)	96 (22.2%)	
Gastrointestinal tract	49 (11.4%)	58 (13.4%)	
Urology	33 (7.7%)	19 (4.2%)	
Hepatobiliary and Pancreatic	27 (6.3%)	24 (5.5%)	
Obstetric	10 (2.3%)	10 (2.4%)	
Thoracic	7 (1.6%)	10 (2.4%)	
Thyroid and breast	7 (1.6%)	6 (1.4%)	
Otolaryngology	6 (1.4%)	2 (0.5%)	
Neurosurgery	5 (1.2%)	2 (0.5%)	
Others	3 (0.7%)	5 (1.2%)	
Malignant Tumour, *n* (%)	33 (7.7%)	30 (6.9%)	0.68
Anaesthesia methods, *n* (%)			0.91
General	403 (93.5%)	402 (92.8%)	
Intraspinal	24 (5.6%)	26 (6.0%)	
Nerve block	4 (0.9%)	5 (1.2%)	

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

TABLE 3 Intraoperative blood salvage transfusion

	POTTS ($n = 431$)	Restrictive transfusion ($n = 433$)	p
Blood loss (ml), median (IQR)	60 (20, 200)	100 (30, 300)	0.12
Intraoperative blood salvage transfusion (%)	35 (8.1%)	41 (9.5%)	0.48
Volume (ml), median (IQR)	750 (400, 1250)	750 (480, 1075)	0.87

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

TABLE 4 Perioperative blood transfusion

	POTTS ($n = 431$)	Restrictive transfusion ($n = 433$)	p
Allogenic red blood cells, *n* (%)	159 (36.9%)	190 (43.9%)	0.036
Amount (U), median (IQR)	3.5 (2.0, 5.5)	4.0 (2.0, 6.0)	0.25
Coagulation factor, *n* (%)	63 (14.6%)	100 (23.1%)	0.001
Plasma transfusion, *n* (%)	62 (14.4%)	98 (22.6%)	0.002
Volume (ml), median (IQR)	600 (400, 1000)	560 (400, 1013)	0.84
Cryoprecipitate transfusion, *n* (%)	7 (1.6%)	17 (3.9%)	0.040
Amount (U), median (IQR)	30 (10, 30)	10 (10, 20)	0.036
Platelet transfusion, *n* (%)	6 (1.4%)	11 (2.5%)	0.22
Amount (U), median (IQR)	1.0 (1.0, 2.3)	2.0 (1.0, 3.0)	0.41

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

after gastrointestinal surgery, intestinal obstruction, chronic osteomyelitis, urethral injury and stricture, mixed haemorrhoids requiring surgical treatment, and active bleeding requiring treatment. The rate of severe surgery-related complications (Clavien-Dindo grade IIIa and higher) was 1.2% in the control group versus 3.9% in the POTTS group ($p = 0.010$). Transfusion-

TABLE 5 Surgery-related complications, mortality, Hb level upon discharge, hospital stay

	POTTS ($n = 431$)	Restrictive transfusion ($n = 433$)	p
Complications			
patient, *n* (%)	24 (5.6%)	21 (4.8%)	0.65
event, *n*	27	33	0.43
Clavien-Dindo classification, *n* (%)			
I, II	12 (2.8%)	16 (3.7%)	0.45
IIIa and higher	5 (1.2%)	17 (3.9%)	0.010*
Mortality, *n* (%)	0 (0%)	1 (0.2%)	0.32
Hb upon discharge (g/dl), median (IQR)	8.5 (5.6, 10.7)	8.5 (4.5, 10.8)	0.43
Hospital stay (day), median (IQR)	14.0 (10.0, 22.0)	15.0 (9.0, 24.0)	0.80

Abbreviation: POTTS, Perioperative Transfusion Trigger Score.

related complication occurred in one patient in the control group (autoimmune haemolysis). The two groups did not differ in Hb levels upon discharge (Table 5).

One patient (a 54-year-old man) in the control group died on the third day after surgery due to upper gastrointestinal bleeding, hemorrhagic shock, and eventually acute respiratory distress syndrome and multiple organ failure.

4 | DISCUSSION

The results from this trial demonstrated that using POTTS as a trigger for perioperative transfusion could reduce the rate of allogeneic RBCs transfusion, without increasing severe surgery-related complications. Lower rate of allogeneic RBCs transfusion was apparent in both the ITT analysis (36.9% vs. 43.9% with restrictive transfusion in the control group, $p = 0.036$) and per-protocol analysis (35.5% vs. 42.8% with restrictive transfusion in the control group, $p = 0.030$).

Allogeneic RBCs transfusion can be lifesaving,[14] but also carries the risk of transfusion-related complications, including transfusion reaction,[15] blood related diseases,[16,17] allergic reaction,[18,19] transfusion-related acute lung injury,[20,21] and transfusion-related circulatory overload.[22–24] Previous studies in patients undergoing orthopaedic surgery showed that improper blood transfusion increases the medical costs.[25,26] In patients undergoing surgery for cancers, improper intraoperative blood transfusion may lead to poor oncologic outcomes and reduce quality of life.[27–32] The risks and benefits of blood transfusion must be carefully weighed.[33]

Another factor that must be considered in blood transfusion is the increasing need for blood transfusion. Since 2015, the number of surgeries in China has been increasing by about 10% per year.[34] In contrast, the increase of blood supply is <3%.[35–37]

Significant research efforts have been devoted to individualise and refine blood transfusion.[38] For example, a revised patient blood management (PBM) programme was launched at Cardiac Surgery Department of Eastern Maine Medical Center and Korea University Anam Hospital to minimise RBCs transfusion.[39,40] The PBM programme relies on three key strategies to achieve its goals: optimise erythropoiesis, minimise blood loss, and manage anaemia.[41] The PBM strategy has since been incorporated in other parts of the world, including the USA, Austria, Australia and Netherlands.[42] Tranexamic acid has also been shown to consistently reduce RBCs transfusion in a wide range of surgical populations.[43] Despite of these advances, Hb at a level between 7 and 10 g/dl represent an area for further refinement in perioperative blood transfusion. The POTTS system included four variables that are readily available during routine practice.[33] All four measures reflects the balance between oxygen supply and demand.[44] Adrenaline infusion reflects insufficient CO. The current study was a proof-of-concept trial that attempted to validate a physiology-based score in managing perioperative blood transfusion. If the concept is validated, the score could be further adjusted for use in centres where vasopressors other than adrenaline is used frequently.

In a previous trial in patients undergoing elective spine surgery with expected blood loss more than 800 ml or exceeding 20% total blood volume,[6,45] the rate of RBCs transfusion was 36.5% in the POTTS group versus 89.4% in the control group with liberal transfusion strategy. The current study compared POTTS versus restrictive blood transfusion, a strategy recommended by major guidelines and widely used in clinical practice. Also, we included emergency surgery in this trial. As a result, reduced RBCs transfusion observed in this trial is more relevant to the real world.

In contrast to reduced transfusion volume with POTTS in a previous trial by Zhu et al,[46] transfusion volume did not differ between the two groups in the current study. Such a discrepancy may be attributed to several reasons, including higher percentage of transfusion due to higher percentage of patients with cancer in the previous trial, and the use of intraoperative blood salvage in the current study.

In a retrospective case–control study of 1049 patients, Hua Xiao et al[47] found that perioperative blood transfusion (OR = 2.13, 95% CI: 1.38–3.29, $p < 0.01$) is an independent risk factor of complications. In another retrospective study of 250 consecutive patients who underwent curative gastric resection for stage II/III gastric cancer, Kanda et al.[30] also showed that blood transfusion is an independent prognostic factor for shorter long-term survival. Consistent with these studies, surgery-related complications did not differ significantly between the two groups in this trial, but the POTTS group had lower

rate of Clavien-Dindo grade IIIa or higher complications (1.2% vs. 3.9% in the control group).

Despite of the lower rate of blood transfusion in the POTTS group, Hb level upon discharge did not differ between the two groups in this trial. Possible reasons for such a phenomenon may include: (1) small amount of blood loss during surgery (100-ml median); (2) 48.5% in the POTTS group and 46.4% in the control group were gynaecological surgery, and postoperative anaemia management of such surgery was often associated with the use of intravenous iron and erythropoiesis-stimulating agents.

The median length of hospital stay was 14.0 and 15.0 days in the POTTS group and control group ($p = 0.80$), respectively (Table 5). The length of hospital stay in this trial was indeed longer than expected in most Western health systems. This could be a source of bias, but in our opinion, does not necessarily undermine either the validity or generalisability of the results since most transfusion occur during the surgery and early days after the surgery.

Other blood products (plasma, cryoprecipitate, platelet) are often transfused together with RBCs in clinical practice. Consistent with the lower rate of allogeneic RBCs transfusion, the use of plasma and cryoprecipitate was lower in the POTTS group than in the control group in this trial. Correlation analysis revealed that consumption of plasma was positively correlated with consumption of RBCs during perioperative period, which suggested that RBCs and plasma were bundling administrated in clinical practice in three centres, and widespread application of POTTS in surgical patients would reduce the RBCs and plasma use. The median of cryoprecipitate transfusion in POTTS group was higher was because of one patient due to cirrhotic patients and oesophagogastric varices underwent laparoscopic total splenectomy, a total of 100 units of cryoprecipitate was infused during the perioperative period. If this patient was excluded, the median of cryoprecipitate transfusion was 25 (10, 30) and 10 (10, 20) units in the POTTS and control groups, respectively ($p = 0.329$).

A major limitation in the current study is that we only included adrenaline but not other types of vasopressors. Secondly, the lack of SvO_2 and lactate metabolism indices is another limitation because of the limited budget. Finally, long-term outcomes will be observed in the long follow-up (more than 12 weeks). More trials are needed in the future.

5 | CONCLUSIONS

This trial demonstrated that a physiology-based score system for perioperative transfusion (POTTS) could reduce the requirement for allogeneic RBCs without increasing severe surgery-related complications in patients undergoing non-cardiac surgery.

