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Received: 23 August 2023 | Revised: 8 January 2024 | Accepted: 15 January 2024

DOI: 10.1111/vox.13594

ORIGINAL ARTICLE

Vox Sanguinis ISBT International Society of Blood Transfusion

Extensive red blood cell matching considering patient alloimmunization risk

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Funding information
Stichting Sanquin Bloedvoorziening, Grant/Award Number: PPOC20-05/2490; NIHR Artificial Intelligence in Health and Care Award, Grant/Award Number: 02331; NIHR BTRU in Donor Health and Behaviour, Grant/Award Number: NIHR203337; NIHR Cambridge BRC, Grant/Award Numbers: NIHR203312, BRC-1215-20014

Abstract

Background and Objectives: Red blood cell (RBC) transfusions pose a risk of alloantibody development in patients. For patients with increased alloimmunization risk, extended preventive matching is advised, encompassing not only the ABO-D blood groups but also the most clinically relevant minor antigens: C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, S and s. This study incorporates patient-specific data and the clinical consequences of mismatching into the allocation process.

Materials and Methods: We have redefined the MINimize Relative Alloimmunization Risks (MINRAR) model to include patient group preferences in selecting RBC units from a finite supply. A linear optimization approach was employed, considering both antigen immunogenicity and the clinical impact of mismatches for specific patient groups. We also explore the advantages of informing the blood bank about scheduled transfusions, allowing for a more strategic blood distribution. The model is evaluated using historical data from two Dutch hospitals, measuring shortages and minor antigen mismatches.

Results: The updated model, emphasizing patient group-specific considerations, achieves a similar number of mismatches as the original, yet shifts mismatches among patient groups and antigens, reducing expected alloimmunization consequences. Simultaneous matching for multiple hospitals at the distribution centre level, considering scheduled demands, led to a 30% decrease in mismatches and a 92% reduction in shortages.

Conclusion: The reduction of expected alloimmunization consequences by incorporating patient group preferences demonstrates our strategy's effectiveness for patient health. Substantial reductions in mismatches and shortages with multi-hospital collaboration highlights the importance of sharing information in the blood supply chain.

Keywords

extensive antigen typing, linear optimization, RBC matching, supply chain

Highlights

- More than 300 red blood cell (RBC) antigens are known, and antibodies against 11 of these are considered to be of great clinical importance.
- Patient group-directed extensive RBC matching can significantly reduce expected alloimmunizations for high-risk patient groups.
- Sharing information on elective transfusions within the blood supply chain reduces both shortages and alloimmunization risk.

INTRODUCTION

Red blood cell (RBC) units are the most commonly transfused blood products. In the Netherlands, there is one organization responsible for the blood supply to 113 hospitals serving a population of 17.6 million inhabitants. There are about 380,000 whole blood donors, and yearly, about 400,000 RBC units are distributed [1]. The blood supply service distributes RBC units to the hospitals daily. These orders are partially based on specific scheduled transfusions, but mainly on order-up-to levels on the 'major' RBC antigens (ABO and D). At the hospitals, products from their inventory are assigned to patients in need of a transfusion, which is generally done by issuing units compatible on these major blood groups. However, more than 300 RBC antigens are known to exist [2]. RBC alloantibodies against 11 of these 'minor' RBC antigens are considered to be of such clinical importance that, for a selection of patient groups, preventive matching on specific subsets of these antigens is part of transfusion guidelines [3]. In general, upon an ABO-D matched transfusion, about 1%–5% of recipients become alloimmunized [4–6], which may increase up to 8%–15% after multiple transfusions [7, 8]. In subsequent transfusion episodes with products containing such antigens, the newly formed antibodies might destroy the transfused RBCs [8–10]. Therefore, before a blood transfusion is administered, the recipient is screened for the presence of alloantibodies to select compatible blood. Because of the transient character of antibodies, over time 70% of alloantibodies will not be detected anymore while still being capable of inducing delayed transfusion reactions [11]. Therefore, in the Netherlands, all identified alloantibodies are registered in a database, which is accessible by all hospitals [12].

