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Preventing alloimmunization using a new model for matching extensively typed red blood cells

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Abstract

Background and Objectives: Alloimmunization is a well-known adverse event associated with red blood cell (RBC) transfusions, caused by phenotype incompatibilities between donor and patient RBCs that may lead to haemolytic transfusion reactions on subsequent transfusions. Alloimmunization can be prevented by transfusing fully matched RBC units. Advances in RBC genotyping render the extensive typing of both donors and patients affordable in the foreseeable future. However, the exponential increase in the variety of extensively typed RBCs asks for a software-driven selection to determine the 'best product for a given patient'.

Materials and Methods: We propose the MINimize Relative Alloimmunization Risks (MINRAR) model for matching extensively typed RBC units to extensively typed patients to minimize the risk of alloimmunization. The key idea behind this model is to use antigen immunogenicity to represent the clinical implication of a mismatch. Using simulations of non-elective transfusions in Caucasian donor and patient populations, the effect on the alloimmunization rate of the MINRAR model is compared with that of a baseline model that matches antigens A, B and RhD only.

Results: Our simulations show that with the MINRAR model, even for small inventories, the expected number of alloimmunizations can be reduced by 78.3% compared with a policy of only matching on antigens A, B and RhD. Furthermore, a reduction of 93.7% can be achieved when blood is issued from larger inventories.

Conclusion: Despite an exponential increase in phenotype variety, matching of extensively typed RBCs can be effectively implemented using our MINRAR model, effectuating a substantial reduction in alloimmunization risk without introducing additional outdating or shortages.

KEYWORDS
alloimmunization, matching, mathematical model, red blood cells

Highlights

- Extended matching is feasible in practice.
- Novel strategy for issuing extensively typed RBCs.

- Extended matching can substantially reduce alloimmunization risks.

INTRODUCTION

Red blood cells (RBCs) are the most common transfused blood product. In most Western countries, between 20 and 40 RBC units per 1000 inhabitants are transfused per year [1]. Nevertheless, blood transfusion can have side effects, of which alloimmunization is one of the most common [2, 3]. Selection of matched blood units is often restricted to the ABO blood group and RhD antigen, and only for certain recipients, more extensively matched units are routinely selected. In case a unit that is mismatched for certain blood group antigens is transfused, there is a risk that the immune system of the recipient will produce red blood cell alloantibodies (alloimmunization) that might result in the destruction of transfused RBCs in subsequent transfusion episodes [4–6]. Therefore, once a patient is alloimmunized against a specific antigen, all subsequent transfusions must be matched for this antigen to prevent acute or delayed transfusion reactions.

Recent advances have resulted in affordable RBC genotyping technology that can be applied on a large scale [7, 8]. In the near future, this technology will allow extensive typing of donors, thereby increasing the availability of typed antigen negative RBC units. But more importantly, when more patients are typed as well, preventive matching for antigens other than A, B and RhD will become possible for more, if not for all patients. However, with the exponential increase in the number of possible phenotype profiles with respect to the antigens considered (for each additional antigen considered, the number of different blood products will roughly double which implies exponential growth per definition), the likelihood of being able to provide all recipients with matched products will diminish.

Another challenge for large-scale extensive matching is that different patient groups have different priorities for receiving extensively matched RBCs. For example, in the Netherlands, female blood recipients aged <45 years receive cEK-matched blood to prevent antibody-mediated haemolytic disease of the foetus and new-born [9]. In many countries, including the Netherlands, certain patient groups at high risk of alloimmunization, such as those with high level of transfusion support (myelodysplasia [10] and thalassemia) and those with higher tendency of alloimmunization (autoimmune haemolytic anaemia [11] and sickle cell disease (SCD) [12]), receive additional matching. The latter group is notoriously hard to match with RBCs of a mainly Caucasian population, as they have a different RBC phenotype profile due to their predominantly African roots [13]. A requirement for the introduction of large-scale extensive matching is that the availability of antigen matched units for the aforementioned patient groups should not decrease when more patients receive extensively matched RBCs.