AUTHOR CONTRIBUTIONS

Kejian Lu and Zehan Huang prepared and written the manuscript. Yanjuan Huang and Ren Liao contributed to the design and development of the study protocol. Zehan Huang, Ailan Huang and Yanjuan Huang supervised and revised the manuscript. Yanjuan Huang, Zehan Huang and Ailan Huang were the head of the three centres and they were responsible for the data of centre respectively. Shucong Liang, Fengting Pan, Huijun Wei participated in the enrollment of patients, execution of the study and management. Jinqing Wei, Chunying Zhang and Yafeng Huang collected the data and follow-up. All authors reviewed the results and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

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Detection frequencies and viral load distribution of parvovirus B19 DNA in blood and plasma donations in England

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Abstract

Background and Objectives: Infections with human parvovirus B19 (B19V) are transmissible by blood components and plasma-derived medicines. The European Pharmacopoeia regulates maximum levels of virus allowed in manufacturers' plasma pools. To evaluate contamination risk prior to re-introduction of UK-sourced plasma for manufacturing, we investigated viraemia frequencies of B19V in plasma samples collected from blood donors before and during COVID-enforced lockdown.

Materials and Methods: Quantitative PCR for B19V DNA was used to screen pools of 96 anonymised plasma samples collected in England from 2017 ($n = 29\,505$), 2020 ($n = 3360$) and 2021 ($n = 43\,200$). Selected positive pools were resolved into individual samples. Data on donor notifications and related lookback investigations were collected from European countries by on-line survey in 2020.

Results: Screening of 76 065 donations identified 80 B19V-positive pools. While most positive samples had low viral loads ($<10^5$ IU ml^{-1}), primarily from 2017 (77/29 505; 0.3%), two contained high levels of B19V DNA (1.3×10^8 and 6.3×10^6 IU ml^{-1}), both likely to contaminate a final manufacturer's pool and lead to discard. The incidence of B19V infection during lockdown was reduced (1/3360 in 2020; 0/43 200 in 2021). Genomic analysis of positive pools resolved to single samples identified B19V genotype 1 in all nine samples. Seroprevalence of anti-B19V IgG antibodies was 75% (143/192). A survey of B19V screening practices in Europe demonstrated considerable variability. Two blood establishments informed infected blood donors of positive B19V results.

Conclusion: Information on seroprevalence, incidence and viral loads of B19V viraemia is contributory the evaluation of alternative operational screening strategies for plasma testing.

1 | INTRODUCTION

Infections with human parvovirus B19 (B19V) are associated with intense viraemia and blood donations collected during the acute

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phase have been shown to transmit infections to recipients of red cells, platelets and plasma-derived blood products.[1] B19V is a small non-enveloped DNA virus, with three known genotypes that infect humans.[2] In immunocompetent individuals, B19V infections are largely asymptomatic although by targeting of erythroid progenitor cells in the bone marrow, B19V creates a temporary reduction in reticulocytes as well as in circulating lymphocytes, neutrophils and platelets.[3] More severe infection outcomes such as prolonged anaemia or transient aplastic crisis may therefore occur in those with pre-existing haematological diseases, such as sickle cell anaemia[4] or autoimmune haemolytic anaemia.[5] Infections acquired during early pregnancy (<18 weeks) may lead to hydrops fetalis.[6]

The intense viraemia that occurs during acute infections has led to documented instances of transfusion transmitted B19V infections, first described in the 1990s.[1] B19V may be transmitted by all blood components (red cells, platelets, fresh frozen plasma, cryoprecipitate) and also through pooled plasma products (reviewed in reference 7). The latter have a high probability of infectivity, given the large pool sizes and individual plasma donations with extremely high viral loads associated with primary infections up to 10^{14} DNA copies /ml[8,9];. These may contaminate an entire manufacturing pool. B19V infectivity is also relatively resistant to inactivation by heat, detergents or commercial pathogen inactivation methods such as Intercept (Cerus) during the fractionation process used to manufacture immunoglobulins and other products from plasma.[10,11] NAT screening to eliminate highly viraemic donations has therefore been widely adopted to reduce the possible risk of B19V transmission by plasma-derived products.[12–14] The European Pharmacopoeia accordingly specifies a requirement that plasma pools used for manufacturing, typically comprising between 6000 and 24 000 individual donations, should contain B19V DNA loads of less than 10 000 international units (IU)/ml.[15,16] This cut-off was determined based on calculations of residual infectivity following virus inactivation. It is mandatory to discard all final manufacturers' plasma pools exceeding these levels of B19V DNA.

Development of effective strategy for B19V screening of plasma destined for fractionation in the UK has become a priority. The use of UK-sourced plasma was discontinued in 1998 in response to concerns over the spread of variant Creutzfeldt Jakob Disease (vCJD). However, the absence of diagnosed cases of vCJD cases in the UK since 2016 after mandatory changes introduced in animal industry led to a comprehensive review of the evidence of the safety of UK plasma for the manufacture of immunoglobulins over 20 years later.[17] It concluded that it would be safe to use UK-sourced plasma providing robust safety standards and other risk mitigation measures remained in place.

However, re-starting plasma product manufacturing from UK-sourced plasma requires consideration of how plasma might be efficiently tested for B19V. A crucial decision is whether to implement testing of component plasma units to identify and exclude highly viraemic donations only (>10^6 IU ml^{-1}) that would contaminate final manufacturing pools over the regulatory threshold. To investigate this, we have evaluated a previously established RT-PCR assay for high-throughput quantitative detection of B19V DNA,[18] and generated baseline data on the incidence of B19V viraemia and associated viral loads in blood donors in England between 2017 and 2021. B19V variants in positive samples were genomically characterised to determine infecting genotypes and any potential epidemiological linkage between infected donors.

The time points were selected to further investigate potential changes in infection frequencies of B19V during the COVID pandemic; elsewhere, there is evidence that incidences of clinically reported cases of both have declined substantially during the prolonged periods of lockdown designed to interrupt the transmission of SARS-CoV-2.[19,20] We have explored the operational implications of introducing B19V screening if it was to be introduced in England for donor follow-up and potential lookback investigations.

2 | METHODS

2.1 | Quantitative B19V PCR

A previously described method for B19V DNA and HAV RNA detection by PCR was used.[18] Analytical sensitivities of the PCRs were determined for all three B19V genotypes by assaying serial dilutions of each WHO International Standard in 50 ng μL^{-1} DNA carrier (Table S1; Supporting Information). Probit analysis was used to determine the 95% limit of detection (LOD) for the assays using SPSS version 26.

International standards for the three B19V genotypes were obtained from the National Institute of Biological Standards and Control (NIBSC, London, UK; code 09/110).

2.2 | B19V testing

A volume of 200 μm of pools comprising 96 plasma samples were initially screened in replicate following nucleic acid extraction using the Quick-DNA/RNA Viral Kit (Zymo Research, Cambridge Bioscience, UK). One fifth of the eluate (representing 40 μl of original sample) was used in the PCR. Pools showing positive reactivity (Ct values <40) in one or both replicates were re-tested. Pools showing positivity in 3/4 or 4/4 combined replicates were assigned as positive; those showing reactivity in 1/4 replicates were assigned as negative. Those positive in 2/4 replicates were retested in replicate in a third PCR. Those showing reactivity in 3/6 or 4/6 of replicates were assigned as positive. Those negative on the third PCR were scored as negative (2/6 reactive overall).

Selected pools showing a range of viral loads were split into their eight component minipools of 12 plasma samples and nucleic acid was extracted from these minipools. Upon identification of one or more positive minipools of 12, the 12 individual samples within each were identified with individual sample PCR.

2.3 | B19V sequencing

B19V DNA from nine positive samples were amplified by nested primers using primers spanning the VP2 region and sequenced via

sanger sequencing (Table S1, Supporting Information). Sequence data were read between positions 3876 and 4953 (positions numbered relative to the AY386330 reference sequence) and compared with available B19V complete genome sequences in this region (sequences listed in Table S2, Supporting Information). Phylogenetic analysis of B19V nucleotide sequences was performed by using the program MEGA6.[21]

2.4 | B19V serology testing

Subsets of donor samples were assayed for B19V IgG ($n = 192$) and IgM ($n = 16$) antibodies using the Serion ELISA for parvovirus B19 IgG/IgM following the manufacturer's instructions (Wurzburg, Germany). Testing was extended to assay IgG and IgM antibodies in the 10 individual samples identified B19V DNA positive by screening. Samples were assigned as positive, indeterminate, or negative based on the manufacturer's criteria.

3 | SUBJECTS STUDIED

3.1 | Plasma samples and controls

Three groups of anonymised plasma samples were obtained from NHS Blood and Transplant (NHSBT):

a. Twenty nine thousand five hundred and ninety two archive donations collected in September 2017 in England in the pre-pandemic period.
b. Three thousand three hundred and sixty samples from plasma donors in 2020 enrolled in the SARS-CoV-2 convalescent antibody programme.
c. One thousand eight hundred residual NAT minipools each containing 24 samples (total 43 200 individual donations) collected betweenJanuary and February 2021 for HBV/HIV/HCV and HEV RNA screening by Roche Nucleic Acid Testing (NAT).

Although the sources of the 76 065 samples at the three points varied, this did not affect the representativeness of donors of blood and plasma over these periods as they were collected from a large number of geographically dispersed donor centres in England, and comparable in age ranges and gender.

3.2 | Ethical statement

Signed consent was obtained from each donor at the time of donation. This included consent to NHSBT to use their data for the purposes of clinical audit to assess and improve our services as well as to increase our knowledge of the donor population.

3.3 | Survey

The potential gain from the introduction of pre-testing of donations before manufacturers' pooling was evaluated against current practice in Europe. In the absence of published data on testing policies as regards to screening methods, assay sensitivities, viral load thresholds and actions taken in the event of positive donations being detected, we performed a survey of current screening practice in European Blood Establishments in September 2020.

4 | RESULTS

4.1 | Sensitivity and reproducibility of the B19V PCR

The analytical sensitivity of the B19V DNA assay was determined using dilution series of the WHO International Standards (Table S3, Supporting Information). From these, the 95% LODs were calculated by Probit analysis for the three B19V genotypes (Table 1). They ranged from 29 IU ml^{-1} in VP2 for B19V genotype 2 to 365 IU ml^{-1} for B19V genotype 1 using NS1 primers (Table 2).