Patients who developed RBC alloantibodies (Allo) will in subsequent transfusion episodes receive units that are, next to D, also matched for CcEe and K and compatible for the implicated antigen. For blood recipients for whom an increased risk of alloantibody formation is expected, the Dutch Blood Transfusion Guideline summarizes advice for preventive extended matching and for patients who do not have alloantibodies [3]. This concerns patients with autoimmune haemolytic anaemia (AIHA), sickle cell anaemia (SCD) or thalassemia (Thal) and patients with myelodysplastic syndrome (MDS). The latter three patient categories are in need of repeated blood transfusions, which increases the exposure to foreign blood group antigens and the risk of developing alloantibodies [8]. In the Netherlands, extended matching for these patient groups includes matching on, in addition to the three major antigens A, B and D, a selection of 11 clinically relevant minor antigens: C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, S and s. Furthermore, RBCs for women aged below 45 years (Wu45) are matched for c, E and K to prevent alloimmunization that may lead to haemolytic disease of the foetus or newborn in future pregnancies. Patients who do not belong to any of these groups (Other) receive RBC units matched for the major antigens only. This group mainly includes elective transfusions, for example, for surgery.

Recently, high throughput genotyping technology has facilitated prediction of the full RBC phenotype of both patients and donors. Using molecular techniques, the presence of hundreds of antigens can be determined in a single assay [13–16]. Although the combinations of 14 antigens proposed theoretically constitute 6566 different blood group combinations, van Sambeeck et al. have shown that most (>95%) of transfusion-induced alloimmunization events can be prevented when both donors and recipients are comprehensively typed and matched [17]. Despite this impressive result, it is impossible to provide fully compatible products to all patients, meaning the challenge will remain how to manage the risk of alloimmunization for individual patients. This is all but a trivial task, not only because of the huge number of possible antigen combinations considered in large-scale extensive matching but also because the risks associated with mismatching differ for each antigen and in particular for each patient group. We therefore propose an issuing strategy that differentiates and prioritizes matching requirements in alignment with the patient groups, as mentioned above.

Aiming to make extensive matching possible in practice, Van de Weem et al. have proposed the 'MINRAR' model (short for MINimize Relative Alloimmunization Risks) to quantify the quality of a match and to determine optimal issuing strategies such that the number of clinically relevant mismatches is minimized [18]. The study at hand shows that, with a straightforward extension of the MINRAR model, offering extensively matched products to all patients does not increase the alloimmunization rate in high-risk groups. In addition, it will demonstrate to what extent the quality of in-hospital matching of RBC products may be improved when hospitals inform the blood bank about future transfusions, which allows for improving the distribution of blood products to the hospitals.

MATERIALS AND METHODS

Constructing the matching model

We propose a modified version of the MINRAR model, as presented in Van de Weem et al. [18], to match extensively typed RBC units to

TABLE 1 Classification of the perceived clinical consequences of incompatible matching for all patient groups considered for different antigens.

	C	c	E	e	K	Fy^a	Fy^b	Jk^a	Jk^b	S	s
Allo	×	×	×	×	×	1	1	1	1	2	3
SCD	×	×	×	×	×	×	1	×	×	1	2
Thal	×	×	×	×	×	2	2	2	2	3	3
MDS	×	×	×	×	×	2	2	2	2	3	3
AIHA	×	×	×	×	×	1	1	1	1	2	2
Wu45	2	×	×	2	×	3	3	3	3	3	3
Other	2	2	2	2	2	3	3	3	3	3	3

Note: Four levels of compatibility are distinguished: ×: mismatching is not allowed; 1: compatible matching is important; 2: compatible matching is preferred; 3: compatible matching has low priority.
Abbreviations: AIHA, autoimmune haemolytic anaemia; MDS, myelodysplastic syndrome; SCD, sickle cell anaemia; Thal, thalassemia; Wu45, women aged below 45 years.

extensively typed patients, while minimizing alloimmunization risk. In the MINRAR model, all products compatible on the major blood group (ABO-D) are considered a valid match for any patient, meaning a shortage is incurred whenever there are insufficient ABO-D compatible products available in the hospital inventory for the patient. The MINRAR model uses antigen immunogenicity (Table S1) to calculate the weight for mismatching on a particular antigen. We extend this approach by also considering the perceived clinical consequences of certain alloantibodies, as estimated by the immunohaematology expert authors (JL, MDH, EvdS and RN). The clinical consequences, as perceived by our experts, are a mixture of pathogenicity and anticipated health implications and are shown in Table 1. When we incorporate this patient group differentiation into our model, we redefine a shortage as a lack of sufficient inventory products available for a patient, all of which must be compatible on the antigens denoted by a × in Table 1 for the corresponding patient group. For a detailed description on how the other preferences are transformed to numerical mismatch weights to be used by the MINRAR model, the reader is referred to Supplement A.

