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The incidence of red cell alloimmunisation and means for its prevention

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In this issue of *The Lancet Haematology*, Johanna van der Bom with Dorothea Evers and colleagues report a cohort study of 21,512 previously non-transfused, non-alloimmunised patients in The Netherlands, who received red cell transfusions matched only for the ABO and D antigens.¹ Many such studies have been reported over more than 60 years² and continue to be worthwhile³ as exemplified by the current study. Beyond the sheer size of the cohort, this study¹ was able to estimate the incidence of alloimmunisation dependent on the cumulative number of antigen-mismatched red cell transfusions, which added much fresh data to the literature.

Prophylactic matching for the C, E, c, e; and K antigens is standard for distinct patient groups in the Dutch¹ and for all women of childbearing age and girls, for instance, in the German health care systems. Only budgetary constraints limited this strategy's application to all recipients of red cell transfusions. The authors recommend prophylactic matching for the C, E, c; K; and Jk^a antigens as the primary and most efficient goal in preventing alloimmunisation.¹ This goal can be achieved with today's immunohaematologic techniques and is an example of precision medicine.

The supply of red cell units typed for the Jk^a antigen may be an issue. Most donors are routinely typed for the C, E, c, e; and K antigens throughout Europe, although less so in North America. Large scale serologic Jk^a antigen typing, however, is rarely performed, as it is technically more demanding and hence unlikely to be performed inexpensively. The authors mention one platform for red cell genotyping⁴ and another large scale, high throughput approach has recently been published in this journal.⁵ While this new technology is transformative, its implementation for routine blood supply has faced impediments for many years in our cost-conscious health care environment.^{6,7} Clinicians need to choose wisely when deciding which resources should be allocated to immunohaematology. Red cell genotyping is more cost effective in the long run. An upfront investment will yield a long term improvement in quality, safety and efficiency.⁶ Why not make a leap forward with a price tag equivalent to what several small steps would cost?

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Estimating the costs of implementing the authors' recommendation in their health care system was beyond the scope of the current study.¹ Although we need cost estimates before we can adopt the authors' recommendation, costs may prove more favourable than anticipated. We can learn from previous lessons in immunohaematology. There are several examples of transformative technologies whose implementation was much delayed by cost considerations but later turned out to be highly cost efficient.⁸ Another pharmacogenomics strategy, precision medicine based on molecular blood group data, was not included in international guidelines or recommendations until 15 years after the technology became available, when, following financial calculations, it was appreciated that such clinically beneficial red cell genotyping could be implemented without increasing overall costs.⁹ After all, don't improvements sometimes cost more? We see that everywhere. Improvements do not have to be cost neutral or save money. A risk-benefit calculation, as much as a cost-benefit calculation, ought to be applied to red cell alloimmunisation.

If prevailing market forces prevent implementation,⁶ one may adjust reimbursement for blood units⁷ or resort to regulation and guidelines.⁸ The preferred approaches will differ, as the structures of health care systems vary. However, the clinical priorities set by haematologists are a key factor in determining the direction and speed of implementation in any health care system. Not capturing cost efficiencies and delaying the implementation of technologies proven to benefit patients¹⁰ are rarely good strategies.

The authors rightfully caution against extrapolating their conclusions to non-Caucasian populations.¹ However, the prevalence of antigens is similar enough to allow the extrapolation to all Caucasian populations. The prevalence of the 2 major antigens in the JK blood group system is comparable and may allow extrapolating to Asian, less so to the African, populations. Adjustments may be needed for matching strategies of the C, E, c, e antigens in Asians and Africans, while the concern for the K antigen is almost exclusive to red cell units from Caucasian donors. Focussing on the Dutch health care system, with Caucasian patients comprising almost 90% of the total, limited extrapolation but strengthened the conclusions: the service was provided to a well-defined population with minimal variation in transfusion policies and laboratory techniques, computerized data management, and consistent patient follow up.¹ These are all features that make the current study worthwhile, despite its topic having been addressed and published quite regularly over many decades.³ Although the details will vary, the overall concept and technologies for avoiding alloimmunisation in non-Caucasian populations may be quite similar to those proposed in the current study.