Multiple testing of the B19V genotype 1 standard produced Ct values with relatively low variability between values on replicate testing (Table 2). For example, a mean Ct value of 28.16 and standard deviation (SD) of ±0.23 was recorded for 5000 IU (1.25×10^5 IU ml^{-1}) dilution of the genotype 1 standard using the NS1 primers and 27.36 (SD ± 0.48) for VP2. Inter-assay variability was comparable for other dilutions (Table 2).

TABLE 1 Sensitivity and reproducibility of B19V PCR—lower limits of detection

Virus	Region	IU	IU mL^{-1}[a]
B19V			
Genotype 1	NS1	14.6	365
	VP2	7.0	175
Genotype 2	NS1	1.3	38
	VP2	1.2	29
Genotype 3	NS1	4.2	105
	VP2	2.7	67

[a]Based on extraction of 200 µl of sample, elution into 50 µl of which 10 µl was amplified by PCR.

TABLE 2 Sensitivity and reproducibility of B19V PCR—assay Ct value and inter-sample variability

IU	N[a]	NS1[b]	VP2
5000	13	28.16 (0.23)	27.36 (0.48)
500	29	32.34 (1.23)	31.20 (0.97)
50	29	35.57 (1.79)	34.84 (1.89)
5	26	38.29 (1.14)	37.48 (1.12)

[a]N: number of replicates tested.
[b]Ct value: mean (± SD).

4.2 | Screening of blood donations

We screened 76 065 plasma samples in pools of 96 for B19V DNA; 29 505 from 2017, 3360 in 2020 and 43 200 in 2021. On initial screening of the 793 pools, a total of 80 positive pools were identified (Table 3; Table S4, Supporting Information). Viral loads obtained by NS1 and VP2 PCRs closely correlated (Figure 1A) and spanned a wide range from <100 to

TABLE 3 Detection frequencies of B19V DNA and HAV RNA in study samples—viraemia frequencies

Virus	Period	Donations	PCR Positive	Frequency	Total > 10^5 IU m^{-1}	Frequency	Sero-positivity
B19V	All	76 065	80	0.11%	2	0.003%	–
	2017	29 505	79	0.27%	2	0.007%	143/192
	2020	3360	1	0.030%	0	–	–
	2021	43 200	0	–	0	–	–

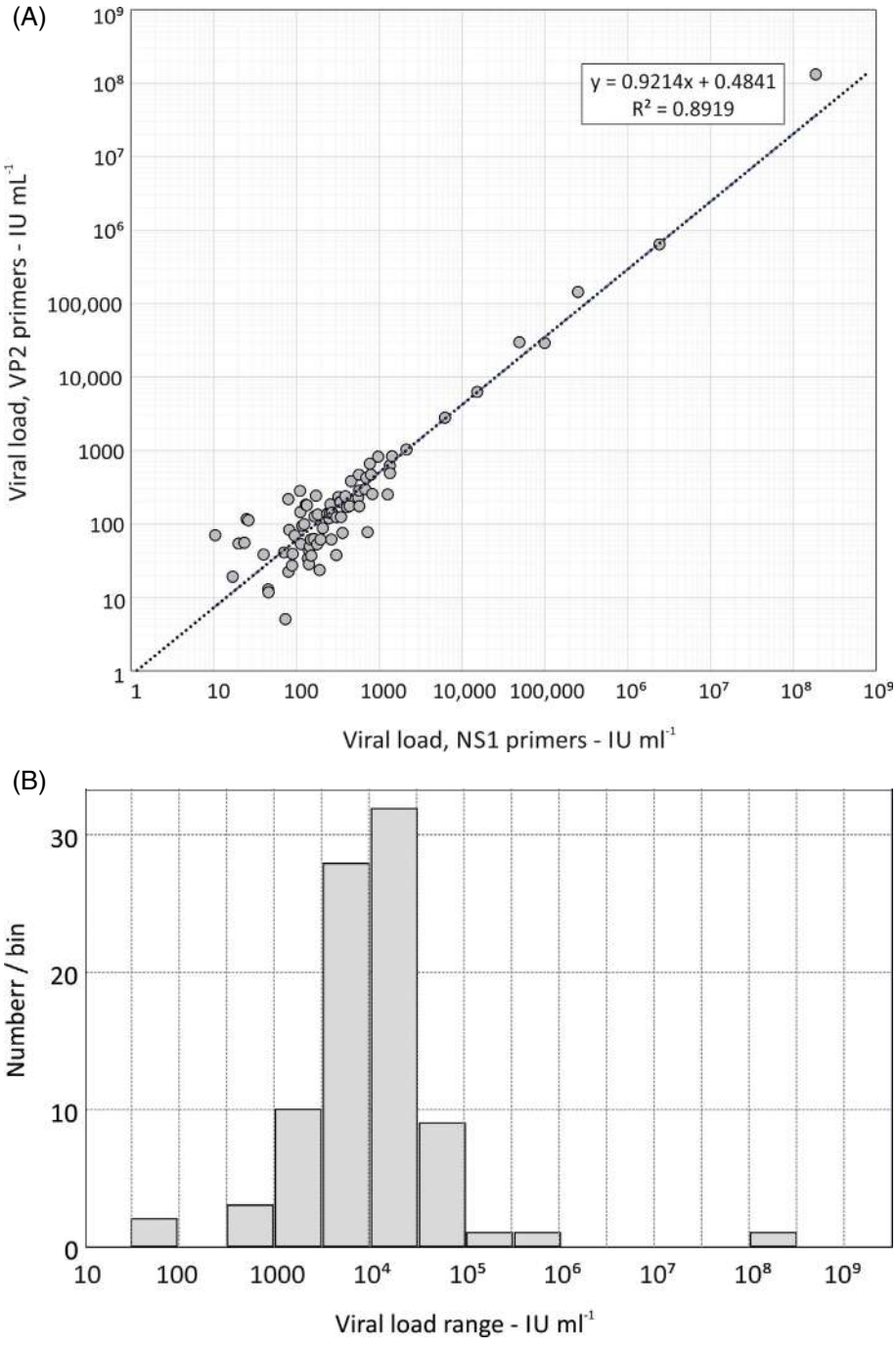

FIGURE 1 (A) Correlation between viral load quantitation in study samples in NS1 and VP2 B19V PCR assays. A regression line of log transformed viral loads in the two assays is shown as a dotted line; the formula for the regression line and correlation coefficient, R^2, are shown in the box. (B) Distribution of viral loads of study samples quantified by NS1 PCR. All viral loads of the B19V positive samples identified on screening were based on values calculated from individual testing or from pooled testing, expressed in IU ml^{-1} by reference to co-tested calibrated run controls of B19V genotype 1

TABLE 4 Detection frequencies of B19V DNA and HAV RNA in study samples—testing of component donations

Pool ID	Pools of 12[a]	Single[a]	Individual donation	NS1 VL[b]	VP2 VL[b]	B19V IgG[c]	B19V IgM[c]
A001	1	1	A001/A10	9.28×10^2	2.07×10^2	Pos (2.1)	Pos (3.2)
B081	1	1	B081/C3	1.25×10^4	2.97×10^4	Pos (2.8)	Neg (0.4)
B110	1	1	B110/C12	1.59×10^c	2.79×10^c	Pos (2.7)	Neg (0.5)
B112	1	1	B112/C2	nd	3.86×10^2	Pos (2.7)	Neg (0.2)
B122	1	2	B122/F2	1.96×10^b	6.60×10^b	Pos (2.6)	Neg (0.3)
			B122/F11	2.52×10^4	2.90×10^4	Pos (2.6)	Pos (1.8)
B219	1	1	B219/D11	4.77×10^7	1.32×10^8	Neg (0.1)	Neg (0.2)
B256	1	2	B256/G5	6.39×10^4	1.44×10^5	Pos (2.6)	Pos (3.2)
			B256/G12	3.89×10^3	6.27×10^3	Pos (2.6)	Neg (0.6)
B280	1	1	B280/E5	6.15×10^5	6.37×10^5	Pos (1.5)	Pos (3.4)

[a]Number of positive sub-pools on splitting.
[b]Units in IU ml^{-1}; shaded by viral loads.
[c]Net ODs after subtraction of substrate blank; shaded by reactivity; OD ranges for result assignments: IgG assay: positive (grey and black filled cells): >0.42; indeterminate: <0.42, >0.29; Negative: <0.29 (unfilled cells); IgM assay: positive: >0.41 (grey and black filled cells); indeterminate: <0.41, >0.29 (unfilled cells); Negative: <0.29 (unfilled cells).

>10^8 IU ml^{-1} (Figure 1B). Two samples containing high levels of B19V DNA (1.32×10^8 IU ml^{-1} and 6.37×10^5 IU mL^{-1} in the VP2-based PCR) were identified from donations collected in 2017 (1:14752). Apart from a single PCR-positive sample from 2020, all other B19 positive samples were also collected in 2017 (79:29505; 0.3%) (Table 3). The remaining sample with low-level B19V DNA was identified in convalescent plasma donor in 2020 (1:3360; 0.03%).

A selection of positive pools of 96 samples over a range of viral loads were split to individual samples of minipools and tested (Table 4); from these, 6 out of 8 minipools yielded single positive sample and the remaining two minipools yielded two. Viral loads in the samples were comparable to those calculated from pooled testing taking the dilution factor into account. Comparison of VP2 sequences from nine of the resolved single donation samples was performed to investigate potential epidemiological linkage between infected donors and rule out contamination as a cause of the observed positive test results. VP2 sequences from nine of the resolved single donation samples were all of genotype 1, but with little apparent linkage between strains infecting different donors (Figure S1, Supporting Information).

High rates of past exposure to B19V were apparent on testing a selection of individual samples from 2017 for B19V IgG antibodies by ELISA (Tables 3 and 4). The overall seropositivity was 74.5% (143/192 samples positive), with a further three showing equivocal reactivity. Individual positive samples identified through splitting pools were assayed for IgG and IgM anti-B19V antibodies by ELISA (Table 4). All seven samples with viral loads <10^5 IU ml^{-1} were seropositive for IgG and either negative or weakly reactive for IgM (2 negative, 2 indeterminate, 3 positive). This contrasts with 15/16 IgM negative, 1/16 IgM indeterminate in 16 randomly selected PCR negative donor samples (data not shown). Contrastingly, the sample with the highest viral load (1.3×10^8 IU ml^{-1}) was seronegative for IgG and IgM, while two samples with viral loads >10^5 IU ml^{-1} were IgG positive and strongly IgM positive, in all three cases consistent with proximity to seroconversion.