The model is designed to match RBC products to requests for a single day, prioritizing the minimization of shortages. This means it focuses on providing all patients with their requested number of products, all of these being compatible on the antigens marked with a × in Table 1. Once the minimum number of shortages is established, four other objectives are minimized simultaneously:

1. mismatches on the minor antigens for which mismatching is allowed, marked with a number in Table 1;
2. antigen substitution: issuing an antigen-negative product to a patient who is positive for that antigen;
3. remaining shelf life of issued products: older products are preferred over fresh products; and
4. major antigen usability of issued products: low usability (e.g., *AB*+) is preferred over high usability (e.g., *O*−).

A full description of the MINRAR model can be found in Supplement E and in the original paper by van de Weem et al. [18]. The mixed-integer linear programming (MILP) model [19] is programmed in Python (version 3.9) [20] and solved using Gurobi Optimization software (version 9.1) [21]. The simulation code is available from https://github.com/Sanquin/blood_matching.

Data on patients and RBC products supplied

The model is designed to be able to match real patients to real products in inventory. For the purpose of model testing, however, data were generated both for demand and for supply. In this section, we elaborate on the considerations for generating the data on patients and supplied products.

When generating patient request data, the distribution of patient groups among all patients needs to be taken into account. Data from two hospitals were available to represent the two distinct hospital types. The Amsterdam UMC, location AMC is chosen to represent university hospitals, and the OLVG, location East to represent regional hospitals. Table S5 in Supplement B shows the distribution of units requested by each patient group in these hospitals.

Considering the antigen profile of simulated patients, phenotypes of all simulated patients are based on antigen frequencies within the Caucasian population, with the exception of the SCD patients. For simulating these patients, we used antigen prevalences for individuals of African ancestry, since SCD mainly occurs in that population. Antigen prevalences for both populations are provided in Supplement F, Table S7.

Transfusions are frequently scheduled in advance, allowing for product requests to be anticipated. The immunohaematology expert authors (JL, MdH, EvdS and RN) estimated lead times for all patient groups, that is, the number of days between the request becoming known and the transfusion. For MDS, SCD and Thal patients, simulated requests become known 1 week before the transfusion. Lead times for the Allo and Other patient groups are uniformly distributed between 0 and 6 days. For Wu45 patients, we assume that the requests are known either on the day of transfusion or 1 day before, each with a 50% probability. Requests for AIHA are not known in advance and only become available on the day of transfusion.