The feasibility of large-scale extensive antigen matching has not yet been widely studied. When investigating the matching of extensively typed RBC units to patients, previous studies first define several stringency levels of antigen matching and subsequently investigate the availability of units for these levels under strict matching regimes [14–16]. In terms of maximizing the matching potential of an extensively typed RBC inventory and patient population, these approaches all have the same limitation: the availability of matching RBC units (and thereby the overall matching quality) is heavily influenced by the (often non-trivial) choice of matching levels. In this study, we present a novel and more flexible issuing strategy that can be used to assign RBC units to patients. The aim of this issuing strategy is to provide all patients with suitable RBC units without introducing any additional shortages or outdating of RBCs. Thus, the objective is to minimize the expected number of alloimmunizations over all transfused patients. This is achieved by using a penalty-based approach to prevent mismatches, instead of forcing strict matching requirements for a fixed set of minor antigens. Although the model does not differentiate between patients of different categories, its penalty-based structure should pave the way for more refined issuing strategies where patient-specific circumstances are taken into consideration as well.

MATERIALS AND METHODS

Managing an RBC inventory involves carefully balancing supply and demand. Hospitals receive daily requests for RBC units that must be allocated from the hospital inventory. To avoid shortages, the inventory is periodically supplied with fresh RBC units, usually triggered by inventory levels. The distribution centres from the blood supplier have a similar balancing process, but instead of daily requests, they must satisfy hospital orders and invite new donors to ensure a steady flow of RBC units. For the purpose of this research, we presume an RBC inventory that is presented with direct requests from patients, and that can only order ABO-RhD-specific blood units. Each day, requests become known at the beginning of the day and a predefined allocation strategy assigns units to requests. As a baseline, we will use the FIFO/MROL model for ABO-RhD matching (further referred to as

TABLE 1 Antigen immunogenicity

Minor antigens	C	c	E	e	K	Fy^a	Fy^b	Jk^a	Jk^b	M	S
Number of alloimmunizations per 1000 patients exposed to two mismatching units (a_k)	2.1	4.3	14.6	5.1	23.4	2.7	0.8	5.1	0.2	1.8	0.8

Note: Clinically relevant minor antigens and their immunogenicity expressed as expected number of patients alloimmunized per 1000 mismatched patients (after exposure to two antigen positive units) [4].

ABOD) of van Sambeeck et al. [14]. This issuing policy forces all units to be matched for ABOD and computes a maximal assignment, meaning that as many matched units are issued as possible. This model ignores all other antigens and is therefore comparable to the matching strategy currently applied for the majority of RBC transfusions in the Netherlands. For further details on the FIFO/MROL model, we refer the reader to the original publication. [14] Our proposed allocation strategy uses antigen immunogenicity to determine the penalty for mismatching on a particular antigen. The antigens considered and their immunogenicities as estimated by Evers et al. [4] in an incident new-user cohort of 21,512 previously non-transfused, non-alloimmunized Caucasian patients receiving ABOD matched red cell transfusions are shown in Table 1. We restricted ourselves to 11 (minor) antigens, as alloimmunization against these antigens represent 95% of the induced clinically relevant alloantibodies. We used the alloimmunization incidence reported for exposure to two units, as this was the only exposure level where data for all 11 antigens considered were available.

The majority of hospitalized patients require more than one RBC unit per transfusion episode (61%, based on Dutch historical in-hospital data from 2012 until 2019) [17]. This implies that the exposure to foreign antigens can range from one to multiple units. In our model, mismatches are presumed to be binary events: a patient is either exposed to a foreign antigen within a transfusion episode or not, and the probability of antibody development is not dependent on the number of mismatched transfusions given during one transfusion episode. This assumption is in line with the recent publication of Yazer et al. who found no significant dosage effect in RhD-alloimmunization rates among exposed transfusion recipients [18]. By ignoring the level of exposure, we maximize the proportion of patients for which exposure is prevented. With these assumptions, we can define the daily allocation problem as an integer linear programming (ILP) model [19] which is solved using Gurobi Optimization software [20].