Matching antigens in large patient cohorts is uncommon beyond ABO and D antigens in North America and beyond ABO; D, C, E, c, e; and K antigens in Europe, because it meets countless logistical and financial challenges.¹ It does not have to be that way. Fatalities caused by transfusions are rare, but non-ABO antibodies have been well documented in all international hemovigilance reports for more than 2 decades as one of the 3 leading causes of such fatalities. Additional cost, delays in supply of compatible blood, and some limited morbidity, such as hemolysis, caused by non-ABO antibodies are common and may affect patient treatment in more ways than we routinely monitor. Have we become complacent because these side effects couldn't be avoided in the past? The rationale to act, despite

additional costs, is obvious for any other drug, if its potentially lethal adverse effect can be prevented by newly available technology and between 2.2% to 7.7% of all treatment-naïve patients¹ are at risk.

The currently proposed routine matching for C, E, c; K; and Jk^a antigens could be implemented using serology, but will fall more easily into place once red cell genotyping becomes standard.¹ Matching patients and blood units by genotype, a process dubbed dry matching,⁸ would benefit patients by reducing 78% of all alloimmunisations, as much as serological matching would in the studied cohort,¹ and cannot hurt any patient with the current safeguards in place. Many similar, small incremental improvements in antigen-matching beyond the C, E, c; K; and Jk^a antigens, to personalize medicine for the transfusion recipients, could add up to an even more substantial benefit for patient care. Education of medical staff and training of laboratory personnel are needed in addition to the resources required for equipment and consumables in the clinical laboratories.

How much more evidence and cost efficiency calculations do we require before addressing the well-defined, potentially lethal, adverse effects of red cell transfusion, such as delayed hemolysis by anti-Jk^a and other blood group antigens? The new technologies available to further curtail and possibly eliminate the major factors of antibody-mediated hemolysis beyond the ABO and D antigens, are ready to be implemented in patient care, whenever the clinical evidence and benefit are considered sufficient by the clinicians. As stated in this journal last year, “implementation of mass-scale genotyping for blood donors as a routine procedure is a win-win situation for patients and hospitals.”⁶ We need to establish means for reimbursing the institutions performing red cell genotyping.

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References

1. Evers D, Middelburg RA, de Haas M, Zalpuri S, de Vooght KM, van de Kerkhof D, Visser O, Péquériau NC, Hudig F, Schonewille H, Zwaginga JJ, van der Bom JG. Red cell alloimmunization in relation to antigens' exposure and their immunogenicity: a cohort study. *Lancet Haematol*. 2016
2. Tormey CA, Stack G. The persistence and evanescence of blood group alloantibodies in men. *Transfusion*. 2009; 49:505–12. [PubMed: 19040411]
3. Flegel WA. A rewarding fresh look at routine blood group data. *Blood Transf*. 2008; 6:182–3.
4. Avent ND, Martinez A, Flegel WA, Olsson ML, Scott ML, Nogues N, Pisacka M, Daniels GL, Muniz-Diaz E, Madgett TE, Storry JR, Beiboer S, Maaskant-van Wijk PM, von ZI, Jimenez E, Tejedor D, Lopez M, Camacho E, Cheroute G, Hacker A, Jinoch P, Svobodova I, van der SE, de HM. The Bloodgen Project of the European Union, 2003–2009. *Transfus. Med. Hemother*. 2009; 36:162–7. [PubMed: 21113258]
5. Flegel WA, Gottschall JL, Denomme GA. Integration of red cell genotyping into the blood supply chain: a population-based study. *Lancet Haematol*. 2015; 2:e282–e8. [PubMed: 26207259]
6. Sandler SG. Blood group genotyping: faster and more reliable identification of rare blood for transfusion. *Lancet Haematol*. 2015; 2:e270–1. [PubMed: 26688381]
7. Westhoff C, Ness PM. The promise of extended donor antigen typing. *Transfusion*. 2015; 55:2541–3. [PubMed: 26559397]

8. Denomme GA, Flegel WA. Applying molecular immunohematology discoveries to standards of practice in blood banks: now is the time. *Transfusion*. 2008; 48:2461–75. [PubMed: 19054376]
9. Kacker S, Vassallo R, Keller MA, Westhoff CM, Frick KD, Sandler SG, Tobian AA. Financial implications of RHD genotyping of pregnant women with a serologic weak D phenotype. *Transfusion*. 2015; 55:2095–103. [PubMed: 25808011]
10. Delaney M. What is the value of a blood type? *Transfusion*. 2015; 55:2057–9. [PubMed: 26372913]