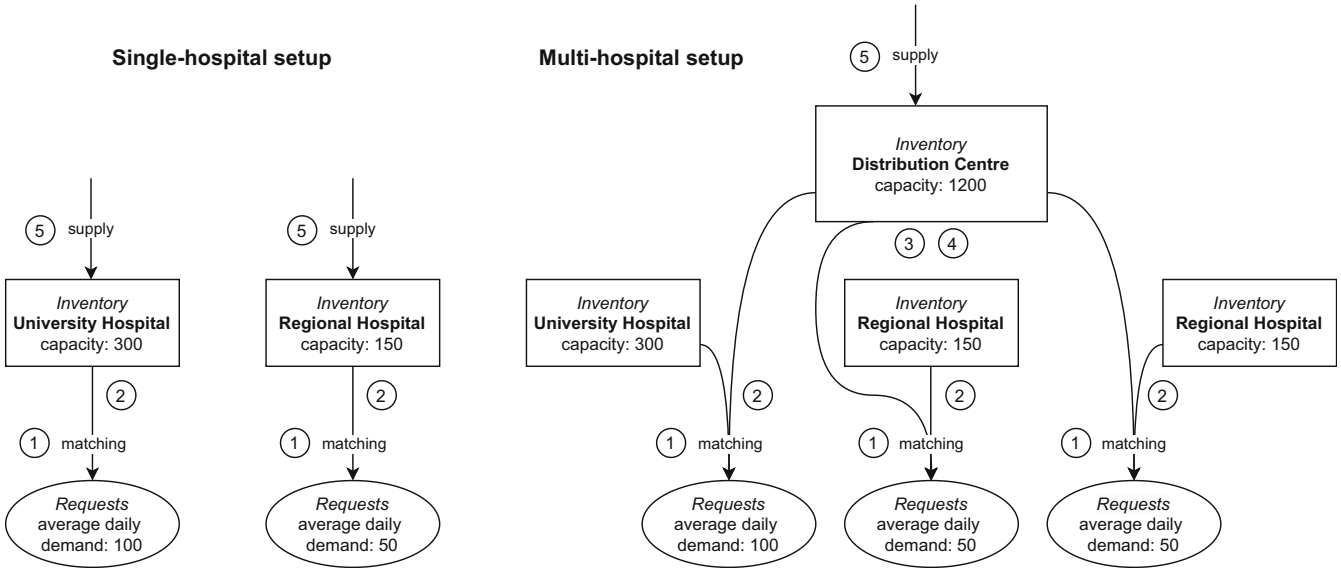

FIGURE 1 Daily tasks performed in both the single- and multi-hospital simulations. (1) Requests are matched from hospital inventory. (2) All products assigned to today's requests are issued and removed from the hospital's inventory. (3) Products assigned to hospital requests to be satisfied tomorrow are shipped to the designated hospital. (4) Supply hospitals to restore target inventory levels. (5) Replenish inventory with random red blood cell units from the donor population.

The number of units requested per patient is sampled from a historical in-hospital distribution using Dutch Transfusion Datawarehouse data, comprising 438,260 transfusions from January 2012 to December 2019 in six Dutch hospitals [22]. For patient groups Allo, Wu45 and Other, the assumed unit requirement ranges from one to four, sampled based on the distribution shown in Supplement B, Figure S1. The remaining groups are assumed to always need two units per patient, the most common request. The phenotypes of the patients are generated at random based on the prevalence of different blood groups among Caucasians (Supplement F, Table S7). Furthermore, we did not model recurring requests for individual patients.

The major antigen profile of the supplied units is sampled in accordance with its prevalence in the donor population, as depicted in Supplement C, Figure S2. As donors are only invited based on their major blood groups, we assume that the minor antigen prevalence in donors mirrors the general population. Minor antigens are therefore sampled based on Caucasian phenotype prevalence for each blood group system (Supplement F, Table S7).

Simulation setup

The performance of the proposed model was assessed through multiple 1-year simulations, where for each separate day an optimal set of products was selected from inventory by the model. A 70-day initialization phase to stabilize inventory levels was applied. Figure 1 illustrates two experimental configurations for the simulations, with numbers 1–5 representing the steps to be executed on each day of the simulation. In the single-hospital setup, matching is performed by the proposed model, and products allocated to today's requests are removed from inventory. At the end of each day, any expired products are removed as well, and the hospital's inventory is replenished with fresh RBC units, as detailed in Section 2.2.

The multi-hospital setup involves three hospitals (two regional, one university) and a distribution centre providing RBC units. The first two steps each day resemble those of the single-hospital setup; however, requests may be matched to products from either the hospital's or the distribution centre's inventory. However, we do assume that requests for today's transfusions can only be satisfied from the hospital's own inventory, as emergency deliveries from the distribution centre are expensive and should be avoided. Next, expired products are removed from all inventories, and products matched from the distribution centre to requests to be satisfied the next day are shipped to the hospitals, along with supplementary products to ensure each hospital's inventory is replenished up to its normal capacity. The selection of products for replenishment is done by preferring older products over younger products and preferring products with low usability on the minor antigens over products with high usability. Finally, the distribution centre's inventory is resupplied with fresh RBC units as discussed in Section 2.2.

RESULTS

In this section, we assess the performance of the modified MINRAR model (as described in Section 2.1.) in matching extensively typed RBC units to extensively typed patients while minimizing alloimmunization risk. First, we will investigate the impact of using patient group-specific weights on the minor antigen mismatches for