4.3 | Survey results

A total of 12 blood establishments providing plasma for fractionation, all members of the European Blood Alliance (EBA), responded to our donor survey. Testing methods (i.e. from individual [ID] NAT to pooling of up to 512 donations, commercial platforms or in-house methods) and policies for the initiation of clinical follow up of viraemic donors and blood component recipients varied greatly between centres (Table 5). Only one blood establishment provided plasma for fractionation without additional B19V testing. The fractionator performed B19V testing for five blood establishments in minipools, but without results being provided back to the blood establishment or blood donors in four cases. One blood establishment receiving results informed their donors of B19V results. Of the remaining six establishments, five undertake B19V testing of their own donations and one sends their samples to another country. A range of commercial (Roche, Grifols) and in-house assays were used. Pool sizes for screening were typically 96. Of these six, only one country informs the donors of their B19V result. None of the respondents of the survey indicated that their blood establishments informed recipients of transfused blood components of their exposure to B19V.

TABLE 5 Survey results of B19V and HAV screening practice in Europe

Country	Estonia	Belgium Croix-Rouge	Belgium Rode Kruis	Portugal	Italy	Switzerland	Finland	France	Germany	Austria	Netherlands	Slovenia
Plasma provided for fractionation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is plasma tested for B19V?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Who does B19V testing?	Fractionator	Fractionator	Fractionator	Fractionator	Fractionator	Referring Laboratories	In-house	In-house	In-house	Other	In-house	
What assay is used for B19V?	Not known	Not known	Not known	Not known	Not known	Commercial	Grifols	Grifols	Roche DPX		In-house	
Confirmatory testing for B19V?						No	No	No	No	No	No	
Pool size for HBV/HCV/HIV NAT?	ID	8	6	ID	ID	ID	ID	ID	96	96	6	ID
Pool size used for B19V testing	Not known	Not known	Not known	96	<512	ID NAT	16	96	96		480/96	
Do you inform donors of B19V result?	No[a]	No[a]	No[a]	Yes	No	Yes (letter)	No	No	No		No	
How long you exclude donor with B19?							None	None	2 months		2 weeks[b]	

[a]We do not receive parvovirus B19 results back from fractionator.
[b]Only if reported symptoms.

5 | DISCUSSION

Detection and quantitation of viraemia by PCR in blood donors provides one metric of the incidence of B19V infections in the survey population. The PCR assay for B19V DNA detection evaluated here showed a robust performance with the sensitivities and reproducibility as expected.[18] The information obtained in the study is vital for the rational planning of the introduction of B19V screening of UK-sourced plasma for manufacturing of medicines. In particular, knowledge of the current and likely future frequencies and viral loads of B19V viraemia are required to guide the choice of effective pool sizes for screening to ensure that final manufacturing pools are not contaminated with B19V leading to their discard.

The current study demonstrated a frequency of high-level B19V viraemia at 1:14 752 in donations collected in 2017 that was comparable to those reported elsewhere in similar screening formats.[22–24] For example, Kooistra et al.[22] reported viral loads of 10^{10} IU ml^{-1} in approximately 1:30 000 donations, >10^{9} IU ml^{-1} in 1:23 600 donations and > 10^{6} IU ml^{-1} in 1:16000 donations in an investigation of 6.5 million blood donations in the Netherlands between 2003 and 2009. B19V infections typically show a 3–4-year incidence cycle[23,25] with highest rates of B19V infection in 2013 and a lower peak in 2017.[25] However, rates of B19V DNA detection varied between countries, with Dutch blood donors showing more frequent peaks of high level viraemia in 2013, 2015, 2017 and 2019,[24] while B19V-associated cases of erythema infectiosum in Belarus peaked in only in 2006 and 2015/2016.[26] In B19V epidemic years more than 1 per 5000 donations have been shown to be viraemic, while only low levels of B19V DNA is evident in other times.[23–25] No B19V DNA was detected in blood donations collected in 2021 in this study and only one low-level positive in 2020. This virtual disappearance of B19V viraemia was much more marked than previously reported changes associated with the 2 or 4 yearly incidence cycle of B19V infections. As previously proposed,[24] implementation of infection control measures to prevent respiratory virus transmission during the COVID-19 pandemic may have had a major effect on B19V transmission too during periods of lockdown.

There was considerable variability of testing strategies for B19V in blood donations destined for fractionation by developed nations; for example NAT on minipools of varying sizes is employed by Germany and Austria, Belgium and the USA.[27] Furthermore, there are examples of alternative testing strategies to pooled NAT; for example, the Netherlands perform IgG testing on individual samples and thus deems plasma safe to use if B19V IgG positive for at least 6 months.[22] Japan performs a haemagglutination assay on individual donations for B19V antigen, with the possible imminent implementation of chemiluminescent enzyme immunoassay on pooled plasma.[28] In contrast, many developed countries do not currently test individual blood donations for B19V DNA, including China, Korea and Australia,[29] where they consider the risk of transfusion-transmitted B19V tolerable, as most transfusion-transmissions of B19V only manifest with mild or no clinical symptoms, and can be readily managed.

Of particular relevance for plasma product manufacturing and the regulations concerning acceptable viral loads in manufacturing pools, we report detection of two donors with high B19V viral loads measured by the VP2 PCR of 1.32×10^8 and 6.37×10^5 IU ml^{-1}. Assuming that manufacturers pool size is at least 6000 donations, B19V screening requires donations with B19V loads over 10^8 IU ml^{-1} to be excluded to avoid contamination of manufacturing pools above the 10^4 IU ml^{-1} threshold specified by the European Pharmacopoeia. In practice, we recommend that B19V screening of plasma prior to supply to manufacturers should identify donations containing B19V DNA loads above 10^6 IU ml^{-1}. This translates to a potential annual rate of around 68 from 2 million donations collected per year in England. This cut-off would provide a 2-log safety margin for screening and hence be capable of reliably detecting such donations while accommodating a parallel requirement not to detect low level of B19V viraemia seen in the much larger number of donations (0.3% in 2017), as their inclusion in manufacturing pools poses no transmission risk.[30,31] B19V DNA can indeed remain detectable in the blood of immunocompetent individuals at lower levels (<10^5 IU ml^{-1}) for months or even years after acute infection; based on one study up to 1% of blood donations contained low levels of B19V DNA[32] and as low as 0.006% in another.[22] B19V DNA is also known to remain detectable life-long in various tissues of immunocompetent adults after infection. These low levels of B19V DNA detected 6 months after the acute infection are considered to be non-infectious DNA remnants.[33] Furthermore, low-level viraemia usually coexists with parvovirus B19V IgG antibodies which will likely further neutralise any potential infectivity of the virus making inclusion of these units in manufacturing even less likely to lead to transmission. Since these donations contain neutralising B19V IgG antibodies· Their removal from fractionation might actually be disadvantageous as it would diminish B19V antibody levels in plasma pools and other plasma-derived products.

Based on our survey results, the proposed testing for B19V DNA in pools of 96 is compatible with plasma screening programmes established elsewhere in Europe. The Red Cross in Germany excluded donations with B19V DNA higher than 10^5 IU ml^{-1} whereas donations containing 2000 IU ml^{-1} of B19V DNA were excluded in Finland. In the Netherlands, the cut-off has been set to around 10^6 IU ml^{-1}. Irrespective of where such testing would be done (in-house, external laboratory or fractionator) and in contrast to some blood establishments in Europe, NHSBT has taken a view that positive results should be reported back to the blood donors and where these results relate to donations of whole blood, appropriate lookback investigations of recipients of blood components should be carried out. Although B19V infections are mostly asymptomatic, they can have severe consequences for an individual's health. Identification of donors with HAV infections or high level B19V viraemia will allow follow-up of potential vulnerable contacts, including immunocompromised individuals, pregnant women and those with underlying haematological disease. However, it is important to note that follow up of donors for mandatory markers also vary significantly across Europe, and by following up donors with high-level positive results, we generally aim to align ourselves to countries with similar epidemiological and public health surveillance systems.

In conclusion, our study provides the first systematic investigation of B19V viraemia frequencies and viral loads in English blood donors, and of the seropositivity for B19V that indicates the proportion susceptible to infection. These are relevant data that will help guide policy for operational screening and strategies for avoiding contaminated manufacturing for medicines pools. The ability to resolve positive pools to the level of individual positive samples enables notification and follow-up of both the infected donors and recipients of blood components produced from the donation. However, the likely retrospective nature of B19V screening may mean that results cannot be provided in time to prevent transfusion of viraemic units. Information on donor infection frequencies nevertheless could further contribute to public health surveillance.

AUTHOR CONTRIBUTIONS

HH conceived of the study and obtained funding and agreement from NHSBT for the project. SW, JR and DN performed the laboratroy work and analysis of the results. SW wrote the Methods section and part of the Results section. PS and HH performed further data analysis and co-wrote and finalised the manuscript.

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CONFLICT OF INTEREST

The authors have no competing interests.

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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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Using a scenario approach to assess for the current and future demand of immunoglobulins: An interview and literature study from The Netherlands

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Abstract

Objectives: To explore the current and future demand of immunoglobulins globally and specifically for the Netherlands by assessing: (I) which specialties contribute to current demand, (II) new areas of medical need, (III) which transformational factors may impact demand and to what effect, by using a scenario approach.

Background: As immunoglobulin demand continues to increase globally, there is concern of increasing shortages and questions of whether and how future demand will continue based on medical need.

Methods/Materials: In line with scenario principles, a scoping review of Pubmed, Web of Science, Embase and Cochrane and grey literature was conducted. Semi-structured interviews with subject matter experts were held. The results of the review and interviews were analysed for major themes.