Matching strategy model

First, we define the decision variables that represent the decisions that must be taken in the allocation problem

$$x_{ij} = \begin{cases} 1 & \text{if patient } i \text{ is assigned unit } j \\ 0 & \text{otherwise} \end{cases}$$

$$s_i = \begin{cases} 1 & \text{if patient } i \text{ cannot beassigned(shortage)} \\ 0 & \text{otherwise} \end{cases}$$

$$y_{ik} = \begin{cases} 1 & \text{if patient } i \text{ is mismatched on antigen } k \\ 0 & \text{otherwise} \end{cases}$$

And the following parameters:

$$u_i = \text{the number of units requested by patient } i$$

$$\varphi_i(k) = \text{presence of antigen } k \text{ in phenotype of patient } i \quad (1 \text{ if present}, 0 \text{ if not present})$$

$$\varphi_j(k) = \text{presence of antigen } k \text{ in phenotype of unit } j \quad (1 \text{ if present}, 0 \text{ if not present})$$

$$\widehat{a}_k = \frac{a_k}{\sum_{k'} a_{k'}} = \text{normalized immunogenicity}$$

$$c_{ij} = \begin{cases} 1 & \text{if unit } j \text{ is ABOD matched with patient } i \\ 0 & \text{otherwise} \end{cases}$$

Now, we can define the objective function to be minimized. This function should firstly minimize the number of shortages and secondly minimize the total mismatch cost:

$$\text{minimize } M\sum_i s_i + \sum_i \sum_k y_{ik}\widehat{a}_k \quad (1)$$

Here, M is a large number to ensure that the prevention of shortages is always prioritized. Lastly, we define the valid solution space by defining the constraints that govern the validity of the decision variables.

$$\sum_j x_{ij} + s_i u_i = u_i \ \forall i \quad (2)$$

$$\sum_i x_{ij} \le 1 \ \forall j \quad (3)$$

$$\sum_j x_{ij}\varphi_j(k) \le y_{ik}u_i \ \forall i \forall k \text{ if } \varphi_i(k) = 0 \quad (4)$$

$$x_{ij} \le c_{ij} \ \forall i \forall j \quad (5)$$

$$x_{ij}, y_{ik}, s_i \in \{0,1\} \ \forall i \forall j \forall k \quad (6)$$

Constraint (2) forces all demand to be satisfied or a shortage is incurred. Constraint (3) allows each unit to be issued no more than once. Constraint (4) forces y_{ik} to one if patient i is mismatched on antigen k. Constraint (5) forbids any ABOD mismatches and constraint (6) forces all variables to be binary. This ILP, which we will refer to as the MINRAR model (MINimize Relative Alloimmunization Risks), can be used to optimally allocate units to patients on a single day. Note that the scope of the model does not have to be a single day. Instead, it can be any period (e.g., the time between two supply moments).

The issuing of RBC units to patients is not a standalone problem as decisions made on the current day will also affect the matching potential for the next day(s). To account for this, we adjust the MINRAR model to perform in an *online* setting. An online problem is one that requires iterative solving as the problem presents itself. In this case, the inventory changes whenever units are being added or issued. This requires taking into account two additional factors:

1. Prevention of outdating: RBC units have a maximum shelf life of 35 days. Thus, there should be a preference for issuing older units.
2. Limiting antigen substitution: The issuing of antigen negative blood to a positive patient (substitution) should be avoided to prevent an accumulation of antigen positive units.

To make older RBC units preferable for issuing, we use the First In First Out (FIFO) discount function as proposed by van Sambeeck et al. [14]:

$$o(r_j) = \left(\frac{1}{2}\right)^{\frac{r_j}{5}} \tag{7}$$

Here, r_j is the remaining shelf life of unit j. This exponential implies that the discount factor for issuing unit j doubles every 5 days, until it is one when the remaining shelf life is zero. Limiting antigen substitution is more complex, as different antigens have different clinical implications. Major antigens A, B and RhD determine whether a match is possible and heavy substitution leads to a reduction of O type blood in inventory which potentially leads to subsequent shortages. Minor antigen substitutions have no effect on shortages. Instead, these will only lead to a reduction of antigen negative blood in stock which will likely increase the number of future mismatches. Hence, we add two penalty terms to address each of these problems separately.