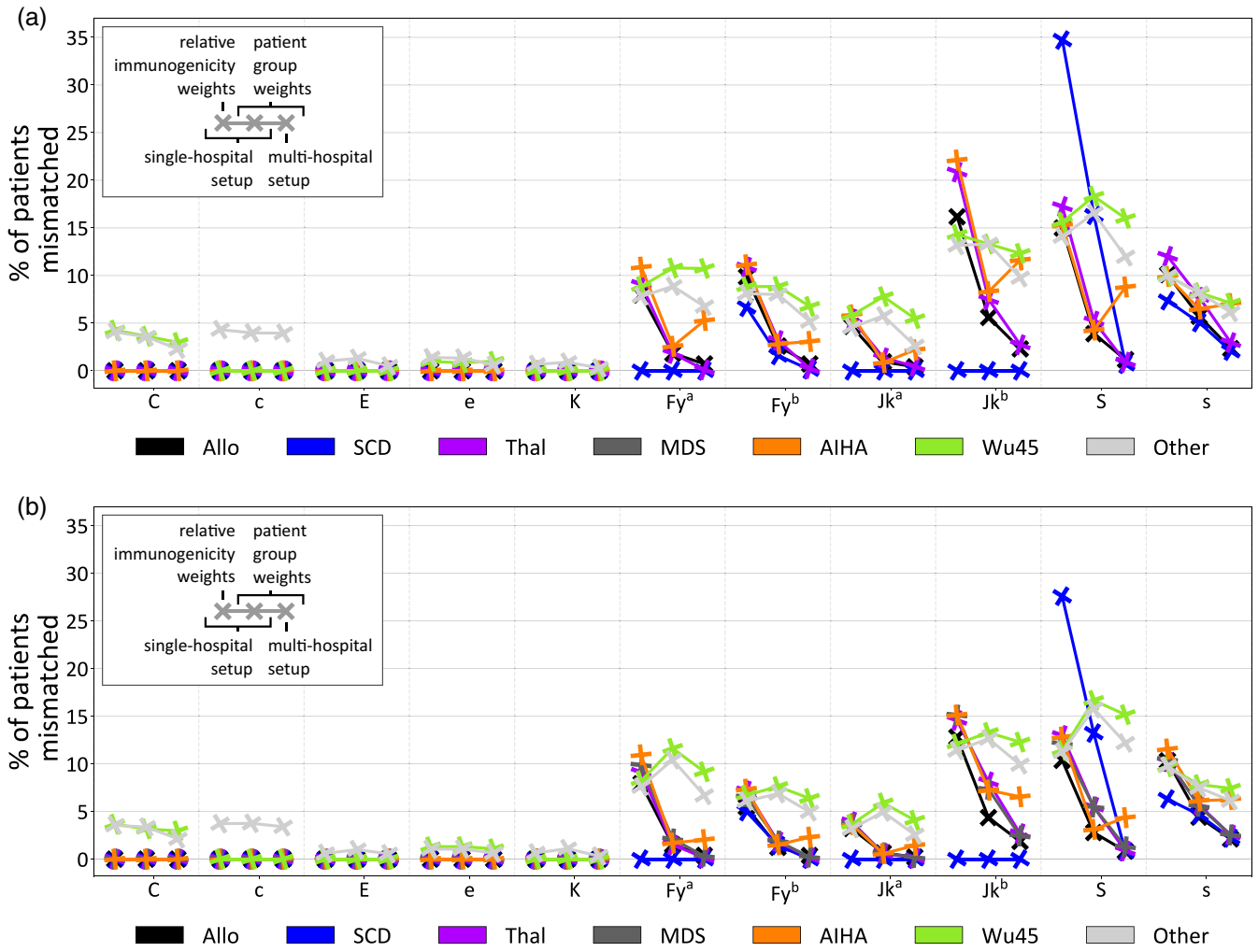

FIGURE 2 Proportion of patients per patient group who received a mismatched red blood cell product. Matching is performed using relative immunogenicity weights (Supplement A, Table S1) or patient group-specific weights (Supplement A, Table S4), either in a single- or multi-hospital setup. In all three scenarios depicted, mismatching was not permitted for matches marked with a × in Table 1. (a) Regional hospitals. (b) University hospitals. AIHA, autoimmune haemolytic anaemia; MDS, myelodysplastic syndrome; SCD, sickle cell anaemia; Thal, thalassemia; Wu45, women aged below 45 years.

each group and then examine the benefits of integrating a distribution centre in the multi-hospital simulation setup.

Impact of patient group-specific weights in the single-hospital scenario

Figure 2 shows the proportion of patients per patient group that is mismatched on each of the minor antigens considered, displayed in sets of three data points. The first data point is the original MINRAR model in a single-hospital setup, and the other two data points represent the new model with patient group-specific mismatch weights, in a single-hospital (second point) or multiple-hospital (third point) setup. First, the effects of employing patient group-specific mismatch weights are compared in the single-hospital setup.