Results: The scoping review resulted in 97 articles, 74 regarding clinical uses, and 23 regarding organisational and other themes. Fifteen clinical and non-clinical experts were interviewed. I) Neurology, immunology, and haematology were specialties that contribute most to current demand. II) Regarding potential new areas of medical need, the literature review resulted in more indications than the interviews, for example, post-renal transplants. III) Four groups of key transformational factors were found: factors that could increase immunoglobulin demand (e.g., EMA revisions), decrease demand (e.g., replacement products, Dutch Transfer Act 2021), factors that remain to be seen how it impacts demand (e.g., further evidence), and miscellaneous factors (e.g., supply-related).

Conclusion: Having identified the specialties and relevant transformational factors that affect immunoglobulin demand, more research is needed on what clinical or organisational strategies would be effective in controlling demand in general for the

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; EMA, European Medicines Agency; fSCIg, facilitated subcutaneous immunoglobulins; GBS, Guillain-Barré syndrome; HLA, human leukocyte antigen; IdeS, immunoglobulin degrading enzyme of Streptococcus pyogenes; Ig, immunoglobulins; ITP, immune thrombocytopenic purpura; IVIGs, intravenous immunoglobulins; MG, myasthenia gravis; MMN, multifocal motor neuropathy; NAITP, neonatal alloimmune thrombocytopenia; PDMPs, plasma-derived medicinal products; PfF, plasma for fractionation; PID, primary immune deficiencies; PSAF, proven specific antibody failure; SC, subcutaneous; SID, secondary immune deficiencies; SmPC, summary of product characteristics.

Netherlands and abroad. Other blood establishments may also use a scenario approach to increase preparedness for future (un)expected developments.

KEYWORDS
immunoglobulins, IVIG, scenario approach

1 | INTRODUCTION

Since the early 2000s, intravenous immunoglobulins (IVIGs), pooled from the plasma of several thousand individuals, has been a 'driver' in determining the demand for plasma for fractionation (PfF) based on medical needs.[1] IVIG has become prominent for its efficacious ability to treat primary and secondary immune deficiencies and be an immunomodulatory agent for various other disorders.[2–4] Over time, uses for IVIGs have increased as it is used for both registered (on-label) treatment and non-registered (off-label) treatments. Furthermore, administration of immunoglobulins (Igs) has expanded to subcutaneous (SCIg) and facilitated subcutaneous options (fSCIg).[5–7] Thus, the global demand of Igs has increased dramatically over time, particularly in high-income countries.[8] A report from MarketsandMarkets™ forecasted that the demand for Ig therapy increased approximately 8% globally and approximately 6% for Europe from 2016 to 2021.[9] This growing demand leads to increasing costs and supply shortages, which are already occurring in the current system.[2,10,11] Furthermore, in 2018, Europe obtained approximately 36% of PfF sourced from the United States,[12] posing challenges for European self-sufficiency and continuity for the availability of these medicines.

Research from the Marketing Research Bureau found that in 2018, the Netherlands was the 11th highest consuming country of Ig usage per capita.[13] The Netherlands has experienced decreasing demand for erythrocyte concentrates[14] which has resulted in fewer recovered plasma (plasma recovered from whole blood collection) and insufficient source plasma (plasma from apheresis). Therefore, with the historical and expected forecast of increased demand for Ig for the Netherlands,[9] Sanquin, the Dutch national blood bank, needed to make decisions regarding its strategy for the future collection of plasma by assessing the future demand of Ig.

Because Ig demand is a complex topic with various factors and stakeholders, quantitative predictions alone are insufficient and requires understanding of the current and future medical need. Therefore, we employed a scenario approach (also called scenario development or scenario planning) which has been used in other fields such as military, oil and transportation. It seeks to explore multiple plausible futures resulting from trends or policies and aids in long-term decision making to increase preparedness and proactivity for (un)expected future developments.[15] This is done by including expert perspectives and systematically identifying relevant transformational factors (broadly defined as developments in society, technology, economy, ecology or politico-legal) that, in this case, may impact future Ig demand and to what effect (e.g., increase or decrease it).[15,16] To the best of our knowledge, no study exists that includes qualitative methods in assessing demand, apart from commercialised reports and a study by Health Canada that addresses Ig supply and demand for Canada.[8] Therefore, the aim of this study is to gain insights into the current and future demand of Ig based on medical need for the Dutch setting. We did this by creating the following research questions:

- Which clinical specialties contribute to the current demand for Ig?
- What are potential new areas of medical need that could be explored?
- What are key transformational factors (from social, technological/clinical, economical, ecological, political, and legal) that would impact Ig demand and to what effect?

2 | MATERIALS AND METHODS

2.1 | Setting

In the Netherlands, Ig is distributed in two main ways with a separate reimbursement scheme for each: (1) Intramurally (within hospitals), where Ig for approved indications is reimbursed by insurance with an 'add-on' while non-approved indications come out of the hospital budget; (2) Extramurally (community pharmacies) where Ig is completely reimbursed by health insurance irrespective of the indication.[17] Ig is reimbursed for on-label usage and for certain off-label indications, which are based on several guidelines and clinicians´ input.[18]

Sanquin is the only blood bank in the Netherlands legally tasked to collect the amount of Dutch plasma necessary for self-sufficiency. Sanquin Plasma Products (SPP) was a pharmaceutical company that was originally part of the Sanquin Blood Supply Foundation. Albeit now separate, SPP (now Prothya Biosolutions) is still connected to Sanquin and continues its role in obtaining Dutch plasma for fractionation in order to manufacture plasma-derived medicinal products (PDMPs) for the Netherlands.[19]

2.2 | Methodology

From February to June 2019, we combined a scoping review with semi-structured interviews. Following scenario principles, this concurrent methodology was considered ideal to answer the research objectives to examine the topic from existing literature and compare it with the perspectives of experts in the field.

- *Scoping review*. A scoping review is a type of literature review that provides a broad overview or map of the evidence with expansive inclusion criteria; it may be a precursor to a systematic review.[20]

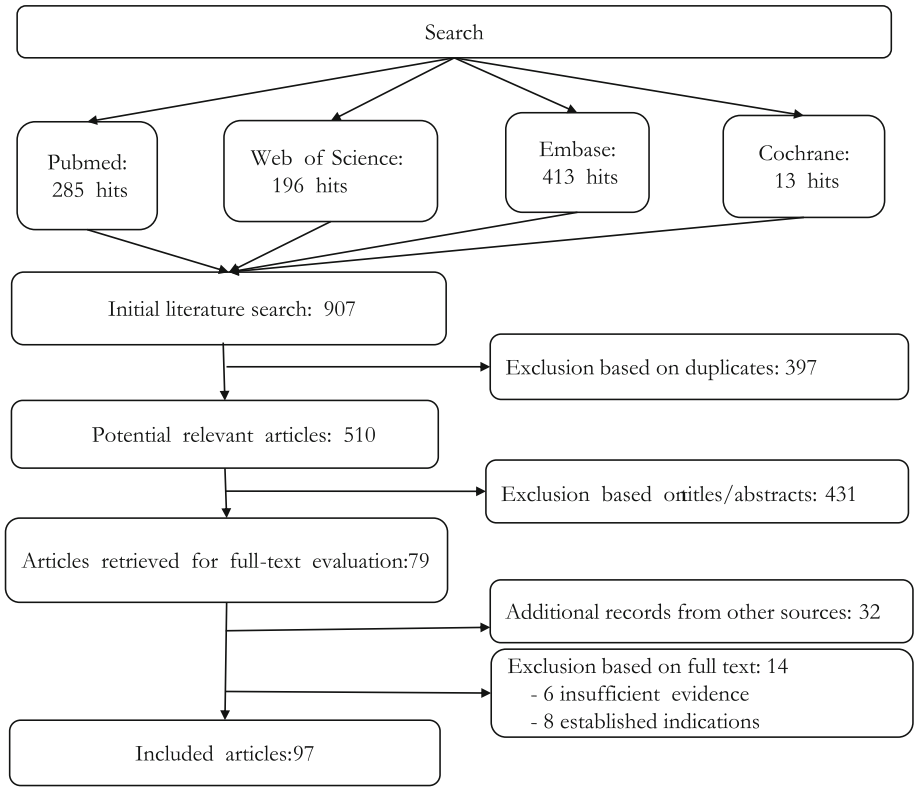

FIGURE 1 Flowchart of literature search

We created a three-part search strategy based on the project's aims regarding PDMPs, supply/demand, and current practice, for the time period between January 2010 until July 2019, and then updated from July 2019 to July 2021 (Appendix A). We applied it to several large-scale databases (Pubmed, Web of Science, Embase, Cochrane). Furthermore, we searched through grey literature (governmental websites, for-profit and not-for-profit plasma websites, presentations from prior conferences). We decided upon three sets of guidelines to be most important for this study: (1) the Australian Criteria (found at https://www.blood.gov.au/igcriteria-version3), which was chosen as the main set of guidelines for referencing other articles to as the 'Criteria' is the most recently updated (in 2018) at the time of this study; (2) the revised European Medicines Agency (EMA) guidelines (released January 2019), applicable for the European setting; (3) The Dutch transfusion guidelines (CBO) 2020, applicable for the Netherlands. For all searches, inclusion criteria included articles from January 2010 to July 2021 in the English and Dutch languages. We excluded studies regarding animals, 'on-label' or 'established' indications with no changes (e.g., dosage) to it, and conference proceedings and abstracts if full text was not available. Literature was also 'snowballed,' meaning that it was obtained through interviews or as a citation from another article. Authors PLS and CSO independently performed the screening of titles, abstracts, and full-text articles. When needed, discussions were held between both authors in order to reach consensus. After eliminating duplicates, and reading for titles and abstracts, 97 articles were chosen for full text (Figure 1).

- *Semi-structured interviews*. We used a purposive sampling strategy[21] to identify experts such as clinicians in specialties known to use (the most) Ig, SPP personnel, and representatives from a patient organisation and a not-for-profit plasma association. All experts were initially approached through a standardised email invitation providing information about the study; if they agreed to participate, each interview would last approximately 30–60 min in length and was recorded with informed consent. Experts were assured of anonymity and confidentiality in the publication of their data and gave verbal consent prior to being interviewed. Interviews were in person or over the telephone, with one expert only accessible through email. Additional respondents were 'snowballed,' a method in which prior respondents were asked to refer other individuals they thought would be appropriate for this study. An interview guide was created in accordance with the research questions comprising of three main sections: (I) current IVIG usage (for clinicians) or distribution/trends (for non-clinicians), (II) transformational factors in society, technology/clinical, economics, politics, or legal that could impact IVIG demand and to what effect, (III) future prediction of IVIG demand (Appendix B). A semi-structured approach was adopted so that the interview guide was followed with additional probing and follow-up questions when appropriate. This allowed for the interviews to be more conversational in nature.[22] Interviews were deemed sufficient in accordance with the project's timeline and the scoping literature review findings.