First, we define the *usability* of a phenotype, which is the probability that the phenotype is matched with a random phenotype on the antigens in set Λ [14].

$$U_\Lambda(\varphi) = \sum_{\varphi' \leq_\Lambda \varphi} p(\varphi) \tag{8}$$

Here, $p(\varphi)$ denotes the prevalence of phenotype φ in the population, and $\varphi' \leq_\Lambda \varphi$ are all phenotypes φ' matching with φ on the antigens in Λ. We can now define the *Major antigen substitution* penalty as the difference in usability between the phenotype of a candidate unit for matching (φ_j) and the phenotype of the patient (φ_i):

$$A_{\text{Major}}(\varphi_j, \varphi_i) = U_{\{A,B,D\}}(\varphi_j) - U_{\{A,B,D\}}(\varphi_i) \tag{9}$$

The value of this term represents the transfusion potential lost by assigning unit j to patient i.

The *Minor antigen substitution* penalty is not determined by the usability of the product, but by its immunogenicity:

$$A_{\text{Minor}}(\varphi_j, \varphi_i) = \sum_{k \mid k \notin \{A,B,D\}} \hat{a}_k \left(1 - \varphi_j(k)\right) \varphi_i(k) \tag{10}$$

The penalty is the sum of all minor antigen substitutions, weighted by their immunogenicity ($\hat{a}_k$). A match without any negative-to-positive antigen combinations will thus have a penalty of zero.

We extend the original objective function (Equation (1)) with these three new terms (FIFO penalty and Major and Minor antigen substitution) as shown in Equation (11). However, we do not change any constraints or decision variables, as the solution space (all allowed combinations of variable values) remains the same, which means that the conditions from Equations (2)–(6) still apply. Note that the additional penalty terms will improve the performance of the model in the long run.

$$\begin{aligned} \text{minimize } & M \sum_i s_i + \sum_i \sum_k [y_{ik} \hat{a}_k] - \sum_j o(r_j) \\ & + \sum_i \sum_j \left[A_{\text{Major}}(\varphi_j, \varphi_i) + A_{\text{Minor}}(\varphi_j, \varphi_i)\right] \end{aligned} \tag{11}$$

Simulations

To assess the performance of the proposed allocation strategy, multiple one-year simulations of different sized RBC inventories were performed. Each simulation is preceded by an initialization period of 1 month to allow the inventory to reach a steady-state distribution for the ABOD blood types. During each simulation, RBC units and patients with random phenotypes are generated. The antigen profiles of RBC units were sampled in accordance with the historical ABOD blood type distribution of RBC units in the Netherlands. The remaining antigens were sampled according to the antigen prevalence in the Caucasian population (also considering the linkage between *RHD* and *RHCE* alleles) [21]. The prevalence per antigen corresponds to the actual distribution of antigens in the donor population, as these play no role in donor selection. Patient phenotypes were fully sampled Caucasian phenotype prevalences [21]. The number of units requested per patient was sampled from an empirical distribution of historical in-hospital requests obtained from the Dutch Transfusion Datawarehouse and consisted of 438,260 transfusions given between January 2012 and December 2019 in six Dutch hospitals [17]. Requests for five or more units (3.07%) were omitted, as these are deemed out of scope for an extensive matching algorithm. Such requests are often not elective, and extensive matching is of less value, since the primary concern in these cases is to maintain the patient's RBC volume. Emergency requests can be allocated from a separate smaller emergency inventory or from the regular inventory followed by a new optimization to reallocate the remaining units to regular patients. Patients with a periodic (chronic) demand for RBC units were not explicitly included, and neither were patients with alloantibodies, mainly due to the absence of historical data for the frequency of these patients and their corresponding alloantibodies.