Figure 2 reveals a substantial number of mismatches for antigens Fy^a, Fy^b, Jk^a, Jk^b, S and s when only applying relative immunogenicity weights. Upon implementing patient group-specific weights, mismatches for patient groups Allo, SCD, Thal, MDS and AIHA are reduced by 65% and 62% for the regional and university hospital, respectively, reducing the number of expected alloimmunizations in these groups by 75% in both hospitals. However, an inverse effect is noted for the larger patient groups Wu45 and Other, which together constitute 94% and 75% of the regional and university hospital patient population, respectively. Application of patient group-specific weights led to a 4% and 17% increase in mismatches and consequently 14% and 35% increase in the number of expected alloimmunizations, in the regional and university hospitals, respectively. This increase is a direct result of the lower patient group-specific weights assigned to these two groups, reflecting their lower risk of mismatching in terms of both antibody formation and consequences of alloimmunization. Changes in both the number of mismatches and expected alloimmunizations as an effect of patient group directed matching, relative to matching based on only relative immunogenicity, are

TABLE 2 Changes (%) in the total number of mismatches and expected alloimmunizations per patient group and hospital type when comparing outcomes from patient group-specific weights to outcomes from relative immunogenicity weights.

		Allo	SCD	Thal	MDS	AIHA	Wu45	Other	Total
Regional	Mismatches	−67.69	−52.83	−64.56	-	−66.34	+4.59	+4.00	−0.13
	Alloimmunizations	−76.51	−56.67	−74.60	-	−78.04	+17.06	+14.26	+11.22
University	Mismatches	−70.15	−50.23	−59.97	−60.16	−67.00	+18.80	+16.32	−1.35
	Alloimmunizations	−78.34	−54.94	−76.98	−74.18	−81.16	+34.58	+35.17	+18.77

Abbreviations: AIHA, autoimmune haemolytic anaemia; MDS, myelodysplastic syndrome; SCD, sickle cell anaemia; Thal, thalassemia; Wu45, women aged below 45 years.

TABLE 3 Changes (%) in the total number of mismatches and expected alloimmunizations per patient group and hospital type when comparing outcomes from where the distribution centres are informed about elective transfusions in each of the connected hospitals included in the multi-hospital setup to outcomes from the single-hospital setup.

		Allo	SCD	Thal	MDS	AIHA	Wu45	Other	Total
Regional	Mismatches	−63.32	−87.50	−72.46	-	+46.14	−14.34	−31.50	−30.76
	Alloimmunizations	−62.91	−95.51	−79.69	-	+94.72	−16.74	−42.39	−41.29
University	Mismatches	−61.09	−84.39	−71.90	−69.63	+13.32	−13.12	−27.69	−29.01
	Alloimmunizations	−69.31	−94.60	−83.94	−78.50	+54.11	−20.51	−40.52	−39.48

Abbreviations: AIHA, autoimmune haemolytic anaemia; MDS, myelodysplastic syndrome; SCD, sickle cell anaemia; Thal, thalassemia; Wu45, women aged below 45 years.

displayed in Table 2. For both Table 2 and Table 3, the number of expected alloimmunizations was estimated by multiplying the number of mismatches by the probability of alloimmunization after receiving two mismatching units [8].

Impact of integrating a distribution centre: The multi-hospital scenario

In Figure 2, the third data point within each set represents the relative number of mismatches in the multi-hospital setup, still using patient group-specific weights for mismatching. Comparing these values to the second data point, representing patient group directed matching in the single-hospital setup, highlights the benefits of informing a distribution centre about blood to be reserved for elective transfusions.

As shown in Table 3, the decrease in the number of mismatches is 61%–87% in the patient groups with highest risk (Allo, SCD, Thal and MDS), leading to an expected decrease of alloimmunizations by 70%–95%. The only increase in mismatches occurs for AIHA patients, being a direct result of all requests for this group becoming known on the day of transfusion. Nevertheless, the overall number of mismatches decreases by 29%–31% and the subsequent number of expected alloimmunizations by 39%–41%. In Supplement H, the change in mismatches between the three scenarios is visualized. Changes in the absolute number of mismatches per year are shown in Supplement H, Figure S5.

Table 4 shows a few simulation characteristics for all patient groups considered in single- and multi-hospital scenarios. It demonstrates that shortages for nearly all patient groups decline significantly when the individual hospitals propagate patient requests to the distribution centre, underlining the benefit of informing distribution centres about the blood required for elective transfusions.

