A feasibility study examining the potential of introducing a whole blood component for the management of traumatic major haemorrhage

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DClinSci 2022

A feasibility study examining the potential of introducing a whole blood component for the management of traumatic major haemorrhage

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A thesis submitted in partial fulfilment of the requirements of Manchester Metropolitan University for the award of Doctorate in Clinical Science.

Department of Life Sciences Manchester Metropolitan University, in collaboration with Barts Health NHS Trust, London.

2022

Acknowledgements

This doctoral thesis completes a 5-year journey through the Higher Specialist Scientific Training (HSST) programme. Throughout this time, I have received support and guidance from numerous people, far too many to thank here, but I would like to thank the following, in particular, for their continued support and advice throughout this 5-year journey, Dr Shubha Allard and Dr Laura Green, without the support of these two fantastic mentors I would not be where I am today.

The research presented in this thesis would not have been possible without the support and guidance of the teams involved in each of the projects. I would like to thank the Systematic Review Initiative (SRI) in particular Susan Brunskill, for imparting their knowledge and time in supporting the scoping review. I would like to thank all the members of the Whole Blood Programme Group, and I would like to express thanks to Dr Nathan Proudlove for imparting his knowledge on quality improvement and operational research methodologies.

I would like to express my deepest gratitude to my doctoral supervisor, Dr Laura Green for giving me the opportunity to undertake this research and for her invaluable guidance and support throughout the course of my research and training.

Last but certainly not least I would like to express my utmost gratitude to my family for their constant love and support, in particular my fiancé Paul. Without his support none of this would have been possible and I dedicate this thesis to him.

Declaration

I, Josephine McCullagh, confirm that the work presented in this thesis is my own. Where information has been derived from other sources; I confirm that this has been indicated in the thesis.

Abstract

Background

The timely and organised approach of transfusing trauma patients in the pre-hospital setting with a 1:1:1 ratio of red blood cells, plasma and platelets has resulted in an increased interest in re-introducing whole blood (WB) components for the management of these patients. WB components are not used routinely in NHS hospitals, but should the blood service decide to implement this component in the prehospital setting, further evidence is required on: a) its safety, because these patients will be transfused group O WB which contains anti-A and anti-B in the plasma that can result in haemolytic transfusion reactions and b) the logistics of supplying group O negative WB to prehospital services, considering that demand for this component currently outstrips supply.

The overall research question in this thesis was to establish whether it is safe and feasible to introduce a WB component in the NHS for the treatment of traumatic major haemorrhage in the pre-hospital setting.

Specific objectives were to:

a) Determine the lowest observable anti-A and anti-B titre (measured by IgG or IgM), and the lowest observable ABO incompatible plasma volume that have been reported in the literature to have resulted in haemolysis in recipients receiving ABO incompatible plasma containing components (scoping review).
b) Determine a) the clinical safety of transfusing LD-RCP to trauma patients; b) whether the component was delivered to hospital on time in full (OTIF) and c) the overall component wastage for the hospital. Through the evaluation of a similar component to WB (i.e., leucocyte-depleted Red Cell and Plasma [LD-RCP]) with regards to shelf life, logistical and serological issues (2-year observational study).
c) Explore the stock management of a WB component using data collected from the 2-year observational study (stock management).

Results

Scoping review

In this first ever systematic scoping review, assessing the risk of haemolysis following the transfusion of ABO incompatible plasma-containing components, 62 eligible cases were identified. There were no completed or ongoing randomised trials. There was heterogeneity between cases in the methods for reporting haemolysis and ABO titration methods, while the volume was poorly reported. Putting all these aside, results showed that platelet components were the most reported components to result in haemolysis in both paediatrics and adults. The lowest anti-A titre reported to cause haemolysis was 32 (paediatrics and adult), while for anti-B it was 512 (IgG and IgM) for adults, 16,384 for paediatrics (IgG and IgM) and 128 (IgM) in cases where the age was not specified. The lowest component volume transfused that was reported to have caused a haemolytic transfusion reaction was 100ml in adults and 15mls in paediatric.

Observational study

Of the 204 patients who were transfused group O RhD negative LD-RCP (a maximum of 4 units), 96 patients had a blood group recorded and were non-group O. Based on the results of haemoglobin, bilirubin and Direct Antiglobulin Tests (DAT), there was no evidence of increased haemolysis compared to patients who were blood group O and who also received group O RhD negative LD-RCP.

During the study, 1208 units (96.5%) of LD-RCP units were delivered to hospital on time and as per specifications, which met the pre-agreed study target of 97% (95% Confidence Interval: 96% - 98%). Despite this, not all units were delivered at age 2 days old with only 64.7% of the total units being delivered on the agreed age. Following the quality improvement work undertaken by the study team, there was a marked improvement in the age of units delivered with 91.7% being delivered at the pre-agreed age towards the end of the study, demonstrating that delivering at age 2 days old is feasible. Component wastage (39%) was a major concern during this study and the pre-agreed wastage level target of <8% was not met. Nevertheless, incremental reductions were demonstrated across the study period, reducing

the weekly wastage from a mean of 8.36 units per week (70%) to 3.19 (27%) by the end of the study period.

Stock management

Based on the data collected from the observational study, evaluation of pre-hospital component demand using ARIMA time series forecasting showed that the demand for pre-hospital transfusion was random and could not be forecasted to a usable degree. Using a combination of a First In First Out (FIFO) inventory model and a Poisson distribution to model component demand, two stock management models were developed (14-day shelf life and 21-day shelf life). Using heuristically generated component supply algorithms the stock management model demonstrated that component wastage could be reduced to 16% and 4% for a 14-day and 21-day shelf-life component, respectively.

Conclusion

Incorporating evidence from a scoping review, data collected as part of a 2-year observational study using a similar component to WB (LD-RCP) and mathematical modelling of the supply and demand, this thesis provides evidence that the transfusion of group O WB components in the prehospital setting is a safe and feasible intervention in the NHS for the treatment of traumatic haemorrhage. However, if the component is only used in this setting, the component wastage level for hospitals is likely to be high, and therefore measures such as extending the shelf-life of the WB component and incorporating a dynamic inventory model for component supply must be considered to minimise the wastage of this precious resource.

Publications arising from this thesis

Papers

McCullagh, J, Proudlove, N, Tucker, H, Davies, J, Edmondson, D, Lancut, J, Maddison, A, Weaver, A, Davenport, R and Green, L. (2021) 'Making every drop count: Reducing wastage of a novel blood component for transfusion of trauma patients', BMJ Open Quality, 10(3), pp. 1–8. Available at: https://doi.org/10.1136/bmjoq-2021-001396. (Appendix 4)

McCullagh, J., Cardigan, R, Brunskill, S.J, Bullock, T, Doree, C, Estcourt, L, Huish, S, Sandercock, J and Green, L. (2022) 'Assessing the risks of haemolysis as an adverse reaction following the transfusion of ABO incompatible plasma-containing components - A scoping review', Blood Reviews, p. 100989. Available at: https://doi.org/10.1016/J.BLRE.2022.100989. (Appendix 5).

Abstracts

McCullagh, J, Cardigan, R, Brunskill, S, Bullock, T, Doree, C, Estcourt, L, Huish, S, Sandercock, J and Green, L. (2022) 'Assessing the risks of haemolysis as an adverse reaction following the transfusion of abo incompatible plasma-containing components—a systematic scoping review', Vox sanguinis, 117, p. 183. Available at: https://doi.org/10.1111/VOX.13285.

McCullagh, J, Davies, J, Edmondson, D, Lancut, J, Maddison, A, Tucker, A and Green, L. (2020) 'Feasibility and safety of leucocyte depleted red cell and plasma transfusion for traumatic major haemorrhage - UK experience', Vox sanguinis, 115, p. 36. Available at: https://doi.org/10.1111/VOX.13031.

Awards

Royal College of Pathologists (RCPath) Advances in Transfusion Medicine 2020 winning poster: Safety of transfusing leucocyte depleted red cell and plasma for traumatic haemorrhage.

Webinars

Making every drop count: Reducing wastage of a novel blood component for transfusion of trauma patients. International Society of Blood Transfusion (ISBT) webinar. 2nd March 2022. https://www.isbtweb.org/resources/isbt-education/webcast-library.html

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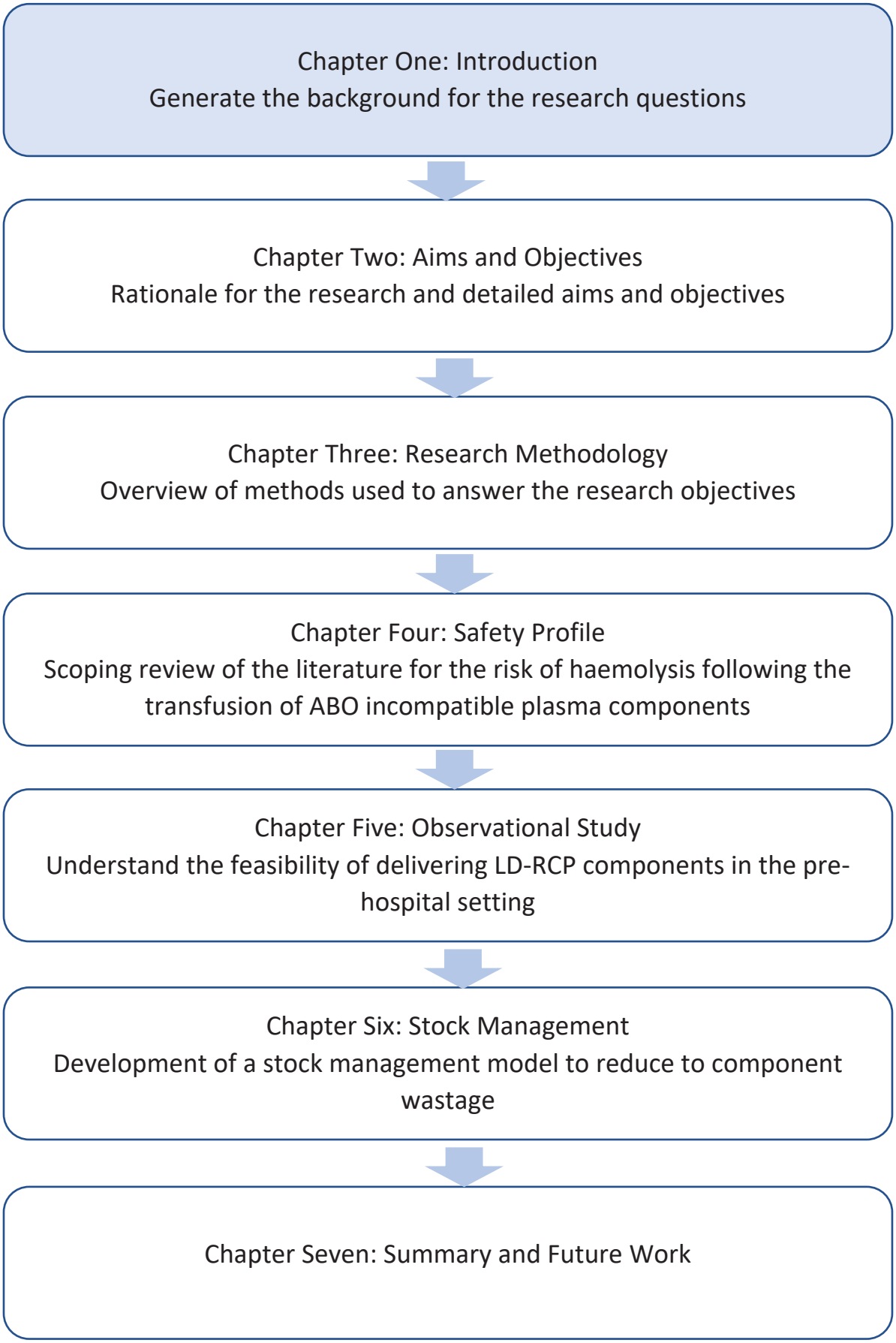
List of abbreviations

ACF	Autocorrelation Function
AHG	Anti-Human Globulin
AIC	Akaike Information Criterion
ANOVA	Analysis of Variance
APTT	Activated Partial Thromboplastin Time
ARIMA	Autoregressive Integrated Moving Average
CJD	Creutzfeldt Jacobs Disease
CRF	Case Report Form
Cryo	Cryoprecipitate
CS	Clinical Symptoms
DAT	Direct Antiglobulin Test
DTT	Dithiothreitol
ED	Emergency Department
EFS	Encrypting File System
FBC	Full Blood Count
FFP	Fresh Frozen Plasma
FIFO	First In First Out
GCP	Good Clinical Practice
Hb	Haemoglobin
HCRW	Health and Care Research Wales
HEMS	Helicopter Emergency Medicine Service
HRA	Health Research Authority
HTR	Haemolytic Transfusion Reaction
IAT	Indirect Antihuman globulin Test
ICTRP	International Clinical Trials Registry Platform
IDE	Integrated Development Environment
IS	Immediate Spin
LAA	London Air Ambulance
LD-RCP	Leucodepleted Red Cell and Plasma
LD-WB	Leucodepleted Whole Blood
LIMS	Laboratory Information Management System
MDT	Multidisciplinary Team
MeSH	Medical Subject Headings
MFI	Model For Improvement
MHP	Major Haemorrhage Protocol
MS	Microsoft
NHSBT	NHS Blood and Transplant
O neg	O RhD negative
OR	Operational Research
OTIF	On Time In Full
PACF	Partial Autocorrelation Function
PAS	Platelet Additive Solution

PDSA	Plan Do Study Act
PICO	Population, Intervention, Comparator and Outcome
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
PT	Prothrombin Time
QI	Quality Improvement
RBC	Red Blood Cells
RCT	Randomised Control Trials
RLH	Royal London Hospital
RSME	Root Mean Square Error
RT	Room Temperature
SPC	Statistical Process Control
SRI	Systematic Review Initiative
TIC	Trauma Induced Coagulopathy
TIMEX	Time Expired
TRF	Trauma Research Fellows
WB	Whole Blood
WILAB	Wasted In Laboratory
WIWARD	Wasted In Ward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Chapter Two: Aims and Objectives
Rationale for the research and detailed aims and objectives
Chapter Three: Research Methodology
Overview of methods used to answer the research objectives
Chapter Four: Safety Profile
Scoping review of the literature for the risk of haemolysis following the transfusion of ABO incompatible plasma components
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Understand the feasibility of delivering LD-RCP components in the pre-hospital setting
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Development of a stock management model to reduce to component wastage
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Chapter 1 Introduction

1.1 Major Trauma

1.1.1 Trauma Induced Coagulopathy

Trauma is the fourth leading cause of mortality worldwide, with 25-40% of trauma deaths being attributed to uncontrolled bleeding (Kauvar and Wade, 2005; Moore *et al.*, 2021). The cost of management being around £150 million for the NHS (Campbell *et al.*, 2015). Uncontrolled or life-threatening bleeding is often associated with abnormalities in the coagulation process (the body's ability to regulate clot formation and break down). These abnormalities following traumatic injury are commonly referred to as Trauma Induced Coagulopathy (TIC). TIC can manifest as a spectrum of phenotypes, ranging from a hypocoagulable state to a hypercoagulable state (Moore *et al.*, 2021).

Early preventable death, defined as death within 24hrs that could have been avoided by the timely implementation of standard practice (Hakkenbrak *et al.*, 2021), is primarily attributable to uncontrolled bleeding/haemorrhage or a hypocoagulable state (Tisherman *et al.*, 2015; Moore *et al.*, 2018a; Sperry *et al.*, 2018). Whereas, later preventable deaths (after 24hrs) are due to a hypercoagulable state associated with venous thromboembolism and organ failure (Moore *et al.*, 2021). Understanding this process is critical in determining the most effective use of blood components and other haemostatic therapies in the treatment of patients with traumatic major haemorrhage. In the past it was believed that during major bleeding, coagulopathy (defined as prolongation of prothrombin time (PT) or activated partial thromboplastin time (APTT) >1.5x mean normal) did not occur until a significant blood volume had been lost, or a patient had received a large volume of blood or fluid. As a result, blood transfusion was given later in the course of bleeding. Between 2003 and 2007 several observational studies in trauma demonstrated that ~25% of bleeding patients present with coagulopathy quite early after injury, before any blood or fluid have been administered, and before significant blood loss has occurred (Brohi *et al.*, 2003; Maegele *et al.*, 2007). The presence of early coagulopathy is strongly associated with a greater need for blood transfusion and higher rate of mortality (independent of injury severity score)(Brohi *et al.*, 2003; Maegele *et al.*, 2007). The pathophysiology of early endogenous coagulopathy is

not well understood, but it is believed to be multi-factorial – induced primarily by tissue trauma, shock and hypoxia (Frith, Cohen and Brohi, 2012).

1.1.2 Damage control resuscitation and transfusion response

A timely and organised approach to transfusion in the management of bleeding is crucial to improving clinical outcomes. Transfusion management during bleeding aims to achieve the following; 1) avoid tissue hypoxia through the transfusion of red blood cells (RBC), which deliver oxygen to tissues; 2) correction of coagulation abnormalities through the transfusion of fresh frozen plasma (FFP, rich in clotting proteins) and cryoprecipitate (cryo, rich in a clotting factor called fibrinogen) and 3) correction of a low platelet count (or thrombocytopenia) through the transfusion of platelets (Hunt *et al.*, 2015).

In order to correct early coagulopathy, in 2007 the major haemorrhage protocol (MHP) was first introduced into clinical care (Cole *et al.*, 2019), providing guidance on the active management of patients with major bleeding to regain haemostasis in trauma. MHP's are designed to provide a more proactive and pragmatic approach to the management of acquired bleeding via the use of treatment algorithms that pre specify the order and ratio of blood components quite early in the course of bleeding (Stanworth *et al.*, 2022). The main aim of the protocols is to enable rapid provision of blood components and improve communications between clinical teams and the transfusion laboratory, thus preventing unnecessary delays in the provision of blood, as well as correcting and preventing early and late coagulopathy.

The implementation of MHP was based on the emerging principles of correcting early coagulopathy through provision of damage control resuscitation (Holcomb, 2007), and this saw the replacement of crystalloids and colloids in the resuscitation of major bleeding with haemostatic resuscitation through blood transfusion resulting in improvements in survival (Brohi, Gruen and Holcomb, 2019). Following this, in 2012 one of London's major trauma centres (Royal London Hospital [RLH]) introduced 'blood on board', an initiative that allowed the London Air Ambulance (LAA) to transfuse RBC to trauma bleeding patients in the pre-hospital setting early in the stage of traumatic injury

(Rehn *et al.*, 2019). This has now become the standard of care for most services in England (Leech and Clarke, 2022).

1.1.3 Optimal Blood Component Ratios

The optimal use of blood component therapy for patients with major haemorrhage remains uncertain. However, in the last decade the research performed in trauma has advanced our understanding of how the ratios of blood components transfused affect patient outcomes. Clinical trials have demonstrated that early and continuous resuscitation with RBC, FFP and platelets in a 1:1:1 ratio, resembling whole blood transfusion (Holcomb *et al.*, 2015; Sperry *et al.*, 2018), can reduce mortality. Holcomb and colleagues conducted the first ever, multicentre randomised control clinical trial (PROPPR) in hospital to assess the safety and effectiveness of a 1:1:1 ratio of RBC, FFP and Platelets (n=338 patients) compared with 1:1:2 ratio (n=342 patients). Although the study found no statistically significant difference in the primary outcome of mortality at 24hrs or 30 days, the study did show that more patients in the 1:1:1 group achieved haemostasis and fewer experienced death due to exsanguination by 24 hours (Holcomb *et al.*, 2015).

In 2018 two randomised control trials evaluating the use of FFP in pre-hospital setting in trauma bleeding patients showed conflicting results on the benefits of plasma on 28-30 days mortality: these were the PAMPer (Prehosptial Air Medical Plasma) trial (Sperry *et al.*, 2018) and the COMBAT (Control of Major Bleeding After Trauma) trial (Moore *et al.*, 2018b). The PAMPer trial was a pragmatic cluster randomised control trial (n=501 patients), comparing early plasma transfusion versus standard care (either RBC or crystalloid resuscitation) showing a significant difference in mortality at 30 days in the plasma arm. The COMBAT trial was a single centre, placebo-controlled trial comparing two units of FFP versus standard care (frozen isotonic saline) in 144 trauma bleeding patients and showed no difference in 28-day mortality (Moore *et al.*, 2018b; Sperry *et al.*, 2018).

As a result of the PROPPR trial, MHP protocols in the UK have since changed to reflect this research. RBC is now given in a 1:1 ratio with thawed FFP as standard practice in the

UK for the management of traumatic major bleeding in a hospital setting (Stanworth *et al.*, 2022). The move to 1:1 ratio of different blood components has created huge interest in the use of Whole Blood (WB) transfusion instead of separate components for early resuscitation, since all blood components are present in one WB unit.

Avery and colleagues (2020) conducted a systematic review to evaluate the efficacy of WB versus individual component therapy on 30-day mortality in adults with traumatic major haemorrhage. The systematic review found only 6 research studies that were of high enough quality, but none of these studies were powered to demonstrate a difference in 30-day mortality (Avery *et al.*, 2020), hence highlighting the need for further trials to evaluate the efficacy and safety of WB versus component therapy in trauma.

1.2 ABO incompatible plasma

1.2.1 ABO blood groups

In 1900 Karl Landsteiner identified the presence of antibodies in blood that gave rise to the discovery of the ABO blood group system. The ABO blood group system is often defined by Landsteiner's Law (Figure 1-1):

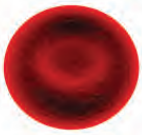
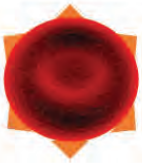
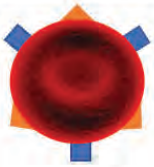
	Group O	Group A	Group B	Group AB
Antigen				
	No antigens	A antigen	B antigen	A & B antigen
Antibody				
	Anti-A & Anti-B	Anti-B	Anti-A	No antibodies

Figure 1-1: A diagram depicting the antigens present on the surface of red blood cells and the antibodies present in the plasma for the different ABO blood groups

1) if an A or B antigen is present on the surface of red blood cells, the corresponding antibody (anti-A or anti-B) must be absent from the plasma;

2) if an A or B antigen is absent on the surface of the red blood cells, the corresponding antibody (anti-A or anti-B) must be present in the plasma.

The anti-A and anti-B are often referred to as 'naturally occurring' antibodies, as they usually develop from 3 months of age without stimulation from pregnancy or blood transfusion. These antibodies can be of the following isotypes, immunoglobulin (Ig)M, IgG or IgA; however, they are predominantly IgM and IgG.

The ABO blood group system remains the most important and clinically significant blood group system in transfusion medicine. The presence of these antibodies almost always results in immune RBC destruction (or haemolysis) following an ABO incompatible RBC transfusion, resulting in significant morbidity and mortality for the recipient. ABO incompatibility can be classified in to two types: major incompatibility and minor incompatibility (Daniels and Bromilow, 2013).

- Major Incompatibility occurs when antibodies in the recipient destroy transfused RBC (e.g. transfusion of group A RBC to a group O recipient - transfusion of ABO incompatible RBC).
- Minor Incompatibility occurs when antibodies in the transfused blood component destroy the recipients RBC (e.g. transfusion of group O plasma to a group A recipient - transfusion of ABO incompatible plasma components)

The risk of haemolysis and serious harm is more likely with the transfusion of ABO incompatible RBC than with ABO incompatible plasma components (Bolton-Maggs, P (Ed), Poles, 2018). However, the risk of haemolysis from a minor ABO incompatible transfusion is still present. The risk and severity of haemolysis from the transfusion of ABO incompatible plasma components (i.e. whole blood, plasma and platelets) can be affected by the isotype, volume transfused, titre (the concentration of an antibody, as determined by the finding of the highest dilution at which it is still able to cause agglutination), and age and weight of the recipient (Mark H. Yazer *et al.*, 2018)

1.2.2 Screening for high titre ABO antibodies

There is currently no international consensus on the clinically safe anti-A/anti-B titres, present in blood donors and no international gold standard for the titration methods.

Caution must be taken when reviewing practices and comparing international guidelines. Inter-laboratory variation in obtaining results from these assays was highlighted in one study that compared pre-transplant median titres from patients in one German and two Swedish blood centres, where the investigators confirmed that the method variation caused significant discrepancy in results (Kumlien *et al.*, 2007). A detailed, standardised procedure for antibody titrations has also been recommended by the Biomedical Excellence for Safer Transfusion Collaborative and the Transfusion Medicine Resource Committee of the American Pathologists. There was particular emphasis on automation, in addition to the need for the implementation of an External Quality Assurance Scheme (AuBuchon, De Wildt-Eggen and Dumont, 2008). As there is a great deal of variation in component titration methods, it is difficult to establish a translatable threshold for the critical high titre classification. Further, there is no internationally recognised 'safe' titre for transfusion of ABO incompatible plasma containing components. When considering a 'safe' titre, the method employed to measure anti-A and anti-B (IgG and IgM) must also be carefully considered (Yazer, Cap and Spinella, 2018).

1.3 Blood components

1.3.1 Whole Blood (WB)

Group O WB was first identified as a 'universal donor' by Ottenberg in 1907. The naturally occurring anti-A and anti-B were assumed to be too diluted to cause haemolysis (Berséus *et al.*, 2013). Fresh WB (i.e. WB collected and transfused within 24 hours of donation) was used routinely by the military between 1940 to 1960. However, in 1944 a severe haemolytic transfusion reaction was reported by the US army when a unit of group O WB, with an anti-A titre of 1:8000, was transfused to a group A recipient (Berséus *et al.*, 2013). The US army since changed their transfusion protocol and only gave group O fresh WB to non-group O recipients if the anti-A and anti-B titres were less than 1:250 (Barnes, 1973). However, by 1965 the use of fresh WB reduced significantly due to the introduction of blood components (i.e. RBC, FFP, Platelet), which made targeted replacement therapy of missing clotting factors possible. This minimised the potential risks and side effects of receiving unneeded blood components and minimised the risks of haemolysis from anti-A and anti-B when transfusing group O. Further, the longer shelf-lives of blood components (varying from 5-7 days for platelets and 35 days for RBC)

compared with fresh WB, made the logistics of supply and demand more manageable for the blood manufacturing units. All these factors contributed to the rapid disappearance of WB.

1.3.2 Platelet

With platelet components, the ABO group of the plasma should also be considered (Stanworth *et al.*, 2015). In the past, platelets have been transfused with much disregard to the ABO group, and in current practice it is routine to make exceptions to ABO matching due to local hospital inventory shortages (Lozano *et al.*, 2010). However, a North American study found that between 1996 and 2006, 6 deaths were reported to the US FDA (Food and Drug Administration) relating to acute transfusion reactions as a result of minor ABO incompatibility in platelet transfusions (Fung, Downes and Shulman, 2007). The most frequent reactions appear to occur when group O single donor apheresis platelets are transfused to group A, B or AB recipients (Cooling *et al.*, 2008). It is recommended that components with low anti-A and anti-B titres may reduce the risk of haemolysis in cases of ABO mismatch. Methods of introducing such recommendations include pre-issue titration and reducing the plasma proportion in the platelet component by introducing the use of platelet additive solutions (PAS). There are also fewer occurrences of haemolysis, allergic and febrile non-haemolytic reactions from platelets stored in 65% PAS, which support the above recommendation (Weisberg *et al.*, 2018). This points to the fact that platelet components are ultimately safer with a lower titre of ABO antibodies.

1.3.3 Plasma

It is highly recommended that patients receive ABO identical plasma as a first choice. Thereafter non-identical plasma may be acceptable in emergency situations if confirmed to be of low titre for anti-A and anti-B. Group O plasma should be transfused only to group O recipients (Green *et al.*, 2018). Group AB plasma is deemed universal as it does not contain anti-A or anti-B (Dunbar *et al.*, 2017). However, due to the low prevalence of group AB blood donors in the population (about 4% of UK population), non-identical plasma other than group AB is frequently used in emergency cases where there is insufficient time to perform blood group analysis. There have been many studies outlining the use of group A plasma instead of AB for emergency use in the civilian

setting, as a 'next best' option for a universal component (Inaba *et al.*, 2010; Chhibber *et al.*, 2014; Dunbar *et al.*, 2017; Yazer, Cap and Spinella, 2018). The risk of haemolysis from non-identical plasma is small but should be considered in settings where large plasma transfusions (including plasma exchange) are given to low plasma volume recipients (neonatal and paediatric recipients) (Win, 2012).

1.3.4 Leucocyte-depleted Red Cell and Plasma (LD-RCP)

In the UK, all blood components undergo a universal removal of leucocytes (called leuco-depletion) as a safety measure to reduce the risk of variant-CJD transmission (Green *et al.*, 2018). The current leuco-depletion filter used by UK blood services removes platelets, producing a component that has RBC and plasma in the same bag (Leucocyte-depleted red cells and plasma or LD-RCP) (Huish *et al.*, 2019). Although LD-RCP does not contain platelets and is therefore not equivalent to a WB component, it still provides some logistical advantages for the pre-hospital community compared to the transport and administration of two separate components (RBC and thawed plasma). It reduces weight for the team and more importantly, minimises time-critical steps for resuscitating bleeding patients at the scene. Thus, freeing up time for the team to do other important tasks and move patients quickly to the hospital.

1.3.5 Transfusing ABO incompatible plasma

Despite stringent regulations within the UK involving high titre testing of components, minor incompatibility still poses an issue with transfusion reactions. Due to the limited supply of Group AB plasma, understandably clinicians have accepted the use of Group A plasma and platelets as the universal group for the management of bleeding patients whose blood group is unknown, and this means that for most patients they will be receiving ABO mismatched plasma components. This is undesirable, given the potential risk of haemolytic transfusion reactions caused by transfusion of ABO incompatible plasma containing components. Further, there is now a huge interest in transfusing WB components in emergency and pre-hospital settings. In such settings, if we are to give WB in the early stage of bleeding, a group O WB component (that contains anti-A and anti-B in the plasma) would be the most logical group to transfuse, as the patient's blood group is likely to be unknown. Therefore, for non-group O recipients there is a potential risk of a haemolytic transfusion reaction occurring. Thus, it is important to quantify this

risk, particularly as these patients are likely to receive a high volume of plasma in the immediate resuscitation period.

The other important factor to consider when transfusing ABO incompatible plasma containing components to patients who develop major bleeding, is the volume administered. Theoretically, one would expect that the higher the volume, the higher the risk of haemolytic transfusion reaction. Yet there is little data in the literature to guide us on the safe volume for ABO incompatible plasma containing components, and none of the national guidelines give any recommendations on this. The volume of plasma administered to bleeding patients has risen recently for all different specialties (Green *et al.*, 2017), driven mostly by studies in trauma (Holcomb *et al.*, 2015; Sperry *et al.*, 2018). For example, one clinical study that described management of major bleeding in different clinical settings, showed that on average, eight units of FFP, two pools of cryoprecipitate, and two pools of platelets are transfused to adult patients who developed major bleeding (defined as ≥5 RBC units in 5 hours and/or ≥10 units in 24 hours) (Green *et al.*, 2017). Currently, a UK multicentre randomised control trial (CRYOSTAT-2, ISRCTN14998314) is assessing the addition of early high doses of cryoprecipitate transfusion (three pools) versus standard care in patients who are bleeding due to trauma. If high dose cryoprecipitate is to become the standard of care in the future (in addition to FFP transfusion), the risks of haemolytic transfusion reactions due to ABO incompatible plasma transfusion is likely to rise. Further work is required to establish the risk of transfusing high volumes of ABO incompatible plasma components and establishing an international standard for a safe titration level and method of testing.

1.4 Stock management of short shelf-life blood components

1.4.1 Whole Blood Component in the UK

As with a WB component, LD-RCP has a shorter shelf life (14 days) than RBC units (35 days) and if either component is to be used only for a limited group of patients (pre-hospital traumatic haemorrhage), it is important that blood services assess its deliverability from a supply and demand point of view, and that hospitals determine its wastage level. Furthermore, in pre-hospital settings, where the blood group of the

patient is unknown, a group O component would be the safest blood group to transfuse. However, there is the potential risk of haemolysis occurring if LD-RCP is transfused to non-group O recipients, due to the presence of anti-A and anti-B in the plasma of group O LD-RCP donated units. Thus, it is important to quantify this risk, particularly as these patients are likely to receive a high-volume transfusion as part of the immediate resuscitation (Mark H. Yazer *et al.*, 2018).

Group O Rh D Negative ('O Neg') is considered the safest group to transfuse to patients with unknown blood groups from the red blood cell perspective (i.e. mainly patients presenting in emergency situations). WB components or LD-RCP in the UK would therefore be produced from group O Neg donations. However, these donations are in short supply, they are a precious resource as they are also required for the manufacture of O Neg RBC used for the transfusion of group O Neg patients, for neonatal and for emergency transfusion of other non-trauma patients with acute bleeding requiring urgent resuscitation. In the UK, 12% of the demand for RBC is for O neg, but this group makes up only 8% of the population (Foukaneli and et al, 2018), so there is a shortage of donors and supply of this type of blood (Foukaneli and et al, 2018), making it a precious resource for the NHS.

