Red blood cell components: time to revisit the sources of variability

Rosemary L. Sparrow

Department of Immunology and Pathology, Monash University, Melbourne, VIC, Australia

Abstract

Quality and safety of red blood cell (RBC) components is managed by screening of donors and strict regulatory controls of blood collection, processing and storage procedures. Despite these efforts, variations in RBC component quality exist as exemplified by the wide range in storage-induced haemolysis. This article provides a brief overview of the variables that contribute or potentially contribute to the quality of stored RBC components, including blood collection, processing, and donor-related variables. Particular focus is made on donor health and lifestyle factors that are not specifically screened and may impact on the physicobiochemical properties of RBCs and their storability. Inflammatory and oxidative stress states may be especially relevant as RBCs are susceptible to oxidative injury. Few studies have investigated the effect of specific donor-related variables on the quality of stored RBC components. Donor-related variables may be unaccounted confounders in the "age of blood" clinical studies that compared outcomes following transfusion of fresher or longer-stored RBC components. The conclusion is drawn that the blood donor is the greatest source of RBC component variability and the least "regulated" aspect of blood component production. It is proposed that more research is needed to better understand the connection between donor-related variables and quality consistency of stored RBC components. This could be very important given the impact of modern lifestyles that sees escalating rates of non-communicable health conditions that are associated with increased oxidative stress, such as hypertension, obesity and diabetes in children and adults, as well as an ageing population in many countries. The effect of these changes to global health and population demographics will impact on blood donor panels, and without significant new research, the consequences on the quality of stored blood components and transfusion outcomes are unknown.

Keywords: blood donor, component processing, red blood cells, transfusion.

Introduction

In many jurisdictions throughout the world, red blood cells (RBCs) for transfusion are regulated as a medicine using similar codes of practice that are applied to the pharmaceutical industry for the manufacture of chemical-based drugs. Unlike a chemical pharmaceutical, in which all raw ingredients and formulations are precisely defined, it is not possible to achieve this same level of precision for complex biological medicines such as RBC components for transfusion. Whereas batch-to-batch variation is minimal for a chemical pharmaceutical, each blood donor and blood donation is biologically unique, and therefore each RBC component is a single batch. Furthermore, unlike the pharmaceutical industry, in which each batch of drug is tested prior to release, this does not occur for RBC components. Nevertheless, with the peace of mind provided by strict regulatory control of blood component production, there has been a tendency to overlook the possible impact of RBC component variability on transfusion outcomes[1]. The common view held by medical personnel is that all RBC components are essentially equivalent.

An exception to the notion of equivalence is the concern about storage duration of RBC components and the associated "storage lesion" that occurs during the permissible shelf-life of up to 42 days[2-5]. Whether shorter-stored RBCs provide improved transfusion outcomes compared to longer-stored RBCs has been a subject of active debate. Recent findings from several large "age of blood" randomised clinical trials (RCTs)[6-9], as well as large observational clinical studies[10], have reported a lack of effect of RBC component storage duration. These findings are somewhat at odds with those expected based on the numerous *in vitro* studies that have documented a progressive decline in RBC component quality caused by the storage lesion[2-5], and results reported by many retrospective "age of blood" clinical studies[11].

Storage duration alone is just one of many factors that impact on RBC component properties and quality. It has long been known that RBCs from some donors store well while others store poorly[12-15]. Evidence of donor-related variability is seen by the haemolysis profiles obtained from large datasets of RBC component quality control information[14,16,17], *in vivo* 24-hour post-transfusion RBC recovery data[12,15], as well as studies in twins[18] and different strains of inbred mice[17]. Donor-related variability may be an unaccounted for confounder in the "age of blood" clinical studies reported to date[5,19]. It is

timely to revisit the vast list of variables that influence RBC component properties and consider the donor-related factors more closely. The following commentary provides a brief overview of the different sources and types of variables, including donor and processing variables, along with the role of regulatory oversight.

Regulatory oversight

Regulatory oversight of donor health screening, blood collection, component processing, testing, quarantine, quality control and storage is intended to ensure blood component purity, potency and safety for the transfusion recipient[20]. Over the past few decades, the implementation of strict regulatory oversight, stream-lining of procedures, and rigorous training of front-line personnel have dramatically reduced technical variabilities in the collection and processing of blood components. Many national blood services and large blood centres have standardised their procedures to increase operational efficiency and improve the consistency of the blood components produced[21,22].