For SCD patients, the proportion of shortages in single-hospital simulations is relatively high compared with other patient groups for both university and regional hospitals. Given that for SCD patients mismatching is not allowed for most minor antigens (Table 1), finding compatible products in a single hospital's inventory proves to be challenging. Consequently, forwarding these requests to the distribution centre is a successful strategy for preventing shortages.

The AIHA patient group suffers a slight increase in the number of shortages for both hospital types. This is likely due to the assumption that these patients' requests cannot be planned in advance and a compatible product can only be found if already in stock. As the distribution centre aims to reserve products with high usability for allocation to hospitals in need, fewer antigen-negative units are stored in hospital inventories, increasing the number of shortages for requests that become known on the day of use. A similar effect can be observed for the Wu45 patient group, as a result of our assumption that 50% of these transfusions are non-elective.

DISCUSSION

In this study, we investigated how the MINRAR model, as proposed by Van de Weem et al. [18], can be extended by applying patient group-specific mismatch weights to minimize the risk of alloimmunization for groups requiring extensively matched RBC products. We used empirical data on the relative immunogenicity, combined with a classification of antigen and patient group importance, to establish patient group-specific mismatch weights. To assess the effectiveness of the

TABLE 4 Number of shortages and units reserved at the distribution centre for various patient groups, as a percentage of the total number of requests for patients of that group (95% CI).

	Regional hospital				University hospital			
	Shortages in single-hospital simulations		Shortages in multi-hospital simulations	Units reserved at distribution centre	Shortages in single-hospital simulations		Shortages in multi-hospital simulations	Units reserved at distribution centre
Allo	1.17	(0.85–1.49)	0.52 (0.16–0.89)	85.72 (84.17–87.27)	0.25	(0.00–0.54)	0.06 (0.00–0.13)	84.52 (83.66–85.39)
SCD	14.34	(10.62–18.05)	0.12 (0.00–0.38)	99.19 (98.48–99.91)	13.19	(12.02–14.35)	0.15 (0.02–0.28)	99.05 (98.63–99.46)
Thal	1.78	(0.00–3.87)	0.00 (0.00–0.00)	99.07 (98.45–99.69)	0.42	(0.13–0.71)	0.00 (0.00–0.00)	99.05 (98.8–99.30)
MDS	-	-	- -	-	0.36	(0.06–0.67)	0.02 (0.00–0.08)	98.75 (98.64–98.86)
AIHA	2.16	(0.17–4.15)	2.51 (1.74–3.27)	0.00 (0.00–0.00)	0.43	(0.02–0.84)	0.75 (0.44–1.07)	0.00 (0.00–0.00)
Wu45	0.11	(0.00–0.32)	0.46 (0.21–0.70)	47.15 (45.15–49.16)	0.00	(0.00–0.00)	0.07 (0.04–0.11)	46.31 (45.38–47.24)
Other	0.14	(0.00–0.29)	0.00 (0.00–0.00)	81.41 (81.03–81.79)	0.00	(0.00–0.00)	0.00 (0.00–0.00)	79.71 (79.15–80.27)
Total	0.33	(0.19–0.48)	0.08 (0.06–0.10)	78.79 (78.3–79.27)	0.83	(0.78–0.89)	0.04 (0.03–0.05)	77.73 (77.39–78.08)

Note: A shortage occurs whenever there is no product available that is compatible on the major antigens A, B and D or on any of the antigens marked with a × in Table 1, for at least one of a patient's requested units. Units that were reserved at distribution centre indicate that for some patient, a better match was available at the distribution centre than in the hospital's inventory, and the product was therefore reserved to be transported to that hospital.

Abbreviations: AIHA, autoimmune haemolytic anaemia; MDS, myelodysplastic syndrome; SCD, sickle cell anaemia; Thal, thalassemia; Wu45, women aged below 45 years.

proposed weights in reducing mismatches for the selected patient groups, multiple 1-year simulations were conducted. The outcomes of these simulations should not be considered practical advice or a prediction of future RBC matching in the blood supply chain. Instead, our objective is to gain insights and illustrate opportunities for RBC matching in a scenario where both donors and patients are extensively typed for clinically relevant minor antigens.

For the single-hospital simulation setup, our method demonstrated an effective reduction in the number of mismatches for all high-risk patient groups considered, mainly on the antigens that either come with a high probability of alloimmunization or where alloimmunization has the most severe consequences. As a result of implementing a patient group directed approach, expected alloimmunization can be reduced by 75% for these groups. However, this benefit leads to an increase of alloimmunization incidence by 14%–35% for patients for whom the effects of mismatching are assumed to be less impactful, being the patient groups Wu45 (women aged below 45 year) and Other (patients not belonging to any of the specific patient groups).