By its nature, demand for blood for pre-hospital/emergency transfusion is inherently both critical and highly variable. There is a fine balance between supply and demand. Ensuring that we have enough LD-RCP (or, eventually, WB) to treat all trauma patients in the pre-hospital setting, whilst minimising wastage. Further, WB has a relatively short shelf-life (14 days, after which it must be disposed of) and will be used for a targeted and limited group of patients. Wastage could therefore be high and result in significant loss to the NHS, both financially and in treatment capacity. Minimising wastage will be crucial in deciding the feasibility of introducing a WB component nationally.

1.4.2 Operational Research

To date, there is no data that have assessed the stock management of WB components. However, a recent systematic review of perishable blood product inventory noted that many modelling methods have been attempted (Flint *et al.*, 2020). The systematic review

identified 24 studies, half of which had been published in the last decade, which could demonstrate an increased interest in the optimisation of blood stock inventory. In the age of 'Big Data' and with easier access to advanced data analysis tool kits, could be one explanation for the increased research in this area. Operational Research emerged as the most common methodology in the 24 papers that were identified in the review.

Operations Research (OR) as defined by Hiller and Lieberman is "research on operations" and is applied to problems that concern how to conduct and coordinate the operations within an organisation (Hillier and Lieberman, 2015). OR methodologies include demand forecasting, simulation, and stochastic modelling to name just a few. However, interestingly the review separated forecasting and simulation as discrete methodologies outside of OR.

OR is used primarily in the world of business to solve logistical problems of supply and demand. The issue we face with regards to perishable stock inventory is no different and could be adapted to suit this logistical problem of WB demand. Over 70% of the studies identified in the systematic review by Flint et al were performed in North America and no studies were identified in the UK (Flint *et al.*, 2020). Although many of the methods used and information gained for this research can be adapted for UK practice, there are many differences in regulatory and clinical practices of transfusion medicine across different countries. Therefore, having UK specific data, and studies performed in the UK will be of huge benefit to UK practice.

1.5 Summary

Major bleeding accounts for 25-40% of all trauma deaths (Kauvar and Wade, 2005; Moore *et al.*, 2021), with the cost of management being around £150 million for the NHS (Campbell *et al.*, 2015). Further research is required to provide answers to the optimal blood component therapy for the management of major traumatic haemorrhage. Questions remain as to whether WB is superior to individual component therapy for the treatment of major haemorrhage in the pre-hospital setting, where time is of the essence.

The logistics and complexities of storage conditions, shelf life, and storage capacity within air ambulances providing individual component therapy in pre-hospital settings could delay transfer to hospital, which for many patients could be detrimental. From a logical point of view, these issues would be resolved with having a single bag which contained all three components (like WB or LD-RCP). Hence the current interest in re-introducing a WB component, as a replacement for individual blood components to resuscitate patients with traumatic major bleeding, particularly those presenting in pre-hospital settings. However, future research should not only assess the efficacy of a WB component, but also the feasibility of delivery compared to the alternative.

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Chapter Two: Aims and Objectives
Rationale for the research and detailed aims and objectives

Chapter Three: Research Methodology
Overview of methods used to answer the research objectives

Chapter Four: Safety Profile
Scoping review of the literature for the risk of haemolysis following the transfusion of ABO incompatible plasma components

Chapter Five: Observational Study
Understand the feasibility of delivering LD-RCP components in the pre-hospital setting

Chapter Six: Stock Management
Development of a stock management model to reduce to component wastage

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Chapter 2 Aims and Objectives

2.1 Rationale and justification for the research

Mortality of trauma patients due to bleeding occur early, and despite the intensive resuscitation of patients by major trauma centres, clinical outcomes remain poor. This study will determine if it is feasible to deliver a WB component to UK hospitals in the future. It will provide much needed insight into the stock management of a short shelf-life component with limited clinical indications and further, the output of this thesis will improve our understanding of the safety of WB transfusion in the resuscitation of trauma bleeding patients. The overall findings will have a direct impact on UK practice on the management of bleeding patients in the pre-hospital setting.

2.2 Problem statement

The optimal use of blood component therapy for the management of major haemorrhage remains uncertain. Following the results of the PROPPR trial (Holcomb *et al.*, 2015), it would be a logical conclusion that a WB component could be the best way forward. However, clearly understanding the stock management of a WB component, which has limited clinical use and a short shelf life, will need to be evaluated to ensure the wastage of limited resources in minimised.

2.3 Aims and Objectives

The overall aim of this thesis is to establish whether introducing a WB component, for the treatment of traumatic major haemorrhage, is feasible in the UK. This will be achieved by better understanding the safety profile and the supply and demand of the leucocyte-depleted red cell and plasma component, which is very similar to the whole blood component.

This thesis is divided into three distinct but related sections.

1. The first section will address the safety of transfusing ABO incompatible plasma components by examining the evidence in the literature (or safety profile).
2. The second element will evaluate data collected as part of a 2-year prospective observational study using LD-RCP (a component with the same shelf life and

logistical and serological issues as WB), specifically examining the usage, wastage, and safety of LD-RCP (Observational Study).

3. The third and final element will explore the stock management of a WB component using data collected from the same 2-year prospective observational study (Stock Management).

More specifically this will include the following objectives:

1) Safety profile

a) Determine the lowest observable anti-A and anti-B titre (measured by IgG or IgM) reported in the literature that has resulted in haemolysis in recipients receiving ABO incompatible plasma containing components.

b) Determine the lowest observable ABO incompatible plasma volume that has resulted in haemolysis, in individuals receiving ABO incompatible plasma containing components

2) Observational Study

a) Evaluate the clinical and serological effects of transfusing group O LD-RCP to non-group O patients

b) Describe and quantify blood component usage, wastage and 'on time in full' (OTIF) delivery of LD-RCP as defined as:

- number of days per-year where the component was delivered in accordance with agreed specification divided by the number of days where the said component was meant to be delivered.

c) Evaluate quality improvement measures introduced to reduce wastage

3) Stock management

a) Evaluate whether the weekly pre-hospital trauma demand can be forecast

b) Develop a statistical model to optimise WB component and minimise component wastage

c) Evaluate the impact of a 21-day shelf life on component wastage using the statistical model developed in 3b).

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Chapter 3 Methods

3.1 Introduction

This chapter provides an overview of all the methods used within this thesis to address the overall aims and objectives outlined in chapter 2. The chapter will begin by providing an overview of the methods used to perform the systematic scoping review that addressed objectives 1a and 1b, examining the safety profile of a WB component. The chapter will then cover the methods used in the 2-year prospective observational study that will address objectives 2a, 2b and 2c. Finally, this chapter will cover the methods used to address objectives 3a and 3b that explore the stock management of a WB component.

3.2 Scoping review principles

The methodologies of scoping and systematic reviews are similar. Both styles of review use systematic methods to collate findings and evidence in the published literature for a given question. However, a scoping review is often more useful when answering much broader questions compared with systematic reviews which are aimed at answering more clearly defined questions (Moher *et al.*, 2009; Tricco *et al.*, 2018).

Systematic review: A form of literature review that uses systematic methods to collate and synthesise findings of studies that address a clearly formulated question (Page *et al.*, 2021).

Scoping review: A knowledge synthesis that follows a systematic approach to map evidence on a topic and identify main concepts, theories, sources, and knowledge gaps (Tricco *et al.*, 2018).

Due to the heterogeneous nature of this review and the complexities around the measurement of anti-A and anti-B titres, it was decided that a scoping review would be most appropriate. The protocol and final write-up of this scoping review were conducted in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Appendix 1). The PRISMA-ScR outlines 20

essential and 2 extra items to include when completing a scoping review (Tricco *et al.*, 2018).

To establish the question and search terms used for the scoping review the PICO (Population, Intervention, Comparator and Outcome) model was used. The search strategy was developed using medical subject headings (MeSH) and text words related to the question (Appendix 2). The literature search was completed by an information specialist at the Systematic Review Initiative (SRI), a clinical research group based within NHS Blood and Transplant's Oxford Blood Centre. The literature search results were uploaded to Covidence, a web-based software platform for literature screening and data extraction.

3.3 Observational study

3.3.1 Ethics

Ethical approval for this study was granted by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW), provided by Dr Laura Green, Consultant Haematologist and Senior Clinical Lecturer, Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London. (REC Reference: 19/HRA/0102; IRAS Project ID: 236783).

The research was conducted in compliance with the approved protocol, the Declaration of Helsinki the Principles of Good Clinical Practice (GCP), European Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, the UK Policy Framework for Health and Social Care Research (V 3.3, 07/11/2017) and any other applicable national regulations.

The primary ethical and management issues surrounding the research were adequate data protection. To address this, all data collected was anonymised and each case was allocated a unique reference number. This number was shared with the clinical team at other sites and was used for all subsequent data collection, storage, and transfer.

The primary study database (MS Access) was stored on a password−protected computer at Barts Health NHS Trust. The study database was encrypted using the Windows XP Encrypting File System (EFS).

The data was accessible only by the key members of the working group, who required access to the data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study was only allowed after a successful application to a Research Ethics Committee.

3.3.2 Study participants

Data for the observational study was collected from two different groups of patients:

1. **Comparator group - RBC cohort (retrospective arm)**
- All trauma patients who were transfused at least one RBC in the pre-hospital setting in London (and emergency department at RLH) from March 2015 to April 2018

2. **Study group – LD-RCP cohort (prospective arm)**
- All trauma patients >1yr old who were transfused at least one LD-RCP unit in the pre-hospital setting because of haemorrhage from November 2018 to October 2020.

Children <1 year old were excluded because the UK national guidelines recommend that these patients should receive RBC units of <5 days old to reduce this risk of hyperkalaemia from large volume transfusion (New *et al.*, 2016). During the study, it was not possible to allocate <5-day old LD-RCP units, hence, this group were excluded.

The routine standard of care for participants was not altered for the purpose of this study, hence study participants were not contacted or approached for consent and no identifiers (i.e. names, addresses, dates of birth, hospital or NHS numbers, or date of death) were collected.

3.3.3 Data collection

Blood component data for patients in both groups were collected as part of this study. To consider seasonal variations and bank holidays, the study data was collected for a period of 24 months and the comparator data was collected for a period of 43 months (prior to the study data).

Comparator group - RBC cohort

Data was collected retrospectively on all trauma patients who were transfused RBC in the pre-hospital setting in London from March 2015 to October 2018, prior to the introduction of LD-RCP into routine practice. Data collected included:

- Components transfused
- Donation number of unit
- Location of unit transfusion (pre-hospital, emergency department (ED))

All data was obtained from the transfusion laboratory information management system (LIMS) WinPath and was stored on a Microsoft Excel spreadsheet.

Study group - LD-RCP cohort

Data was collected on all trauma patients who were transfused LD-RCP in London from November 2018 – October 2020. Data collected included:

- Date of injury
- Components transfused
- Number of components transfused in 24hrs
- Laboratory results (Full blood count (FBC), bilirubin, Direct Antiglobulin Test (DAT) and Blood group).

The pre-hospital critical care team in London can transfer traumatically injured bleeding patients directly from scene to the four major trauma centres (i.e. the Royal London Hospital, St Georges Hospital, St Mary's hospitals and Kings College Hospital).

If a patient who required blood in the pre-hospital setting in both groups survived and were admitted to any of these hospitals, further data was collected from hospitals on a

case report form (CRF) on Microsoft Access. All patients were given a unique identification number. The following information was collected on the CRF:

- Donation number of unit
- Date of unit delivery
- Age of unit on delivery
- Fate of unit (used, wasted)
- Date of fate
- Location of wastage
- Reason for wastage
- Location of unit transfusion (pre-hospital, emergency department (ED))
- Date the unit was transferred to ED fridge
- Age of unit on transfer

Data was obtained from the transfusion laboratory information management system (LIMS) in each hospital and was stored on a Microsoft Excel spreadsheet.

3.3.4 Evaluation of haemolysis

The clinical and serological effects of transfusing a group O WB component to non-group group O patients was assessed through statistical analysis of the laboratory results collected as part of the observational study. The statistical analysis was performed using IBM SPSS statistics (Version 27) predictive analytics software. Continuous variables were summarised as medians [interquartile range] and compared using Mann-Whitney U tests.

3.3.5 Quality improvement

To understand the pathway of the LD-RCP component and explore the different elements of the pathway that could contribute to component wastage, a process map was produced of the end-to-end journey of LD-RCP. Starting with the initial blood donation and ending with the final fate of the component (transfused or discarded). Using the Model for Improvement (MFI) developed by Langley et al, 1996, Plan Do Study Act (PDSA) cycles were conducted using the data collected on wastage. Each quality improvement idea was discussed and decided by the whole blood program group prior

to implementation. Data was presented using Statistical Process Control Charts (SPC) developed in MS Excel.

3.3.6 On Time in Full (OTIF)

On Time in Full (OTIF) is a key supply chain metric that the blood supplier NHSBT use to determine if they are meeting the expectations of customer demand for blood components. OTIF is normally defined as a simple percentage:

$$\text{OTIF \%} = \left[\frac{\text{Orders delivered on time}}{\text{Total number of orders}} \right] \text{x } 100.$$

In the case of this observational study, OTIF was measured only for the LD-RCP plasma components and was defined as:

$$\text{OTIF \%} = \left[\frac{\text{Days per-year where the component was delivered}}{\text{Number of units ordered}} \right] \text{x } 100.$$

Equation 1: On Time In Full (OTIF) formula

3.4 Supply and Demand of LD-RCP

3.4.1 Evaluation of component usage

Component usage data collected as part of the observational study and was used to evaluate the component demand. Counts and percentages were used to summarize the distribution of categorical variables. Mean and standard deviation were used for continuous data. To determine the differences in component usage for the day of the week and month, one-way analysis of variance (one way ANOVA) was used. Statistical analysis was performed using IBM SPSS statistics (Version 27) predictive analytics software.

3.4.2 Demand forecasting

Demand forecasting is a systematic method of evaluating future demand that can be used to support more accurate stock management, enhance inventory planning, and

meet service demands. Demand forecasting uses historical data to evaluate future demand. There are qualitative and quantitative/statistical methods available for demand forecasting. This thesis will explore the use of quantitative/statistical methods to forecast future demand, specifically looking at an econometric forecasting technique known as Autoregressive Integrated Moving Average (ARIMA) to determine if the component usage data for pre-hospital trauma could be forecast to a useful degree to support stock management.

An ARIMA model is a demand forecasting model that is comprised of a combination of AR (Autoregression) and MA (moving averages) with the addition of Integration (I) which uses differencing of the raw observations to make the time series stationary. Each of the three components AR, MA and I is specified in the model as a parameter, with standard notation being ARIMA(p,d,q). Whereby:

- **p** = the lag of observations included in the model, represents AR and is obtained from the partial autocorrelation plot
- **d** = the order of differencing, represents I and is obtained from the Augmented Dickey-Fuller test:

$$y_t = c + \beta_t + \alpha Y_{t-1} + \phi \Delta Y_{t-1} + \phi_2 \Delta Y_{t-2} \ldots + \phi_p \Delta Y_{t-p}$$

Equation 2: Augmented Dickey-Fuller Test formula

- **q** = the order of moving average, represents MA and is obtained from the autocorrection plot.

Building an ARIMA model is completed in two stages: 1) Identifying whether the data is stationary and 2) Generating and testing the model. Stage 1, Identifying if the data is stationary is an important part of building a forecasting model with some degree of accuracy. To build an ARIMA model the data must be stationary, if the data is not stationary then differencing (d) is required to remove non-stationary features.

The time series data used for the ARIMA model was the component usage data collected as part of the observation study. Models were generated for both the comparator group (RBC cohort) and the study group (LD-RCP) cohort using both daily and weekly

component usage time series data to determine if future demand for each component could be forecast.

The ARIMA forecasting model was solved using Python - a general-purpose programming language often used to conduct data analysis, on Anaconda3 - an open-source distribution platform for Python and R programming languages, using the integrated development environment (IDE) Spyder 4, included with Anaconda3.

3.4.3 First In First Out Model

First in first out (FIFO) is a method of handling inventory whereby the first stock item to be delivered, in this case a blood component, is the first item to be used. Blood supply, as a perishable product with a short shelf life, lends itself to a FIFO style stock management model (Simonetti *et al.*, 2014). This method is generally applied throughout hospital laboratories to manage stock levels and minimise component wastage. Its application being primarily manual.

A FIFO stock management model was created using MS Excel. Under a FIFO stock management model, it is assumed that the oldest units in stock will be the first units used/issued thereby reducing unnecessary wastage due to outdating. The FIFO stock management model was used to:

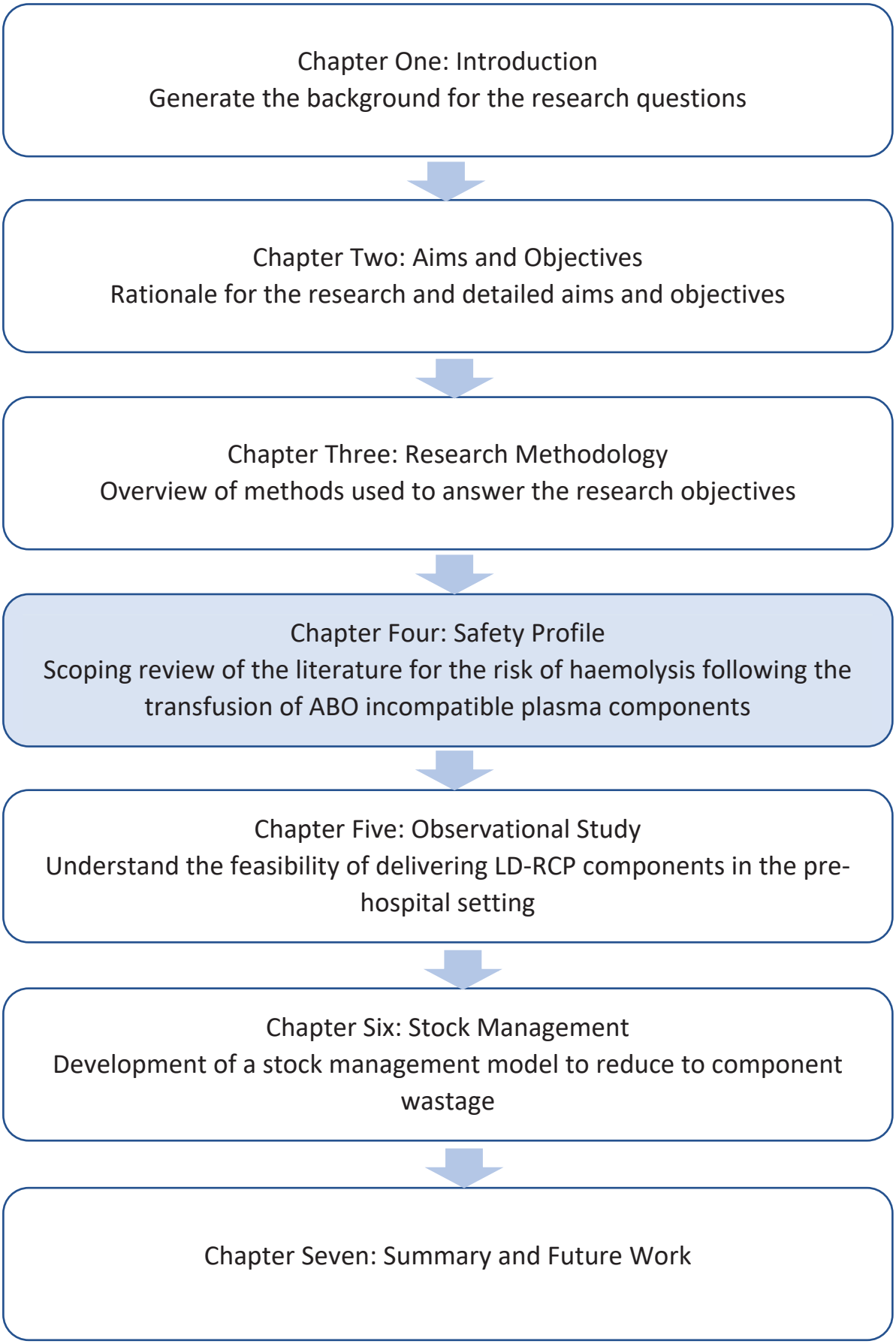
1) Evaluate the effectiveness of the current stock management system to follow a strict FIFO stock management policy.
2) Determine the lowest possible LD-RCP wastage for pre-hospital demand using the static supply of LD-RCP component used throughout the study period
3) Test different algorithms of adjusted component supply to determine an optimal supply to meet demand and reduce component wastage

Seven FIFO models were developed with a 14-day shelf life to mirror the actual shelf life of the WB component. The supply of WB component for each of the seven models was altered with different algorithms based on stock levels. Each model was assessed to determine the optimal model for minimising component wastage whilst ensuring that demand was met. A further seven models were developed with a 21-day shelf and the

same stock management algorithm to evaluate whether an extended shelf-life would influence the potential wastage levels of the component.

3.4.4 Simulation

Simulation is an operational research technique that is used to imitate (simulate) the operation of a process or system (Hillier and Lieberman, 2015). Simulation can be used to experiment with and test the suitability of mathematical models to determine the most optimum model for the problem to be solved. In this thesis simulation was used to generate WB component demand for each of the FIFO models. A Monte Carlo simulation was developed using MS Excel. A Poisson probability distribution was used to generate the random variables for the component demand. This randomly generated demand data was then used as demand input for the FIFO model to generate various outcome profiles. Effectiveness of each FIFO model was determined by the sum of component wastage plus the unmet demand.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Chapter 4 Assessing the risks of haemolysis as an adverse reaction following the transfusion of ABO incompatible plasma-containing components - A scoping review

4.1 Introduction

The ABO blood group system remains the most important and clinically significant due to the naturally occurring presence of anti-A and anti-B in donors and recipients. These antibodies can result in immune red blood cell destruction (or haemolysis) leading to significant morbidity and mortality for the recipient if ABO incompatible components are transfused. ABO incompatibility can be classified into two types: major incompatibility, where antibodies in the recipient bind to transfused red cells and minor incompatibility where antibodies in the transfused blood component bind to the recipients red cells (Daniels and Bromilow, 2013).

Whilst the risk of haemolysis and serious harm is higher with the transfusion of ABO incompatible red blood cells (RBC) than with ABO incompatible plasma components (Bolton-Maggs, P (Ed), Poles, 2018), there is still a risk of haemolytic transfusion reactions with components containing plasma (i.e. fresh frozen plasma and platelets). Currently, national guidelines recommend that patients should receive ABO identical plasma and platelet components as a first choice (Nahirniak *et al.*, 2015; Estcourt *et al.*, 2017; Green *et al.*, 2018; The Australian and New Zealand Society of Blood Transfusion, 2020; Cardigan *et al.*, 2021) and for patients with an unknown blood group, group AB is the universal and ideal blood group to transfuse. However, the prevalence of group AB donors in the population is very low. Therefore, several guidelines and blood services now recommend that group A plasma, which is negative for high titre Anti-B could be used as an alternative to reduce the risk of haemolysis due to the transfusion of non-ABO identical plasma/platelets. This, however, introduces complexity in finding suitable ABO groups of the components based on the recipients ABO group and specifying that the components are ‘high titre negative’ for anti-A/B. Further, not all blood providers

routinely screen for high-titre anti-A/B and the cut-off level for what is defined as 'low titre' or 'high titre negative' remains unknown and lacks international consensus.

Most international blood services have accepted an anti-A and anti-B titre of <100 for IgM and <400 for IgG antibodies as a safe cut-off (Berséus *et al.*, 2013; Yazer and Spinella, 2020; Cardigan *et al.*, 2021). However, there is a great deal of variation in component titration methods, and it is therefore, difficult to establish a threshold for the critical high titre classification. Furthermore, the relationship between the titre and the risk of haemolysis is not absolute and the severity of haemolysis from a transfusion of ABO incompatible plasma/platelets components can be affected by other factors, including, the isotype, volume transfused, age and weight of the recipient as well as underlying pathology (Mark H Yazer *et al.*, 2018). A further consideration in determining an appropriate cut-off for high titre screening is drawing a balance between removing high titre donations and ensuring an adequate supply of components.

There is now interest in transfusing whole blood (WB) components in emergency and pre-hospital settings, as this allows for the 1:1:1 resuscitation of bleeding patients with red cells, plasma, and platelet transfusion (Holcomb *et al.*, 2015). In such settings, if we are to transfuse WB in the early stage of bleeding, a group O WB component (that contains both anti-A and anti-B in the plasma) would be the most appropriate group to transfuse, as the patient's blood group is likely to be unknown. Therefore, for non-group O recipients there is a potential risk of a haemolytic transfusion reaction occurring due to the transfusion of ABO incompatible plasma. Thus, it is important to quantify this risk, particularly as these patients are likely to receive a high volume of plasma in the immediate resuscitation period.

This scoping review aims to assess the evidence on the impact of ABO incompatible plasma/platelets and determine the lowest observable anti-A or anti-B titre levels and the lowest volume that have resulted in haemolytic transfusion reactions (both laboratory and clinical). This review has concentrated only on minor ABO incompatibility and therefore, restricted the review to the transfusion of ABO incompatible plasma-containing blood components (platelets, plasma, cryoprecipitate, and whole blood) and the risk of haemolysis associated with anti-A and anti-B in the transfused component

only. Other adverse reactions associated with the transfusion of blood components were not considered.

4.2 Objectives

Objectives of this scoping review were to answer the following questions:

1. In individuals receiving ABO incompatible plasma containing components, what is the lowest observable anti-A and anti-B titre (measured by IgG or IgM) reported in the literature that has resulted in haemolysis (clinical or laboratory)?

2. In individuals receiving ABO incompatible plasma containing components, what is the lowest observable ABO incompatible plasma volume that has resulted in a haemolysis?

4.3 Methods

4.3.1 Review Protocol

The protocol was written using the PRISMA extensions for Scoping Reviews.

4.3.2 Eligibility Criteria

Studies were eligible if they included patients of any age, who received a transfusion of an ABO incompatible plasma containing component where haemolysis was reported. Paediatric population was defined as ages 0-17 years.

“Plasma containing component” was defined as, fresh frozen plasma (FFP), thawed plasma, FFP24 (plasma frozen within 24hrs), lyophilised plasma, freeze dried plasma, pathogen inactivated plasma, cryoprecipitate, apheresis platelet, pooled platelet, or whole blood.

4.3.3 Exclusion Criteria

Studies were excluded if they addressed: ABO incompatible packed red cell transfusions; intravenous immunoglobulins; anti-D administration; haematopoietic stem cell transplants, and studies using animal models. Haemolysis was defined as described in each individual study.

Studies were included if they were randomised control trials (RCTs), cluster-RCTs with at least two interventions, non-RCTs, repeated measures studies, controlled before-and-after studies, case reports, case control studies, reports from hemovigilance schemes if published as a paper and any other study type that has assessed the risk of haemolysis with ABO incompatible plasma transfusion.

4.3.4 Information Source and Search Strategies

An information specialist (Carolyn Doree) searched the following databases from their inception to 24 April 2022; MEDLINE (OvidSP), PubMed (pre-MEDLINE publications only), Embase (OvidSP), CENTRAL (The Cochrane Central Register of Controlled Trials) & CDSR, *The Cochrane Library* (Wiley interface, 2022, Issue 4), Transfusion Evidence Library (Evidentia Publishing, Web of Science (Thomson Reuters), Scopus (Elsevier), Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). There were no restrictions on publication date, language, publication status or study design. Search terms, inclusions and exclusions are presented in Appendix 2.

4.3.5 Selection of sources and evidence

Search results were uploaded to Covidence, a web-based software platform, to facilitate the screening process. Three review authors (Myself (JM), Tom Bullock (TB) and Sian Huish (SH)) independently screened abstracts and then the full text of potentially eligible studies, with one reviewer (JM) screening all abstracts and full texts. Any disagreements were resolved by consensus.

4.3.6 Data extraction process

A data-extraction form was developed by three reviewers (JM, TB and SH) with input from Susan J. Brunskill. The three reviewers (JM, TB and SH) independently extracted the data, discussed the results, and continuously updated the data-extraction form. A pilot of the data-extraction form was completed by all three reviewers prior to starting the extraction process.

4.3.7 Data Items

The following parameters were collected: study ID, study setting and country, date of publication, study participant demographics, details of component transfused, the volume of component transfused, details of assays used to measure anti-A and anti-B titre, recipient and component blood type, and details of diagnostic tests used to measure haemolysis markers. Data on clinical outcomes where available, were also collected and this included mortality, morbidity and whether a haemolytic transfusion reaction was reported. Due to constraints on time, resources, and the age of some papers we did not contact the authors of the papers if missing data was identified or suspected.

4.3.8 Synthesis of Results

The extracted data was summarised in a table format, grouping studies by type and ABO blood group of the component transfused, age of patients, method of measuring the titre levels and volume of plasma component transfused. The primary outcome of this review was anti-A and anti-B titre (measured by IgM or IgG) that resulted in measurable haemolysis following ABO incompatible plasma transfusion The secondary outcome was assessing the association between volume of ABO incompatible plasma administered and haemolysis.

4.3.9 Statistics

As this is a scoping review, we have not statistically analysed the data, rather we have reported the findings in tables and plots and commented narratively on the findings in the text. The focus of the reporting is the anti-A and anti-B titre, volume of ABO-incompatible plasma transfused, and patient outcome. Data for adult patients is reported separately from data for paediatric patients, as we considered the volume and titre of anti-A/B that may cause haemolysis to be different.

4.4 Results

4.4.1 Study Selection

5,681 citations were identified (including 224 ongoing trials), which were reduced to 3,712 citations after duplicates were removed (Figure 4-1). Three review authors (JM, TB and SH) excluded 3262 citations based on the abstract, leaving 450 full text articles for review. The full text of 93 records could not be found: thus, 357 full text articles were reviewed for eligibility. Of the 357 citations, 308 studies were excluded because; 279 did not report haemolysis and 29 reported haemolysis due to something other than ABO-incompatible plasma containing transfusion. Of the 49 eligible papers, all were case reports/short case series. No completed or ongoing RCTs were identified.

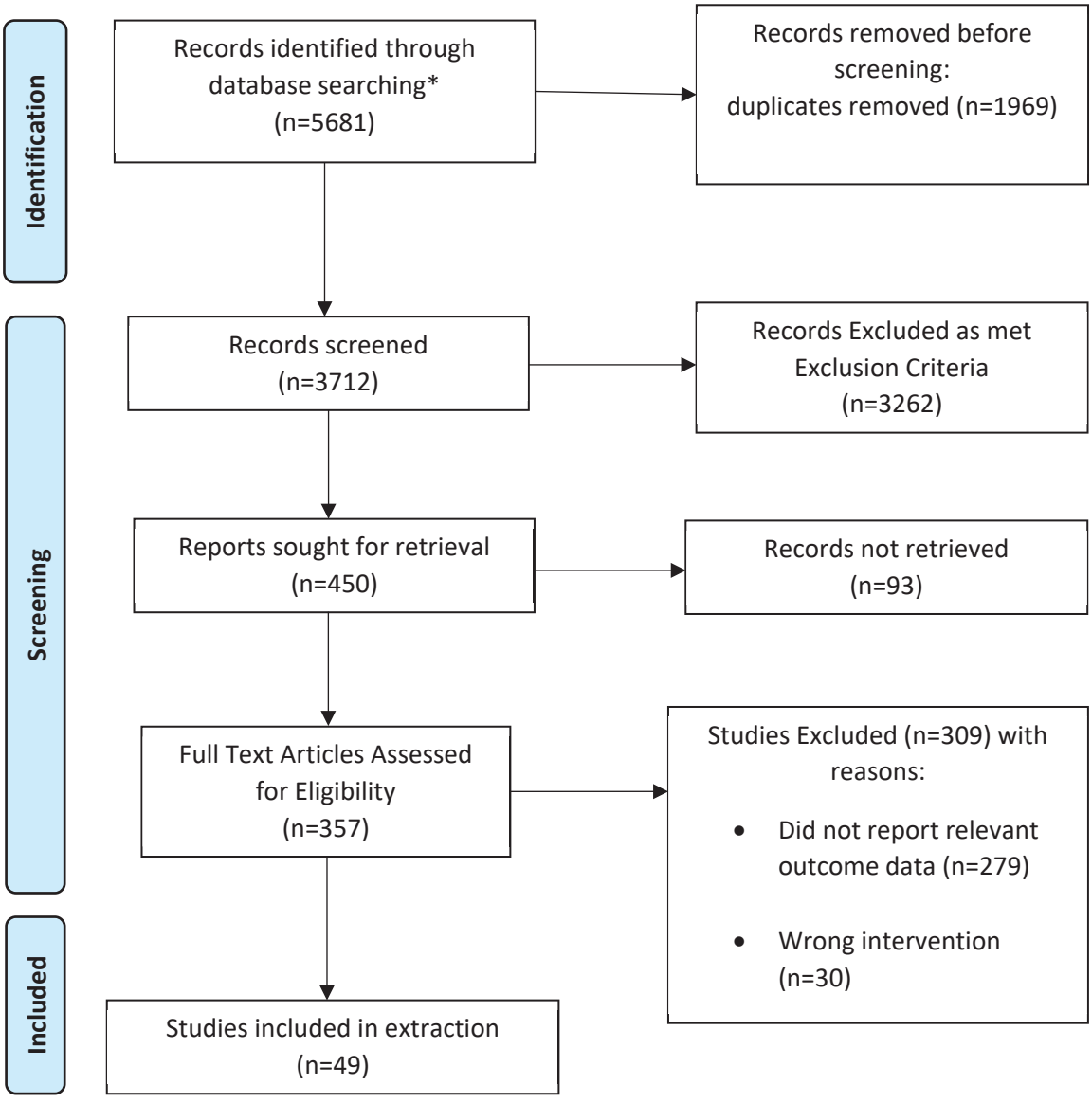


Figure 4-1: Prisma Flow Diagram

4.4.2 Synthesis of Results

A total of 49 papers, all case reports, published between 1946 and 2022, were included, of which eight reported more than one case of haemolysis, thereby 62 cases of haemolysis provided the data for this review. 34 (53%) cases involved adult patients (Table 4-1), 14 (22%) were paediatric patients (Table 4-2) and 14 (22%) cases did not specify the age of the patient (Table 4-3).