Analysis of interviews. All recorded interviews were transcribed verbatim and coded using qualitative software MAXQDA 2018 (VERBI Software GmbH, Germany). Several rounds of coding were applied to understand the data in their context. First cycle coding

followed a pre-determined coding framework based on the research aims.[23] Author PLS and two other researchers assessed three transcripts initially to review and revise the coding framework. Coding differences were settled through consensus and adjustments were made to the framework. The framework was expanded to allow for inductive themes that arose. Author PLS coded the rest of the transcripts with this adjusted framework, and author MvK checked five random transcripts for quality assurance.

3 | RESULTS

Of the 15 experts interviewed, 8 (53%) were clinician-researchers representing 6 specialties; almost all experts had 11+ years working in their respective fields (Table 1).

Of the 97 articles obtained from the scoping review, 74 concerned clinical factors, subdivided by specialty, and 23 regarded supply, demand, or organisational actions (Supplementary Table 1).

To answer the research questions, the literature is reviewed (*a*) followed by the interviews (*b*). For *b*, all quotations were directly taken from the experts.

3.1 | Clinical specialties that contribute to Ig demand

a. From both the literature and interviews, it was found that there is no centralised monitoring system that monitors Ig demand across the different specialties in the Netherlands—only national numbers of certain product usage (i.e., Nanogam)[24] and private, hospital-based numbers. However, it was assumed that the Dutch setting was similar to other high-income countries like the UK: the National Database Annual Reports for 2017–2020 reported Ig use by specialty by volume were (in order of) neurology, immunology, and haematology.[25–27]

Further, documents such as the EMA Guidelines and Dutch transfusion guidelines (CBO Consensus 2020) are applicable for the Dutch setting. As of January 2019, the EMA Guidelines have been amended and expanded for the European setting[28] (Table 2 describes these changes including its impact for multiple specialties). The CBO Consensus 2019 (unchanged from 2011) also specifies Ig to be indicated in pregnancy when fetal and neonatal alloimmune thrombocytopenia (FNAIT) is suspected,[35] which is also an established therapeutic role in the Australian Criteria[36] and literature.[27,37]

b. Clinicians could provide examples of specific specialties in which demand has grown, including internal medicine (specifically oncology, humoral immune deficiencies and haematology). Furthermore, 6 experts described the increased demand in neurology, where the amount of CIDP and MMN patients are fewer but have higher consumption: *'When it comes to number of patients, those with [primary] immune deficiencies is a high number. But if you look into usage of grams or kilograms of products, then the neuromuscular disorders (the MMN or CIDP) consume more. There are less patients, but the dosage is much higher'. (Expert 5)* Moreover, the growth in neurology underlies another significant growth in the area of secondary immune deficiencies (SIDs). Five experts had noticed this trend with similar explanations surrounding patient numbers (*'for 1 PID patient, you have 20 or 30 SIDs' (Expert 5)*) and Ig's efficacy in treating SIDs (*'we learned from experience that Ig really works not only in PIDs but also in SIDs' (Expert 14).*

TABLE 1 Descriptives of interviewed experts

Expert characteristics	Number of Experts from total ($n = 15$)
Male	10 (67%)
Female	5 (33%)
Occupation	
Clinician-researcher	8 (53%)
Hospital pharmacist	1 (7%)
Patient organisation representative	1 (7%)
Not-for-profit plasma association representative	1 (7%)
Sanquin Plasma Products employees	3 (20%)
Immunoglobulin scientist	1 (7%)
Years of experience	
0–10	1 (7%)
11–20	8 (53%)
21+	6 (40%)
Clinical specialties represented	Neurology, Nephrology, Dermatology, Immunology, Haematology, and Haemato-oncology

3.2 | Potential new areas of medical need for immunoglobulins

With regards to potential new areas of medical need and new indications for Ig, the literature search provided more indications than the interviews.

- The literature provided a number of possible Ig treatment options in infectious diseases such as encephalitis,[38,39] in solid organ transplant patients,[40,41] in dermatology such as atopic dermatitis,[42–45] in immunology and rheumatology, such as systemic lupus erythematosus,[46–48] to treat sepsis,[49–51] and in women with reproductive failure.[52,53]
- Nine of the 15 experts gave suggestions on new areas of medical need, although only a few (3/9) could provide specifics: in dermatology, soft tissue infections; in neurology, small fibre neuropathy or myositis; in infectious diseases, Ebola or dengue (with convalescent plasma). The other experts provided generalised ideas for

TABLE 2 Description of European Medicines Agency Guideline revisions and the specialties affected

Indication type	Definition	Specialties affected
I) Replacement therapy in adults, and children and adolescents age 0–18 years	For replacement therapy, IVIG should be initiated in A. Primary immunodeficiency syndromes (PID) with impaired antibody production and B. Secondary immunodeficiencies (SID) in patients who have proven either specific antibody failure (PSAF) or serum IgG level of <4 g/L *and* suffer from severe or recurrent infections, ineffective antimicrobial treatment**	Immunology, oncology, haematology, haemato-oncology, paediatrics
II) Immunomodulation in adults, and children and adolescents age 0–18 years.	For immunomodulation, IVIG is indicated in five specific diseases in which they need maintenance dosages for longer periods of time due to the chronic nature of the diseases. 1. Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count (including ITP in pregnancy[29]) 2. Guillain Barré syndrome (GBS) 3. Kawasaki disease (in conjunction with acetylsalicylic acid) 4. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)[30–33 a] 5. Multifocal motor neuropathy (MMN)[33,34 a]	Haematology, neurology, paediatrics

[a]Newly-added indications as part of the 2019 revisions.

'new indications' in the realms of aging-related, autoimmune, and/or immune-modulating diseases, and other SIDs.

3.3 | Key transformational factors that could impact immunoglobulin demand and its subsequent effect

When literature was searched and experts were asked regarding transformational factors that could impact Ig demand and to what effect, three groups emerged: factors that could increase Ig demand, factors that could decrease Ig demand, and factors that remain to be seen how it impacts demand. (Supplementary Tables 2–4 list these factors in-depth and by which method they were found - scoping review or interview).

3.3.1 | Factors that could increase demand

Both the literature review and interviews revealed social, technological, economic, political, and legal factors that could increase demand (shown in the 'up' arrows in Figure 2). With regards to social factors, both methods described demographic factors, such as age (the growing elderly patient population,[6,40,51,54] the older age of women becoming pregnant[52] and heightened age limits for various therapies) and increasing weight (as treatment is weight-based).[51,54] From a communication perspective, experts shared that increasing physician awareness (through education, diagnostic tools) and interactions (word-of-mouth) may also contribute to increasing demand.[51] Two clinician-researchers cautioned that while these factors may increase demand, this may not be entirely applicable to paediatrics due to the small number of paediatric patients with PIDs, whereas another clinician-researcher stated that as more adults are being diagnosed with PIDs, there would be heightened demand due to the chronic and weight-based natures of treatment.

Linking both social and technological/clinical factors, experts stated that as increasing age is no longer a limiting factor for treatments, and as new cellular and immunosuppressant therapies and drugs are developed, patients endure a prolonged immunosuppressive state that possibly warrant Ig as secondary support.[6,51,55–59] Lastly, one expert familiar with the EMA Guideline revisions stated it could justify increased Ig demand in Europe, particularly for SIDs.

3.3.2 | Factors that could decrease demand

Both the literature review and interviews revealed technological/clinical, and economic-political factors that could decrease demand (shown in the 'down' arrows in Figure 2). With regards to technological/clinical factors, alternative therapies were found that overlap with Ig's mechanisms of action, such as the neonatal receptor (FcRn)[60] and other Fc receptor blockers,[61] complement-inhibiting drugs,[62,63] and reduction of antibody production.[64] A clinical expert spoke of the value of trials seeking to taper/stop neurology patients off of Ig or switching to Rituximab instead (which would impact demand as neurology is the highest consuming specialty). Interestingly, from both interviews and the literature, limitations of these treatments or therapies were found: certain treatments (e.g., FcRn, Rituximab) held a 'double edge' in being a possible alternative for patients, and yet also causing immunosuppression (as described previously), which could still warrant Ig, albeit reduced.

Further, while gene-correcting options are available for PIDs,[65] it is only suitable for a minority: *'Only 10 to 15% of patients have a monogenetic cause of the diseases, and that means that only that*