We investigated to what extent the matching quality improves for various patient groups when information on requested products is propagated to the distribution centre and incorporated into supply decisions for specific hospitals. For the majority of patient groups, this results in an increased number of antigens that could be matched compatibly. Additionally, the number of shortages can be significantly reduced, in particular for the SCD patient group, as most minor antigens considered are not allowed to be mismatched for these patients. Note that in reality, a shortage does not imply that a patient will receive either an incompatible product or no product at all; hospital staff will make sure to obtain a compatible product, by requesting an emergency delivery of a compatible product from the distribution centre. Nonetheless, it is highly desirable to avoid such measures to provide patients with appropriate blood products. The observed effects of information sharing on the reduction of both mismatches and shortages can be used by blood supply services to drive changes in information sharing within the supply chain design.

It is crucial to emphasize that the results and improvements as demonstrated by our simulations are confined within the specific parameters and assumptions decided for this study. As each of these decisions stems from simulations being an approximate representation of reality, both necessary and unavoidable simplifications were incorporated in the simulations. These assumptions impact the way model outputs should be interpreted with respect to the real world, rather than their potential for practical applicability. First, the model optimizes matching over a day, as if all requests for a given day were known and could be optimized together. In reality, orders may come in one after the other, and units already given are not available anymore. Second, the data used to represent patients and supplied RBC products are limited. Data on patient group distributions were based only on two hospitals, and actual lead times for requests likely exhibit greater variation than included in our simulations. In addition, for patient groups SCD, Thal, AIHA and MDS, we assumed a demand of two units for each request, whereas in reality, there is more variation in the number of units requested. Finally, we did not account for units

that are requested for transfusion but are returned to hospital stock, which is quite common in practice. Particularly for patients undergoing surgery, a surplus of blood products is typically reserved for use only in cases of excessive blood loss. Unused units will return to inventory and a foreseen mismatching unit will in fact not result in a mismatch, indicating that the estimated number of mismatches is an overestimation. However, the risk of outdating will increase when issued units are (repeatedly) not transfused. Neither of these effects is accounted for in our model and will be a topic for future research.

In this study, we considered patient group-specific mismatch weights, which are calculated as the product of three elements: relative immunogenicity, antigen weight and patient group weight (as discussed in Supplement A). It is important to acknowledge that only one of these elements (immunogenicity) is obtained from empirical experiments and that the other two rely on expert opinion. Future research might aim to investigate and improve these estimates (and weights). Moreover, the model's second objective function balances the number of mismatches, minor antigen substitution, the age of the issued products and their usability. The overall matching quality is likely to benefit from more research on how to best balance these objectives.

More research is necessary to support steps towards potential implementation of (automated) extended matching in hospital practice. In an ideal world, information regarding RBCs is included in the planning for the distribution of all RBCs throughout the supply chain, as soon as it becomes available. In a future where all donors have been typed on all clinically relevant antigens and information on RBC requests is shared immediately with the blood bank, it may even become possible to guide donor invitations to provide the best quality blood products to all patients.

ACKNOWLEDGEMENTS

The work presented in this paper is inspired by the work performed by R.H.G.W. for his master's degree in Computing Science at Utrecht University (the Netherlands) under supervision of H.H. and M.P.J. This work was established as part of the Stichting Sanquin Bloedvoorziening grant PPOC20-05/L2490. The work of F.B.O. was funded by the NIHR under an Artificial Intelligence in Health and Care Award (AI Award 02331) and through the NIHR BTRU in Donor Health and Behaviour (NIHR203337) and the NIHR Cambridge BRC (BRC-1215-20014; NIHR203312).

M.L.W. wrote the initial draft for this article in collaboration with M.P.J; data on donor and patient distributions were obtained by J.S.L. All authors contributed to, revised and approved the final manuscript. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The simulation code is available from https://github.com/Sanquin/blood_matching.

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SUPPORTING INFORMATION

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

How to cite this article: Wemelsfelder ML, van de Weem RHG, Luken JS, de Haas M, Niessen RWLM, van der Schoot CE, et al. Extensive red blood cell matching considering patient alloimmunization risk. Vox Sang. 2024.