Donor selection

For blood collection centres, the objective of donor selection is equally focused to provide a safe and efficacious product for the recipient of the donation as well as to avoid any harm to the health of the donor[23]. Donor acceptance criteria depend heavily on the donor reporting to be well at the time of blood donation and identifying certain risks that could harm the recipient, such as transmission of infectious disease or allo-antibody reactivity.

Donation acceptance

Physical criteria for acceptable donations rely on the donor's haemoglobin (Hb) level measured at donation and the volume of blood collected, both of which must be within defined limits that may vary between jurisdictions[23,24]. For example, the prescribed volume of blood collected for a whole blood (WB) donation is typically 450 mL with a ±10% margin; in other words the acceptable volume range is 405-495 mL, which equates to a 90 mL difference between the smallest and largest acceptable donations[25]. In many jurisdictions, the minimum Hb limit is lower for female donors than male donors[24], and is inherently variable between donors and donations. Thus, the total Hb content of individual RBC components can differ markedly simply based on the variability of the volume of blood collected and the donor Hb level[26].

Routine quality control of RBC components

Only a small proportion of randomly selected RBC components are checked for quality control purposes. The intention of quality control is to provide assurance that the manufacturing system is performing within specification and looks for shifting trends rather than deviations of individual products. Some RBC components may be checked prior to storage to verify acceptable leucoreduction, while other tests are conducted at product expiry. The panel of expiry quality control measurements may simply include product volume, cell count, haematocrit and Hb content. Some blood centres perform additional quality measurements, such as percent haemolysis[14]. An array of other tests, such as pH, levels of RBC metabolites and membrane properties may be used for validation or research studies; however, the cost implications of a more expansive quality control testing regime would be prohibitive. Regardless of this, it is still unclear which, if any, of the available tests predict efficacy of the component when transfused[27,28]. Thus, for the vast majority of RBC components, specific information about RBC content and quality is not known.

Collection and processing variables

There are numerous sources of "allowable" variables within the collection and processing stages of blood component production that can influence the biological properties of the finished product (Table I).

In addition to the variables of blood volume and total Hb content mentioned above, other examples of variables include the elapsed time between WB collection and processing, temperature and handling conditions during the hold period. In many countries, including Europe, the United Kingdom, Canada and Australia, WB can be held for up to 24 hours at room temperature prior to processing, whilst other countries, such as the United States of America (USA), require that if WB is not processed within 8 hours of collection it must be refrigerated. Longer hold time is known to affect RBC biochemical properties; however, the RBC components meet accepted quality criteria[29]. Differences in the processing procedures used, such as the buffy coat method, plasma-reduction or apheresis, and types of leucocyte-reduction filter (WB-filter or RBC component filter) influence the characteristics of the final product[30,31]. A recent Canadian clinical study has highlighted that differences in processing methods of RBC components may have a greater impact on recipient outcome than previously appreciated[32]. This Canadian study is noteworthy. However, a caveat regarding its conclusions is necessary because the handling and processing of donations in Canada may be different to those used in other jurisdictions, and the study did not attempt to account for donor-related variables.

Donor-related variables

Some of the donor variables that potentially contribute to RBC component composition and quality are listed in

Table I - Blood collection and processing variables that contribute or potentially contribute to red blood cell component composition and quality.

Collection/processing step	Variables
Collection	
Type of donation	Whole blood, RBC apheresis
Venepuncture patency	Phlebotomy; donor venous accessibility
Blood volume collected	Set target volume±10% margin, e.g. 450±45 mL
Blood collection/storage pack	Different manufacturers, configurations, plastics, plasticisers, etc.
Anti-coagulant	Different formulations and manufacturers (CPD, CP2D, CPDA-1, ACD, etc.)
Hold time and temperature prior to processing	Varies within and between jurisdictions, e.g. up to 24 hours hold at room temperature or cooled
Handling and transportation prior to processing	Varies within and between jurisdictions
Processing	
Processing method	Packed RBCs, buffy coat method, apheresis
Processing conditions (centrifugation settings, temperature, etc.)	Varies within and between jurisdictions
Additive solution	Different formulations and manufacturers (SAGM, AS-1, AS-3, AS-5, AS-7, PAGGSM, MAP, CPDA-1, etc.)
Pre-storage leucoreduction	Universal leucoreduction is not mandated in all countries, e.g. USA
Type of pre-storage leucoreduction filter	Different manufacturers, filter chemistries, specifications for use, etc.
Final component volume, RBC and Hb content	Dependent on donation and processing variables
Post-processing manipulations (irradiation, washing, cryopreservation/thaw, etc.)	Procedures and revised component out-date varies between jurisdictions
Maximum storage time and inventory management	Varies between jurisdictions
Storage conditions, handling, transport prior to transfusion	Varies within and between jurisdictions

RBC: red blood cell; Hb: haemoglobin.