The data extracted is presented in Figure 4-2 and discussed separately for adults and children below.

Table 4-1: A table compiling all the papers reporting on adult cases.
The volumes recorded in the table are those of the whole component except for those highlighted * which report the plasma volume of the component. ^Multiple units of different blood group were transfused. IAT (Indirect Antihuman globulin Test), RT (Room Temperature), IS (Immediate Spin), DAT (Direct Antiglobulin Test) and CS (Clinical Symptoms). Data not reported in the cases is represented by (–).

Author	Country	Component Type	Volume	Component Blood Group	Patient Blood group	Antibody	Method of Measurement	Inferred Antibody Isotype	Antibody Titre	Mortality (Y/N)	Measure of Haemolysis
Haemolytic transfusion reactions due to anti-B											
(Pierce et al., 1985)	-	Pooled Platelet	-	O	B	Anti-B	-	-	16384	-	DAT
(Reis & Coovadia, 1989)	Canada	Apheresis Platelet	-	O	B	Anti-B	IAT	IgG	4096	No	DAT/eluate/CS
(Sauer-Heilbom et al., 2002)	US	Apheresis Platelet	526ml	O	B	Anti-B	DTT/Saline IAT	IgM/IgG	2048/4096	-	DAT/eluate/CS
(Daniel-Johnson et al., 2008)	USA	Apheresis Platelet	100ml	A	B	Anti-B	IgG/Saline	IgG/IgM	16384/16384	No	DAT/eluate/CS
(Milkins et al., 2017)	UK	Apheresis Platelet		A	AB	Anti-B	-	-	512	-	CS
(Shachner & Clark, 2018)	US	Apheresis Platelet	135ml	A	B	Anti-B	Saline Tube	IgM	512	No	DAT/CS
(Balbuena-Merle et al., 2019)	USA	Apheresis Platelet	367ml	O	B	Anti-B	Tube IAT	IgG	512	Yes	DAT/eluate/CS
(Swain et al., 2019)	Australia	Apheresis Platelet	-	A	AB	Anti-B	IAT/Saline	IgG/IgM	32000	No	DAT/eluate/CS
Haemolytic transfusion reactions due to anti-A											
(Ebert & Emerson Jr., 1946)	USA	Whole Blood	350ml	O	A	Anti-A	-	-	2048	No	CS
(McLeod et al., 1982)	USA	Apheresis Platelet	100-200ml*	O	A	Anti-A	IAT/Saline	IgG/IgM	10240/640	No	DAT/eluate/CS
(Ferguson, 1988)	Canada	Apheresis Platelet	-	O	A	Anti-A	IAT/RT	IgG/IgM	4000/256	No	DAT/eluate/CS
(Murphy et al., 1990)	UK	Apheresis Platelet	255ml	O	A	Anti-A	IAT/Saline	IgG/IgM	1024/256	-	DAT/eluate/CS
(Mair & Benson, 1998)	USA	Apheresis Platelet	225ml	O	A	Anti-A	Saline	IgM	128	-	DAT/eluate/CS
(Williamson et al., 1999)	UK	Apheresis Platelet	-	O	A	Anti-A	-	-	-	-	Eluate/CS
(Larsson et al., 2000)	USA	Apheresis Platelet	371ml	O	A	Anti-A	Saline RT	IgM	16384	No	DAT/eluate/CS
(Valbonesi et al., 2000)	Italy	Apheresis Platelet	30-35ml*	O	A	Anti-A	37°C/RT	IgG/IgM	128/8000	-	DAT/eluate/CS
(Zubair et al., 2004)	USA	Apheresis Platelet	150ml	O	A	Anti-A	37°C/RT	IgG/IgM	2048/512	-	DAT
(Sadani et al., 2006)	UK	Apheresis Platelet	-	O	A	Anti-A	IAT/DTT	IgG/IgM	640/1280	Yes	DAT/eluate/CS
(Rosen & Indrikovs, 2008)	USA	Pooled Platelets	-	^O, B	A	Anti-A	-	-	-	-	DAT/eluate/CS
(Losada et al., 2010)	USA	Apheresis Platelet	-	O	A	Anti-A	AHG	IgG	32	-	CS
(Fontaine et al., 2012)	USA	Apheresis Platelet	231ml	O	A	Anti-A	Tube IgG/IgM	IgG/IgM	2048/512	Yes	DAT
(Piskorski & Sweeney, 2014)	USA	Pooled Platelets	-	O	A	Anti-A	-	-	-	-	DAT/CS
(Kundrapu et al., 2017)	USA	Apheresis Platelet	-	O	A	Anti-A	IgG/IgM	IgG/IgM	1024/256	No	DAT/CS
(Cumming et al., 2018)	USA	Apheresis Platelet	-	O	A	Anti-A	-	-	-	-	CS
(Peedin et al., 2018)	US	Pooled Platelet	-	O	A	Anti-A	IgG/IS	IgG/IgM	2048/64	No	DAT/eluate/CS
(Basu et al., 2019)	India	Apheresis Platelet	-	O	A	Anti-A	IAT/Saline	IgG/IgM	1024/128	-	DAT/eluate/CS
(Gammon et al., 2019)	USA	Pooled Platelet	-	O	A	Anti-A	37°C/IS	IgG/IgM	2048/256	No	CS
(Guarente et al., 2019)	USA	Pooled Platelet	-	O	A	Anti-A	Saline	IgM	64	-	DAT/eluate/CS
(Moinuddin et al., 2019)	USA	Apheresis Platelet	280ml	O	A	Anti-A	Saline RT	IgM	512	No	DAT/eluate/CS
(Hou et al., 2019)	Taiwan	Platelet	-	B	A	Anti-A	IgM/IgG	IgM/IgG	256/2048	-	DAT/eluate/CS
(Pasion et al., 2021)	USA	Apheresis Platelet	-	O	A	Anti-A	RT/IAT	IgM/IgG	32/256	-	DAT/eluate/CS
Haemolytic transfusion reactions due to anti-A/anti-B											
(Chow et al., 1991)	-	Pooled and Apheresis		^O, A, B	AB	Anti-A/Anti-B	-	-	1024	No	Eluate
(McManigal & Sims, 1999)	USA	Apheresis Platelets		^O, A, B	AB	Anti-A/Anti-B	-	-	-	No	DAT/Eluate

Table 4-2: A table of the papers reporting on paediatric cases.
The volumes recorded in the table are those of the whole component except for those highlighted * which report the plasma volume of the component. ^Multiple units of different blood group were transfused. IAT (Indirect Antihuman globulin Test) and RT (Room Temperature), DAT (Direct Antiglobulin Test), CS (Clinical Symptoms). Data not reported in the cases is represented by (–).

Author	Country	Age	Weight	Component Type	Volume	Component Blood Group	Patient Blood Group	Antibody	Method of Measurement	Inferred Antibody Isotype	Antibody Titre	Mortality (Y/N)	Measure of Haemolysis
Haemolytic transfusion reactions due to anti-B													
(Boothe et al., 1995)	USA	6yrs		Whole Blood	-	O	B	Anti-B	IgG	-	>64000	-	Eluate/CS
(J. Daniel-Johnson et al., 2008)	USA	5yrs	26kg	Apheresis Platelet	37ml	A	B	Anti-B	IgG/Saline	IgG/IgM	16384/16384	No	DAT/Eluate/CS
Haemolytic transfusion reactions due to anti-A													
(Wood et al., 1967)	US	9yrs		Pooled Plasma	5700ml	-	A	Anti-A	-	-	32	Yes	DAT/Eluate/CS
(Burman et al., 1973)	UK	5yrs		Cryoprecipitate	15ml*	O	AB	Anti-A	-	-	-	No	DAT/CS
(Pierce et al., 1985)	-	2yrs	25.5kg	Apheresis Platelet	-	O	A	Anti-A	-	-	32000	Yes	Eluate
(Duguid et al., 1999)	UK	5wks		Apheresis Platelet	-	O	A	Anti-A	-	-	-	No	DAT/Eluate/CS
(Duguid et al., 1999)	UK	9dys		Apheresis Platelet	-	O	AB	Anti-A	-	-	-	No	DAT/Eluate/CS
(Duguid et al., 1999)	UK	4m		Thawed Plasma	90mls*	O	A	Anti-A	-	-	-	No	DAT/Eluate/CS
(Valbonesi et al., 1978)	Italy	16yrs		Apheresis Platelet	-	O	A	Anti-A	37°C/RT	IgG/IgM	128/8000	Yes	DAT/Eluate/CS
(Angiolillo & Luban, 2004)	USA	8m	9kg	Apheresis Platelet	107ml*	O	A	Anti-A	-	-	128	Yes	DAT/Eluate/CS
(Sapatnekar et al., 2005)	US	2yrs	12kg	Apheresis Platelet	145ml	O	A	Anti-A	IAT/Saline RT	IgG/IgM	16384/1024	No	CS
(Harris et al., 2007)	USA	8yrs	30kg	Apheresis Platelet	300ml	O	A	Anti-A	IAT	IgG	4096	No	DAT/Eluate/CS
(Piskorski & Sweeney, 2014)	USA	11yrs		Pooled Platelets	-	O	AB	Anti-A	-	-	-	-	DAT
(Augustine et al., 2021)	India	9yrs	35kg	Apheresis Platelets	-	^O, B	AB	Anti-A	RT	IgM	128/32	No	DAT/CS

Table 4-3: A table of the papers reporting on cases where age of the patient was not specified.
IAT (Indirect Antihuman globulin Test), DAT (Direct Antiglobulin Test), RT (Room Temperature) and CS (Clinical Symptoms). Data not reported in the cases is represented by (–).

Author	Country	Component Type	Volume	Component Blood Group	Patient Blood group	Antibody	Method of Measurement	Inferred Antibody Isotype	Antibody Titre	Mortality (Y/N)	Measure of Haemolysis
Haemolytic transfusion reactions due to anti-B											
(Ruby et al., 2021)	USA	platelet	-	O	B	Anti-B	-	-	-	Yes	
(Daniel-Johnson et al., 2009)	USA	Apheresis Platelet	-	A	B	Anti-B	-	-	-	-	DAT/Eluate/CS
(Ruby et al., 2021)	USA	platelet	-	A	B	Anti-B	-	-	2048	Yes	
(Storch & Eder, 2021)	USA	Apheresis Platelet	-	O	B	Anti-B	IS/AHG	IgM/IgG	128/512	Yes	
(Malvik et al., 2020)	USA	Apheresis Platelet	-	O	B	Anti-B	-	-	-	-	
Haemolytic transfusion reactions due to anti-A											
(Bachowski et al., 2010)	Canada	Apheresis Platelet	-	O	A	Anti-A	IS/IAT	IgM/IgG	512/4096	-	CS
(Bachowski et al., 2010)	Canada	Apheresis Platelet	-	O	A	Anti-A	IS/IAT	IgM/IgG	128/512	-	CS
(Ruby et al., 2021)	USA	platelet	-	O	A	Anti-A	IgM/IgG	IgM/IgG	512/2048	Yes	
(Ruby et al., 2021)	USA	platelet	-	O	A	Anti-A	-	-	-	Yes	
(Ruby et al., 2021)	USA	platelet	-	O	A	Anti-A	-	-	2048	Yes	
(Malvik et al., 2020)	USA	Apheresis Platelet	-	B	A	Anti-A	-	-	-	-	
Haemolytic transfusion reactions due to anti-A/anti-B or no antibody specified											
(Ruby et al., 2021)	USA	platelet	-	O	AB	anti-A and anti-B	-	-	128	Yes	
(Ruby et al., 2021)	USA	platelet	-	O	AB	-	-	-	32000	Yes	
(Malvik et al., 2020)	USA	Apheresis Platelet	-	O	AB	-	-	-	128	-	

4.4.3 Adult cases

- *Component & Blood Group*

The blood components responsible for the haemolysis reported in 34 adult cases were apheresis platelets (24, 70%), pooled platelets (7, 20%) both apheresis and pooled platelets (1, 3%) whole blood component 1 (3%) and platelet that was not further specified as apheresis or pooled 1 (3%). Of the components transfused, 26 (76%) were group O, 4 (13%) were group A, 1 was group B and 3 (9%) were reported as multiple units transfused of different groups (O, A & B).

- *Haemolysis and clinical outcomes*

Of the 34 adult cases, 20 (59%) reported both clinical symptoms, DAT, and eluate results. 26 (72%) reported a positive DAT, 24 (70%) reported an eluate result and 29 (85%) reported clinical symptoms of haemolysis. Patient outcomes were reported in only 14 (41%) cases and 3 (9%) reported the death of the patient associated with haemolyis. These 3 cases were all following the transfusion of group O apheresis platelets, haemolysis resulting from anti-A in 2 cases and anti-B in 1 case, all with a titre of >500.

- *Antibody titre*

Of all adult cases, 28 (82%) reported the antibody titre of the unit responsible for causing the haemolysis (Table 4-1), of which 19 were due to anti-A, 8 were due to anti-B and 1 was due to anti-A and anti-B. However, only 24 (71%) cases reported the method of measurement, temperature, or the isotype. The antibody isotype (IgG or IgM) was only directly reported in 5 cases, the temperature (37^{o}C or room temperature (RT)) of the method was recorded in 6 cases and the methods recorded in the papers were as follows; saline (11), Anti-Human Globulin (AHG)/IAT (10), immediate spin (1), 2 cases specifically reported that testing was carried out using the tube method and 2 cases reported the use of Dithiothreitol (DTT). The lowest antibody titre reported in the literature for adult patients was an anti-A titre of 32 measured by AHG and an antibody titre of 32 measured at RT and for anti-B it was 512 IgG and IgM.

- *Component Volume*

13 (41%) cases reported the volume of the component or the volume of plasma in the component. The lowest component volume transfused that was reported in the adult literature was 100ml of a group A apheresis platelet unit transfused to a group B patient with an anti-B titre of 16384 measured by IgG. The transfusion reaction was characterised by dark brown urine and a grossly haemolysed sample with a positive DAT. The patient was reported to have made a full recovery.

4.4.4 Paediatric cases

- *Component & Blood Group*

The blood components responsible for the haemolysis reported in the 14 paediatric cases were apheresis platelets (9), pooled platelets (1), whole blood component (1), cryoprecipitate (1), pooled plasma (1), and thawed plasma (1). Of the components transfused, 13 were group O and 1 was group A.

- *Haemolysis*

Of the 14 paediatric cases included in this review, 11 reported a positive DAT, 10 reported an eluate result and 13 reported clinical symptoms of haemolysis. A total of 6 cases reported clinical symptoms, DAT, and eluate results. Patient outcome was reported in 11 cases and 4 cases reported the death of the patient due to haemolysis.

- *Antibody titre*

Of the 14 paediatric cases reported, 9 reported the antibody titre of the unit responsible for causing the haemolysis of which 7 were due to anti-A and only 2 were due to anti-B (Table 4-2). However, only 2 cases reported the isotype measured. The temperature of the method was recorded in 3 cases and the method was reported in 3 cases (Saline and IAT/AHG). The lowest antibody titre reported in the literature for paediatric patients was an anti-A titre of 32, although no measurement method was provided from these cases: one of the transfusions resulted in the death of the patient due to haemolysis. For anti-B the lowest antibody titre reported to cause haemolysis was 16,384 as measured by saline.

- *Component Volume*

A total of 8 paediatric cases reported the volume of the component or the volume of plasma in the component. The lowest component volume transfused that was reported to have caused a haemolytic transfusion reaction (HTR) in the paediatric literature was 15mls of a unit of cryoprecipitate, no antibody titre was reported, and the patient was reported to have made a full recovery.

4.4.5 Age not specified cases

- *Component & Blood Group*

The blood components responsible for the haemolysis reported in the 14 cases where age was not specified were apheresis platelets (7) and platelets that were not further specified into apheresis or pooled (7). Of the components transfused, 11 were group O 2 were group A and 1 group B.

- *Haemolysis*

Of the 14 cases where age was not specified, 1 reported a positive DAT and eluate result and 3 reported clinical symptoms of haemolysis. A total of 8 cases reported patient outcome and 8 reported the death of the patient due to haemolysis.

- *Antibody titre*

Of the 14 cases where age was not specified, 8 reported the antibody titre of the unit responsible for causing the haemolysis, of which 4 were due to anti-A and only 2 were due to anti-B (Table 4-3). However, only 1 case reported the isotype measured. The method was reported in 3 cases (Immediate spin and IAT/AHG). The lowest antibody titre reported in the literature for this group was an anti-A titre of 512 and .an anti-B titre of 128 as measured by immediate spin.

4.4.6 Relationship between volume and titre

There was a paucity of data reported on the volume of the components transfused in each of the cases identified, with only 43.8% reporting the volume of the component transfused or the volume of plasma in the component. The lowest volume that resulted in haemolysis for both the adult and paediatric populations were 100mls and 15mls respectively. With this very limited sample, there were no obvious relationships between volume and titre (Figure 4-2).

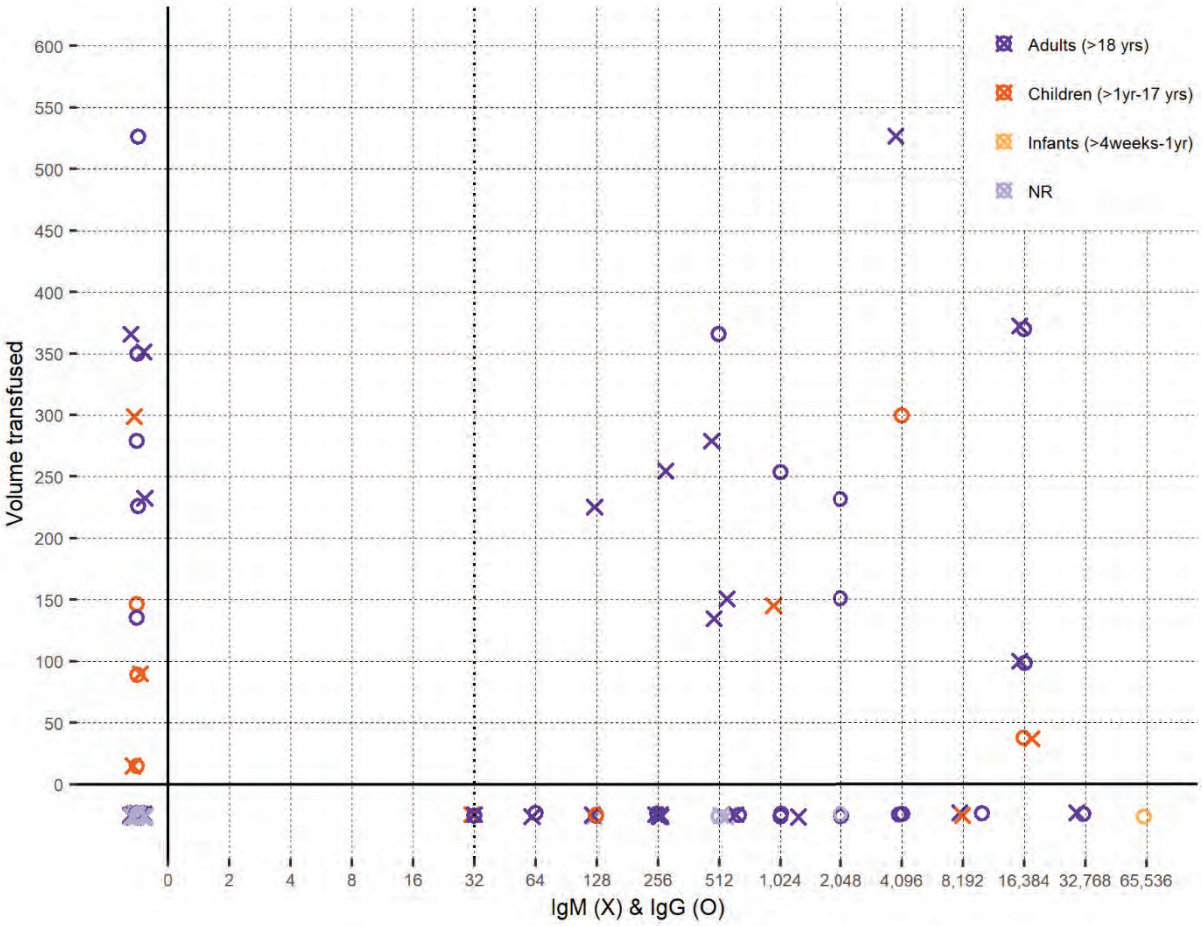


Figure 4-2:A graph showing the relationship between volume of component transfused and IgM/IgG titre.
Reported titres (IgM and IgG) plotted against reported volume with missing values replaced by negative numbers so that a volume with no reported titre will be plotted to the left of the y-axis and a titre with no reported volume will be plotted below the x-axis. The x-axis is on a log scale to make the lower titres more readable. Excludes one very high volume (5,700ml) with no reported titres.

4.5 Discussion

4.5.1 Summary of Evidence

In this first systematic scoping review the objectives were to determine a) the lowest observable anti-A and anti-B titre reported in the literature with ABO-incompatible plasma-containing components that resulted in a HTR (based on clinical or laboratory definitions), and b) the relationship between titre and volume and lowest observable ABO incompatible plasma volume that has resulted in a HTR.

The findings identified 62 case reports (34 adults and 14 paediatric, with 14 cases not reporting age) where ABO incompatible plasma containing components have resulted

in haemolysis. There was heterogeneity in the methods for reporting haemolysis and the ABO titration methods. The volume of the components transfused in each of the cases was poorly reported with only 19 (31%) providing this information. Antibody titre was also poorly reported with 47 (74%) of cases providing this information and only 23 (37%) reporting the titres for both IgG and IgM isotypes. Platelet components were the most reported components to result in haemolysis in both paediatrics and adults. The lowest anti-A titre reported to cause haemolysis was 32 (paediatrics and adult), while for anti-B it was 512 (IgG and IgM) for adults 16,384 for paediatrics (IgG and IgM) and 128 (IgM) in cases where the age was not specified. The lowest component volume transfused that was reported to have caused a haemolytic transfusion reaction was 100ml in adults and 15mls in paediatric. Clinical outcomes were also poorly reported, but of the 34 (55%) cases that reported these, 15 (24%) cases reported that the patient had died.

4.6 Discussion of the results

In this first scoping review, 62 case reports were identified between 1946 and 2022 where ABO incompatible plasma/platelet components have resulted in haemolysis. There were no completed or ongoing randomised trials. As expected, platelet components were the most reported components to result in haemolysis in both the paediatrics and adults, as ABO-incompatible platelet transfusions are components more often given compared to ABO-incompatible plasma due to limitations in supply including HLA requirement. There were also two cases that reported haemolysis from a unit of whole blood (1 adult case with an anti-A titre of 2048 and 1 paediatric case with an anti-B titre of >64000 IgG). These cases were reported in 1946 and 1995 (Ebert and Emerson Jr., 1946) (Boothe et al., 1995) respectively, prior to more recent requirements to screen such donations for high titre anti-A/B.

With increasing interest in the use of whole blood for resuscitation of trauma patients who are bleeding, it is very important to put these results into perspective. A systematic review conducted to assess the difference in safety outcomes with the transfusion of WB compared to blood components for any bleeding patient regardless of age or clinical condition identified six RCTs with a total of 618 participants, none of which were reported to have suffered from a haemolytic transfusion reaction (Geneen *et al.*, 2022). Similar results have been reported in recent observational studies of whole blood transfusion in trauma patients (Harrold *et al.*, 2020). It is important to acknowledge that during bleeding there is a significant blood volume loss and therefore it could be argued that the risk of haemolysis in such patients could be lower compared to patients who are not bleeding. Furthermore, an international survey on the use of group O whole blood for the resuscitation of civilian trauma patients in 2020, showed that the definitions for 'low titre anti-A and anti-B' varied between <50 and <256 with the two main methods being Saline tube without anti-human globulin (AHG) or Saline tube with AHG (Yazer and Spinella, 2020).

Group O was the most common blood group to cause haemolysis and many clinical guidelines indeed advise against the use of group O plasma containing components for non-group O patients (Green *et al.*, 2018; The Australian and New Zealand Society of

Blood Transfusion, 2020) unless a significant amount of plasma has been removed for example by suspending platelets in platelet additive solution (PAS). Anti-A was the antibody responsible for most cases of haemolysis, which supports the existing knowledge base that anti-A is more immunogenic than anti-B. Group A was responsible for 7 (4 adult, 1 paediatric and 2 age not specified) cases of haemolysis, all reported within the last 12 years from the transfusion of apheresis platelets. All these cases had an anti-B titre above the level considered 'safe' by most international blood services with the lowest titre to result in haemolysis reported as 512 measured by saline tube (Shachner and Clark, 2018).

There was huge heterogeneity in the way that ABO titration methods were reported, with some papers only reporting the temperature and others reporting the isotype of the antibody being measured. Some papers reported two methods and titre levels however, there was often no explicit reference to the isotype measured although this could be inferred from the data. Further, the methods for reporting haemolysis varied between papers. Some papers reported serological haemolysis with DAT and an eluate being the most common laboratory tests, others reported only clinical haemolysis, and some reported both laboratory and clinical haemolysis. The details on clinical recovery were not provided for all cases, and where it was provided (34 cases), a full recovery was reported in 19 cases, and 15 patients (3 adult, 4 paediatric and 8 no age specified) died due to haemolysis, highlighting the need for caution when transfusing ABO incompatible plasma components and the importance of establishing safe ABO titres.

Results of the review showed that 88% of cases reported the titre of the ABO antibody responsible for haemolysis and the lowest titre reported to cause haemolysis in both the paediatric and adult cases was an anti-A IgG titre of 32. Based on the current evidence and taking into considerations the limitations mentioned above, we can conclude that an anti-A titre of less than 32 could be considered the lowest cut-off to minimise the risk of haemolysis associated with ABO incompatible plasma transfusion. A recent international forum that assessed the policies for the transfusion of ABO or RhD non-identical platelets, reported the current methods and cut offs for measuring high titre anti-A and anti-B from eight different respondents. The majority of countries routinely test for IgM only, with all having a cut off between 64 and 128 equivalent to

saline tube agglutination method. These cut offs are at a level chosen to achieve a pragmatic balance between reducing risk of haemolysis as far as possible on the one hand, whilst maintaining an adequate supply of components on the other hand (Cardigan *et al.*, 2021).

The findings from this review suggest that in order to fully mitigate the risk of haemolysis from ABO incompatible plasma transfusion, a lower cut off of 32 may be required. This could theoretically be achieved through more selective screening of donations, but this will result in too many donations being unable to be used due to the likely limited proportion of the donor population with values below 32, especially for group O donors. Although the lowest titre of anti-A that was implicated in a HTR was as low as 1/32 IgG, reports at this level are rare, most being associated with higher titres. Therefore, there needs to be a balanced consideration between the titre at which risk reduction for HTR is likely to be maximised and the ability to have sufficient donations to make such products from.

The case reports within this review are too few to draw conclusions on the relationship between IgG and IgM in blood donors, and whether there is a need to review policies for whether IgG as well as IgM should be screened for. In fact, large data sets on this aspect are lacking. Alternatively, another way of addressing this issue is to consider methods to further dilute or remove anti-A/B from plasma-rich blood components.

No strong conclusions can be drawn about the importance of volume, or the relationship between volume and titre, with respect to risk of haemolysis due to limited data provided in the case reports. We considered that it is likely that not only the titre of anti-A/B in the component is important, but also the volume of the component transfused i.e. the dose of antibody transfused. Additionally, factors such as avidity of the antibodies and recipient factors would also likely be important in determining whether a reaction would occur. Defining a critical cut off is challenging, in part because as this review suggest, and others have postulated, there is no definitive relationship between titre and risk of HTR (Karafin *et al.*, 2012). Although volume and titre of incompatible plasma transfused are related to risk, this relationship is not absolute and recipient factors such as ABO zygosity and complement regulatory deficiencies are thought to play

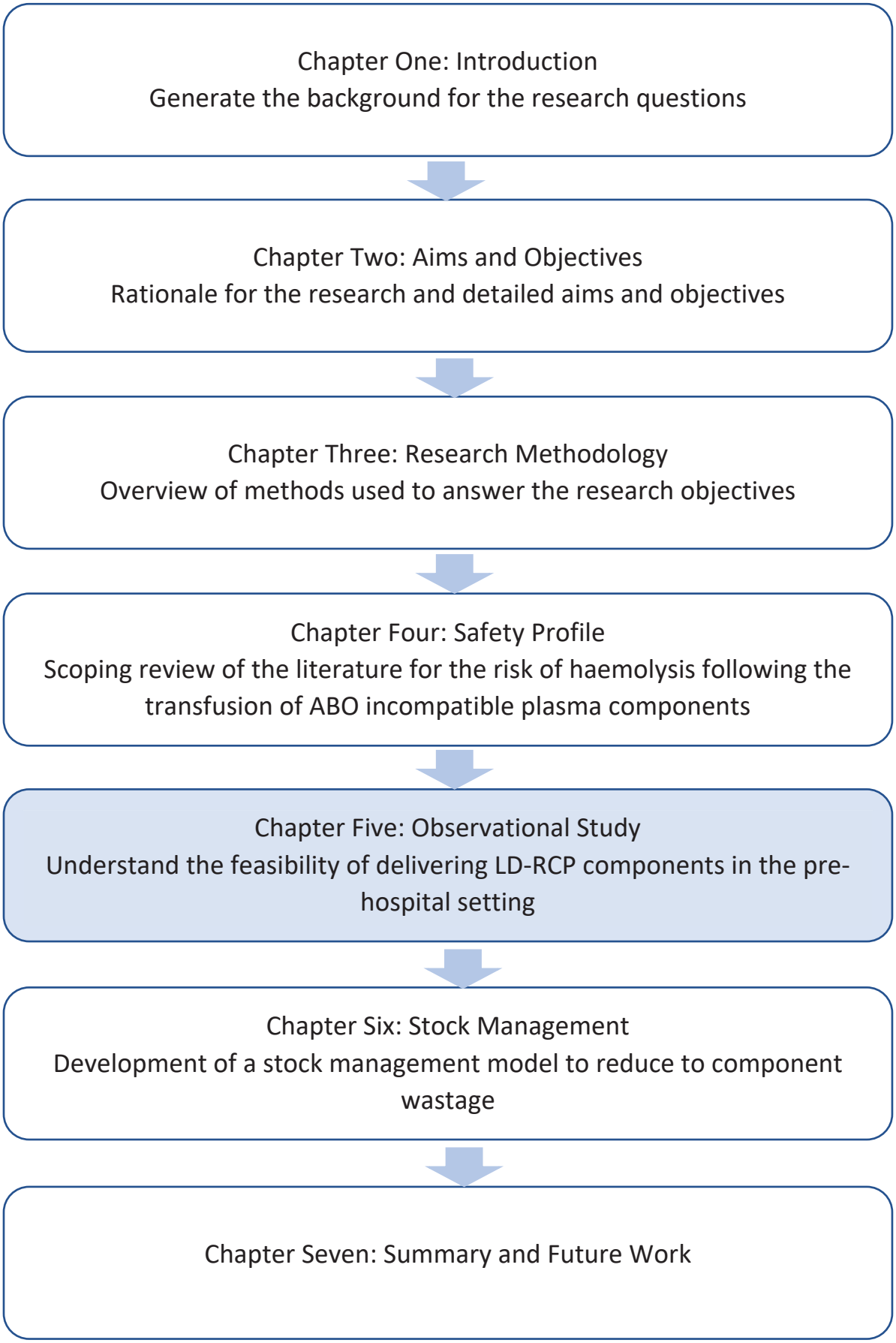
a role in determining the likelihood of a HTR occurring (Pandey *et al.*, 2017; Branch *et al.*, 2018). Further, adsorption of anti-A and B through soluble A and B antigens on the endothelium of patients of mis-matched ABO group are thought to contribute to the low level of HTR observed. We note that there are several points on the plot in Figure 4-3 which correspond to fairly low titres transfused in fairly low volume and so it is clear that there is a risk even when volume*titre is relatively small. We cannot reliably quantify that risk.