Five different sized inventories with an average daily demand of 25, 50, 100, 200 and 500 RBC units, respectively, were simulated. In each simulation, the inventory size used is equal to five times the average daily demand, which is most common in the Netherlands. In the Netherlands, hospital inventories are relatively small, as they can have units delivered from Sanquin distribution centres within 1 h if necessary. We have not implemented this feature in our simulations, as it confounds the capability of the matching policy itself. In our simulations, units with major antigens issued (or outdated) on the previous day are replenished at the beginning of each day. Each of these units has a set of randomly assigned minor antigens in accordance

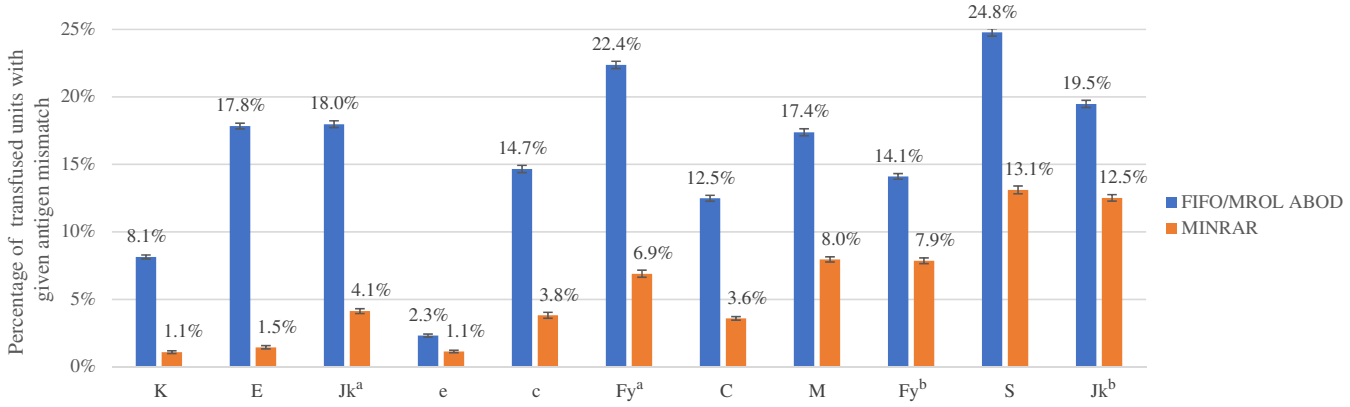

FIGURE 1 Percentage of transfused units with antigen mismatches using the FIFO/MROL ABOD and MINRAR issuing strategies for a random average daily demand of 100 red blood cell units (inventory size 500 units)

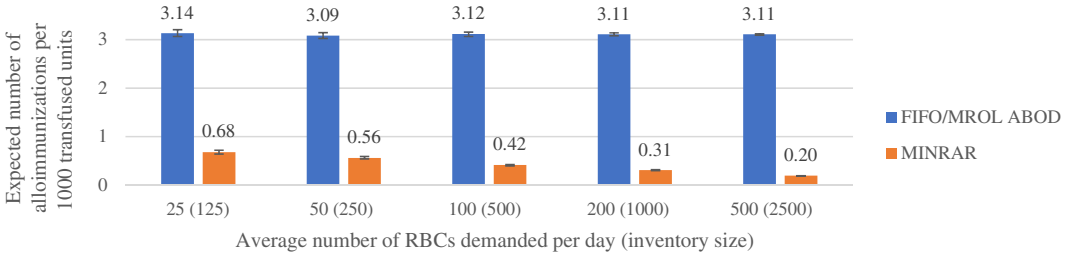

FIGURE 2 Approximation of the expected number of alloimmunizations per 1000 transfused units using the FIFO/MROL ABOD and MINRAR issuing strategies for five different sized inventories

with the donor population prevalence. This policy eliminates shortages and outdating caused by supply irregularities. The daily demand was sampled from fitted distributions per day of the week based on historical data (total issued RBC units per day by Sanquin, the Dutch blood bank, during 2009 and 2019, obtained from *eProgesa*, the ICT management system of Sanquin), and downscaled to match the average daily demand of 25, 50, 100, 200 and 500 RBC units used in the simulations.