Table II. Only a few of the donor characteristics listed are used as selection criteria, including donor age, weight and Hb level. Typically, donors are between 18 and 70 years old. Some jurisdictions allow donors as young as 16 years to donate providing parental or medical consent is obtained. Donors older than 70 years may donate providing they are well and/or obtain medical consent. Acceptable donor weight is usually at least 50 kg to donate a full WB unit (i.e. 450 mL) or over 70 kg for double RBC apheresis. An upper weight limit is not usually defined. Blood pressure is recorded in some jurisdictions, several of which accept donors with moderately abnormal readings if the donor is otherwise well[23]. Selection limits for Hb levels may be sex specific and vary in different jurisdictions[24]. The minimum inter-donation interval varies between jurisdictions; for example, 56 days in Canada, the Netherlands and the USA, compared to around 120 days in Croatia, Israel, Luxembourg, Malta and Slovenia[24,25]. Higher donation frequency tends to correlate with increased rate of donor deferral due to unacceptably low Hb levels, particularly in female donors[24]. Certain diseases, such as previous leukaemia, trigger permanent deferral. Acceptance of donors with other diagnosed diseases, medical conditions or traits varies between jurisdictions, but the donor must report to be in good health in the weeks prior to donation, and where applicable, their condition controlled by prescribed medication[23]. As indicated in Table II, there are a myriad of other variables that contribute to donor health, and could potentially influence RBC properties and their storability positively or negatively, which are not considered in the selection process. It is reasonable to hypothesise that the blood donor is the greatest source of variability of RBC component quality rather than collection or processing variables.

Donor factors and transfusion outcomes: recent research

To date, very few studies have specifically addressed the influence of donor variables on RBC transfusion outcomes[33]. New research is beginning to emerge that will fill this void, but already, seemingly contradictory results are being reported. For example, RBC components from young female donors have been reported to be more resilient to mechanical or osmotic stresses and have lower *in vitro* haemolysis[17,34]. Such attributes could be expected to favour improved function and survival of stored RBCs following transfusion. However, a large longitudinal cohort study of 30,503 transfusion recipients in Canada reported that RBC components from female donors or young donors less than 30 years of age were associated with increased mortality[35]. In

Table II - Donor variables that contribute or potentially contribute to red blood cell component composition and quality.

Donor variable	Used as selection criteria	Acceptance limits or information documented by blood centre
Sex	No	Documented
Age	Yes	Minimum-maximum limits apply; limits vary between jurisdictions
Body weight	Yes	Minimum weight limit; varies between jurisdictions
Body mass index	No	Not systematically documented
Blood pressure	Yes/No	May be documented; varies between jurisdictions
Blood group antigens	No	ABO, Rhesus D are documented; other alloantigens are documented if extended typing performed
Hb level	Yes	Different acceptance limits for female and male donors; varies between jurisdictions
Other RBC indices (cell concentration, cell size, haematocrit, etc.)	No	Not routinely measured for whole blood donations
Iron deficiency	Yes*	*Applies only to centres that have implemented routine screening
Diagnosed RBC pathologies or carrier traits (G6PD deficiency, haemochromatosis, sickle cell trait, thalassaemia carriers, etc.)	Yes/No	Acceptance of donors varies between jurisdictions
Diagnosed medical conditions (diabetes; obesity; metabolic syndrome; inflammatory conditions; immunosuppressive conditions; allergy; respiratory conditions; auto-immune diseases; hormonal imbalance; hypertension; hyperlipidaemia; periodontitis; previous non-haematologic cancer; intestinal, kidney, liver conditions)	No**	Not systematically documented **Donor acceptance dependent on the donor reporting to be well at the time of donation
Health and lifestyle choices (diet; vitamins and supplements; contraceptive/ hormonal therapies; tobacco intake; alcohol consumption; physical activity)	No	Not systematically documented
Immediately prior to donation (food, drink consumed; high physical activity; vitamins, supplements, medication taken; tobacco intake; anxiety, stress level)	No	Not systematically documented
Inter-donation interval	Yes	Minimum time period since previous donation varies between jurisdictions
Seasonality of donation	No	Documented
Unknown or undisclosed variables (undiagnosed conditions or diseases, e.g. cardiovascular disease, diabetes, RBC or haematologic pathologies, inflammatory or immunosuppressive disorders, auto-immune diseases, lung, intestinal, kidney or liver conditions, etc.; pre-clinical conditions, e.g. pre-diabetes; metabolic variants; genetic variants)	Not possible	Unknown variable; cannot be documented