The evidence in this review consists largely of case reports, less than half of which reported both volume and titre(s), and there will be some bias inherent in the decision to publish a case report at all. Very high volumes transfused imply very sick recipients and it is possible that haemolysis is less likely to be considered a notable outcome worth publishing for this group, especially when weighed against the ability to obtain large quantities of blood products in an emergency. Conversely, very high titres ordered or supplied in error, or because the risk was perceived to be small for low volume transfusions, might be less likely to be published because the motivation of case reports is often an interesting or unexpected outcome, and not a confession of clinical error. The non-random sample of cases reported in the literature means that we cannot conclude that the relatively high proportion of deaths (15%) in this review is at all representative of the true underlying risk from ABO-incompatible plasma transfusions.

4.7 Limitations

This scoping review has some limitations. Firstly, to make the review more feasible, only papers that were written in English were included and secondly, only papers that were available online were included. Thirdly, due to large number of abstracts and papers that were screened and reviewed and because most of the missing data would not exist due to the nature of case reports and the age of many of these papers, it was not possible to approach authors for incomplete data. The year that the cases were published also poses as a limitation due to the fact that transfusion practices have developed over the years and some of these case may not directly reflect current transfusion practices. The impact of these limitations to the overall findings of the review cannot be reliably quantified. Moreover, we need to recognise that the rate of under recognition and /or

under reporting of this complication is probably significant (Lozano *et al.*, 2010), and therefore would not have been captured by this review.


Chapter One: Introduction
Generate the background for the research questions
Chapter Two: Aims and Objectives
Rationale for the research and detailed aims and objectives
Chapter Three: Research Methodology
Overview of methods used to answer the research objectives
Chapter Four: Safety Profile
Scoping review of the literature for the risk of haemolysis following the transfusion of ABO incompatible plasma components
Chapter Five: Observational Study
Understand the feasibility of delivering LD-RCP components in the pre-hospital setting
Chapter Six: Stock Management
Development of a stock management model to reduce to component wastage
Chapter Seven: Summary and Future Work

Chapter 5 Feasibility of delivering combined Red Cell and Plasma Component for pre-hospital service

5.1 Background

There is now a huge interest in re-introducing a whole blood (WB) component as a replacement for current blood components to resuscitate patients with traumatic major bleeding, particularly those presenting in pre-hospital settings. In pre-hospital settings the deliverability of a 1:1:1 ratio of individual components (i.e., RBC, plasma and platelets) poses logistical challenges as this would: a) necessitate additional weight for the pre-hospital personnel approaching the scene of the accident; b) increase the complexity of resuscitating patients because several bags (blood and fluid) would need to be administered to a patient who may not have enough intravenous access, and the clinical team are occupied doing other important tasks; and c) delay the transfer of patients to hospital because the clinical team would attempt to transfuse both RBC and FFP at the scene, which could potentially be detrimental to outcome. A combined component like WB or LD-RCP may reduce these logistical complexities.

In England, all blood components are manufactured by NHS Blood and Transplant, who supply blood throughout the NHS. The manufacture of WB is more complicated than other components, due to the current manufacturing process involved with leucocyte depletion, introduced in 1999 to reduce the risk of variant CJD (vCJD) transmission. The leucocyte-depleted (LD) filter used to manufacture current components also removes 80% of the platelets. So, in addition to the individual components of RBC, platelets and plasma, NHSBT can produce LD-RCP (RBC + plasma in the same bag) that could potentially overcome the logistical challenges of administering blood in the prehospital environment. However, studies comparing its efficacy and safety, against standard blood components, have not been conducted.

Group O Rh D Negative ('O Neg') is considered the safest group to transfuse to patients with unknown blood groups. However, transfusing group O LD-RCP or LD-WB (both contain anti-A and anti-B in the plasma) can give rise to the potential risk of haemolysis

due to anti-A and anti-B in non-group O recipients. Thus, it is important to quantify this risk, particularly as these patients are likely to receive a high volume of the components in the immediate resuscitation period (Yazer et al., 2018). A recent systematic review aimed at assessing the difference in safety outcomes with the transfusion of WB compared to blood components for any bleeding patients, reported that none had suffered from a haemolytic transfusion reaction (n= 618 participants) (Geneen et al., 2022). Similar results have also been reported in recent observational studies of whole blood transfusion in trauma patients (Harrold et al., 2020)(Yazer *et al.*, 2016). Despite these studies demonstrating the safety of transfusing a group O WB component to trauma patients it's important to recognise the variation in component manufacture and the non-standardised methods for measuring low titre components in different countries, as shown in chapter 4.

In addition, group O Neg red cell donations are also required for the manufacture of O Neg RBC used for the transfusion of group O Neg patients, for neonatal and for emergency transfusion of patients with acute bleeding requiring urgent resuscitation. In the UK, 12% of the demand for RBC is for O neg. This group makes up only 8% of the population (Foukaneli and et al, 2018), so there is a shortage of donors and supply of this type (Foukaneli and et al, 2018) making donated O Neg blood is a precious resource for the NHS.

LD-RCP and LD-WB have a much shorter shelf life than RBC: 14 days compared with 35 days. In the US, unused WB is re-processed after 10 days to produce RBC (Yazer *et al.*, 2016), minimising component wastage of WB if the latter is not used within its shelf life. However, this is not possible in the UK due to regulatory constraints on hospital blood banks and hospital blood establishments. Therefore, if LD-RCP/WB components are used for one group of patients (i.e. pre-hospital trauma bleeding patients) one would anticipate the wastage level to be high due to their shorter shelf life than RBC, however this has not been assessed before. For long term sustainability, minimising LD-RCP wastage is crucial in deciding the feasibility of introducing a WB component nationally for the future.

5.2 Aims and Objectives

The overall aim of this chapter was to assess the feasibility to deliver LD-RCP components (and eventually LD-WB by extension) to patients who are bleeding in the pre-hospital setting, so as to lay the groundwork for a future trial that will compare the efficacy and safety of LD-WB versus other different transfusion strategies.

The objectives of the study were to:

1) Evaluate the clinical and serological effects of transfusing group O LD-RCP to non-group O patients
2) Describe and quantify blood component usage, wastage and 'on time in full' (OTIF) delivery of LD-RCP defined as:
    - number of days per-year where the component was delivered in accordance with agreed specification divided by the number of days where the said component was meant to be delivered.
3) Evaluate quality improvement measures introduced to reduce wastage
    - Project A: widening access to the blood product (and thus increasing demand)
    - Project B: maximising the useful availability of the product by adjusting the delivery schedule.

5.3 Methods

5.3.1 Study Setting

A 'Whole Blood Programme Group' was established to evaluate new strategies to reduce the LD-RCP wastage, deal with other issues arising during the study and feedback results and progress to key stakeholders. This group was a multi-disciplinary team consisting of the key study members (Haematology consultants, Emergency Medicine & Trauma consultants, transfusion scientists, a research fellow, blood component development scientists and blood component manufacturing specialists). The group met every four months to review the overall progress of the study and formulate new actions plans. Key members directly involved in the management of LD-RCP delivery and stock management met more regularly to discuss compliance and review the data prior to the Group's main meetings.

5.3.2 Observational study

Prior to this study, the London Air Ambulance (LAA), a helicopter emergency medicine service (HEMS) based at the Royal London Hospital (RLH), carried group O RBC on board as part of a 'blood on board' initiative established in 2012 (Rehn *et al.*, 2019). The service delivers advanced trauma care in the pre-hospital setting to London's most seriously injured patients. In November 2018, HEMS, made a clinical decision to change transfusion management of trauma bleeding patients in the pre-hospital setting from RBC only to LD-RCP. This was part of the 'Whole Blood Programme' agreed between NHSBT and RLH emergency team.

All LD-RCP issued by NHSBT were low titre (<1/128 for anti-A and B) group O RhD negative, K negative. These were supplied from NHSBT to the transfusion laboratory at RLH. The supply chain was managed daily through standing order utilising the routine online blood ordering system, as illustrated in Appendix 3.

The LD-RCP units were boxed in transport containers, known as Golden Hour Boxes™ (Pelican BioThermal, MN, USA) for transport by the LAA and Emergency Response vehicles. These boxes maintain a steady state temperature of 4^{O}C (±2^{o}C) for 48-72 hours. Each box was validated to carry two units of LD-RCP for 24 hours. There were always three boxes in circulation: one for the helicopter, one for the road vehicle and a third as a spare. A total of 6 units of LD-RCP were in circulation at one time. At day 10 of the LD-RCP shelf-life, units were transferred to remote blood fridges in the Emergency department (ED) at RLH for use in trauma bleeding patients only, to reduce component wastage.

5.3.2.1 Study participants

All trauma patients >1yr old requiring prehospital transfusion for major haemorrhage following traumatic injury were included in the study. Patients could receive a maximum of four units of LD-RCP (each unit 470±50 mL) during the study, while those patients who were <50kg could receive a maximum 40 ml/kg.

5.3.2.2 Data collection

Data was collected between November 2018 to October 2020 prospectively. LD-RCP component usage, wastage, and data on the level of haemolysis were obtained from the Laboratory Information Management System (LIMS), WinPath at RLH. Data from the hospital end comprised of the following information:

Component specific

- number of units transfused
- number of units transferred to Golden Hour Boxes™
- age of unit when transferred to the ED blood fridge
- number of components transferred to the ED fridge
- number of units wasted
- number of units used in ED for non-trauma or non-bleeding patients

Component wastage was categorised as either wasted in lab (WILAB), units that expired whilst still in the laboratory stock fridge or wasted in ward (WIWARD), units that expired outside of the laboratory and differentiated into; out of temperature control, where transfusion cold chain requirements were not met or time expiry, where the units had past their expiry dates.

The number of units transfused was categorised as transfused pre-hospital or transfused in-hospital.

Patient specific data collected were

- number of patients who received >4 LD-RCP units
- reason for transfusion
- patient blood group
- direct antiglobulin test (DAT)
- haemoglobin (g/L)
- bilirubin levels (µmol/l)

If a patient had multiple measurements of Hb or bilirubin taken on the same day, the lowest Hb level and the highest bilirubin level were recorded, as these could potentially indicate haemolysis. Measurements were recorded on Day 0, Day 1, Day 2 and Day 3.

The data collected from NHSBT was comprised of the number of LD-RCP units delivered, the number of units requested and the age of units on delivery. During set-up agreements for the study, supply of LD-RCP to RLH was agreed at 12 units per week. This being a new product, with a short shelf-life and targeted use, the potential level of wastage had only been speculated at a level that would have been considered acceptable. Figure 5-1 illustrates a high-level process map, indicating the main steps involved in the journey of LD-RCP. It also indicates the areas where data collection was used to assess the efficiency of the process and the outcome of any interventions to improve the primary outcomes.

5.3.2.3 Feasibility criteria

The feasibility objectives and criteria related to the data collected are presented in Table 5-3. The objectives were split into three categories: Component wastage, stock management and clinical factors. Three criteria for progression were established and agreed before the start of the study, these were established in line with the conceptual framework for defining feasibility and pilot studies (Eldridge *et al.*, 2016).

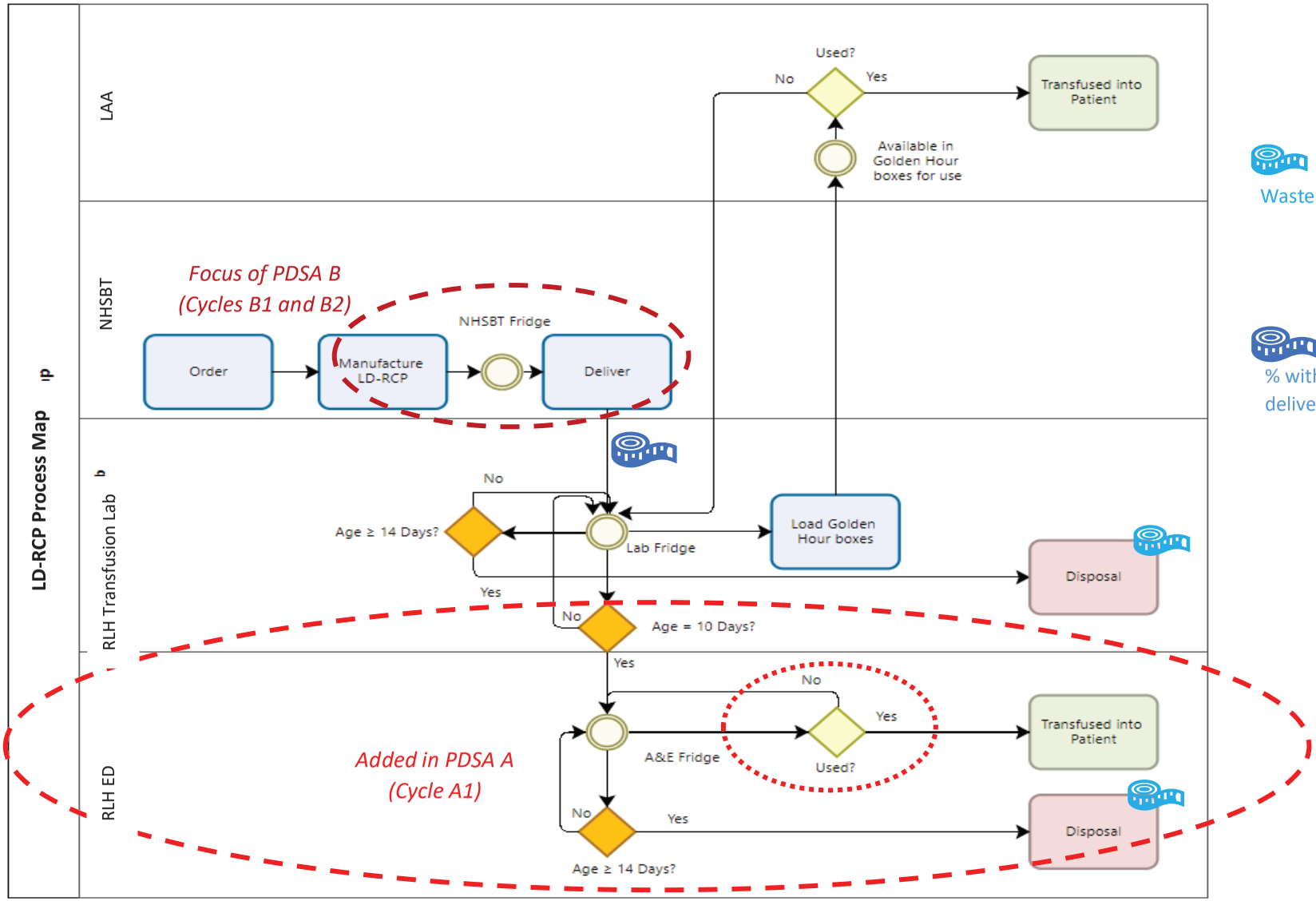


Figure 5-1: Process map depicting the flow of LD-RCP.
RLH (Royal London Hospital) ED (Emergency Department), LAA (London's Air Ambulance) LD-RCP (Leucocyte depleted red cell and plasma), NHSBT (NHS Blood and Transplant) and PDSA (Plan–Do–Study–Act)

Feasibility objectives and related data to be collected	***Go criteria to proceed to full trial (Eldridge, et al 2016)***	***Criteria to reassess and adjust full trial protocol (Eldridge, et al 2016)***	***Stop criteria (Eldridge, et al 2016)***	***Rationale***
Component Wastage				
i) Rate of component wastage	*≤8% wastage*	*9% - 30% wastage*	*>30% wastage*	*On average RBC wastage is 2.5%. With the shorter shelf life of RC/Plasma at 14 days it was decided that 8% wastage would be the acceptable limit*
Stock Management				
ii) Days where demand is not met	*0 -5 days*	*6 - 15 days*	*>15 days*	*Ideally for the study to work and to assess feasibility of using this component there should be 0 days with no component.*
iii) Number of components being transferred to ED (not used in the pre-hospital setting)	*<30% of components*	*30-50% of components*	*>50% of components*	*If the number of units being transferred to A&E exceeds 50% this would be a good indication to evaluate stock levels and reduce ordering.*
iv) On time in full delivery (OTIF)	*>96%*	*94% - 95%*	*95%*	*The current NHSBT OTIF standard is 97%*
Clinical Factors				
vi) Number of components used inappropriately in ED to non-trauma, but bleeding patients	*≤ 10% of units.*	*10 -25% of units*	*>25% of units*	*In 2016 of the Incorrect blood components transfused 20% were the wrong component and of that 10% were given by the clinical team.*

Table 5-1: Feasibility objectives for the observational study

5.3.3 Quality Improvement

The quality improvement measures introduced to reduce wastage of the LD-RCP component were divided into two main projects: project A and project B:

5.3.3.1 Project A

The main idea for Project A was to widen access to the LD-RCP units beyond the pre-hospital setting, so that a unit approaching the end of its shelf-life (and so becoming increasingly unlikely to be used for the targeted pre-hospital transfusion) could be used by other patients who could benefit. The first Plan Do Study Act (PDSA) cycle in project A (A1), was to identify a way of expanding the use of the LD-RCP units to trauma patients.

The first group that were captured were patients who presented at the ED with trauma-induced major haemorrhage. The units were stored in the ED blood fridge and the ED staff were expected to use any LD-RCP available in preference to RBC. It was identified that without the necessary training to introduce this new procedure, many staff may have been unaware or reluctant to use the new component. A second PDSA cycle (A2) was therefore initiated, with the Trauma Research Fellows (TRF) working with ED staff with the aim of making preferential use of LD-RCP, when available, in routine practice. This cycle involved MDT education, targeted messaging at handovers, weekly focus on blood transfusion, and targeted teaching at new staff induction. If the wastage level was still above the 8% target, then the last strategy and third PDSA cycle (A3) was to transfuse LD-RCP at the end of its shelf-life to other non-trauma patients and trauma patients who were bleeding in hospital and needed ongoing transfusion treatment with RBC and thawed plasma as part of routine care.

5.3.3.2 Project B

Following this focus on a new pathway to ED use, the Group agreed that another reconsideration of the whole process was required to attempt to reduce the wastage further. Project B therefore focused on a greater system process change rather than solely a local trust process change, focusing on LD-RCP delivery to RLH to increase and adjust its window of availability for use (particularly for pre-hospital use). The weekly LD-RCP delivery had been a standard order delivered along with other routine products (Appendix 3). The first PDSA cycle of project B (B1) was to work with NHSBT to

coordinate the manufacture and delivery schedule, instituting a dedicated LD-RCP delivery schedule. On further analysis and reflection, it was identified that more trauma cases occurred (and therefore more blood was administered) on Saturday and Sunday than any other days of the week. A second PDSA cycle (B2) was introduced to adjust the LD-RCP delivery day to allow the 14-day shelf-life to span two Saturday and Sundays.

5.3.4 Analysis

The serological data comparing the Hb levels and bilirubin levels of group O patients and group non-O patient who were transfused LD-RCP were summarised as medians [interquartile range] and compared using Mann-Whitney U tests. Counts and percentages were used to summarise component usage, wastage, and delivery. Mean [standard deviation] were used for continuous data as appropriate. The statistical analysis was performed using IBM SPSS statistics (Version 27) predictive analytics software. Data was presented using Statistical Process Control Charts (SPC) developed in MS Excel. On time in full (OTIF) delivery was calculated using the formula below:

$$\text{OTIF \%} = \left[\frac{\text{Days per-year where the component was delivered}}{\text{Number of units ordered}} \right] \times 100.$$

5.4 Results

5.4.1 Risk of Haemolysis

A total of 204 patients were transferred to RLH and transfused LD-RCP. Of this 177 had a blood group recorded: 81 patients were group O and 96 were non-group O. An average of 2 [1.12] LD-RCP units were transfused for both group O and non-group O cohorts. Of the 177 that had a recorded blood group 170 patients received less than or equal to 4 units of LD-RCP and 7 patients received >4 units. Of the 7 patients who received >4 units, 6 were group O and 1 patient was group B. At least one Hb (g/l) and bilirubin (µmol/l) measurement were available from the 177 patients at day 0, day 1, day 2, day 3 or all 4 time points (Figure 5-2 and Figure 5-3).

Distributions of the Hb and Bilirubin levels for group O and non-group O patients were similar. Median Hb for group O (92g/l [80-113]) and non-group O (95g/l [79-109]) were not significantly different, between the two groups p =0.422.

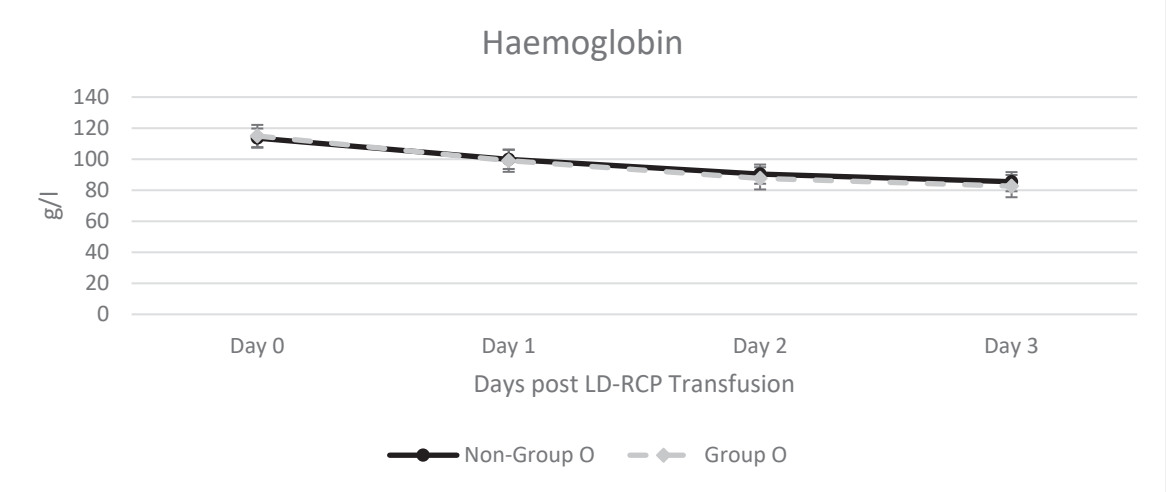


Figure 5-2: Laboratory markers of haemolysis - Haemoglobin
Laboratory markers of haemolysis (haemoglobin) in non–group O (n =96) and group O (n =81) recipients of at least one unit of LD-RCP. Using a Mann Whitney U test there were no statistically significant differences in haemoglobin levels between the non–group O recipients and the group O recipients at any of the four time points

Median bilirubin for group O (14µmol/l [8-20.1]) and non-group O (16µmol/l [9-27]) was also not significantly different, p = 0.084.

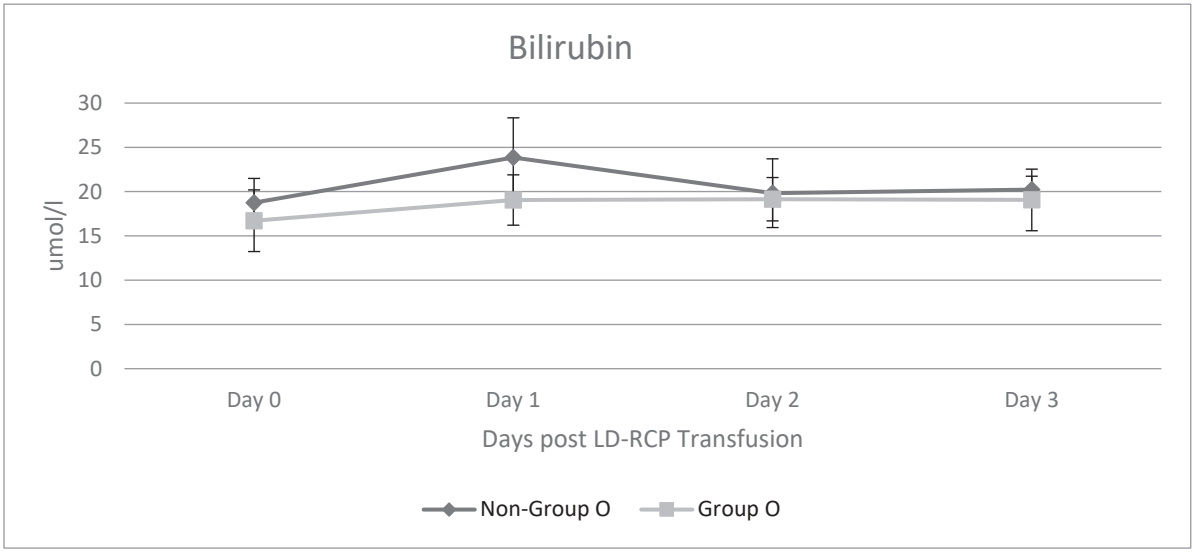


Figure 5-3: Laboratory markers of haemolysis - Bilirubin
Laboratory markers of haemolysis (bilirubin) in non–group O (n =96) and group O (n =81) recipients of at least one unit of LD-RCP. Using a Mann Whitney U test there were no statistically significant differences in bilirubin levels between the non–group O recipients and the group O recipients at any of the four time points

A DAT result was recorded in 31 (34.1%) of the non-group O patients, of which 6 were positive. Of the 6 positive DAT results, 4 patients were group A and 2 patients group B, none of these 6 patients had received more than 4 units of LD-RCP and the DAT strength was less than 2 in all 6 cases. No transfusion reactions were reported during the study period for these patients.

5.4.2 On Time in Full Delivery

Throughout the study period a total of 1253 LD-RCP units were requested from the blood service by the hospital (average of 52 [5] units per month), of which 96.5% (n = 1208 units, n= 604 days) of these orders were delivered on time in full. There were 45 (3.6%) units that were ordered and not delivered. Of the 1208 units that were delivered, 781 (64.7%), 259 (21.5%), 104 (8.61%) and 64 (5.29%) were delivered at 2 days old, 3 days old, 4 days old and >4 days old respectively (Figure 5-4).

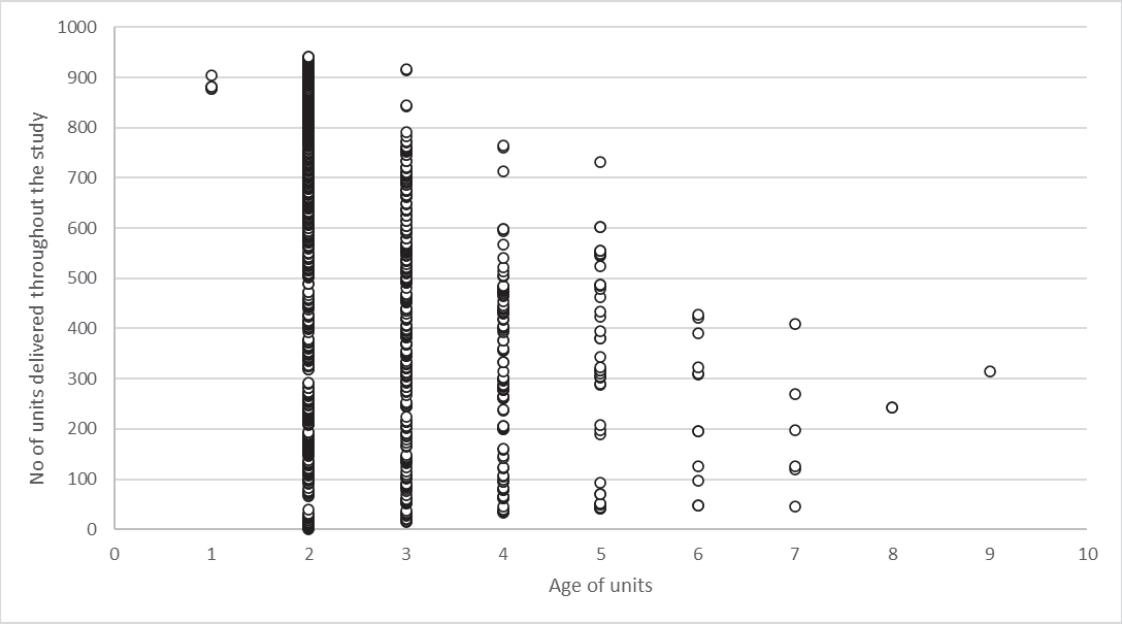


Figure 5-4: A strip plot showing the age of LD-RCP components on delivery throughout the study period (November 2018 – October 2020) .

The age of units on delivery gradually improved throughout the study period (Figure 5-5), with fresher units (age 2 days old) being delivered more often. Looking at the data in 6-month periods there were a total of 147 (43.75%), 140 (45.6%), 246 (82.0%) and 243 (91.7%) units delivered age 2 days old in the first, second, third and the fourth 6-month time periods, respectively.

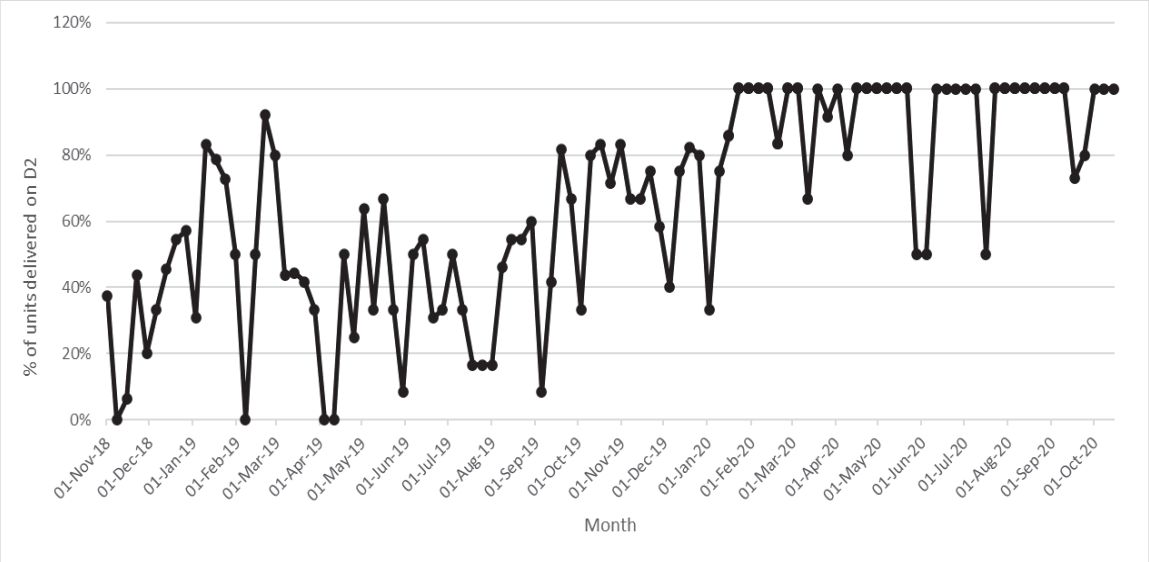


Figure 5-5: The % number of LD-RCP components delivered to RLH Laboratory on a weekly basis. The % of components delivered on day 2 (D2) improved throughout the study.

5.4.3 Component usage and wastage

Of the 1208 LD-RCP units that were delivered over the 24-month study period, 733 (60.68%) were transfused (Figure 5-6) and 475 (39.3%) units were wasted (Figure 5-7). 1180 were transferred to a Golden Hour box at least once, 28 units were sent directly to the ED blood fridge from the lab bypassing the HEMS boxes completely. Of the total number of units that were transferred to the HEMS boxes, 826 (70%) were transferred to their first HEMS box at ≤4days old. A total of 549 (45.4%) units were administered in the pre-hospital setting and 236 (19.5%) were wasted in the lab (WILAB), of which 60 (25.4%) were out of temperature control (this was mainly due to an issue with the Golden Hour boxes) and 176 (74.6%) had time expired (TIMEX).