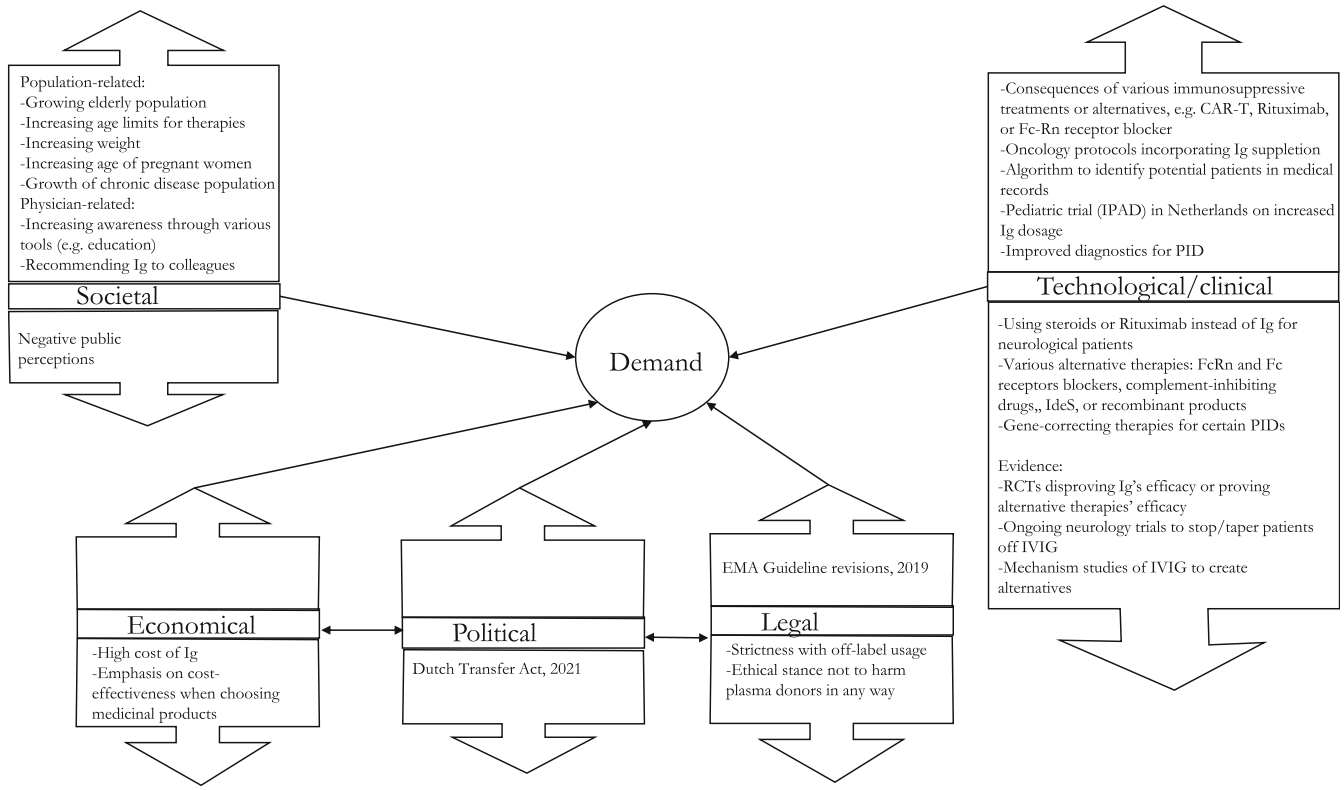

FIGURE 2 Relevant transformational factors that could increase ("up" arrows) or decrease ("down" arrows) demand

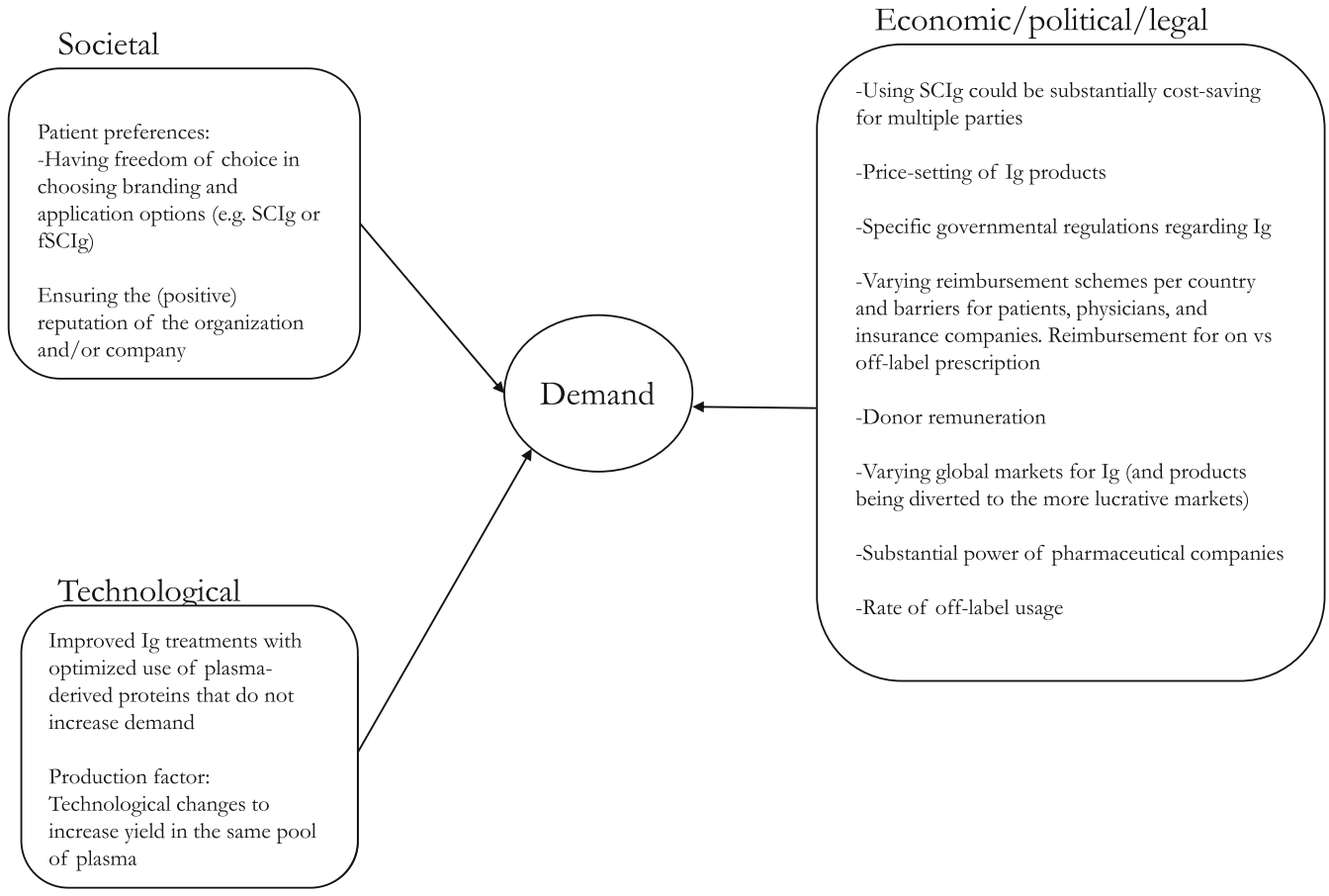

FIGURE 3 Miscellaneous transformational factors that impact demand

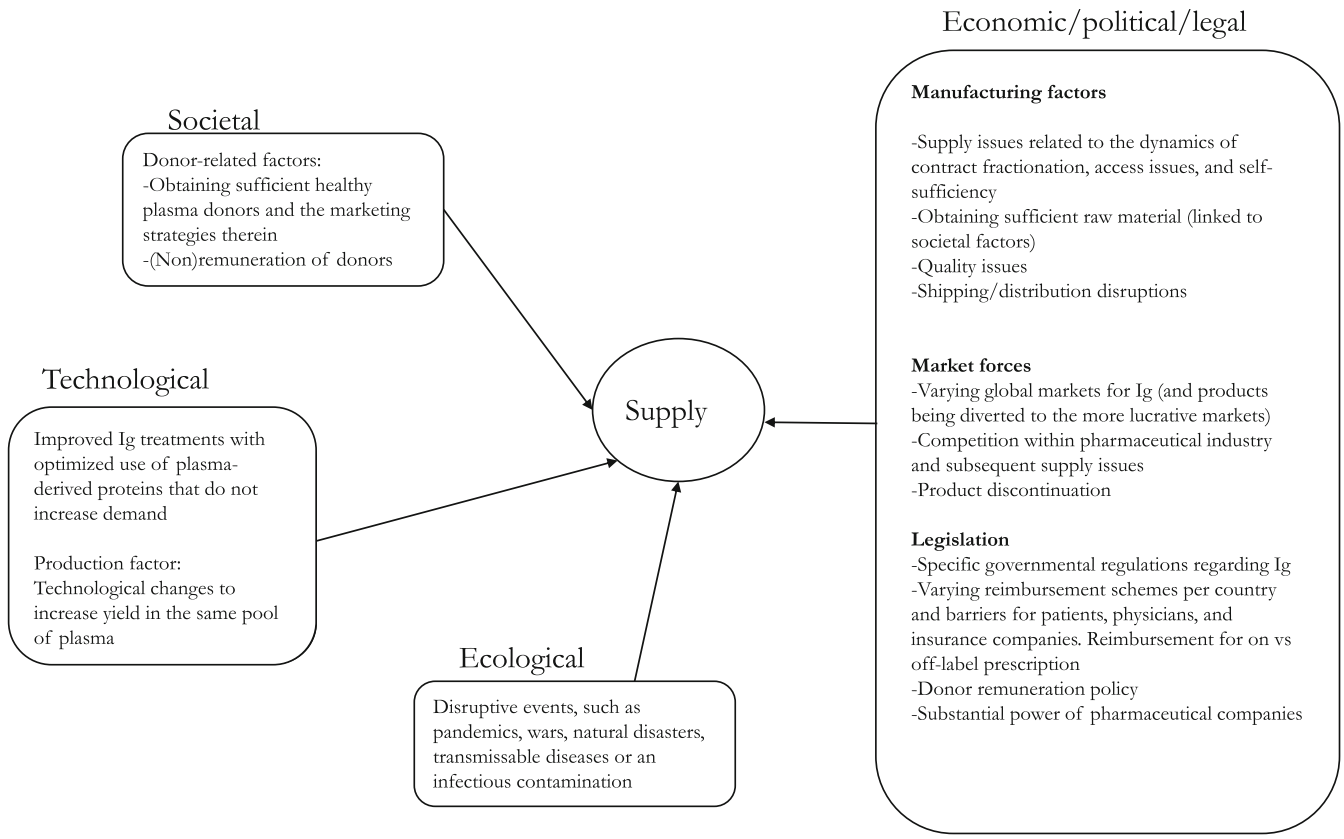

FIGURE 4 Miscellaneous transformational factors that impact supply

percentage would be suitable to undergo these procedures. That's one. Second, there's no gene therapy for CVID or XLA'. (Expert 12) Overall, while experts acknowledged the possibilities of alternative therapies and its impact on decreasing Ig demand, many expressed they see no real competition that would displace Ig within the next 3–10 years.