Hb: haemoglobin; RBC: red blood cell.

contrast, a large retrospective study of 136,639 RBC transfusion recipients in Sweden and Denmark did not find an effect of donor age on 30-day or 1-year mortality[36]. Similarly a smaller French retrospective cohort study of 2,715 cardiac surgery patients did not find an effect of donor age, sex or component storage duration on 1-year mortality[37].

The effect of sex mismatch between donor RBCs and patient-recipient has also been investigated. In the French study[37], a trend towards increased risk of death was noted for female recipients (n=247) of male-only RBCs compared to male recipients (n=237) of female-only RBCs (hazard ratio [HR] 2.03, 95% CI: 0.87-4.73 *vs* 0.96, 95% CI: 0.57-1.61, respectively), but the effect did not reach statistical significance in this study cohort. In a Swedish retrospective study of 5041 cardiac surgery patients followed for up to 12 years after transfusion, there was a significant association of

increased long-term mortality in patients who received only sex-mismatched RBC components (HR 1.08, 95% CI: 1.03-1.14; p=0.003)[38]. This study did not differentiate the direction of sex mismatch (i.e. female RBCs-male recipient or male RBCs-female recipient). These recent studies add to an earlier Dutch study that reported significantly increased mortality at 90 days and 6 months after transfusion in male recipients less than 55 years old who received female RBCs[39]. The association was not significant at 5 years after transfusion, nor was it significant at any of the time points for female recipients who received only male RBCs.

Based on findings to date, the influence of donor age or donor sex on transfusion outcomes remains unclear. It may be too simplistic to select only one or two basic donor-related variables when there are many more donor variables that could influence the properties of RBC components, such as indicated in Table II.

Changing donor demographics and potential impact on RBC component quality

With the exception of donor age and donor sex noted above, very few studies have specifically investigated the effect of donor-variables on the quality of stored RBC components. The significantly changing demographics of the global population, including an increasing proportion of the elderly age group[40,41], and escalating rates of non-communicable health conditions, such as hypertension, obesity and type-2 diabetes in children and adults[42], raises questions about the potential impact of these evolving changes on the demographic profile of blood donor panels and the possible implications for the quality of blood components for the future.

For example, in many countries, the obesity rates have doubled since 1980; as of 2012, the average rate of adult obesity of 34 countries of the OECD (Organisation for Economic Co-operation and Development) was 18%, with countries such as Canada, Australia and the United States having much higher rates of 25%, 28% and 35%, respectively[43]. Likewise, the rate of metabolic syndrome, which is defined as having three or more risk characteristics that include excess abdominal adiposity, hypertension, raised blood lipids, raised fasting plasma glucose or diabetes, is also rapidly rising, particularly in countries with higher incidence of obesity, such as the United States and Australia[44-46]. Based on 2012 data, the prevalence of metabolic syndrome in the United States is reported to be 35% of the adult population and 50% in adults aged 60 years or older[44].

Cardiovascular disease, obesity and diabetes individually and combined are associated with numerous biochemical changes, including increased oxidative stress and inflammatory markers, that affect blood characteristics, together with RBC properties[47-50]. The extent of the changes to RBCs caused by these health conditions is further influenced by genetic and inherited metabolic differences between individuals[51-57], and even seasonal effects[58]. It is very likely that the numbers of blood donors with undiagnosed or pre-clinical stages of these and related health conditions is increasing. The direct effect of these health conditions on the quality of stored RBC components has not been specifically investigated.

Donor lifestyle variables and RBC component quality

Blood donors are not routinely asked about lifestyle variables such as diet, physical activity, alcohol and tobacco intake, although all of these variables can significantly influence RBC physicochemical properties[19]. Decreased RBC anti-oxidant capacity and increased oxidative stress markers are consistent characteristics of unhealthy lifestyle choices, such as poor or unbalanced diet, excess alcohol, tobacco intake or physical inactivity.