For each antigen, we report the percentage of units transfused that mismatch on that antigen. Furthermore, we computed an estimate of the expected number of alloimmunizations per 1000 transfused units. Translating the number of mismatches into an expected number of alloimmunizations is not straightforward. However, an approximation can be made using the alloimmunization incidence estimates from Table 1. First, we assume that within a single transfusion episode, a patient can only be exposed once per foreign antigen, meaning that the transfusion of 1, 2, 3 or 4 mismatching units is treated as one exposure. This approach is used as we presume that in general, the level of exposure needed to potentially trigger alloimmunization is already reached with the transfusion of one mismatching unit. Although the risk of alloimmunization increases with the amount of exposure, this concerns exposures over time rather than the level of exposure within a single transfusion episode. To estimate the total number of alloimmunizations, the number of patients exposed per antigen is multiplied with the corresponding alloimmunization incidence from Table 1. Note that the data presented in Table 1 from the original paper [4] reflect an exposure to two units. As we only model one exposure event, the final penalty is therefore divided by two.

The C++ code for the simulations can be obtained from the corresponding author upon request.

RESULTS

In Figure 1, the percentage of transfused units that mismatch on a particular antigen is shown for both issuing strategies. These results are averages of 1-year simulations of a 500-unit inventory with an average daily demand of 100 random units. The figure shows a reduction in mismatches for every antigen in line with the aim of the MINRAR issuing strategy (which is to minimize the risk of alloimmunization over all patients). The effect of these reductions in terms of the expected number of alloimmunizations prevented is shown in Figure 2. A table with more details on the outcomes of the simulations (including the percentage of shortage and outdating) can be found in Supplementary Materials (Appendix S1). Our results show that the gain of extensive matching with the MINRAR issuing strategy compared with a matching policy limited to antigens A, B and RhD can, even for small inventories, provide a decrease in alloimmunization risk of 78.3%. This risk can be further reduced when the matching is

performed more centralized, for example in distribution centres with larger inventories. In the largest scenario that was analysed (2500 RBC unit inventory and average daily demand 500 units), the expected number of alloimmunizations is 0.20 per 1000 transfused units, compared with 3.11 for the FIFO/MROL ABOD policy, which implies a reduction of the alloimmunization risk of 93.7%. Note that this reduction is achieved without an increase in shortages or outdating and pertains to a demand of RBCs with a previously unknown phenotype profile.

DISCUSSION

In this study, we investigated the feasibility of extensive RBC matching for genotyped donors and patients. We proposed the MINRAR model for allocation of RBC units to patients to minimize the risk of alloimmunization for all patients. Figure 1 shows that substantial reductions in antigen mismatches are possible, while Figure 2 shows that these reductions translate to a substantial reduction in alloimmunization incidence. We note that the approximation used to estimate the expected number of alloimmunizations ignores the magnitude of antigen exposure per transfusion episode. This favours the results of the MINRAR issuing strategy, as this strategy will actively 'bundle' antigen mismatches such that exposure can be prevented for a maximum number of patients whenever mismatch-free issuing is not possible. However, we argue that ignoring the magnitude of antigen exposure within a transfusion episode is both justifiable (as was explained earlier) and favourable for the overall patient population in terms of preventing alloimmunization and therefore the best method of approximation.

As mentioned in the introduction, patient-specific circumstances play an important role in determining the clinical implication of a mismatch on a particular antigen. Currently, mismatch penalties in the MINRAR model are solely based on immunogenicity. However, the MINRAR model can be easily adapted to weigh clinical aspects that determine the implications of a mismatch for a specific patient group. For example, mismatches for SCD patients could be given much larger penalties than similar mismatches for regular patients. Although the effect of such an extension to the MINRAR model with penalties dependent on both the mismatched antigen and transfusion recipient patient group has already been preliminary studied [22], the viability of extended matching hinges on the availability of extensively matched units for patient groups for which there is an increased incentive for preventing alloimmunization. Further research should provide insight into how extended matching can be implemented without a loss of matching quality for those patient groups.