Additionally, the expense of Ig was an important economic factor with many ramifications[1,66–70] which could potentially force economies to curb their demand: *If the cost is higher, the consumption can decline because countries cannot afford it (Expert* 3). One clinician particularly tied evidence, economic and legal aspects together by advocating for a strict evidence-based approach to prescribing Ig, which would dampen demand: '*I think we should strive for more evidence-baseness of using the IVIG, I think the present situation is still a little bit wild and uncontrolled…there will be a stop on that, it will be more strictly regulated…If IVIG would not be reimbursed for specific indications because the evidence is meagre or shallow, then of course, that will influence prescription'. (Expert 10)* Literature provides examples of how some hospitals have initiated various stewardship programs to monitor and curb demand.[59,71,72]

More social, ecological, political, legal factors were found from the interviews. Particular for the Netherlands, experts shared how an important healthcare change was to occur in 2021, called the *overheveling*, or the Transfer Act, motioned by the Ministry of Health in 2017 to curb Ig demand by narrowing Ig prescription and distribution to the hospitals only. This act would eradicate the local pharmacy scheme, a 'black box' where reimbursement occurs regardless of the indication. Those patients and their treatment costs would be transferred to the hospital budget instead. Experts hypothesized of the upcoming effects, with some perceiving advantages such as providing insights into patient care and usage, '*to give a bigger opportunity to actually cut down on cost'* (*Expert 13*). However, they seemed quite wary of the disadvantages, such as patients being referred from hospital-to-hospital or patients having limited product options.

3.3.3 | Factors that remain to be seen on how it impacts demand

Both the literature and interviews stated that evidence from more high-quality RCTs is needed[30,38,44,49,51,73,74] and would impact demand in the direction of the results (i.e., if the evidence proved that Ig is truly efficacious and/or have increased dosage of the product, then it would potentially increase demand, but if the evidence proved otherwise, then it would decrease demand). Further, if studies could clearly elucidate IVIG's mechanisms of action,[75] then viable alternatives could be created. Additionally, some experts noted a trend in their patients regarding increased usage of SCIg or fSCIg. A study of Dutch neurologists stated that the effects of the PATH study[30] could

result in increased usage of SCIg amongst CIDP patients.[76] Further, more studies are being done with fSCIG as the hyaluronidase allows for larger volumes at singular subcutaneous sites and thus, fewer doses.[6,7,77] Literature states that SCIg is cost-saving[31,78–81] with yet unknown consequence on demand.

3.3.4 | Miscellaneous but important factors

As demand is linked with supply, relevant factors arose that affect both (Figures 3 and 4). These include supply shortages due to the 'system obstructions', as coined by one expert, which reflect societal,[82–84] economic/political/legal[25,27,59,85–89] and ecological factors embedded and interrelated within the dynamics of contract plasma fractionation,[1] such as market forces, manufacturing issues and infectious contamination[59] (Figure 4). Overcoming shortages, therefore, require attention to these various systemic elements.

4 | DISCUSSION

This study sought to gain insights into the future demand of Ig in the Netherlands by using a scenario approach. This led to the identification of relevant groups of transformational factors that could increase, decrease, or impact (with yet unknown effect) the future demand of Ig for the Netherlands, with global implications as well.

Although there is no Dutch centralised monitoring system, current demand lies within the specialties of neurology, immunology, and haematology similar to other countries.[8,25,27,54] As the latter two are part of 11 sub-specialties within Internal Medicine, it is conceivable that Internal Medicine and neurology are the main consumers of Ig in the Dutch context. In a study amongst Dutch neurologists treating CIDP, substantial variation in diagnosis and treatment options were found, with authors stating there is potential in decreasing IVIG usage if there was clearer advice in the European Federation of Neurological Societies/Peripheral Nerve Society guidelines.[76] Healthcare Institute Netherlands has a database that shows how Nanogam's users have increased from 2016–2020 and it is the third most expensive drug to reimburse.[24] Hence, at the beginning of this study in 2019, the then-upcoming Transfer Act in 2021 was perceived as a major political change to create transparency and oversight into Ig prescription to reduce demand from unnecessary indications[90] but it was cancelled indefinitely due to COVID-19.[91]

What is applicable for both the Netherlands and high-income countries are the following transformational factors, subdivided into specific factors for immune deficiencies and immunomodulation. With regards to PIDs, there could be increased demand as experts highlighted that clinicians are growing in awareness of diagnosing PIDs and using Ig treatment which may lead to increased demand,[92] particularly in diagnosing and treating *adult* patients.[93] A study using latent therapeutic demand modelling showed that the potential demand for treating CVID or XLA (two of the most common PIDs using Ig) actually exceed current demand, meaning that more Ig could be used to treat these conditions.[94,95] Conversely, gene-correcting therapies could counterbalance this demand, although it is currently suitable for certain monogenetic causes of disease and is not yet applicable for CVID or XLA.[65] As SIDs occur as a consequence of disease or therapy,[4] SID demand could continue increasing with the rise of immunosuppressive therapies, such as CAR-T cell,[56,57] compounded with the effects of socio-demographic factors (increasing age, weight). The effect of the latter could be hampered if there was standardisation of dosing based on ideal or adjusted body weight but wide variations in practice still persist.[96–98] Arguably, Ig need not be the first line of treatment options,[4,99] but the broadened EMA definition for SIDs[28] provides allowance for it to be.

Furthermore, we found four transformational factors that impact both immune deficiencies and immunomodulation. First is the EMA 2019 guideline revisions, which gives prescribing justification for reimbursement agencies, physicians, and other stakeholders in Europe. Its inclusion of CIDP and MMN into its approved indications reflect current practice and justifies its continual (and possibly, increased) use. This latter point is reflected in CSL Behring's growth of IVIG and SCIg sales in early 2020 due to the inclusion of CIDP in its product labeling.[100] However, the impact for possible increase within Europe will vary depending upon country-specific reimbursement policies. Secondly, the rise of possible alternative therapies, particularly, FcRn receptor blocker[61,101] and complement inhibiting drugs,[63] could curb demand significantly if it were successful. Whatever replacement or alternative products or therapies are produced must be proven to be safe and (cost) effective in order to be truly viable options. One example of such is eltrombopag, found to be a noninferior but more cost-effective option than IVIG as bridging therapy for ITP.[102] The evidence from trials of these alternatives or basal studies of Ig's mechanisms will contribute to a body of evidence (the third element) that will be tale-telling to the direction of demand. Lastly, the rising popularity of SCIg[103] and fSCIg[7,77] have a questionable impact on demand, although studies show its economic beenfit.[7,31,78–80] Pharmacokinetic and clinical studies suggest that switching from IVIG to SCIg requires a higher dosage,[104,105] which would result in increased demand,[104] whereas others found that a 1:1 dosage is comparable and/or equally effective.[30,79,106] and the FDA recommends a conversion rate of 1.4. Further RCTs are needed to determine the most beneficial or personalised dosing strategy.

Hence, future demand for the Netherlands and other high-income countries is likely to increase given strong demand patterns,[9,13] and the aforementioned factors that could increase demand. However, the growth of the demand will also be abated by the individual and cumulative effects of the transformational factors noted above. Thus, for clinicians and policy makers, it is necessary to monitor both aspects in making decisions regarding Ig sufficiency. For the Netherlands, one way would be to create a centralised monitoring system, such as the UK's National Immunoglobulin Database.[27] Such a system could also monitor the factors mentioned here, include changes to guidelines or in prescribing practices, for the sake of assessing effect and making more accurate predictions for the country's future demand. Furthermore, measures to steward

its use are necessary, and a first step would be to conduct local/regional audits regularly. One promising area is further research into clinician awareness and prescribing behaviour, the core activity of Ig demand. This includes better understanding of psychological factors, group dynamics, and even logistical reasons for why various initiatives in hospitals to control demand are not successful for the long-term.[54] Additionally, lessons can be learned and replicated from the hospital stewardship programs/organisational interventions that have sprung up, which exhibits varying levels of (dramatic) success in curbing Ig usage.[59,71,72]

Strengths of this study include using the combination of a scoping review and interview study that allowed for identifying the contextual factors related to Ig demand. This methodology is customizable for any country, in that it highlights country-specific issues regarding the future demand of Ig and the implications thereof. Using this approach could be an alternate, and more independent (non-biased) approach to purchasing reports from commercial companies. Other blood establishments could use this work as a starting point and modify it accordingly, even taking it further by assessing the mitigating measures to mitigate the threats and embrace the opportunities,[107] or using traditional scenario methodology and choosing to focus on certain transformational factors to create specific future scenarios.[15] This methodology was used by Sanquin to make recommendations to the Ministry of Health regarding the need for increased plasma collections, which resulted in the opening of the first plasma-only collection in the Netherlands center in 2020.

The main limitation of this study was its lack of numerical data for the Dutch setting for questions such as the number of patients requiring Ig, estimates of future demand or extrapolating trends. Further, in interviewing 15 experts, of which 8 are clinicians, with one neurologist and two haematologists, we may have missed other, or more nuanced, perspectives. Due to the limited time frame of this study, we made choices to interview a wide range of key experts and chose these clinicians as representatives of their fields due to their reputation and output, which may have introduced a selection bias. Additionally, including SPP employees may have also introduced bias, but these persons were chosen for their content knowledge and their remarks were compared and validated with clinicians and the other representatives during interviews.

5 | CONCLUSION

Using a scenario approach, we have identified that neurology, immunology, and haematology are the main drivers of Ig demand along with four groups of transformational factors that may impact demand. Future demand for the Netherlands and other high-income countries is expected to continue, but may be abated by the individual and cumulative effects of the other factors. Hence, monitoring demand patterns and its contributing factors are needed to facilitate responsible use of Ig along with thinking of various long-term strategies on the local, clinical, and national levels that will aid in preparing for future Ig developments, whatever they may be.

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AUTHOR CONTRIBUTIONS

MvK conceived the initial idea of the study, and all authors designed the methodology. PLS conducted the interviews and analyses and MvK partially reviewed analysis. PLS and CSO conducted the scoping review and analyses. PLS wrote the manuscript while CSO and MvK critically reviewed and revised the manuscript.

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CONFLICT OF INTEREST

No conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Further data concerning the scoping review is available from the corresponding author, CSO, upon reasonable request.

ETHICS STATEMENT

This study did not require ethical approval due to its scoping review nature, and lack of personal contact with donors, patients, or vulnerable groups.

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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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