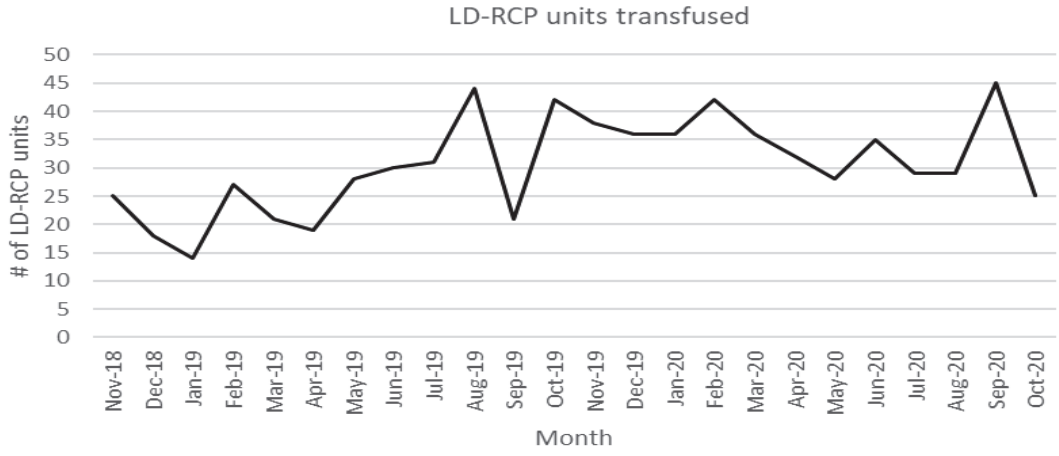


Figure 5-6: Number of LD-RCP components transfused per month throughout the 24-month study period

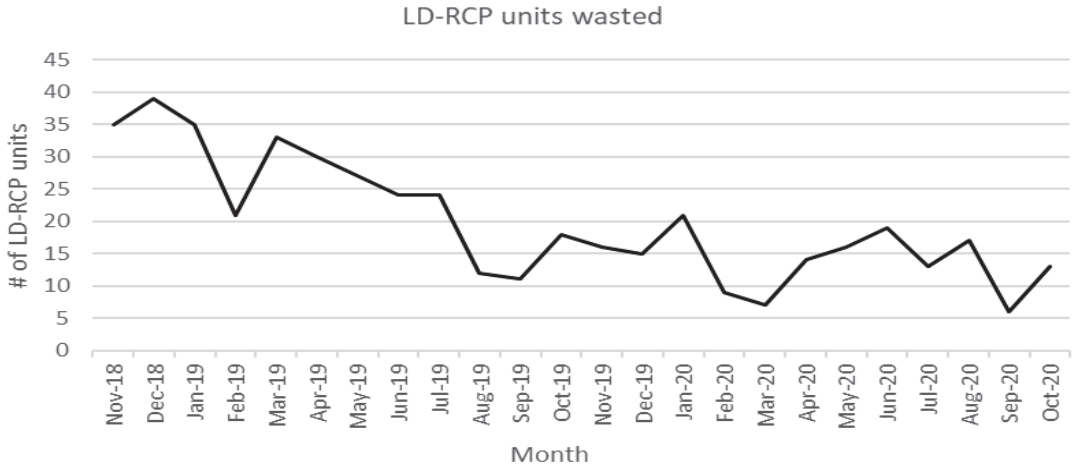


Figure 5-7: Number of LD-RCP components wasted per month throughout the 24-month study period

For the first four months of the study LD-RCP component was used solely in the pre-hospital setting. Following this introductory period and to help reduce the level of component wastage, units were transferred to the ED blood fridge at day 10 of their shelf-lives for transfusion to trauma patients only. A total of 423 (35%) units were transferred to the ED blood fridge, of which 70 (16.5%), 81 (19.1%), 118 (27.9%) and 154 (36.4%) units were transferred on days 10, 11, 12 and 13 days old, respectively. Of the units that were transferred to the ED fridge 184 (43.5%) units were transfused and 239

(56.4%) were wasted, of which 7 (2.9%) were out of temperature control and 232 (97.1%) due to TIMEX.

A mean [Standard Deviation] of 20 [9.32] units a month were wasted throughout the 24-month study period. Despite this the total component wastage level did reduce significantly throughout the study period with the component wastage per month for the first 12 months being 26 [9.07] units versus 14 [5.13] units in the last 12 months of the study period (p=0.001).

5.4.4 Quality Improvement

The two main metrics of interest from a quality improvement (QI) standpoint were total component wastage and age of units on delivery (% Age ≤ 2 Days old at delivery), measured on a weekly and monthly basis. In the first phase of this QI programme, the Current Condition of the new process was established: mapping the LD-RCP flow (Figure 5-1) and establishing baseline performance on the metrics (Figure 5-7 and Table 5-1: Feasibility objectives for the observational study).

Once the project started, it was found that the initial (baseline) wastage was very high (70%) and that many units had limited shelf-life remaining at delivery (only 42% were age ≤ 2 days old and therefore having at least 12 days of opportunity for use). It became evident, therefore, that very considerable improvements were necessary.

5.4.4.1 Project A

The aim of Project A was to extend the LD-RCP pathway by moving remaining units down to the ED fridge at 10 days old (only 4 days of shelf-life remaining). Note: this never emptied the Transfusion Lab and HEMS stock as by Age 10 days a subsequent delivery would have occurred, and units were used oldest-first (FIFO stock management method). The first statistical process chart (SPC) demonstrated that the level of wastage was much higher than had first been anticipated, with a mean weekly wastage of 8.36 units per week (70%). The baseline data demonstrated a high level of component wastage; however, it did demonstrate a stable baseline, a good platform to perform any QI work.

The first PDSA cycle (A1) established the transfer of LD-RCP units to the ED blood fridge at day 10 and tested the impact. It achieved the first modest, interim target of 50% component wastage, reaching a mean weekly component wastage of 5.88 units (49%). During this phase, it was picked up that ED staff were not always using LD-RCP when it was available.

Cycle A2 took the remedial step of having trauma research fellows (these are 24hrs, 7 days a week on duty) working with ED staff to educate and encourage take-up, a challenging task in an area of rapid staff turnover. The SPC chart highlights that following the start of this cycle, the impact of this step was delayed. Despite this delay in reducing the wastage level, A2 did achieve a reduction in wastage, reducing the mean component wastage from 5.88 units (49%) to 4.54 units per week (38%) (Figure 5-8 upper graph).

The total wastage of LD-RCP units was reduced over the length of the study. However, on 17 weeks throughout this study period (103 weeks in total) the target wastage level of ≤1 unit per week was achieved. Although, the overall target level of 8% total component wastage was never reached. It was not possible to test the impact of the last QI step on wastage levels (i.e. transfusing LD-RCP to other non-trauma patients in hospital who are bleeding) due to the impacts of the COVID-19 pandemic on staffing and resourcing levels towards the end of this study period. Later, further analysis established that not all LD-RCP wastage had occurred at the end of shelf life: 5.7% of LD-RCP units were discarded due to failures in cold chain (these units were not kept at the appropriate temperature when stored). Furthermore, it was also found that only 16.5% of transfers of units to ED occurred at the intended 10 days old (and 36% were > 12 days old) representing opportunities for further improvement within the local system.

5.4.4.2 Project B

The baseline data highlighted that LD-RCP was not being delivered to RLH as fresh as desirable. One unit was already 9 days old, so only having 5 days of shelf-life left (and, under the new pathway, only 1 day for pre-hospital use before transfer to the ED blood fridge). The baseline data highlighted that a mean of only 42% of units were delivered at age ≤ 2 days (Figure 5-8 lower graph).

A year after the study commenced, cycle B1 and B2 addressed the age of units on delivery (% Age ≤ 2 Days Old) through changes to the transport and delivery arrangements with NHSBT. The number of units delivered at age ≤ 2 days improved from the baseline of 42% to 86%. As demonstrated in Figure 5-8, the number of data points above the new mean suggested that the process was making further good progress towards an ultimate target of 100% of LD-RCP units being delivered at age ≤ 2 days old. The change in total number of units delivered at age ≤ 2 days also had an impact on reducing the weekly component wastage. The aim was to reduce the mean weekly wastage to 3 units per week (25%). This target was narrowly missed, with actual mean weekly wastage achieving a reduction from 4.54 (38%) to 3.19 (27%).

As summarised in Table 5-2 and shown in Figure 5-8, over the four PDSA cycles LD-RCP unit wastage reduced, from a mean weakly wastage of 8.36 units (70%) to 5.88 units per week (49%), then 4.54 (38%), 3.38 (28%) and, finally, 3.19 units (27%).

A third PDSA cycle was due to be implemented (A3), however, due to the COVID-19 pandemic this third PDSA (i.e. transfusing LD-RCP to non-trauma patients with bleeding) was unable to be implemented. In the end two PDSA projects were completed, each with two cycles. Each cycle was discussed and agreed in the WB Programme Group multi-disciplinary meetings prior to commencement.

5.4.5 Feasibility Outcomes

The criteria for study feasibility are outlined in Table 5-1 which describes five key objectives and criteria to proceed (green), criteria to reassess (amber) and stop criteria (red) for the study. At the end of the study period three of the study outcomes; days with unmet demand (0%), percentage of components used inappropriately (0%) and OTIF (96.5%), all achieved the proceed criteria (green). One outcome; number of units transferred to ED (35%) achieved the reassess criteria (amber) and one outcome, percentage component wastage (39.3%) achieved the stop criteria (red). The monthly results of each of these feasibility outcomes are reported in Table 5-3.

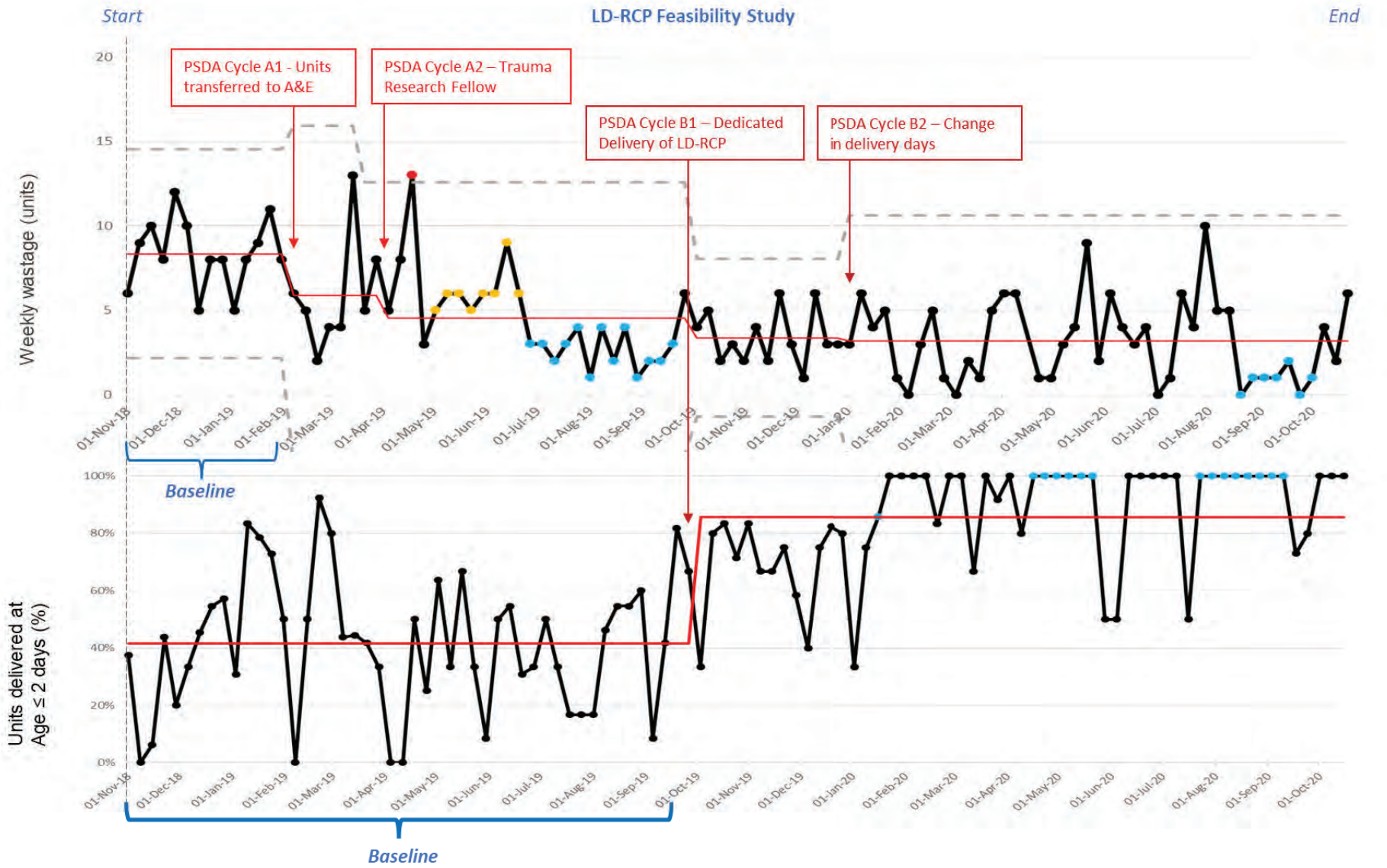


Figure 5-8: Performance metrics over the timeline of the project.
Top: SPC chart of the weekly component wastage. Bottom: SPC chart of % of components delivered at age ≤2 days. The mean is represented by the red line in both graphs. ED (emergency department) and PDSA (Plan–Do–Study–Act) cycles clearly indicated).

PDSA Cycle	Plan / Prediction	Do	Study	Act	Time Required
Baseline	Establish Current Condition (map blood flow and analyse baseline performance)	'Go and See' analysis	Mean Weekly Wastage = **8.36** units (**70**%). Mean % Age ≤ 2 Days = 42% per week [Oldest = 9 Days]	Embark on cycles of improvement, aiming for Mean Weekly Wastage ≤ 1 units (8%) by November 2020	14 weeks
A1	Transfer near-expiry units to A&E Hypothesis: A&E staff can make good use of LD-RCP for trauma patients First target: Mean Weekly Wastage = 6 units (50%)	At Age = 10 Days move LD-RCP to the A&E fridge	Mean Weekly Wastage = **5.88** units (**49%**) (Mean % Age ≤ 2 Days = no change) Some A&E patients eligible to receive LD-RCP had not, despite availability in the A&E fridge	First target achieved, but capability low (achieved in 6 out of the 8 weeks). Review highlighted that further work was required: conduct another cycle with modified plan and more ambitious target.	8 weeks
A2	Encourage use by A&E staff Hypothesis: Trauma Research Fellows could establish LD-RCP use as routine practice for A&E staff. Second target: Mean Weekly Wastage = 4 units (33%)	Existing TRFs work in A&E to assist with education, training and prompting use of LD-RCP	Mean Weekly Wastage = **4.54** units (**38%**) (Mean % Age ≤ 2 Days = no change)	SPC (Fig 2) suggests effective after a time lag: 4 units achieved most weeks in second half, but capability low (little safety margin). Further improvement ideas needed; tighten target a little.	26 weeks
A3	Further extend the LD-RCP pathway to include non-trauma patients with major bleeding. Hypothesis: Will further increase in demand for LD-RCP. Fifth target: Mean Weekly Wastage = 1 unit (8%)	Units Age ≥ 10 Days to be used for non-trauma bleeding patients in-hospital.	Not able to carryout final improvement cycle due to the COVID-19 pandemic.		
B1	Dedicated LD-RCP delivery slot Hypothesis: More LD-RCP received at Age ≤ 2 if had dedicated delivery slots Third target: Mean Weekly Wastage = 3 units (25%)	Work closely with NHSBT (supplier) using RLH metrics and data, agree dedicated delivery slot rather than the general delivery slots	Mean Weekly Wastage = **3.38** units (**28%**) Median % Age ≤ 2 Days = 80% per week	Big improvement in % Age ≤ 2 Days (process metric), but only small improvement in Mean Weekly Wastage. Further improvement ideas needed; tighten target a little.	13 weeks
B2	Change LD-RCP delivery days Hypothesis: since pre-hospital trauma incidence highest on Fridays and Saturdays, delivery to cover two weekends would decrease wastage Fourth target: Mean Weekly Wastage = 3 units (25%)	Change dedicated delivery days, Tue: 2 units, Wed: 4 units, Thu: 2 units, Fri: 2 units, Sat: 2 units	Mean Weekly Wastage = **3.19** units (**27%**) [5 weeks with 0 wastage] (Median % Age ≤ 2 Days : no change expected)	Ultimate target still not met, but great improvement in Mean Weekly Wastage overall. Variation still high. (% Age ≤ 2 Days appears to continue to improve)	17 weeks

Table 5-2: Improvement cycles for project A and project B.
ED (Emergency Department), NHSBT (NHS Blood and Transplant), PDSA (Plan–Do–Study–Act), RLH (Royal London Hospital) and SPC (Statistical Process Control).

	2018		2019												2020									
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O
% Total Component Wastage	58	68	71	44	61	61	49	44	44	21	25	22	30	29	37	18	16	30	36	35	31	37	12	34
% Days where demand not met	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
% Components being transferred to ED	0	0	0	38	35	69	53	39	33	27	23	53	56	29	39	33	42	54	43	39	45	22	20	47
% Of units OTIF	100	100	92	94	93	100	100	98	95	100	98	96	100	92	95	92	100	98	96	100	95	97	98	100
% Components used in ED to non-trauma, but bleeding patients	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 5-3: Feasibility criteria and outcomes reported monthly throughout the study period
Criteria to proceed (green), criteria to reassess (amber) and stop criteria (red). Emergency department (ED), On time in full (OTIF).

5.5 Discussion

This chapter set out to answer the following objectives:

a) Evaluate the clinical and serological effects of transfusing group O LD-RCP to non-group O patients
b) Describe and quantify blood component usage, wastage and 'on time in full' (OTIF) delivery of LD-RCP.
c) Evaluate quality improvement measures introduced to reduce wastage

For the first objective, a total of 204 patients were transferred to RLH and transfused LD-RCP, but of this only 96 patients who had a blood group were non-group O. In this cohort, based on the results of haemoglobin, bilirubin and DAT, there was no evidence of increased haemolysis compared to patients who were blood group O and who received group O negative LD-RCP. These results are very similar to the other studies (Harrold *et al.*, 2020), (Yazer *et al.*, 2016) who have also demonstrated that low titre LD-WB components are safe to transfuse to non-group O patients. However, it is important to recognise that there are some limitations to this assessment. First the pre-study criteria restricted the number of LD-RCP components per patient to 4 units to reduce the risk of haemolysis from the anti-A and anti-B in this component and therefore beyond 4 units no conclusion can be made on the risk of haemolysis with LD-RCP or LD-WB. Second, an extensive haemolytic screen on all patients who received group O LD-RCP, was not able to be performed, because some patients died before any blood samples could be taken from them and the study design and approval did not allow for further research sample to be taken.

In this study that saw the introduction of LD-RCP for all trauma patients in London, 96.5% (n = 1208 units) of LD-RCP unit orders were delivered on time in fill which met the pre-agreed study target of 97%; 95%CI: 96% - 98%). Despite this not all units were delivered at age 2 days old with only 64.7% of the total units being delivered on the agreed age resulting in fewer opportunities for the component to be used, and thus impacting on the level of component wastage seen throughout the study. Following the quality improvement work and interventions in project B, there was a marked improvement in

the age of units delivered with 91.7% being delivered at the pre-agreed age towards the later end of the study period. Demonstrating that delivering at age 2 days old is feasible.

Component wastage was a major concern during this study. A short shelf-life component limited to trauma patients only was always going to provide a challenge. Managing the supply and demand of this component was a fine balance. The pre-agreed wastage level target of 8% was set rather optimistically too low considering the supply strategy used throughout the study period. The mean wastage for the 24-month study period was 20 [9.32] units per month, with the last 12 months of the study period showing a mean wastage of 14 [5.13] units per month. Component wastage was the only feasibility outcome that resulted in a stop criteria at the end of the study. Nevertheless, reductions in component wastage were shown across the study period, demonstrating that component wastage could be minimised.

The biggest impact on wastage was increasing the availability of the units to be used in the ED (project A2), and thus increasing the demand. Indeed, when looking at wastage level in hospitals for the current blood components that have a shorter shelf-life than LD-RCP (i.e., FFP 5 days after thawing and platelets 7 days), they are quite low (lower than 8%) and one of the main reasons for this is the fact that they can be transfused to any bleeding patients and not just a selective group. However, more than 30% of all components throughout the study period were transferred to the ED blood fridge, suggesting that the number of components being ordered and delivered outstretched the demand in the pre-hospital setting. The SPC chart highlights that there was a delay in the impact seen following the start of this cycle (A2). This lag in wastage reduction could demonstrate the time lapse between training/education and the application of the knowledge gained and in particular could be an example of how hard it is to change habits and to establish new routines, even with frequent practice and interaction with ‘coaches’ (Rother, 2018) .

One area not well investigated in advance of the observational study was the actual demand for blood for major trauma in the pre-hospitals setting. The agreement on a constant delivery level of 12 units per week was based on a quick analysis of Golden Hour box provision rather than a detailed analysis of historical demand (i.e. use of RBC).

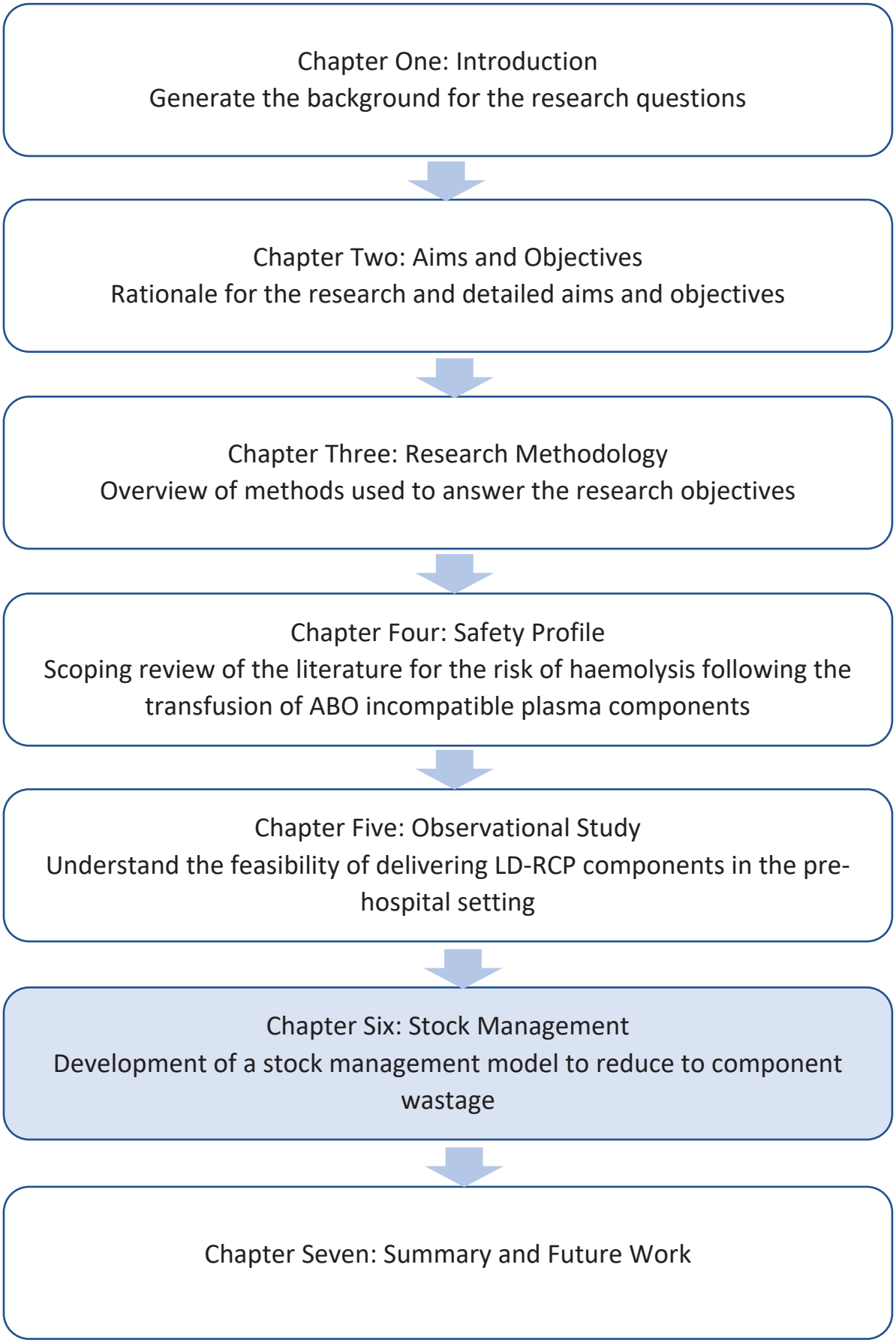
This did ensure, however that 100% of the demand for the component was met (Table 5-2). Such an analysis could have examined weekly demand level and variation, together with any trend and patterns analysis.

Similarly, prior analysis of within-week demand cycles might have prompted, in the setup, designing delivery cycles to this and then, in turn, fitting the manufacturing schedule to the delivery cycle. This was only addressed half-way (a year) through the study, with Project B. The widening-demand work (Project A) had a big impact on wastage (as expected), so starting with this seemed sensible. However, the length of time until delivery root-causes were addressed is an example of the conflict between i) very fast cycle experimentation and improvement and ii) disentangling the effects of a single change (or a single closely related bundle of changes) and being able to demonstrate the effects (e.g. with SPC) (Rother, 2010; Provost and Murray, 2011). This was compounded in this study by it being of a new product/service, so there was felt to be no already- existing (historical) baseline performance data and that new data points accrued only once a week.

More detailed data analysis during the project might have picked this up and suggested additional process metrics. Cold-chain failures could have been another target for QI cycles, discovering root causes and reducing their incidence. Additional cycles of the 'Project A' work (transfer to ED) might have targeted compliance with the 10-day action point, perhaps considering QI ideas like visual management cues, 5S organisation and poka yoke mistake-proofing (NHS Institute for Innovation and Improvement, 2005).

In conclusion this study demonstrated that providing LD-RCP is feasible and safe. However, moving forward, NHSBT will need to ensure that they maintain the supply and demand chain for group O RhD negative and establish whether it is feasible to increase the scale of production of LD-RCP to meet national demand whilst maintaining suitable stock levels for the much-needed group O RhD negative red cells. Hospitals will need to demonstrate a robust stock management system and be able to provide alternatives to use in the pre-hospital setting to keep wastage levels at a minimum. There will always be some degree of component wastage. This is seen more often with short shelf-life components; the question is, what level of wastage is acceptable? And

what steps can be put in place to minimise the level of wastage. The stock management of short shelf-life components is not a new issue and is well documented in the literature. A recent systematic review looking at outdated platelets documented that component wastage due to TIMEX has been an issue for 4 decades (Flint *et al.*, 2020). In an ideal world we would replicate the system currently in place in the US, where WB components are re-manufactured at day 10 to produce RBC (Yazer *et al.*, 2016). This would remove the issue of blood component wastage, however, due to the regulatory constraints surrounding hospital blood banks and hospital blood establishments in the UK this is currently not achievable.


Chapter One: Introduction
Generate the background for the research questions
Chapter Two: Aims and Objectives
Rationale for the research and detailed aims and objectives
Chapter Three: Research Methodology
Overview of methods used to answer the research objectives
Chapter Four: Safety Profile
Scoping review of the literature for the risk of haemolysis following the transfusion of ABO incompatible plasma components
Chapter Five: Observational Study
Understand the feasibility of delivering LD-RCP components in the pre-hospital setting
Chapter Six: Stock Management
Development of a stock management model to reduce to component wastage
Chapter Seven: Summary and Future Work

Chapter 6 Development of stock management model

6.1 Introduction

The perishable nature and short shelf life of LD-RCP or LD-WB components makes stock management a complex task and increases the risk of component wastage due to time expiry. Blood donation in the UK relies solely on the good nature of volunteers. Studies looking at the motivations behind people's willingness to donate blood have demonstrated that the most common reason to donate is altruism (Carver *et al.*, 2018; Padilla-Garrido *et al.*, 2021). The knowledge that the act of donating a unit of blood could potentially save another's life. The realisation that a high proportion of components are wasted, could have detrimental impacts on people's willingness to donate and thus the supply of blood components in the UK could be severely affected. Employing strategies to minimise component wastage wherever possible is a critical task for any blood service or hospital transfusion laboratory.

Analysing the trade-off between unmet demand and component wastage due to time expiry (TIMEX) is a type of problem that has been investigated using Operational Research modelling (Dijk, Wal and Sibinga, 2009; Qin *et al.*, 2011; Osorio, Brailsford and Smith, 2015; Brailsford *et al.*, 2017; Dillon, Oliveira and Abbasi, 2017). A recent review of modelling of perishable blood product inventory, in that case platelets, notes that many modelling methods have been attempted and that simulation methods were one of the most effective methods at reducing component wastage due to outdating (Flint *et al.*, 2020). Other methods looking at reducing the component wastage of RBC have explored demand forecasting methods, that include time series analysis methods such as ARIMA (Pereira, 2004; Filho *et al.*, 2013; Shih and Rajendran, 2019; Nandi, Roberts and Nandi, 2020).

Inventory models are important to support supply chains and, in this case, support to reduce unnecessary wastage of a perishable short shelf-life component such as LD-WB or LD-RCP due to outdating. If demand could be predicted and determined ahead of time, then deterministic inventory methodologies can be used to develop a model.

However, if demand is random and cannot be predicted to a useful degree, stochastic methodologies should be used in developing inventory models. Although there are mathematical solutions available to resolve most supply and demand problems, these solutions can add an extra layer of complexity to routine stock management (Blake, 2009). Simplifying these mathematical models using heuristic approaches can support in achieving a more pragmatic solution to real life problems. In fact, in economics, simple heuristic models have performed better than some of the more complicated mathematical models when it comes to predicting consumer demand (Dosi *et al.*, 2020; Gigerenzer, 2022).

UK data establishing the effect of storing RBC and platelets with plasma in the same bag has demonstrated that, considering the functionality of clotting factors and platelets, the shelf-life of a LD-WB component should be between 14- and 21-days shelf life (Huish *et al.*, 2019). This data is also supported by international practice of WB, with Norway and the United States storing units for 21 days and 14 days, respectively (M. H. Yazer *et al.*, 2018). The current shelf life for the LD-RCP component used in the observational study had a shelf life of 14 days. Having the ability to potentially extend that shelf life to 21 days would have a greater impact on variables such as logistics of supply and potential component wastage. Evaluating the potential benefits on the stock management of a LD-WB component by extending the shelf -life from 14 days to 21 days could support our understanding of how this component could be used more efficiently in the future. Therefore, the models developed within this chapter will consider both a 14 day and 21-day shelf life for LD-WB to evaluate the potential wastage.

6.2 Aims and Objectives

The overall aim of this chapter was to determine to what extent component wastage could be minimised for pre-hospital transfusion and to determine the effects of altering the supply of LD-RCP/WB component would have on component wastage. To enable this, a better understanding of the demand for LD-RCP/WB would be required.

The objectives of this chapter were to:

1) Evaluate whether the daily and weekly pre-hospital trauma demand was forecastable to a usable degree
2) Develop a statistical model to optimise LD-WB component supply and minimise component wastage
3) Evaluate the impact of a 21-day shelf life on component wastage using the statistical model developed in 2).

6.3 Methods

To address the aims and objectives of this chapter the daily and weekly pre-hospital demand for blood components was evaluated. This included the LD-RCP (study group) data as well as the RBC (comparator group) data. The purpose of including the RBC data, from the three-year period prior to the observational study, was to determine if this data was similar enough to the LD-RCP data to be used as training data for any forecasting models.

For the analysis of component demand, data was collected from the observational study as described in Chapter 3.3.3 and analysed as described in 3.4.1. Only the data for pre-hospital transfusion component usage was used in this Chapter as the pre-hospital transfusion data represents the true pre-hospital trauma demand for blood. During the study period component usage within ED was only introduced as a quality improvement measure to reduce the overall component wastage and therefore not a true reflection of the pre-hospital demand.

6.3.1 Analysis

6.3.1.1 Component Demand

Component usage data collected as part of the observational study was used to evaluate the component demand. Counts and percentages were used to summarize the distribution of categorical variables. Mean and standard deviation were used for continuous data. To determine the differences in component usage for the day of the week and month, one-way analysis of variance (one way ANOVA) was used. Statistical analysis was performed using IBM SPSS statistics (Version 27) predictive analytics software.

6.3.1.2 ARIMA

An ARIMA (AR (Autoregression), MA (moving averages), I (differencing)). forecasting model was solved using Python. Each of the three components AR, MA and I was specified in the model as a parameter, using the standard notation (p,d,q). Whereby:

- **p** = the lag of observations included in the model, represents AR and is obtained from the partial autocorrelation plot
- **d** = the order of differencing, represents I and is obtained from the Augmented Dickey-Fuller test:

$$y_t = c + \beta_t + \alpha Y_{t-1} + \phi \Delta Y_{t-1} + \phi_2 \Delta Y_{t-2} \ldots + \phi_p \Delta Y_{t-p}$$

Equation 3: Augmented Dickey-Fuller Test formula

- **q** = the order of moving average, represents MA and is obtained from the autocorrection plot.

Models were generated for both the comparator group (RBC cohort) and the study group (LD-RCP) cohort using both daily and weekly component usage time series data to determine if future demand for each component could be forecast.

6.3.1.3 First In First Out Model

A First In First Out (FIFO) stock management model was created using MS Excel. Seven FIFO models were developed with a 14-day shelf life to mirror the actual shelf life of the WB component. The supply of the WB component for each of the seven models was altered with different algorithms based on stock levels. Each model was assessed to determine the optimal model for minimising component wastage whilst ensuring that demand was met. A further seven models were developed with a 21-day shelf and the same stock management algorithms to evaluate whether an extended shelf-life would influence the potential wastage levels of the component.

6.3.1.4 Simulation

A Monte Carlo simulation was developed using MS Excel. A Poisson probability distribution was used to generate the random variables for the component demand for input into the FIFO model to generate various outcome profiles. Effectiveness of each FIFO model was determined by the sum of component wastage plus the unmet demand.

6.4 Results – Demand Forecasting

Total prehospital component demand of RBC, for all London Major Trauma Centres, between April 2015 and October 2018 was 1586 units, transfused to a total of 415 patients, averaging 3.8 units per patient equating to roughly 1064ml of volume. In contrast the total pre-hospital demand of LD-RCP between November 2018 and October 2020 was 549 units, transfused to a total of 291 patients, averaging 1.8 units per patient, equating to roughly 855ml of volume. Data for RBC and LD-RCP demand was analysed for any obvious trends and to determine the similarity between the two data sets. Times series graphs were used to illustrate the daily demand (Figure 6-1) and weekly demand (Figure 6-2).