Hyperlipidaemia

Red blood cell components prepared from donors with hyperlipidaemia, particularly raised triglycerides, have been found to have increased haemolysis early in storage that can reach unacceptably high levels before component out-date[59]. The lipid content of RBC membranes is known to vary according to the relative concentrations of lipid species in the extracellular milieu[60,61], and this in turn can alter RBC membrane fluidity. Furthermore, hypercholesterolaemia is associated with increased oxidative stress and inflammatory mediators that can damage RBCs and increase RBC membrane rigidity[47]. Plasma lipid levels can be transiently raised by the consumption of a high fat meal[62,63], which is relevant in the context of blood donation and variability in the quality of RBC components[59,64]. Although very turbid plasma products are discarded by some blood centres, the RBC components prepared from the same donations are not usually discarded.

Diet and alcohol

The physicobiochemical properties of RBCs can be significantly affected by diet. A high fat diet may not necessarily result in raised plasma lipids, but can still contribute to significant RBC dysfunction *via* increased inflammatory and oxidative stress mechanisms[65]. On the other hand, a healthy diet and one that is rich in natural antioxidants may enhance the capacity of RBCs to counter the damage inflicted by oxidative stresses[66-69]. However, dietary antioxidants, preservatives and colourants included in the "Western" diet may

influence immune regulation, including the development of allergic, inflammatory or immunosuppressed responses[70,71].

Moderate consumption of red wine can improve RBC membrane fluidity[72], but excess ethanol negatively affects RBC rheology by inducing macrocytic morphological changes with reduced RBC deformability and aggregation, reduced RBC anti-oxidant capacity, increased oxidative markers, and increased blood viscosity[73-75].

Physical activity

Insufficient physical activity and extreme exercise are each associated with raised oxidative stress markers, which negatively impact on RBCs[76,77]. Moderate and regular exercise and physical activity has significant benefits on RBC redox homeostasis[78,79].

Tobacco smoking

Tobacco smoking causes marked changes to RBC rheological properties due to the consequences of inhaled toxins that increase the levels of oxidants and plasma lipids[80,81]. The levels of induced oxidants has been shown to vary with the age and sex of the smoker, with young female smokers being the most adversely affected[82]. Oxidant levels are further exacerbated in smokers after ingestion of a meal, which can be alleviated by moderate exercise[83]. Furthermore, consumption of red wine prior to smoking can reduce the negative haematologic changes associated with smoking[84].

Donor medical conditions and RBC component quality

In addition to the medical conditions mentioned above (i.e. hypertension, obesity, diabetes, etc.), there is a plethora of other ailments that can affect RBC physicochemical properties (Table II). Furthermore, an unknown proportion of donors will have undiagnosed or pre-clinical forms of these medical conditions. Given that progressively increased oxidative stress is a feature of the RBC storage lesion[4,85], it is reasonable to hypothesise that RBCs collected from donors with inflammatory conditions, including autoimmune and hyperallergic predisposition, may be more susceptible to storage-induced injury. Detailed studies of stored RBC components prepared from donors with inflammatory profiles have not been reported. A few studies have been reported concerning RBCs collected from donors with certain inherited disorders that affect RBCs and these are briefly discussed below.

Genetic pathologies

Donors who disclose genetic pathologies that affect RBCs, such as hereditary haemochromatosis (HH), sickle cell trait (SCT), and glucose-6-phosphate dehydrogenase (G6PD) deficiency, are accepted in many jurisdictions providing the donor feels well at the time of donation, and where applicable their condition is controlled[19,24]. Many more donors may be unaware of their conditions as clinical symptoms are often not apparent.

Iron overload is the hallmark of HH and exposes RBCs to increased oxidative challenge[86,87]. HH is one of the most common genetic diseases that affect RBCs, with a prevalence of around 0.6% in individuals of European ethnicity. As it is an autosomal recessive disorder, HH is significantly more frequent in males. Irreversible organ damage may have already occurred before clinically significant symptoms become apparent, which tend to emerge in mid-life or later. HH is associated with a heightened risk of other diseases, including type-2 diabetes[88]. However, individuals homozygous for the common HH-related *HFE* gene C282Y mutation have been reported to have lower total lipid and low-density cholesterol levels[89], which may be advantageous. Phlebotomy is standard therapy for the treatment of HH. Patients with HH are often referred to blood centres for their phlebotomy therapy. In many jurisdictions, blood collected from patients with controlled HH is deemed acceptable and is processed as a routine blood transfusion component. Thus, the frequency of HH in blood donor panels is likely to be higher than the frequency in the general population. Although RBC components from HH donors appear to display acceptable quality following storage[90,91], extensive investigations have not been reported.