The results in Figures 1 and 2 show that the application of the MINRAR model leads to a substantial reduction in the expected number of alloimmunizations. More difficult to see is how well the MINRAR model performs in absolute sense. To evaluate the quality of allocation, we can compare the matching result to the *best possible allocation* for a given simulation by assigning RBC units to patients retrospectively. Looking back on the RBC supply and demand over a finished simulation, one can determine what the very best allocation possible would have been if one would have been able to look into the future. In Appendix S2, we show a comparison between the MINRAR model and this optimal (retrospective) allocation. These results show that the allocation obtained by the MINRAR strategy is close to the best possible allocation. The amount of alloimmunization preventable by retrospective issuing—relative to the MINRAR strategy—is comparable to the expected alloimmunization induced by ignoring antigens M, S or C. Considering that the MINRAR model has no knowledge of future supply and demand, we can conclude that the MINRAR strategy provides a near-optimal solution.

In addition to optimizing specific allocation strategies, the MINRAR model can also be used to address policy issues. One example is how antigen matching is affected by the heterogeneity of donor and recipient populations. In Appendix S3, we show the impact of a varying mix of Caucasians and individuals of African descent on the level of alloimmunization for both ethnic groups. These results show that the alloimmunization risk for individuals of African descent increases substantially (up to 60%) when supplied from a 98% Caucasian population, whereas in a more heterogeneous population (80% Caucasian, 20% African descent), this increase is limited (4.9%). Lastly, we note that all the results presented are limited to alloimmunization against the antigens included in Table 1, which are most relevant for Caucasians. However, the MINRAR model can be applied for any mixture of ethnic populations and number of antigens, given that their immunogenicity can be estimated.

With the advancements in genotyping technology and foreseen reduction in its costs, the implementation of extensive antigen matching becomes more and more realistic. In contrast, the exponential increase in the number of phenotypes when considering more minor antigens—with the 14 antigens considered, there are 3168 different blood groups in Caucasians alone—would suggest that extensive matching would not be feasible in practice. However, we have shown that matching on all clinically relevant antigens can almost fully eliminate the risk of transfusion induced alloimmunization. Using the MINRAR allocation model to iteratively compute an assignment of RBCs to patients even for a small inventory, one can prevent 78.3%, and possibly even up to 93.7% of expected alloimmunizations that would have occurred when matching for antigens A, B and RhD alone. The decrease in alloimmunization risk for larger inventories indicates that more advanced matching strategies, whereby the decision on RBC allocation is organized at a more centralized level (e.g., at a large distribution centre), may reduce this risk even further. In addition, the model and current simulations presume that all RBC requests are non-elective and that the antigen composition of patient RBCs is unknown until requested. As in practice, a substantial proportion of transfusions are elective; the potential alloimmunization reduction achievable by extended matching will be higher than indicated by our current results. At present, however, most effort should be directed towards investigating the financial viability of large-scale

extensive matching as well as other operational and organizational challenges resulting from changes in matching policy. Nonetheless, our research shows that a substantial reduction in alloimmunization can be achieved without any increase in outdating or shortages, even if RBC allocation remains at hospital level. With such promising results, we have demonstrated the practical feasibility and potential in alloimmunization prevention of extended matching which should lead to an improved safety of future RBC transfusions.

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CONFLICT OF INTEREST

We declare no conflict of interest.