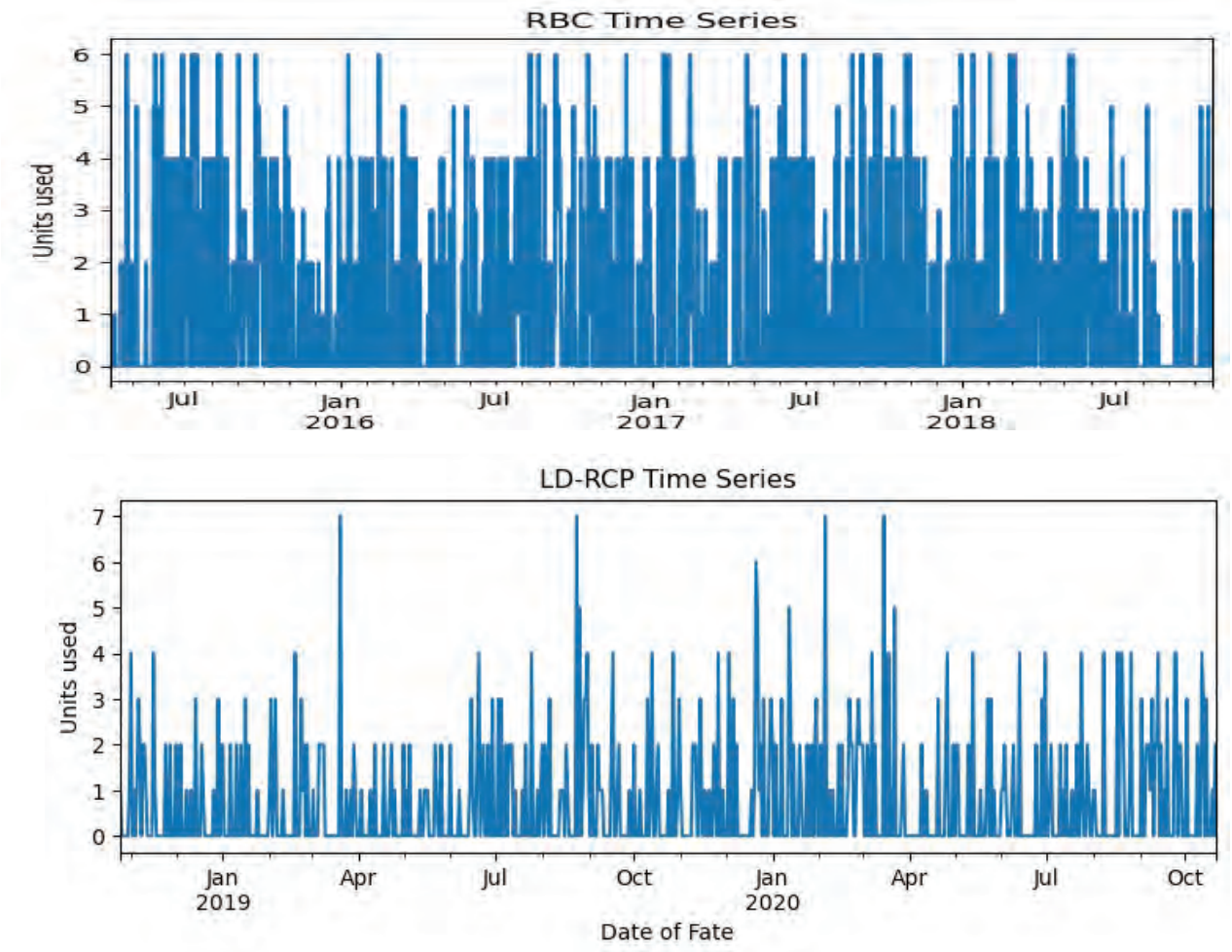


Figure 6-1: Time series graphs of daily component usage.
Top: RBC component usage between April 2015 and October 2018. Bottom: LD-RCP component usage between November 2018 – October 2020

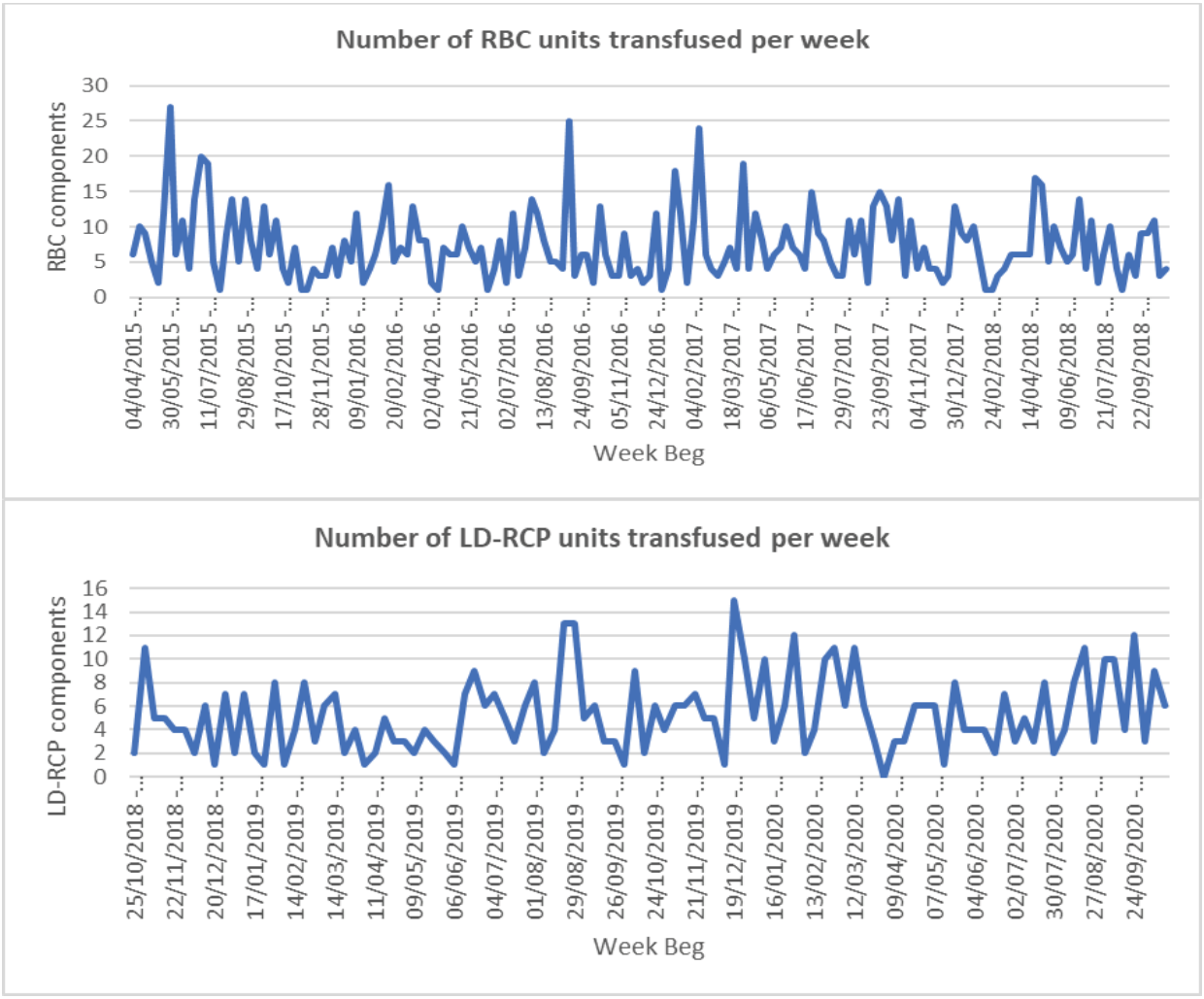


Figure 6-2: Time series graph of weekly component demand.
Top: RBC component demand between April 2015 and October 2018. Bottom: LD-RCP component demand between November 2018 and October 2020

Data for all RBC and LD-RCP time points highlight what looks like stationary data for both components and every time point (daily and weekly). The data for daily demand was explored further to determine if there were any statisitically significant differences in component demand for each day of the week.

6.4.1 Daily RBC and LD-RCP Demand

Component demand of RBC for each day of the week was as follows: Monday (1.25 ± 1.77), Tuesday (1.09 ± 1.64), Wednesday (1.12 ± 1.69), Thursday (1.13 ± 1.69), Friday (1.27 ± 1.67), Saturday (1.35 ± 1.76), Sunday (1.33 ± 1.72), (Figure 6-4). There was a

higher mean demand of RBC on Saturday and Sunday, however, the difference in demand for each day of the week was not statistically significant p = 0.646.

Component demand of LD-RCP for each day of the week was as follows: Monday (0.54 ± 1.07), Tuesday (0.66 ± 1.15), Wednesday (0.84 ± 1.39), Thursday (0.67 ± 1.19), Friday (0.73 ± 1.11), Saturday (0.95 ± 1.39), Sunday (0.88 ± 1.40), (Figure 6-4). There was a higher mean component demand of LD-RCP on Saturday, Sunday and Wednesday, however, the differences between component demand for each day of the week was not statistically significant, p = 0.217.

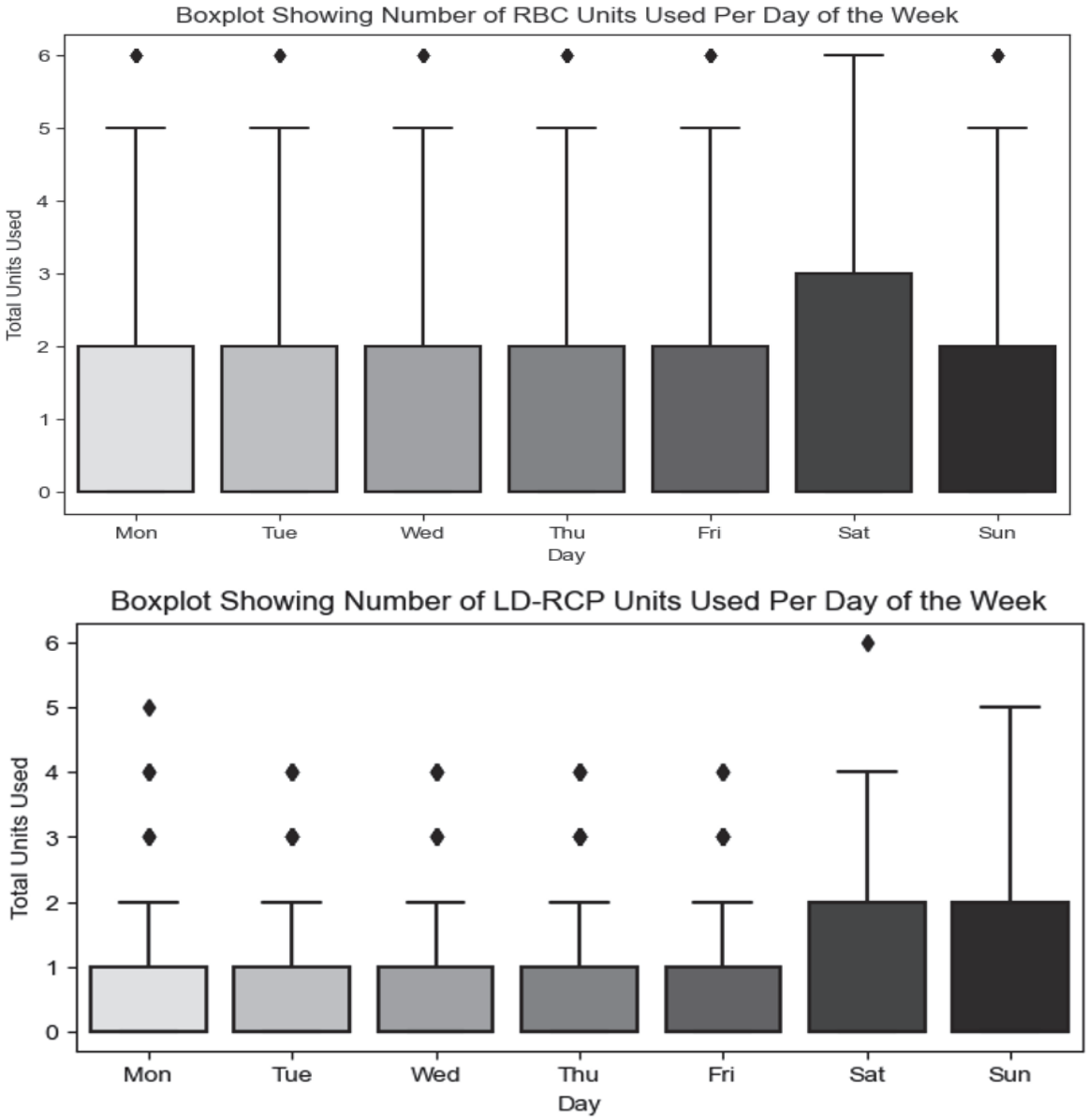


Figure 6-3: Boxplots of the number of RBC and LD-RCP demand for each day of the week Top: RBC component demand Monday – Sunday between April 2015 and October 2018. Bottom: LD-RCP component demand Monday-Sunday between November 2018 – October 2020

The total mean daily component usage differed significantly between RBC (1.22 ± 1.71) and LD-RCP (0.75 ± 1.253) (p=0.001), indicating that the usage patterns between the two components were not the same and therefore the three-year RBC data, collected retrospectively, could not be used to support any predictions in demand forecasting of the LD-RCP component usage moving forward.

6.4.2 Forecasting of the data

For the analysis of demand forecasting only the daily and weekly LD-RCP demand data was used. This decision was made following the results of the daily component demand analysis which highlighted the differences in RBC demand versus LD-RCP component demand. The two data sets were too different for the RBC component demand to be useful in predicting the demand of LD-RCP. Also predicting monthly demand would not provide much benefit for a component with a 14-day shelf life and therefore a more frequent demand such as weekly or daily would be more appropriate.

The ARIMA (p,d,q) statistical analysis model was used to generate the time series forecast for both the daily and weekly LD-RCP demand. Building an ARIMA model is completed in two stages: 1) Identifying whether the data is stationary and 2) Generating and testing the model. Stage 1, Identifying if the data is stationary is an important part of building a forecasting model with some degree of accuracy. To build an ARIMA model the data must be stationary, if the data is not stationary then differencing (d) is required to remove non-stationary features.

6.4.2.1 Stage 1 – Stationary Data

As highlighted in the time series graphs and analysis, component demand appeared to be stationary without any obvious trends. To confirm that it is in fact stationary, an Augmented Dickey-Fuller (ADF) test was performed as described in Table 6-1.

	ADF statistic	**p-value**
Daily LD-RCP	-27.488751	0.000000
Weekly LD-RCP	-9.965013	0.000000

Table 6-1: A table containing the results of the ADF (Augmented Dickey Fuller) statistic and corresponding p-value for daily and monthly LD-RCP demand. ADF p-values are both <0.5.

As the Dickey fuller p-value is <0.5 for both daily and monthly LD-RCP time series, both data series were classified as stationary and therefore no differencing was required. Resulting in a 0 for the d element of the model (p,0,q).

6.4.2.2 Stage 2 – Generating and testing the model

The next step was to identify the AR (p) terms and MA (q) terms of the model by interpreting the Partial Autocorrelation function (PACF) and Autocorrelation Function (ACF) plots respectively. The AR and MA terms were selected by the automatic algorithm in Python. The models with the best fit, represented by the lowest AIC (Akaike Information Criterion) value and the smallest forecasting error, represented by the lowest root mean square error (RMSE) for both daily and weekly demand (Table 6-2 and Table 6-3, respectively) were selected to test the forecast. All the models generated were very similar in terms of AIC and RMSE. In theory the best models for both daily and weekly demand were ARIMA (0,0,1) and (1,0,0).

Daily LD-RCP Demand		
ARIMA model (p,d,q)	**Model goodness of fit (AIC)**	**Forecasting error (RMSE)**
0,0,1	2398.750	1.268
0,0,2	2400.258	1.269
1,0,0	2398.769	1.268
1,0,1	2400.643	1.273
2,0,1	2401.795	1.275
3,0,1	2402.975	1.274
4,0,1	2404.968	1.273
5,0,1	2405.159	1.274
1,0,2	2401.908	1.273
1,0,3	2403.171	1.272
1,0,4	2404.676	1.274

Table 6-2: Daily LD-RCP demand ARIMA models
AIC: Akaike Information Criterion; RMSE: Root Mean Square Error; p: Autoregression term (MA); d: order of differencing (I) and q: Moving averages (MA).

Weekly LD-RCP Demand		
ARIMA model (p,d,q)	**Model goodness of fit (AIC)**	**Forecasting error (RMSE)**
0,0,1	544.027	3.147
0,0,2	545.001	3.127
1,0,0	544.024	3.147
1,0,1	545.925	3.163
2,0,1	545.478	3.207
3,0,1	546.371	3.118
4,0,1	547.819	3.124
5,0,1	548.913	3.233
1,0,2	547.849	3.206
1,0,3	546.634	3.099
1,0,4	547.877	3.315

Table 6-3: Daily LD-RCP demand ARIMA models
AIC: Akaike Information Criterion; RMSE: Root Mean Square Error; p: Autoregression term (MA); d: order of differencing (I) and q: Moving averages (MA).

6.4.2.3 ARIMA model results

The results of the ARIMA model to forecast demand are presented in Figure 6-4 and Figure 6-5. The ARIMA forecasts sit very closely around the mean unit usage for both daily (0.75 ± 1.25) and weekly (5.28± 3.23) LD-RCP unit usage, with a small element of noise and randomness around that mean. On a practical level, due to the level of noise and randomness in the original dataset, the forecast models would likely perform little better than simply using mean unit usage when making ordering decisions to satisfy component demand.

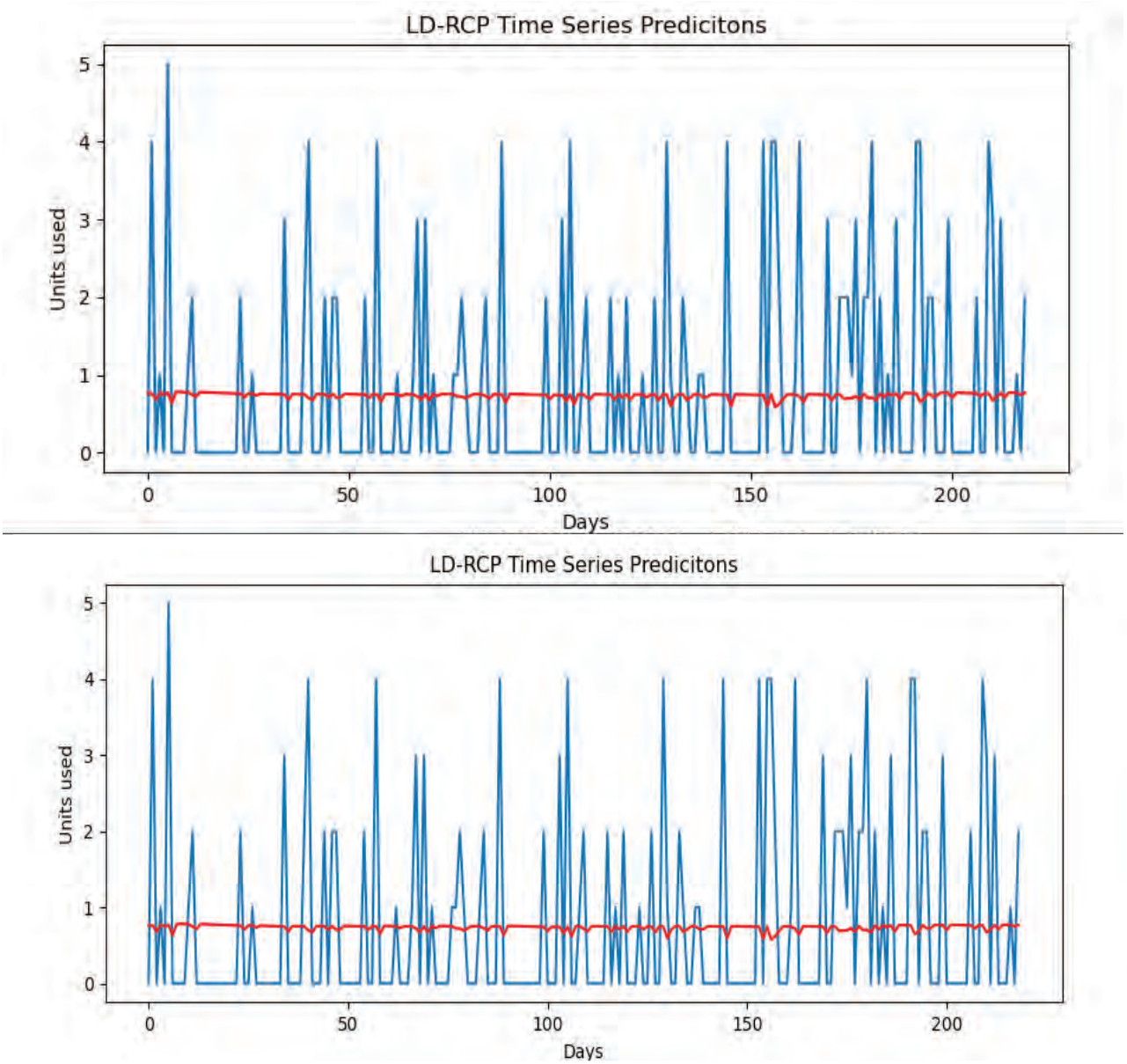


Figure 6-4: Daily LD-RCP time series ARIMA predictions
Top: ARIMA (1,0,0) and Bottom: ARIMA (0,0,1)

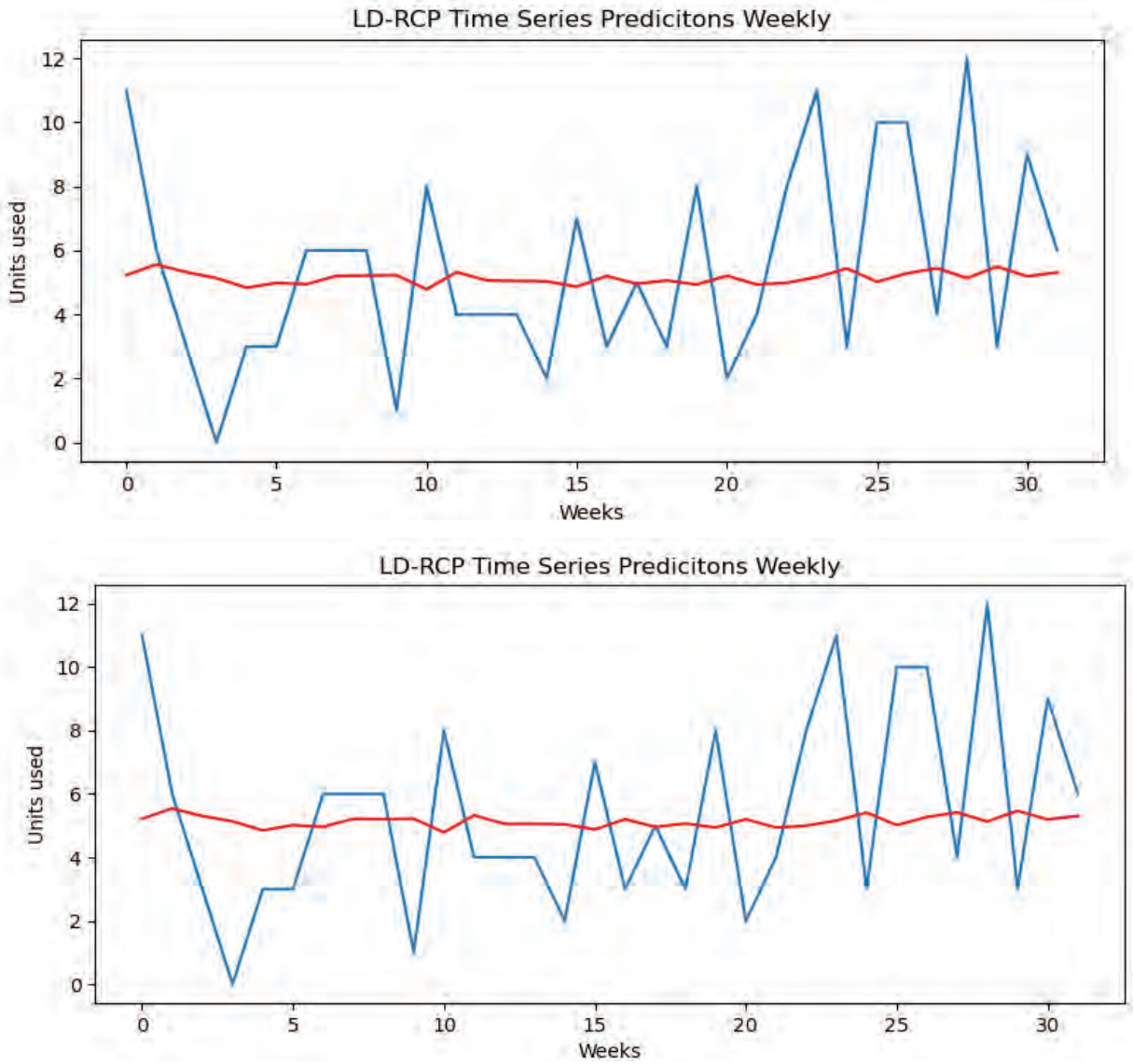


Figure 6-5: Weekly LD-RCP time series predications
Top: ARIMA (1,0,0) and Bottom : ARIMA (0,0,1)

If the demand of future component usage could be forecast with a considerable degree of precision, then it would be reasonable to use an inventory policy that assumes that all forecasts will be accurate (Hillier and Lieberman, 2015). A deterministic inventory model would then be appropriate as the variable would be known. In this case the demand could not be predicted, as determined by the ARIMA model results, and a stochastic inventory model would be more appropriate due to the random nature of the demand variable.

6.5 Results - Stochastic model development

6.5.1 FIFO model

A First In First Out (FIFO) stock management model for a 14 day shelf life LD-RCP component was developed in MS Excel. The model was validated using the study supply and demand data. The component demand and supply inputs were the exact daily demand and supply during the 24-month study period. The outputs from the actual study versus the outputs from the FIFO model are represented in Table 6-4.

	Supply	Demand	Wastage	Unmet demand
Actual study	1208	733	475	0
FIFO model	1208	733	465 (+10 inventory)	0

Table 6-4: Verification of the FIFO model compared with the actual study results.

Table 6-4 validates the FIFO model. With the same input data for daily component supply and demand the wastage level for the actual study was 475 units and using the FIFO model was 465 plus 10 units in inventory at the end of the 24-month study period. These 10 units in inventory would eventually have contributed to the overall wastage level. This model was developed to mimic the inventory management of the component in real time. It was then used as part of a bigger model for further analysis, to evaluate how component supply levels could impact unit wastage.

6.5.2 Stochastic Model

Forecasting demand for LD-RCP/WB is important for inventory control, however the uncertainty of the variable is so high that forecasting techniques could lead to unsatisfactory results as demonstrated by the ARMIA models discussed in 6.3.4. The forecasting approach demonstrated in the ARIMA models closely followed the mean daily and weekly component usage and therefore did not demonstrate a suitable model for forecasting. Due to the highly variable and random nature of the LD-RCP component demand, it cannot be forecast to a reliable level and therefore it is necessary to consider a stochastic inventory model to approach this problem. The model developed was a combination of FIFO and Monte Carlo simulation.

6.5.2.1 Problem formulation

The objective was to optimise LD-RCP/WB component supply and minimise component wastage due to TIMEX (TIMEX [Time Expired]: defined as components not utilised before the end of their shelf life).

6.5.2.2 Generating the Demand Variable

Demand was modelled as a discrete random variable using a Poisson distribution with a λ of 0.70 (daily mean LD-RCP component usage). The RAND function in MS Excel was used to generate different demand profiles using parameters set by the Poisson distribution.

$$f(x) = P(X = x) = (e^{\lambda}\lambda^{x})/x!$$

Equation 4: Poisson Distribution

6.5.2.3 Generating the Supply Variable

Heuristic methods were used to determine the algorithms used for component supply. The supply algorithms were generated around the following basic parameters:

- 3-day lead time on orders
- Each unit was delivered at 2days old
- 24hrs ad-hoc orders were possible

Each model was adjusted based on the outcome (wastage and unmet demand) of the previous model.

6.5.2.4 Simulation

For the simulation exercise, supply models were tested. Each model had a run length of 732 days (as did the original LD-RCP observational study). Random demand profiles following a Poisson distribution were generated for each model. These demand profiles were used as input values for the demand element of the FIFO model to generate outputs of mean component wastage; mean component usage and mean unmet demand. All outputs were based on the average of 1000 replications. The sum of the mean component wastage and the mean unmet demand were used to measure the performance of each model. Seven different supply models were generated, for each

model tested, the algorithms were adjusted following the analysis of the output parameters

6.5.3 Model outputs – 14-day shelf life

6.5.3.1 Baseline

The first stage was to use the model to evaluate the potential outputs from the study if the component was used for pre-hospital demand only (baseline). For this, only the demand variable was generated. The supply variable remained as it was during the study, roughly a static delivery of 12 units per week. The model run length was 732 days with 1000 repetitions. Results from this initial model demonstrated a mean component usage of 515.79 [26.88] 95% CI [514.12 - 517.45], a mean component wastage of 682.81 [26.8] 95% CI [681.14 - 684.47] and no unmet demand. Component wastage was calculated at 57%, this was considerably more component wastage than seen throughout the study period as would have been expected with the same supply and a reduced level of demand (no ED usage).

6.5.3.2 Models 1-7

The next stage was using the full model to test different supply strategies to optimise the model using a heuristic approach. The algorithms used for each model are shown in Table 6-5.

	Basic Order	Ad hoc orders
Model 1	If inventory <10 order 3	If inventory ≤6 order 2
Model 2	If inventory <12 order 2	If inventory ≤6 order 2
Model 3	If inventory <12 order 3	If inventory ≤6 order 2
Model 4	If inventory <12 order 2	If inventory ≤8 order 2
Model 5	If inventory <14 order 2	If inventory ≤6 order 2
Model 6	If inventory <6 order 2	-
Model 7	If inventory <8 order 2	-

Table 6-5: A table of the heuristic algorithms used for generating the supply variable for each model. No data is represented by (-).

The results of each of these models are displayed are Table 6-6. The score was generated by taking the sum of the mean component wastage and the mean unmet demand. For this analysis the lowest scores represent the best performing models.

	Component Wastage			Component Usage			Unmet Demand			% Wastage	Score
	Mean	*SD*	*95% CI*	*Mean*	*SD*	*95% CI*	*Mean*	*SD*	*95% CI*		
Baseline	682.81	26.8	[681.14 - 684.47]	515.79	26.88	[514.12 - 517.45]	-	-	-	57%	682.81
Model 1	278.02	21.84	[276.66 - 279.37]	516.05	26.36	[514.41 - 517.68]	0.086	0.39	[0.06 - 0.11]	35%	278.10
Model 2	249.36	20.77	[248.07 -250.65]	516.51	27.46	[514.81 - 518.21]	0.025	0.20	[0.01 - 0.03]	33%	249.39
Model 3	340.31	22.33	[338.92 - 341.69]	516.73	26.81	[515.07 - 518.39]	0.026	0.21	[0.01 - 0.03]	40%	340.33
Model 4	263.48	20.20	[262.23 - 264.74]	518.07	26.01	[516.45 - 519.68]	0.009	0.13	[0.00 - 0.01]	34%	263.49
Model 5	308.59	20.40	[307.33 - 309.86]	517.27	26.44	[515.63 - 518.91]	0.005	0.08	[0.00 - 0.01]	37%	308.60
Model 6	97.00	14.45	[96.10 - 97.89]	515.04	26.48	[513.40 - 516.68]	5.795	3.53	[5.57 - 6.01]	16%	102.79
Model 7	153.95	17.55	[152.86 - 155.03]	513.72	27.09	[512.0 - 515.40]	1.024	1.44	[0.93 - 1.11]	23%	154.97

Table 6-6: A table representing the output data for the baseline model and models 1-7 with adjusted supply, for a 14-day shelf-life component Baseline – the component supply for the observational study. Models 1-7 – altered component supply as described in Table 6-5. No data is represented by (-).

The outputs for each of the models are represented in Table 6-6. The results of % wastage and the model score indicate that all of the models 1-7 outperform the baseline model. This demonstrates that altering the supply variable can have the desired impact on minimising component wastage. Although the results of models 1-5 showed a reduced level of overall component wastage and a lower score compared to the baseline, the component wastage was still relatively high and similar to the wastage levels seen in the observational study (39.3%) when only the demand variable was altered.

Models 6 and 7 start to explore the trade-offs between unmet demand and wastage:

1) The risk of inventory levels falling to zero and therefore not being able to supply the component when needed, opting instead for a potentially suboptimal component
2) The risk of excess inventory, thereby incurring wastage of the component and holding excess units that could have been used elsewhere.

This trade-off is accomplished by minimising the effects of the sum of unmet demand and component wastage as shown by scoring each model. These two models demonstrate a larger reduction in the mean component wastage and % wastage than the other 5 models, however, they both have a larger mean unmet demand when compared with the other 5 models and the baseline.