Sickle cell trait, or sickle cell carrier, is the heterozygous form of sickle cell disease, which is one of several types of haemoglobinopathies. Due to the presence of the abnormal sickle haemoglobin gene (HbS), RBCs from SCT individuals tend to be more rigid[92]. SCT is particularly prevalent in individuals of African black ethnicity; the incidence of SCT in the African-American population is estimated to be around 7-9%[93,94]. For RBC components prepared from SCT donors, the increased rigidity of the RBCs can be problematic during pre-storage leucoreduction filtration, with increased risk of filter blockages and damage to the RBCs[95,96]. Recent studies using a mouse SCT model have demonstrated increased haemolysis and post-transfusion clearance of stored SCT RBCs[97]. Transfusion of SCT-RBC components to sickle cell disease recipients is avoided, particularly during a sickling crisis, due to the risk of exacerbation of vascular occlusion. The world-wide incidence of other haemoglobinopathies, including the thalassaemias, is increasing and becoming more diversified due to immigration, mixed-ethnic births, and improved medical standards in developing

countries where many of the haemoglobinopathies have a higher frequency[98]. The effect on the quality of RBC components prepared from donors with genetic variants of Hb has not been investigated in detail.

Glucose-6-phosphate dehydrogenase deficiency is the most common genetic enzyme defect in humans. It is an X-linked recessive inheritance and consequently affects males, while females are more likely to be heterozygous carriers. G6PD is part of the pentose phosphate pathway (PPP) that is active in all cells. RBCs rely on the PPP to generate large amounts of NADPH required to produce the anti-oxidant, glutathione. Consequently, G6PD-deficient RBCs are vulnerable to oxidative stress and ultimately, haemolysis[99]. Individuals with G6PD-deficiency are usually asymptomatic, and for this reason are accepted as blood donors in most jurisdictions. However, recent studies have questioned the safety and efficacy of stored G6PD-deficient RBC components[100-102].

Future focus

It is clear that the blood donor is likely to be the greatest source of variability of RBC component quality and arguably is the least "regulated" step in the production line of blood components. Research focused to better understand the effect of donor-related variables is needed.

To obtain meaningful results will require collection of additional health, medical and lifestyle information from blood donors as well as certain biochemistry tests, such as plasma lipids and oxidative markers. More detailed studies could utilise the power of "omics" technologies (proteomics, metabolomics, lipidomics and transcriptomics) to reveal biological patterns associated with good or poor "storers". Some research is already being undertaken in this direction, such as the large USA-based "RBC-Omics" project within the REDS III programme that will use a genome-wide association study (GWAS) approach to investigate the genetic basis of RBC storage variability and haemolysis of 14,000 US blood donors[103].

These research approaches could lead to the identification of markers in donor blood that predict the storability of blood components. To be fully informative, these endeavours will need to gather together the expertise of a range of disciplines, including medical, scientific, public health, sociology and bioinformatics. It is a major exercise that will require much planning and investment of resources. However, it will be worth the effort. Not only might this research be of great benefit to Transfusion Medicine, but will potentially be of enormous value to public health research and programmes to deal with the implications of the sizeable shifts that are occurring in the health demographic profiles of the global population.

Conclusions

There are a multitude of variables that contribute or potentially contribute to the quality of stored RBC components. Many variables related to collection and processing of blood are managed by strict regulatory controls and standardised procedures, and, to some extent, by donor selection criteria. However, the blood donor remains the greatest source of variability of RBC component quality. Donor selection criteria are principally focused on avoiding the transmission of infectious diseases to the transfusion recipient as well as avoiding harm to the health of the blood donor in the context of blood depletion. Few studies have investigated the effect of specific donor-related variables on the quality of stored RBC components. Donor-related variables have not been accounted for in the 'age of blood' RCTs, or in many of the observational studies.

With the changing demographics of the global population, that is seeing more aged people, and rapidly rising rates of non-communicable medical conditions such as hypertension, obesity and diabetes, in children and adults, more research is needed to understand how these changes in population health impact on the quality of stored RBC components and transfusion outcomes. Identification of donor-related markers that are predictive of RBC storability could be invaluable in achieving improved consistency of RBC component quality and recipient outcomes. The challenge is there for us to grasp.

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Correspondence: Rosemary Sparrow
Department of Immunology, Monash University, AMREP
89 Commercial Road
Melbourne, Victoria 3004, Australia
e-mail: rosemary.sparrow@monash.edu