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REFERENCES

1. Janssen M, Rautmann G. The collection, testing and use of blood and blood components in Europe. Eur Dir Qual Med Healthc EDQM Counc Eur; 2014.
2. Serious Hazards Of Transfusion. SHOT report 2019. Available from: https://www.shotuk.org/shot-reports/report-summary-and-supplement-2019/
3. Transfusion and Transplantation Reactions in Patients TRIP Hemovigilance report 2020. Available from: https://www.tripnet.nl/wp-content/uploads/2020/08/Trip.HEMO_uitgebreid_ENGdef2020-4.pdf
4. Evers D, Middelburg RA, de Haas M, Zalpuri S, de Vooght KM, van de Kerkhof D, et al. Red-blood-cell alloimmunisation in relation to antigens' exposure and their immunogenicity: a cohort study. Lancet Haematol. 2016;3:e284–92.
5. Giblett ER. A critique of the theoretical hazard of inter vs. intra-racial transfusion. Transfusion. 1961;1:233–8.
6. Tormey CA, Stack G. Immunogenicity of blood group antigens: a mathematical model corrected for antibody evanescence with exclusion of naturally occurring and pregnancy-related antibodies. Blood. 2009;114:4279–82.
7. Flegel WA, Gottschall JL, Denomme GA. Implementing mass-scale red cell genotyping at a blood center. Transfusion. 2015;55:2610–5.
8. Lane WJ, Vege S, Mah HH, Lomas-Francis C, Aguad M, Smeland-Wagman R, et al. Automated typing of red blood cell and platelet antigens from whole exome sequences. Transfusion. 2019;59:3253–63.
9. Luken JS, Folman CC, Lukens MV, Meekers JH, Ligthart PC, Schonewille H, et al. Reduction of anti-K-mediated hemolytic disease of newborns after the introduction of a matched transfusion policy: a nation-wide policy change evaluation study in the Netherlands. Transfusion. 2021;61:713–21.
10. Evers D, Zwaginga JJ, Tijmensen J, Middelburg RA, de Haas M, de Vooght KMK, et al. Treatments for hematologic malignancies in contrast to those for solid cancers are associated with reduced red cell alloimmunization. Haematologica. 2017;102:52–9.
11. Engelfriet CP, Reesink HW, Garratty G, Knight R, de Silva M, Contreras M, et al. The detection of alloantibodies against red cells in patients with warm-type autoimmune haemolytic anaemia. Vox Sang. 2000;78:200–7.
12. Meinderts SM, Gerritsma JJ, Sins JWR, de Boer M, van Leeuwen K, Biemond BJ, et al. Identification of genetic biomarkers for alloimmunization in sickle cell disease. Br J Haematol. 2019;186:887–99.
13. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4:327–55.
14. van Sambeeck JHJ, van Brummelen SPJ, van Dijk NM, Janssen MP. Optimal blood issuing by comprehensive matching. Eur J Oper Res. 2022;296:240–53.
15. Klapper E, Zhang Y, Figueroa P, Ness P, Stubbs J, Abumuhor I, et al. Transfusion practice: toward extended phenotype matching: a new operational paradigm for the transfusion service. Transfusion. 2010;50:536–46.
16. Wilkinson K, Harris S, Gaur P, Haile A, Armour R, Teramura G, et al. Molecular blood typing augments serologic testing and allows for enhanced matching of red blood cells for transfusion in patients with sickle cell disease. Transfusion. 2012;52:381–8.
17. van Hoeven LR, Hooftman BH, Janssen MP, de Bruijne M, de Vooght K, Kemper P, et al. Protocol for a national blood transfusion data warehouse from donor to recipient. BMJ Open. 2016;6:e010962.
18. Yazer MH, Triulzi DJ, Sperry JL, Seheult JN. Rate of RhD-alloimmunization after the transfusion of multiple RhD-positive primary red blood cell-containing products. Transfusion. 2021;61:S150–8.
19. Schrijver A. Theory of linear and integer programming. Chichester: John Wiley & Sons; 1998.
20. Gurobi Optimization L. Gurobi optimizer reference manual; 2021. Available from: http://www.gurobi.com
21. Reid ME, Lomas-Francis C, Olsson ML. The blood group antigen factsbook. San Diego, CA: Elsevier Science and Technology; 2012.
22. Van de Weem RHG. Comprehensive red blood cell matching. Utrecht: Utrecht University; 2020 Available from: https://dspace.library.uu.nl/handle/1874/401212

SUPPORTING INFORMATION

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

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