The best performing model was model 6 with a score of 102.79, a mean wastage of 97.00 [14.45], 95% CI [96.10 - 97.89] representing 16% component wastage. The model also had the largest mean unmet demand of 5.795 [3.53], 95% CI [5.57 - 6.01] representing <1% unmet demand over the 732-day run period.

The model scoring was set using arbitrary values for component wastage and unmet demand, attributing a value of 1 for each. The scores were used as a method to easily identify well-performing models. However, depending on the impact that unmet demand could have on clinical practice and patient outcomes, the value of unmet demand as a factor may need to be weighted more heavily when assessing each model.

6.5.4 Model outputs - 21-day shelf life

The third and final objective for this chapter was to evaluate the impact of a 21-day shelf life on component wastage using the statistical model developed. All variables (demand and supply) were generated in exactly the same way as for the 14-day model, demand was generated from a Poisson distribution and the heuristic supply algorithms outlined in Table 6-5 were used for each of the 21-day models. Each model had a run length of 732 days, and all outputs were based on the average of 1000 replications. The only change was to the FIFO model, which was adapted from a 14-day shelf life to a 21-day shelf life.

6.5.4.1 Baseline

The first stage was again to use the model to evaluate the potential outputs from the study if the component was used for pre-hospital demand only (baseline) with a shelf-life of 21 days rather than 14 days. Results from this initial model demonstrated a mean component usage of 517.36 [27.16] 95% CI [515.68 - 519.05], a mean component wastage of 670.17 [27.16] 95% CI [668.48 - 671.85] and no unmet demand. Component wastage was calculated at 55%, this was similar but slightly less than the component wastage seen with the baseline model for the 14-day shelf, which resulted in 57% component wastage. Again, as seen with the 14-day shelf-life baseline model, this wastage level was considerably more than that seen throughout the study period, as would have been expected with the same supply and a reduced level of demand.

6.5.4.2 Models 1-7

The outputs for each of the models are represented in Table 6-7. The results of % wastage and the model score indicate that all of the models 1-7 outperform the baseline model. This again, demonstrates that altering the supply variable can have the desired impact on minimising component wastage. The % wastage and model score for all the 21- day shelf-life models all perform better than their 14-day shelf-life counter parts. This highlights that although the baseline data didn't show promising improvements with a static component supply and an extended shelf life, altering the supply using the algorithms described in Table 6-5 did have the desired effect on minimising component wastage will all models achieving a mean component wastage of ≤20%.

	Component Wastage			Component Usage			Unmet Demand			% Wastage	Score
	Mean	*SD*	*95% CI*	*Mean*	*SD*	*95% CI*	*Mean*	*SD*	*95% CI*		
Baseline	670.17	27.16	[668.48 - 671.85]	517.36	27.18	[515.68 - 519.05]	-	-	-	55%	670.17
Model 1	94.28	15.79	[93.30 - 95.25]	516.47	26.80	[514.81 - 518.13]	0.05	0.31	[0.03 - 0.07]	15%	94.33
Model 2	86.21	15.08	[85.27 - 87.14]	516.09	26.80	[514.42 - 517.75]	0.02	0.16	[0.01 - 0.03]	14%	86.22
Model 3	132.89	16.92	[131.84 - 133.94]	517.28	25.83	[515.68 - 518.88]	0.02	0.19	[0.01 - 0.03]	20%	132.91
Model 4	89.71	15.21	[88.76 - 90.65]	516.15	26.68	[514.50 - 517.80]	0.00	0.07	[0.00 - 0.01]	15%	89.71
Model 5	123.27	17.29	[19.49 - 124.34]	515.16	27.40	[513.46 - 516.86]	0.00	0.04	[0.00 - 0.00]	19%	123.27
Model 6	19.97	7.68	[96.10 - 20.44]	516.12	27.23	[514.44 - 517.81]	4.42	3.12	[4.22 – 4.61]	4%	24.38
Model 7	39.94	10.46	[39.29 - 40.58]	516.25	26.34	[514.62 - 517.88]	0.76	1.27	[0.68 – 0.84]	7%	40.70

Table 6-7: A table representing the output data for the baseline model and models 1-7 with adjusted supply for a 21-day shelf-life component. Baseline – the component supply for the observational study. Models 1-7 – altered component supply as described in Table 6-5. No data is represented by (-).

The best performing models with the lowest scores were model 6 (score 24.38) and model 7 (score 40.7) with % wastage figures of 4% and 7% respectively. Again, as with the 14-day shelf-life models, both model 6 and model 7 explored the trade-off between unmet demand and wastage and both models had higher unmet demand when compared with the other 5 models. The unmet demand for model 6 was the highest with a mean of 4.42 [3.12], 95% CI [4.22 – 4.61], however, this only translates to an unmet demand of <1% over a 732-day run period.

6.6 Discussion

Analysis of the RBC and LD-RCP weekly and daily demand data demonstrated that the two data sets differed significantly, and RBC data collected over the 3-year period prior to the introduction of LD-RCP could not be used as training data for the ARIMA forecasting models. To some degree this was not a surprise. Although the two components were both used for the management of bleeding in trauma patients in the pre-hospital setting, the components themselves are fundamentally different. LD-RCP contains the addition of plasma and was of a larger volume than a standard bag of RBC. Perhaps the lower mean usage over the 2-year study period is an early indication that the administration of the LD-RCP components resulted in a lower demand for blood components.

By its nature, demand for blood for pre-hospital transfusions is inherently both critical and highly variable. The ARIMA models highlighted that the demand for pre-hospital transfusion was random and could not be forecasted to a usable degree. On a practical level, due to the level of noise and randomness, the forecast models would likely perform little better than simply using mean unit usage when making ordering decisions to satisfy component demand. Therefore, a stochastic inventory model was chosen to optimise component supply and minimise component wastage. Although there are mathematical solutions available to resolve most supply and demand problems such as the supply of perishable blood components, these solutions can add a layer of complexity to the routine management of stock. It is important that the search for an idealised solution does not hamper day to day practice and the simpler the solution the better chance it has of being utilised to make the changes required.

Current practice for ordering decisions of units to satisfy demand are based on previous average units used, and a level of heuristics by both hospitals and the centralised blood service, NHSBT. If ordering decisions are to be improved upon to improve stock management and reduce wastage of a precious resource, any forecasting model must improve upon this current practice. This chapter has shown that, due to the randomness and element of noise within component usage, creating a robust prediction model using the ARIMA method, is likely to perform little better than current standard practice, and would likely serve to only increase complexity in the unit ordering process. However, the stochastic models developed, using a level of simple heuristics, demonstrated huge improvements in component wastage.

There is a fine balance between supply and demand: ensuring that we have enough LD-RCP (or, eventually, LD-WB) to treat all trauma patients in the pre-hospital setting, whilst minimising wastage. Clinical output from the observational study (not reported in this thesis), demonstrates there being no difference in clinical outcome between patients who received LD-RCP and patients who received red cell and plasma components. There was however, a statistically significant difference between both LD-RCP and red cell and plasma versus RBC component only in the 24-hour mortality but not 30-day mortality, with plasma arms being better than RBC only (data submitted for publication to Annals of Surgery). To date, there is still no data in the UK that indicates how a LD-WB component would affect clinical outcomes compared to LD-RCP or red cell and thawed plasma. Therefore, when using a model such as this for future studies, it is important to take into consideration this trade-off between unmet demand and the alternative component that is being administered.

For future studies, if there is found to be no significant differences in clinical outcomes between LD-WB and RBC and plasma, wastage levels for LD-WB units would need to be at a comparable level to currently accepted wastage levels for red cells. Whole blood units would still have the small logistical advantages over RBC and plasma (1 bag instead of 2) and would therefore likely still be preferred. But, as demonstrated in this thesis, due to the shorter shelf life of whole blood units, it would be expected that unmet demand would occur which would need to be filled by individual component therapy.

Chapter One: Introduction
Generate the background for the research questions

Chapter Two: Aims and Objectives
Rationale for the research and detailed aims and objectives

Chapter Three: Research Methodology
Overview of methods used to answer the research objectives

Chapter Four: Safety Profile
Scoping review of the literature for the risk of haemolysis following the transfusion of ABO incompatible plasma components

Chapter Five: Observational Study
Understand the feasibility of delivering LD-RCP components in the pre-hospital setting

Chapter Six: Stock Management
Development of a stock management model to reduce to component wastage

Chapter Seven: Summary and Future Work

Chapter 7 Summary and future directions

7.1 Summary

The overall aim of this thesis was to establish whether introducing a leucocyte depleted Whole Blood (LD-WB) component, for the treatment of traumatic major haemorrhage, is feasible in the UK. To establish this, I went on to answer three distinct but related questions to address the main areas that would affect the introduction of the LD-WB in the UK. These were:

1. Evaluate the safety of transfusing ABO incompatible plasma components by examining the evidence in the literature with regards to:
    a) Determining the lowest observable anti-A and anti-B titre (measured by IgG or IgM) reported in the literature that has resulted in clinical haemolysis in recipients receiving ABO incompatible plasma containing components.
    b) Determining the lowest observable ABO incompatible plasma volume that has resulted in haemolysis, in individuals receiving ABO incompatible plasma containing components

2. As part of a 2-year prospective observational study, I evaluated the logistical elements and safety of delivering another blood component called leucocyte-depleted red cell and plasma in one bag (or LD-RCP) that has the same shelf-life and serological challenges as the LD-WB, specifically examining the safety of LD-RCP, its delivery from the blood service to hospital and wastage in hospital

3. Based on the results of the 2-year observational study, I went on to explore the stock management of a LD-WB component, aiming to:
    a) Evaluate whether the weekly pre-hospital trauma demand can be forecasted
    b) Develop a statistical model to optimised WB component and minimise component wastage
    c) Evaluate the impact of a 21-day shelf life on component wastage using the statistical model developed in 3b).

As far as the safety of transfusing a group O leucocyte-depleted red cell and plasma (LD-RCP) component is concerned, the scoping review of the literature identified only 49 papers representing a total number of 62 case reports. There were no completed or on-going randomised control trials (RTCs) identified. Based on the 62 cases, platelet components were the most reported components to result in haemolysis in both paediatrics and adults. The lowest titre reported to cause haemolysis in both paediatrics and adults was an anti-A titre of 32, while the lowest component volume to result in haemolysis was 100ml in adults and 15mls in paediatric cases. Of the 62 cases reported, 15% of cases died, highlighting the clinical importance of the risk of harm due to haemolysis associated with ABO-incompatible plasma-containing components, although we cannot provide any meaningful estimate of the true risk of death in these cases.

However, it is important to emphasise that results of the systematic review showed significant heterogeneity in the methods for reporting clinical and laboratory haemolysis and the ABO titration methods and the information on volumes transfused and clinical recovery were also poorly reported. Therefore, further research is needed to a) standardise the methods for the measurement of ABO titrations and b) agree the lowest cut-off levels for high titre negative components internationally.

The observational study, which saw the introduction of LD-RCP in the pre-hospital setting, as a replacement for red blood cells (RBC), was the first and only study in the UK to assess the safety and feasibility of introducing such a component into clinical practice. From the safety perspective, the study demonstrated that LD-RCP component was not associated with increased haemolytic adverse events in non-group O recipients compared with group O recipients. Putting aside the limitations that have been acknowledged in Chapter 5, this data provides new evidence into the safety of transfusing a maximum of 4 units of ABO incompatible plasma (i.e., LD-RCP or LD-WB) to trauma bleeding patients.

As part of the 2-year observational study, I also went on to evaluate the feasibility of delivering the LD-RCP to support trauma patients who are bleeding in the prehospital

setting, aiming to determine the overall blood component usage, wastage and 'on time in full' (OTIF) delivery of LD-RCP as well as evaluate quality improvement measures introduced to reduce wastage. Overall, three out of five feasibility outcomes (i.e., days with unmet demand, percentage of components used inappropriately, and OTIF) established prior to the start of the study period were met. The two remaining outcomes that were not fully met were number of units transferred to ED (35%) and percentage component wastage (39.3%). Nevertheless, incremental reductions were demonstrated across the study period, reducing the weekly wastage from a mean of 8.36 units per week (70%) to 3.19 (27%) by the end of the study period. The biggest impact on component wastage was increasing the availability of the units to be used in ED, and thus increasing the demand through cascading what would likely have been surplus to a secondary use.

Despite the slightly higher transfer of LD-RCP to the ED fridge and the high component wastage, this data demonstrated that the transfusion of LD-RCP (hight titre negative for anti-A and anti-B) in the prehospital environment is safe, and that the wastage level for the component can be kept low, if it is transfused to other patients in hospital who are bleeding. Moving forward, hospitals will need to demonstrate a robust stock management system to keep wastage levels at a minimum. More detailed analysis of historical transfusion demand in both pre-hospital and ED settings will be required to refine the supply of a WB component.

The final section of my thesis was to develop a stock management model based on the observational study data and the detailed analysis of the component demand from historical data. The aims of this further analysis were to establish if there were any trends in the data that could support the forecast of future component demand. The data demonstrated that the demand for pre-hospital blood component was random in nature and that forecasting the data using an ARIMA model was not possible beyond predicting the mean daily and weekly demand. This was very similar to the stock supply approach used within the study, which demonstrated high component wastage levels despite efforts to increase demand by using the component in different settings.

Due to the random nature of pre-hospital blood demand, a dynamic stochastic inventory model was developed. The model aimed to minimise wastage levels by generating different component supply algorithms for a 14-day and 21-day shelf-life component. The models developed highlighted that component wastage for the 2-year study period could have been reduced to 16% and 4% for a 14-day and 21-day shelf life, respectively. However, both models demonstrated unmet demand and started to explore the trade-offs between unmet demand and component wastage. For future trials looking at the use of LD-WB it will be important to take into consideration this trade-off between component wastage and unmet demand. Understanding the risks associated with excess component wastage versus the use of any alternative component that would be administered to meet demand.

7.2 Future directions

Future studies should concentrate on standardising the methods for the measurement of ABO titrations in plasma and gaining international consensus on the lowest cut-off levels for high titre negative components. More work is needed to explore opportunities to manage the high demand for group O RhD negative red cell-containing components (like LD-RCP, or LD-WB) as well as reduce component wastage and validating the stock management model developed in chapter 6 to ensure that a dynamic supply can be easily utilised in hospital settings.

I am aware that the output of this work has directly impacted on the design of the multicentre randomised control trial (SWiFT) that is due to start in England in November 2022. The trial will compare the LD-WB transfusion versus standard of care (red cell and thawed plasma) in prehospital setting, aiming to recruit a total of 850 patients. To address the high wastage level we saw as part of the 2-year feasibility study, the trail will a) use a longer shelf-life LD-WB component (21 days) than the LD-RCP, and b) transfuse the LD-WB to other bleeding patients in hospital, if the safety outcome data of the first 200 patients recruited to the trial, showed no safety concerns.

To address the high demand for the group O RhD negative components, NHSBT has recently evaluated the clinical risks and benefits as well as health economic benefits of

transfusing group O RhD positive to all individuals who present with trauma and who require blood as part of their resuscitation outside hospitals. Such strategy would increase the risk of D alloimmunisation for recipients who are RhD negative, and in particular for women of child-bearing potential where D alloimmunisation could cause harm to the unborn child. The results of the clinical risk assessment have shown that if NHSBT implements an RhD positive strategy for prehospital services, then for every 14,000 D-positive transfusions administered to all trauma patients of any sex and age, one harm would occur (95% CI 5,600 – 42,000). The main risk in the population was that of haemolytic disease of foetal and newborn, where for every 570 transfusions, one foetal death or disability would occur (Cardigan *et al.*, 2022). Implementation of group O RhD positive red cells or WB in prehospital setting would require that these risks and benefits are discussed with other key stakeholders and patients to determine what is acceptable and not acceptable.

Another option that one could consider to reduce wastage of group O RhD negative LD-WB, would be to re-manufacture LD-WB back into red cells in additive at either days 14 or 21, which is what some countries are currently doing (USA). However, in the UK hospitals are not permitted to return red cells to NHSBT and for these to be re-manufactured and re-issued. This is to ensure the integrity and safety of the unit. Re-manufacturing of units cannot be completed by hospitals as this would require them to hold a Blood Establishment licence, which >95% of hospitals are not. Whilst it may be possible to put in place systems to take blood back from hospitals and re-manufacture units, this will require significant assurance with respect to the audit trail and tracking of units via suitable IT management systems but would provide an option to significantly reduce component wastage due to time expiry.

Chapter 8 Bibliography

Angiolillo, A. and Luban, N.L. (2004) 'Hemolysis following an out-of-group platelet transfusion in an 8-month-old with Langerhans cell histiocytosis', *Journal of Pediatric Hematology/Oncology*, 26(4), pp. 267–269.

AuBuchon, J.P., De Wildt-Eggen, J. and Dumont, L.J. (2008) 'Reducing the variation in performance of antibody titrations', *Vox Sanguinis*, 95(1), pp. 57–65. Available at: https://doi.org/10.1111/j.1423-0410.2008.01043.x.

Augustine, M. *et al.* (2021) 'Case report and strategies to mitigate passive hemolysis with platelet transfusions in children', *Asian journal of transfusion science*, 15(2), pp. 229–232. Available at: https://doi.org/https://dx.doi.org/10.4103/ajts.ajts_25_21.

Avery, P. *et al.* (2020) 'Whole blood transfusion versus component therapy in adult trauma patients with acute major haemorrhage', *Emergency Medicine Journal*, 37(6), pp. 370–378. Available at: https://doi.org/10.1136/emermed-2019-209040.

Bachowski, G. *et al.* (2010) 'Determination of anti-A and anti-B titers in random donors and donors involved in hemolytic reactions from platelets', *Transfusion*, 2), pp. 160A-161A. Available at: https://doi.org/http://dx.doi.org/10.1111/j.1537-2995.2010.02833-1.x.

Balbuena-Merle, R. *et al.* (2019) 'Fatal acute hemolytic transfusion reaction due to anti-B from a platelet apheresis unit stored in platelet additive solution', *Transfusion*, 59(6), pp. 1911–1915. Available at: https://doi.org/https://dx.doi.org/10.1111/trf.15240.

Barnes, A. (1973) 'Status of the Use of Universal Donor Blood Transfusion', *CRC Critical Reviews in Clinical Laboratory Sciences*, 4(2), pp. 147–160. Available at: https://doi.org/10.3109/10408367309151555.

Basu, D. *et al.* (2019) 'Incompatible crossmatch: First sign of a hemolytic transfusion reaction due to out-of-group platelet transfusion', *Asian Journal of Transfusion Science*, 13(1), pp. 57–59. Available at: https://doi.org/https://dx.doi.org/10.4103/ajts.AJTS_36_17.

Berséus, O. *et al.* (2013) 'Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma', *Transfusion*, 53(SUPPL. 1). Available at: https://doi.org/10.1111/trf.12045.

Blake, J.T. (2009) 'Editorial On the use of Operational Research for managing platelet inventory and ordering', *Transfusion*, 49, pp. 396–401. Available at: www.scienceofbetter.org.

Bolton-Maggs, P (Ed), Poles, D. et al (2018) *Serious Hazards of Transfusion (SHOT) Steering Group Chair Professor Steering Group (SG) during 2017*.

Boothe, G. *et al.* (1995) 'Acute hemolysis due to passively transfused high-titer anti-B causing spontaneous in vitro agglutination', *Immunohematology*, 11(2), pp. 43–45.

Brailsford, S.C. *et al.* (2017) 'An analysis of the academic literature on simulation and modelling in health care', *https://doi.org/10.1057/jos.2009.10*, 3(3), pp. 130–140. Available at: https://doi.org/10.1057/JOS.2009.10.

Branch, D.R. *et al.* (2018) 'ABO zygosity, but not secretor or Fc receptor status, is a significant risk factor for IVIG-Associated hemolysis', *Blood*, 131(7), pp. 830–835. Available at: https://doi.org/10.1182/blood-2017-07-796151.

Brohi, K. *et al.* (2003) 'Acute Traumatic Coagulopathy', *Journal of Trauma*, 54(6), pp. 1127–1130. Available at: https://doi.org/10.1097/01.TA.0000069184.82147.06.

Brohi, K., Gruen, R.L. and Holcomb, J.B. (2019) 'Why are bleeding trauma patients still dying?', *Intensive Care Medicine*, 45(5), pp. 709–711. Available at: https://doi.org/10.1007/s00134-019-05560-x.

Burman, D. *et al.* (1973) 'Acute anaphylaxis, pulmonary oedema, and intravascular haemolysis due to cryoprecipitate', *Archives of Disease in Childhood*, 48(6), pp. 483–485.

Campbell, H.E. *et al.* (2015) 'Quantifying the healthcare costs of treating severely bleeding major trauma patients: A national study for England', *Critical Care*, 19(1), pp. 1–14. Available at: https://doi.org/10.1186/s13054-015-0987-5.

Cardigan, R. *et al.* (2021) 'International Forum on Policies and Practice for Transfusion of ABO and RhD Non-Identical Platelets: Summary', *Vox Sanguinis*, (April), pp. 1–9. Available at: https://doi.org/10.1111/vox.13129.

Cardigan, R. *et al.* (2022) 'Estimating the risks of prehospital transfusion of D-positive whole blood to trauma patients who are bleeding in England', *Vox Sanguinis*, 117(5), pp. 701–707. Available at: https://doi.org/10.1111/vox.13249.

Carver, A. *et al.* (2018) 'What motivates men to donate blood? A systematic review of the evidence', *Vox sanguinis*, 113(3), pp. 205–219. Available at: https://doi.org/10.1111/VOX.12625.

Chhibber, V. *et al.* (2014) 'Is group A thawed plasma suitable as the first option for emergency release transfusion? (CME).', *Transfusion*, 54(7), pp. 1751–5; quiz 1750. Available at: https://doi.org/10.1111/trf.12537.

Chow, M.P. *et al.* (1991) 'Hemolysis after ABO-incompatible platelet transfusions.', *Zhonghua yi xue za zhi = Chinese medical journal; Free China ed*, 48(2), pp. 131–134.

Cole, E. *et al.* (2019) 'A Decade of Damage Control Resuscitation', *Annals of Surgery*, Publish Ah(Xx), pp. 1–6. Available at: https://doi.org/10.1097/sla.0000000000003657.

Cooling, L.L. *et al.* (2008) 'Anti-A and anti-B titers in pooled group O platelets are comparable to apheresis platelets', *Transfusion*, 48(10), pp. 2106–2113. Available at: https://doi.org/10.1111/j.1537-2995.2008.01814.x.

Cumming, M. *et al.* (2018) 'Acute hemolytic transfusion reactions in massachusetts, 2015-2017', *Transfusion*, 58 (Supple, p. 16A. Available at: https://doi.org/http://dx.doi.org/10.1111/trf.14903.

Daniel-Johnson, J. *et al.* (2008) 'Probiotic-associated high-titer anti-B in a group a platelet donor as a cause of severe hemolytic transfusion reactions', *Transfusion*, 48(2), pp. 260A-260A.

Daniel-Johnson, J. *et al.* (2009) 'Probiotic-associated high-titer anti-b in a group a platelet donor as a cause of severe hemolytic transfusion reactions', *Transfusion*, 49(9), pp. 1845–1849. Available at: https://doi.org/10.1111/j.1537-2995.2009.02208.x.

Daniels, G. and Bromilow, I. (eds) (2013) *Essential Guide to Blood Groups*. Oxford: John Wiley & Sons. Available at: https://doi.org/10.1002/9781118688915.

Dijk, N. van, Wal, J. van der and Sibinga, C.S. (2009) 'Blood platlet production: a novel approach for practical optimisation', *Transfusion*, 49(March), pp. 411–420. Available at: https://doi.org/10.1111/j.1537-2995.2008.01996.x.

Dillon, M., Oliveira, F. and Abbasi, B. (2017) 'A two-stage stochastic programming model for inventory management in the blood supply chain', *International Journal of Production Economics*, 187(May 2016), pp. 27–41. Available at: https://doi.org/10.1016/j.ijpe.2017.02.006.

Dosi, G. *et al.* (2020) 'RATIONAL HEURISTICS? EXPECTATIONS AND BEHAVIORS IN EVOLVING ECONOMIES WITH HETEROGENEOUS INTERACTING AGENTS', *Economic Inquiry*, 58(3), pp. 1487–1516. Available at: https://doi.org/10.1111/ECIN.12897.

Duguid, J.K., Minards, J. and Bolton-Maggs, P.H. (1999) 'Lesson of the week: incompatible plasma transfusions and haemolysis in children.', *BMJ (Clinical research ed.)*, 318(7177), pp. 176–177.

Dunbar, N.M. *et al.* (2017) 'Safety of the use of group A plasma in trauma: the STAT study', *Transfusion*, 57(8), pp. 1879–1884. Available at: https://doi.org/10.1111/trf.14139.

Ebert, R. v and Emerson Jr., C.P. (1946) 'A Clinical Study of Transfusion Reactions: The Hemolytic Effect of Group-O Blood and Pooled Plasma Containing Incompatible Isoagglutinins', *Journal of Clinical Investigation*, 25(4), pp. 627–638.

Ebert, R. V. and Emerson, C.P. (1946) 'a Clinical Study of Transfusion Reactions: the Hemolytic Effect of Group-O Blood and Pooled Plasma Containing Incompatible Isoagglutinins', *The Journal of clinical investigation*, 25(4), pp. 627–638. Available at: https://doi.org/10.1172/JCI101745.

Eldridge, S.M. *et al.* (2016) 'Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework'. Available at: https://doi.org/10.1371/journal.pone.0150205.

Estcourt, L.J. *et al.* (2017) 'Guidelines for the use of platelet transfusions', *British Journal of Haematology*, 176(3), pp. 365–394. Available at: https://doi.org/10.1111/bjh.14423.

Ferguson, D.J. (1988) 'Acute intravascular hemolysis after a platelet transfusion.', *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 138(6), pp. 523–524.

Filho, O.S.S. *et al.* (2013) 'Demand Forecasting for Blood Components Distribution of a Blood Supply Chain', in *6th IFAC Conference on Management and Control of Production and Logistics*. Available at: https://doi.org/10.3182/20130911-3-BR-3021.00092.

Flint, A.W. *et al.* (2020) 'Is Platelet Expiring Out of Date? A Systematic Review', *Transfusion Medicine Reviews*, 34(1), pp. 42–50. Available at: https://doi.org/10.1016/j.tmrv.2019.08.006.

Fontaine, M J *et al.* (2012) 'How we treat: risk mitigation for ABO-incompatible plasma in plateletpheresis products', *Transfusion*, 52(10), pp. 2081–2085. Available at: https://doi.org/https://dx.doi.org/10.1111/j.1537-2995.2012.03596.x.

Fontaine, Magali J. *et al.* (2012) 'How we treat: Risk mitigation for ABO-incompatible plasma in plateletpheresis products', *Transfusion*, 52(10), pp. 2081–2085. Available at: https://doi.org/10.1111/j.1537-2995.2012.03596.x.

Foukaneli, D. and et al (2018) *National Comparatie Audit of Blood Transfusion - 2018 survey of group O D negative red cell use*. Available at: https://hospital.blood.co.uk/audits/national-comparative-audit/medical-audits/2018-survey-of-group-o-d-negative-red-cell-use/.

Frith, D., Cohen, M.J. and Brohi, K. (2012) 'Animal models of trauma-induced coagulopathy', *Thrombosis Research*, 129(5), pp. 551–556. Available at: https://doi.org/10.1016/J.THROMRES.2011.11.053.

Fung, M.K., Downes, K.A. and Shulman, I.A. (2007) 'Transfusion of platelets containing ABO-incompatible plasma: a survey of 3156 North American laboratories.', *Archives of pathology & laboratory medicine*, 131(6), pp. 909–916. Available at: https://doi.org/10.1043/1543-2165(2007)131[909:TOPCAP]2.0.CO;2.

Gammon, R. *et al.* (2019) 'Acute hemolytic transfusion reaction due to prepooled platelets (PLTS): Very rare event', *Transfusion*, 59 (Supple, p. 196A. Available at: https://doi.org/http://dx.doi.org/10.1111/trf.15462.

Geneen, L.J. *et al.* (2022) 'The Difference in Potential Harms between Whole Blood and Component Blood Transfusion in major Bleeding: A Rapid Systematic Review and Meta-Analysis of RCTs', *Transfusion Medicine Reviews*, 36(1), pp. 7–15. Available at: https://doi.org/10.1016/j.tmrv.2021.10.003.

Gigerenzer, G. (2022) *One Data Point Can Beat Big Data*, *Behaviouralscientist.org*. Available at: https://behavioralscientist.org/gigerenzer-one-data-point-can-beat-big-data/ (Accessed: 16 September 2022).

Green, L. *et al.* (2017) 'Aetiology and outcome of massive transfusion in two large London teaching hospitals over a 3-year period (2012-2014)', *Transfusion Medicine*, 27(5), pp. 342–347. Available at: https://doi.org/10.1111/tme.12434.

Green, L. *et al.* (2018) 'British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding', *British Journal of Haematology*, 181(1), pp. 54–67. Available at: https://doi.org/http://dx.doi.org/10.1111/bjh.15167.

Guarente, J. *et al.* (2019) 'Dilution is not the solution: acute hemolytic transfusion reaction after ABO-incompatible pooled platelet transfusion', *Immunohematology*, 35(3), pp. 91–94.

Guarente, J. *et al.* (2020) 'Dilution is not the solution: Acute hemolytic transfusion reaction after ABO-incompatible pooled platelet transfusion', *Immunohematology*, 35(3), pp. 91–94. Available at: https://doi.org/http://dx.doi.org/10.21307/IMMUNOHEMATOLOGY-2020-020.

Hakkenbrak, N.A.G. *et al.* (2021) 'Preventable death in trauma: A systematic review on definition and classification', *Injury*, 52(10), pp. 2768–2777. Available at: https://doi.org/10.1016/J.INJURY.2021.07.040.

Harris, S.B. *et al.* (2007) 'Nonfatal intravascular hemolysis in a pediatric patient after transfusion of a platelet unit with high-titer anti-A', *Transfusion*, 47(8), pp. 1412–1417.

Harrold, I.M. *et al.* (2020) 'Hemolytic markers following the transfusion of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients', *Transfusion*, 60 Suppl 3, pp. S24–S30. Available at: https://doi.org/https://dx.doi.org/10.1111/trf.15629.

Hillier, F.S. and Lieberman, G.J. (2015) *Introduction to Operations Research*. 10th edn. 2 Penn Plaza, New York: McGraw-Hill Education.

Holcomb, J.B. (2007) 'Damage control resuscitation', *Journal of Trauma - Injury, Infection and Critical Care*, 62(6 SUPPL.), pp. 38–39. Available at: https://doi.org/10.1097/TA.0b013e3180654134.

Holcomb, J.B. *et al.* (2015) 'Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma', *JAMA*, 313(5), p. 471. Available at: https://doi.org/10.1001/jama.2015.12.

Hou, K. *et al.* (2019) 'Hemolytic transfusion reaction caused by ABO non-identical platelet transfusion-a case report', *Vox sanguinis*, 114(SUPPL, pp. 123–124. Available at: https://doi.org/https://dx.doi.org/10.1111/vox.12847.

Huish, S. *et al.* (2019) 'Effect of storage of plasma in the presence of red blood cells and platelets: re-evaluating the shelf life of whole blood.', *Transfusion*, 59(11), pp. 3468–3477. Available at: https://doi.org/10.1111/trf.15549.

Hunt, B.J. *et al.* (2015) 'A practical guideline for the haematological management of major haemorrhage', *British Journal of Haematology*, 170(6), pp. 788–803. Available at: https://doi.org/10.1111/bjh.13580.

Inaba, K. *et al.* (2010) 'Impact of ABO-identical vs ABO-compatible nonidentical plasma transfusion in trauma patients', *Archives of Surgery*, 145(9), pp. 899–906. Available at: https://doi.org/10.1001/archsurg.2010.175.

Karafin, M.S. *et al.* (2012) 'ABO antibody titers are not predictive of hemolytic reactions due to plasma-incompatible platelet transfusions.', *Transfusion*, 52(10), pp. 2087–2093. Available at: https://doi.org/10.1111/j.1537-2995.2012.03574.x.

Kauvar, D.S. and Wade, C.E. (2005) 'The epidemiology and modern management of traumatic hemorrhage: US and international perspectives', *Critical Care*, 9(SUPPL. 5), pp. 1–9. Available at: https://doi.org/10.1186/cc3779.

Kumlien, G. *et al.* (2007) 'Comparing the Tube and Gel Techniques for ABO Antibody Titration, as Performed in Three European Centers', *Transplantation*, 84(Supplement), pp. S17–S19. Available at: https://doi.org/10.1097/01.tp.0000296019.85986.af.

Kundrapu, S. *et al.* (2017) 'Possible immune-mediated hemolysis due to platelet transfusion masked by underlying hemolysis in a patient with blast crisis', *Transfusion*, 57 (Supple, pp. 180A-181A. Available at: https://doi.org/http://dx.doi.org/10.1111/trf.14286.

Larsson, L.G., Welsh, V.J. and Ladd, D.J. (2000) 'Acute intravascular hemolysis secondaryto out-of-group platelet transfusion', *Transfusion*, 40(8), pp. 902–906.

Leech, C. and Clarke, E. (2022) 'Pre-hospital blood products and calcium replacement protocols in UK critical care services: A survey of current practice', *Resuscitation Plus*, 11, p. 100282. Available at: https://doi.org/10.1016/J.RESPLU.2022.100282.

Losada, E. *et al.* (2010) 'Operational impact of a policy requiring avoidance of group O apheresis platelets for group A patients', *Transfusion*, 2), p. 161A. Available at: https://doi.org/http://dx.doi.org/10.1111/j.1537-2995.2010.02833-1.x.

Lozano, M. *et al.* (2010) 'Practices associated with ABO-incompatible platelet transfusions: a BEST Collaborative international survey', *Transfusion*, 50(8), pp. 1743–1748. Available at: https://doi.org/https://dx.doi.org/10.1111/j.1537-2995.2010.02642.x.

Maegele, M. *et al.* (2007) 'Incidence and Outcome of Traumatic Brain Injury in an Urban Area in Western Europe over 10 Years', *European Surgical Research*, 39(6), pp. 372–379. Available at: https://doi.org/10.1159/000107097.

Mair, B. and Benson, K. (1998) 'Evaluation of changes in hemoglobin levels associated with ABO-incompatible plasma in apheresis platelets.', *Transfusion*, 38(1), pp. 51–55.

Malvik, N. *et al.* (2020) 'ABO-incompatible platelets are associated with increased transfusion reaction rates', *Transfusion*, 60(2), pp. 285–293. Available at: https://doi.org/https://dx.doi.org/10.1111/trf.15655.

McLeod, B.C. *et al.* (1982a) 'Haemolytic transfusion reaction due to ABO incompatible plasma in a platelet concentrate.', *Scandinavian journal of haematology*, 28(3), pp. 193–196.

McLeod, B.C. *et al.* (1982b) 'Haemolytic transfusion reaction due to ABO incompatible plasma in a platelet concentrate', *Scandinavian Journal of Haematology*, 28(3), pp. 193–196.

McManigal, S. and Sims, K.L. (1999) 'Intravascular hemolysis secondary to ABO incompatible platelet products. An underrecognized transfusion reaction', *American Journal of Clinical Pathology*, 111(2), pp. 202–206.

Milkins, C. *et al.* (2017) 'Risk and impact of haemolytic transfusion reaction due to passive ABO antibodies as evidenced by serious hazards of transfusion data', *British Journal of Haematology*, 176 (Suppl, pp. 21–22. Available at: https://doi.org/http://dx.doi.org/10.1111/bjh.14613.

Moher, D. *et al.* (2009) 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement', *Annals of Internal Medicine*, 151(4), pp. 264–269. Available at: https://doi.org/10.7326/0003-4819-151-4-200908180-00135.

Moinuddin, I.A., Millward, P. and Fletcher, C.H. (2019) 'Acute Intravascular Hemolysis Following an ABO Non-Identical Platelet Transfusion: A Case Report and Literature Review', *The American Journal of Case Reports*, 20, pp. 1075–1079. Available at: https://doi.org/https://dx.doi.org/10.12659/AJCR.915521.

Moore, E.E. *et al.* (2021) 'Trauma-induced coagulopathy', *Nature Reviews Disease Primers 2021 7:1*, 7(1), pp. 1–23. Available at: https://doi.org/10.1038/s41572-021-00264-3.

Moore, H.B. *et al.* (2018a) 'Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial', *Lancet (London, England)*, 392(10144), p. 283. Available at: https://doi.org/10.1016/S0140-6736(18)31553-8.

Moore, H.B. *et al.* (2018b) 'Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial', *The Lancet*, 392(10144), pp. 283–291. Available at: https://doi.org/10.1016/S0140-6736(18)31553-8.

Murphy, M.F. *et al.* (1990) 'Acute haemolysis after ABO-incompatible platelet transfusions', *Lancet*, 335(8695), pp. 974–975.

Nahirniak, S. *et al.* (2015) 'Guidance on Platelet Transfusion for Patients With Hypoproliferative Thrombocytopenia', *Transfusion Medicine Reviews*, 29(1), pp. 3–13. Available at: https://doi.org/10.1016/j.tmrv.2014.11.004.

Nandi, Anita K, Roberts, D.J. and Nandi, Asoke K (2020) 'Blood donors and blood collection', *Transfusion*, 60(March), pp. 535–543. Available at: https://doi.org/10.1111/trf.15705.

New, H. V *et al.* (2016) 'Guidelines on transfusion for fetuses, neonates and older children', *British Journal of Haematology*, 175(5), pp. 784–828. Available at: https://doi.org/10.1111/bjh.14233.

NHS Institute for Innovation and Improvement (2005) *Improvement Leaders' Guide Process mapping, analysis and redesign General improvement skills*. Coventry. Available at: www.institute.nhs.uk/improvementguides (Accessed: 14 August 2022).

Osorio, A.F., Brailsford, S.C. and Smith, H.K. (2015) 'A structured review of quantitative models in the blood supply chain: A taxonomic framework for decision-making', *International Journal of Production Research*, 53(24), pp. 7191–7212. Available at: https://doi.org/10.1080/00207543.2015.1005766.

Padilla-Garrido, N. *et al.* (2021) 'Motivators, barriers and communication channels for blood donation in relation to students at a university in Spain', *Transfusion and Apheresis Science*, 60(6). Available at: https://doi.org/10.1016/J.TRANSCI.2021.103270.

Page, M.J. *et al.* (2021) 'PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews', *BMJ*, 372, p. n160. Available at: https://doi.org/10.1136/bmj.n160.

Pandey, P. *et al.* (2017) 'Potential impact of complement regulator deficiencies on hemolytic reactions due to minor ABO-mismatched transfusions', *Blood Advances*, 1(23), pp. 1977–1982. Available at: https://doi.org/https://dx.doi.org/10.1182/bloodadvances.2017008805.

Pasion, J.O. *et al.* (2021) 'When O Bites Back: Unrecognized Acute Hemolytic Reaction from Out-of-Group HLA-Compatible Platelet Transfusion', *Annals of clinical and laboratory science*, 51(2), pp. 267–270.

Peedin, A.R. *et al.* (2018) 'Dilution is not the solution: Acute hemolytic transfusion reaction after abo-incompatible prepooled platelet transfusion', *Transfusion*, 58 (Supple, p. 114A. Available at: https://doi.org/http://dx.doi.org/10.1111/trf.14903.

Pereira, A. (2004) 'Performance of time-series methods in forecasting the demand for red blood cell transfusion', *Transfusion*, 44(May), pp. 739–746.

Pierce, R.N., Reich, L.M. and Mayer, K. (1985) 'Hemolysis following platelet transfusions from ABO-incompatible donors.', *Transfusion*, 25(1), pp. 60–62.

Piskorski, A. and Sweeney, J. (2014) 'Intravascular hemolysis from prepooled platelets', *Transfusion*, 2), p. 142A. Available at: https://doi.org/http://dx.doi.org/10.1111/trf.12845.

Provost, L.P. and Murray, S.K. (2011) *The health care data guide: learning for data improvement*. San Francisco: Jossey Bass.

Qin, Y. *et al.* (2011) 'The newsvendor problem: Review and directions for future research', *European Journal of Operational Research*, 213(2), pp. 361–374. Available at: https://doi.org/10.1016/j.ejor.2010.11.024.

Rehn, M. *et al.* (2019) 'EFFECT OF PREHOSPITAL RED BLOOD CELL TRANSFUSION ON MORTALITY AND TIME OF DEATH IN CIVILIAN TRAUMA PATIENTS', 51(3), pp. 284–288. Available at: https://doi.org/10.1097/SHK.0000000000001166.

Reis, M.D. and Coovadia, A.S. (1989) 'Transfusion of ABO-incompatible platelets causing severe haemolytic reaction', *Clinical & Laboratory Haematology*, 11(3), pp. 237–240.

Rosen, D. and Indrikovs, A. (2008) 'Acute immune hemolysis in an adult due to transfusion of ABO-incompatible platelets', *Transfusion*, 48(2), pp. 75A-75A.

Rother, M. (2010) *Toyota Kata: managing people for improvement, adaptiveness and superior results.* New York: McGraw-Hill.

Rother, M. (2018) *Toyota Kata practice guide.* New York: McGraw-Hill.

Ruby, K.N., Harm, S.K. and Dunbar, N.M. (2021) 'Risk of ABO-Incompatible Plasma From Non-ABO-Identical Components', *Transfusion medicine reviews*, 35(4), pp. 118–122. Available at: https://doi.org/https://dx.doi.org/10.1016/j.tmrv.2021.06.006.

Sadani, D.T. *et al.* (2006a) 'Repeat ABO-incompatible platelet transfusions leading to haemolytic transfusion reaction.', *Transfusion medicine (Oxford, England)*, 16(5), pp. 375–379. Available at: https://doi.org/10.1111/j.1365-3148.2006.00684.x.

Sadani, D.T. *et al.* (2006b) 'Repeat ABO-incompatible platelet transfusions leading to haemolytic transfusion reaction', *Transfusion Medicine*, 16(5), pp. 375–379.

Sapatnekar, S. *et al.* (2005) 'Acute hemolytic transfusion reaction in a pediatric patient following transfusion of apheresis platelets', *Journal of Clinical Apheresis*, 20(4), pp. 225–229. Available at: https://doi.org/10.1002/jca.20072.

Sauer-Heilbom, A. *et al.* (2002) 'Passive antibody, aggressive hemolysis: An ABO-incompatible platelet transfusion', *Transfusion*, 42(9), pp. 112S-112S.

Seheult, J.; Triulzi, D. J.; Alarcon, L. H.; Sperry, J. L.; Murdock, A.; Yazer, M.H. (2016) 'ABO antibody-mediated hemolysis is not detectable following cold-stored uncrossmatched whole blood transfusion in civilian trauma patients', *Transfusion*, 56(Supplement S4), p. 16A. Available at: https://doi.org/10.1017/CBO9781107415324.004.

Shachner, T.R. and Clark, C.T. (2018) 'Acute Hemolytic Transfusion Reaction in Group B Recipient Associated with Group A Apheresis Platelet Donor: Case Report and Literature Review', *Case Reports in Medicine*, 2018, p. 8259531. Available at: https://doi.org/https://dx.doi.org/10.1155/2018/8259531.

Shih, H. and Rajendran, S. (2019) 'Comparison of Time Series Methods and Machine Learning Algorithms for Forecasting Taiwan Blood Services Foundation ' s Blood Supply', *Journal of Healthcare Engineering*, 2019, pp. 1–6.

Simonetti, A. *et al.* (2014) 'A stock-and-flow simulation model of the US blood supply', *Transfusion*, 54(March), pp. 828–838. Available at: https://doi.org/10.1111/trf.12392.

Sperry, J.L. *et al.* (2018) 'Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock', *New England Journal of Medicine*, 379(4), pp. 315–326. Available at: https://doi.org/10.1056/NEJMoa1802345.

Stanworth, S.J. *et al.* (2015) 'Platelet refractoriness - practical approaches and ongoing dilemmas in patient management', *British Journal of Haematology*, 171(3), pp. 297–305. Available at: https://doi.org/http://dx.doi.org/10.1111/bjh.13597.

Stanworth, S.J. *et al.* (2022) 'A guideline for the haematological management of major haemorrhage : a British Society for Haematology Guideline', (May), pp. 1–14. Available at: https://doi.org/10.1111/bjh.18275.

Storch, E. and Eder, A. (2021) 'Abo-incompatible platelet and plasma transfusion-related fatalities reported to the FDA, 2011-2020', *Transfusion*, 61(SUPPL 3, pp. 218A-219A. Available at: https://doi.org/http://dx.doi.org/10.1111/trf.16623.

Swain, F. *et al.* (2019) 'Acute haemolytic reaction secondary to an ABO minor mismatched platelet transfusion from a group A blood donor', *Transfusion Medicine*, 29(2), pp. 133–135. Available at: https://doi.org/https://dx.doi.org/10.1111/tme.12591.

The Australian and New Zealand Society of Blood Transfusion (2020) *Guidelines for Transfusion and Immunohaematology Laboratory Practice*. First Edit. Australian and New Zealand Society of Blood Transfusion Ltd.

Tisherman, S.A. *et al.* (2015) 'Detailed Description of all Deaths in Both the Shock and Traumatic Brain Injury Hypertonic Saline Trials of the Resuscitation Outcomes Consortium', *Annals of surgery*, 261(3), p. 586. Available at: https://doi.org/10.1097/SLA.0000000000000837.

Tricco, A.C. *et al.* (2018) 'PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation', *Annals of Internal Medicine*, 169(7), pp. 467–473. Available at: https://doi.org/10.7326/M18-0850.

Valbonesi, M. *et al.* (2000) 'Acute intravascular hemolysis in two patients transfused with dry-platelet units obtained from the same ABO incompatible donor.', *The International journal of artificial organs*, 23(9), pp. 642–646.

Weisberg, S.P. *et al.* (2018) 'PAS-C platelets contain less plasma protein, lower anti-A and anti-B titers, and decreased HLA antibody specificities compared to plasma platelets', *Transfusion*, 58(4), pp. 891–895. Available at: https://doi.org/https://dx.doi.org/10.1111/trf.14523.

Williamson, L.M. *et al.* (1999) 'Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports', *BMJ*, 319(7201), pp. 16–19.

Win, N. (2012) 'High Titre Anti-A / B Testing of Donors within NHS Blood and Transplant (NHSBT) High Titre Anti-A / B Testing of Donors within NHS Blood and Transplant (NHSBT)', pp. 1–13.

Wood, M., Price, W.R. and Childers, D. (1967) 'A hidden danger of pooled plasma', *American Journal of Surgery*, 114(5), pp. 629–635.

Yazer, M.H. *et al.* (2016) 'Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients', *The Journal of Trauma and Acute Care Surgery*, 81(1), pp. 21–26. Available at: https://doi.org/https://dx.doi.org/10.1097/TA.0000000000001100.

Yazer, Mark H. *et al.* (2018) 'How do I implement a whole blood program for massively bleeding patients?', *Transfusion*, 58(3), pp. 622–628. Available at: https://doi.org/10.1111/trf.14474.

Yazer, Mark H *et al.* (2018) 'How do I implement a whole blood program for massively bleeding patients?', *Transfusion*, 58(3), pp. 622–628. Available at: https://doi.org/10.1111/trf.14474.

Yazer, M. H. *et al.* (2018) 'Vox Sanguinis International Forum on the use of prehospital blood products and pharmaceuticals in the treatment of patients with traumatic haemorrhage', *Vox Sanguinis*, 113(7), pp. 701–706. Available at: https://doi.org/10.1111/VOX.12678.

Yazer, M.H., Cap, A.P. and Spinella, P.C. (2018) 'Raising the standards on whole blood', *The Journal of Trauma and Acute Care Surgery*, 84(6S Suppl 1), pp. S14–S17. Available at: https://doi.org/https://dx.doi.org/10.1097/TA.0000000000001778.

Yazer, M.H. and Spinella, P.C. (2020) 'An international survey on the use of low titer group O whole blood for the resuscitation of civilian trauma patients in 2020', *Transfusion*, 60(S3), pp. S176–S179. Available at: https://doi.org/10.1111/trf.15601.

Zubair, A. *et al.* (2004) 'Severe acute hemolytic transfusion reaction following ABO-mismatched platelet transfusion: Should ABO-mismatched platelet transfusion policy be evaluated', *Blood*, 104(11), pp. 110B-110B.

Chapter 9 Appendices

9.1 Appendix 1 :Preferred Reporting Items for Systematic Reviews (PRISMA ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

9.2 Appendix 2: Search Strategy for the scoping review

The following databases were searched on 11.4.22 for all types of studies:

- MEDLINE (Ovid, 1946 to present)
- PubMed (pre-MEDLINE publications only)
- Embase (Ovid, 1974 to present)
- CENTRAL (The Cochrane Central Register of Controlled Trials) & CDSR, *The Cochrane Library* (Wiley interface, 2022, Issues A 3 & 4 respectively)
- Transfusion Evidence Library (Evidentia Publishing, 1950 to present)
- Web of Science (Thomson Reuters, 1990 to present)
- Scopus (Elsevier, 1970 to present)
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP)

SEARCH STRATEGIES

MEDLINE (Ovid)

1. Blood Transfusion/
2. Blood Component Transfusion/
3. Platelet Transfusion/
4. Plateletpheresis/
5. *Plasma/
6. Plasma/ and (transfus* or blood component* or blood product*).mp.
7. (FFP* or fresh plasma or frozen plasma or plasma-PLT* or thawed plasma or lyophilised plasma or freeze dried plasma or plasma-containing or plasma-rich or cryoprecipitate or whole blood).tw,kf.
8. ((plasma or platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor* or random donor*)).tw,kf.
9. ((plasma or platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf.
10. (thrombo?ytopheres* or plateletpheres* or (plasma adj3 platelet*)).tw,kf.
11. (group A plasma or group O plasma or group B plasma or AB plasma or "A/B plasma")).tw,kf.
12. ((group A or group O or group B or group AB or "group A/B") adj6 (donor* or plasma*)).tw,kf.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Blood Group Incompatibility/
15. ABO Blood-Group System/
16. ((ABO or blood group* or group O or group A* or group B) adj5 (compatib* or incompatib* or noncompatib* or match* or typing or unmatch* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or mismatch* or mis-match* or identical or nonidentical or unidentified or unknown)).tw,kf.
17. (ABO group-specific or group match* or group crossmatch* or group cross-match* or out-of-group*).tw,kf.

18. ((anti-A or anti-B or anti-AB or "anti-A,B" or "anti-A/B") adj5 (titer* or titre*)).tw,kf.

19. 14 or 15 or 16 or 17 or 18
20. Hemolysis/
21. exp Transfusion Reaction/
22. Blood Transfusion/ae or Blood Component Transfusion/ae or Platelet Transfusion/ae
23. (hemoly* or haemoly* or (transfus* adj3 reaction*)).tw,kf.
24. 20 or 21 or 22 or 23
25. 13 and 19 and 24
26. (((ABO or blood group* or group O or group A* or group B) and (compatib* or incompatib* or noncompatib* or match* or unmatch* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or mismatch* or mis-match* or identical or nonidentical or "out-of-group" or unidentified or unknown) and (transfus* or blood component* or blood product* or plasma* or FFP* or cryoprecipitate or platelet* or whole blood)) not transplant*).ti.
27. 25 or 26

PubMed

#1 (FFP* OR "fresh plasma" OR "frozen plasma" OR plasma-PLT* OR "thawed plasma" OR "lyophilised plasma" OR "freeze dried plasma" OR "plasma-containing" OR "plasma-rich" OR cryoprecipitate OR "whole blood")
#2 ((plasma OR platelet* OR thrombocyte*) AND (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product* OR component* OR concentrate* OR apheres* OR pooled OR single donor* OR random donor*))
#3 ((plasma OR platelet* OR thrombocyte*) AND (protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization))
#4 (thrombocytopheres* OR thrombocytapheresis OR plateletpheres* OR (plasma AND platelet*))
#5 ("group A plasma" OR "group O plasma" OR "blood group B plasma" OR "AB plasma" OR "A/B plasma")
#6 ((group A OR group O OR group B OR group AB OR "group A/B") AND (donor* OR plasma*))
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 ((ABO OR "blood group" OR "blood groups" OR "group O" OR "group A" OR "group AB" OR "group B") AND (compatib* OR incompatib* OR noncompatib* OR match* OR unmatch* OR mismatch* OR mis-match* OR crossmatch* OR cross-match* OR uncrossmatch* OR uncross-match* OR identical OR nonidentical OR "out-of-group" OR unidentified OR unknown))
#9 (ABO group-specific OR group match* OR group crossmatch* OR group cross-match* OR out-of-group*)
#10 ((anti-A OR anti-B OR anti-AB OR "anti-A,B" OR "anti-A/B") AND (titer* OR titre*))
#11 #8 OR #9 OR #10

#12 (hemoly* OR haemoly* OR (transfus* AND reaction*))
#13 #7 AND #11 AND #12
#14 medline[sb]
#15 #13 NOT #14

Embase (Ovid)
1. Blood Transfusion/
2. Blood Component Therapy/
3. Plasma Transfusion/
4. Thrombocyte Transfusion/
5. Thrombocytopheresis/
6. *Plasma/
7. Plasma/ and (transfus* or blood component* or blood product*).mp.
8. (FFP* or fresh plasma or frozen plasma or plasma-PLT* or thawed plasma or lyophilised plasma or freeze dried plasma or plasma-containing or plasma-rich or cryoprecipitate or whole blood).tw,kw.
9. ((plasma or platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor* or random donor*)).tw,kw.
10. ((plasma or platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kw.
11. (thrombo?ytopheres* or plateletpheres* or (plasma adj3 platelet*)).tw,kw.
12. (group A plasma or group O plasma or group B plasma or AB plasma or "A/B plasma")).tw,kw.
13. ((group A or group O or group B or group AB or "group A/B") adj6 (donor* or plasma*)).tw,kw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Blood Group Incompatibility/ or Blood Group ABO Incompatibility/
16. Blood Group ABO System/
17. ((ABO or blood group* or group O or group A* or group B) adj5 (compatib* or incompatib* or noncompatib* or match* or unmatch* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or mismatch* or mis-match* or identical or nonidentical or unidentified or unknown)).tw,kw.
18. (ABO group-specific or group match* or group crossmatch* or group cross-match* or out-of-group*).tw,kw.
19. ((anti-A or anti-B or anti-AB or "anti-A,B" or "anti-A/B") adj5 (titer* or titre*)).tw,kw.
20. 15 or 16 or 17 or 18 or 19
21. Hemolysis/
22. exp Blood Transfusion Reaction/
23. Blood Transfusion/ae or Blood Component Therapy/ae or Thrombocyte Transfusion/ae
24. (hemoly* or haemoly* or (transfus* adj3 reaction*)).tw,kw.
25. 21 or 22 or 23 or 24
26. 14 and 20 and 25

27. (((ABO or blood group* or group O or group A* or group B) and (compatib* or incompatib* or noncompatib* or match* or unmatch* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or mismatch* or mis-match* or identical or nonidentical or "out-of-group" or unidentified or unknown) and (transfus* or blood component* or blood product* or plasma* or FFP* or cryoprecipitate or platelet* or whole blood)) not transplant*).ti.
28. 26 or 27

CENTRAL & CDSR

#1 MeSH descriptor: [Blood Transfusion] this term only
#2 MeSH descriptor: [Blood Component Transfusion] this term only
#3 MeSH descriptor: [Platelet Transfusion] this term only
#4 MeSH descriptor: [Plateletpheresis] this term only
#5 MeSH descriptor: [Plasma] this term only
#6 (FFP* or "fresh plasma" or "frozen plasma" or plasma-PLT* or "thawed plasma" or "lyophilised plasma" or "freeze dried plasma" or "plasma-containing" or "plasma-rich" or cryoprecipitate or "whole blood")
#7 ((plasma or platelet* or thrombocyte*) NEAR/5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor* or random donor*))
#8 ((plasma or platelet* or thrombocyte*) NEAR/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation))
#9 (thrombo?ytopheres* or plateletpheres* or (plasma NEAR/3 platelet*))
#10 ("group A plasma" or "group O plasma" or "blood group B plasma" or "AB plasma" or "A/B plasma")
#11 ((group A or group O or group B or group AB or "group A/B") NEAR/6 (donor* or plasma*))
#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 or #11
#13 MeSH descriptor: [Blood Group Incompatibility] this term only
#14 MeSH descriptor: [ABO Blood-Group System] this term only
#15 ((ABO or "blood group" or "blood groups" or "group O" or "group A" or "group AB" or "group B") NEAR/5 (compatib* or incompatib* or noncompatib* or match* or unmatch* or mismatch* or mis-match* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or identical or nonidentical or "out-of-group" or unidentified or unknown))
#16 (ABO group-specific or group match* or group crossmatch* or group cross-match* or out-of-group*)
#17 ((anti-A or anti-B or anti-AB or "anti-A,B" or "anti-A/B") NEAR/5 (titer* or titre*))
#18 #13 OR #14 OR #15 OR #16 OR #17
#19 MeSH descriptor: [Hemolysis] this term only
#20 MeSH descriptor: [Transfusion Reaction] this term only
#21 MeSH descriptor: [Blood Transfusion] this term only
#22 MeSH descriptor: [Blood Component Transfusion] this term only and with qualifier(s): [adverse effects - AE]

#23 MeSH descriptor: [Platelet Transfusion] this term only and with qualifier(s): [adverse effects - AE]
#24 (hemoly* or haemoly* or (transfus* NEAR/3 reaction*))
#25 #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26 #12 AND #18 AND #25
#27 (((ABO or "blood group" or "blood groups" or "group O" or "group A" or "group AB" or "group B") and (compatib* or incompatib* or noncompatib* or match* or unmatch* or mismatch* or mis-match* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or identical or nonidentical or "out-of-group" or unidentified or unknown) and (transfus* or blood component* or blood product* or plasma* or FFP* or cryoprecipitate or platelet* or whole blood)) NOT transplant*):ti
#28 #26 OR #27

TRANSFUSION EVIDENCE LIBRARY

Subject Area: Blood Components / Plasma/FFP OR Cryoprecipitate OR Platelets AND title:(hemolysis OR haemolysis OR hemolytic OR haemolytic OR reaction OR compatible OR incompatible OR unmatched OR mismatched OR crossmatched OR uncrossmatched) OR article_abstract:(hemolysis OR haemolysis OR hemolytic OR haemolytic OR reaction OR compatible OR incompatible OR unmatched OR mismatched OR crossmatched OR uncrossmatched)
OR
Subject Area: Clinical Practice / Adverse Effects of Transfusion AND title:(hemolysis OR haemolysis OR hemolytic OR haemolytic OR reaction OR compatible OR incompatible OR unmatched OR mismatched OR crossmatched OR uncrossmatched) OR article_abstract:(hemolysis OR haemolysis OR hemolytic OR haemolytic OR reaction OR compatible OR incompatible OR unmatched OR mismatched OR crossmatched OR uncrossmatched)

WEB OF SCIENCE

1 TS=(FFP* or "fresh plasma" or "frozen plasma" or "thawed plasma" or "lyophilised plasma" or "freeze dried plasma" or "plasma-containing" or "plasma-rich" or cryoprecipitate or "whole blood")
2 TS=((plasma or platelet* or thrombocyte*) AND (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor))
3 TS=((plasma OR platelet* OR thrombocyte*) AND (protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization))
4 TS=(thrombo?ytopheres* or plateletpheres* OR (plasma* AND platelet*))
5 TS=("group A plasma" or "group O plasma" or "blood group B plasma" or "AB plasma" or "A/B plasma")
6 TS=((group A or group O or group B or group AB or "group A/B") AND (donor* or plasma*))
7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
8 TS=((ABO or "blood group" or "blood groups" or "group O" or "group A" or "group

AB" or "group B") AND (compatib* or incompatib* or noncompatib* or match* or unmatch* or mismatch* or mis-match* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or identical or nonidentical or "out-of-group" or unidentified or unknown)) OR TS=((anti-A or anti-B or anti-AB or "anti-A,B" or "anti-A/B") AND (titer* or titre*))
9 TS=(hemoly* or haemoly* or (transfus* AND reaction*))
#10 #7 AND #8 AND #9
11 TI=(((ABO or "blood group" or "blood groups" or "group O" or "group A" or "group AB" or "group B") AND (compatib* or incompatib* or noncompatib* or match* or unmatch* or mismatch* or mis-match* or crossmatch* or cross-match* or uncrossmatch* or uncross-match* or identical or nonidentical or "out-of-group" or unidentified or unknown) AND (transfus* or blood component* or blood product* or plasma* or FFP* or cryoprecipitate or platelet* or "whole blood")) NOT transplant*)
12 #10 OR #11

SCOPUS

1. TITLE-ABS-KEY ((FFP* OR "fresh plasma" OR "frozen plasma" OR "thawed plasma" OR "lyophilised plasma" OR "freeze dried plasma" OR "plasma-containing" OR "plasma-rich" OR cryoprecipitate OR "whole blood"))
2. TITLE-ABS-KEY (((plasma OR platelet* OR thrombocyte*) W/5 (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product* OR component* OR concentrate* OR apheres* OR pooled OR "single donor" OR "single donors" OR "random donor" OR "random donors")))
3. TITLE-ABS-KEY (((plasma OR platelet* OR thrombocyte*) W/5 (protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization)))
4. TITLE-ABS-KEY ((thrombo?ytopheres* OR plateletpheres* OR (plasma* W/3 platelet*)))
5. TITLE-ABS-KEY (("group A plasma" OR "group O plasma" OR "group B plasma" OR "AB plasma" OR "A/B plasma"))
6. TITLE-ABS-KEY ((("group A" or "group O" or "group B" or "group AB" or "group A/B") W/6 (donor* or plasma*)))
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. TITLE-ABS-KEY (((ABO OR "blood group" OR "blood groups" OR "group O" OR "group A" OR "group AB" OR "group B") W/5 (compatib* OR incompatib* OR noncompatib* OR match* OR unmatch* OR mismatch* OR mis-match* OR crossmatch* OR cross-match* OR uncrossmatch*)))
9. TITLE-ABS-KEY (((ABO OR "blood group" OR "blood groups" OR "group O" OR "group A" OR "group AB" OR "group B") W/5 (uncross-match* OR identical OR nonidentical OR "out-of-group" OR unidentified OR unknown)))
10. TITLE-ABS-KEY ((ABO group-specific or group match* or group crossmatch* or group cross-match* or out-of-group*))
11. TITLE-ABS-KEY (((anti-A or anti-B or anti-AB or "anti-A,B" or "anti-A/B") W/5 (titer* or titre*)))
12. #8 OR #9 OR #10 OR #11
13. TITLE-ABS-KEY ((hemoly* OR haemoly* OR (transfus* W/5 reaction*)))
14. #7 AND #10 AND #11

15. TITLE (((ABO OR "blood group" OR "blood groups" OR "group O" OR "group A" OR "group mab" OR "group B") AND (compatib* OR incompatib* OR noncompatib* OR match* OR unmatch* OR mismatch* OR mis-match* OR crossmatch* OR cross-match* OR uncrossmatch* OR uncross-match* OR identical OR nonidentical OR "out-off-group" OR unidentified OR unknown) AND (transfus* OR "blood component" OR "blood components" OR "blood product" OR "blood products" OR plasma* OR FFP* OR cryoprecipitate OR platelet* OR "whole blood")))
16. #12 OR #13

ClinicalTrials.gov

Title: ABO OR blood group OR group O OR group A OR group AB OR group B OR hemolysis OR haemolysis OR hemolytic OR haemolytic OR transfusion reaction
Intervention: transfusion OR blood component OR blood product OR plasma OR FFP OR cryoprecipitate OR platelet OR platelets OR whole blood
Other Terms: compatible OR incompatible OR noncompatible OR matched OR unmatched OR mismatched OR mis-matched OR crossmatched OR cross-matched OR uncrossmatched OR uncross-matched OR identical OR nonidentical OR out-of-group OR unidentified OR unknown
OR
Intervention: transfusion OR blood component OR blood product OR plasma OR FFP OR cryoprecipitate OR platelet OR platelets OR whole blood
Other Terms: compatible OR incompatible OR noncompatible OR matched OR unmatched OR mismatched OR mis-matched OR crossmatched OR cross-matched OR uncrossmatched OR uncross-matched OR identical OR nonidentical OR out-of-group OR unidentified OR unknown
Outcomes: hemolysis OR haemolysis OR hemolytic OR haemolytic OR transfusion reaction

WHO ICTRP

Title: ABO compatible OR ABO incompatible OR ABO noncompatible OR matched OR unmatched OR mismatched OR mis-matched OR crossmatched OR cross-matched OR uncrossmatched OR uncross-matched OR out-of-group OR hemolysis OR haemolysis OR hemolytic OR haemolytic OR transfusion reaction
Intervention: transfusion OR blood component OR blood product OR plasma OR FFP OR cryoprecipitate OR platelet OR platelets OR whole blood
Recruitment Status: ALL
OR
Title: transfusion OR blood OR plasma OR FFP OR cryoprecipitate OR platelet OR platelets
Intervention: ABO compatible OR ABO incompatible OR ABO noncompatible OR matched OR unmatched OR mismatched OR mis-matched OR crossmatched OR cross-matched OR uncrossmatched OR uncross-matched OR out-of-group OR hemolysis OR haemolysis OR hemolytic OR haemolytic OR transfusion reaction
Recruitment Status: ALL

9.3 Appendix 3: Delivery schedule for LD-RCP during the observational study

			Bank Holiday Monday			Bank Holiday Monday
		Option 1 Cover	**Cover**	**Option 2 Cover + Plus Demand**	**My Logic**	**Option 2 Cover + Plus Demand**
Bled Day	Delivery Day	Units to send	Units to send	Units to send		Units to send
Fri	Mon	0	0	0	Already Sent Sunday	0
Sat/Sun	Tue	2	2	2	Only able to ensure 2 from weekend Collection. Under review if session mix is changed	2
Mon	Wed	2	2	4	To prime system for demand, plus replace 4 from Friday bled (week before) that will be day 10 .i.e. into A/E supply	2
Tue	Thu	2	2	2		4
Wed	Fri	2	2	2	Prime for weekend demand	2
Thu	Sat	2	2	2		2
Fri	Sun	2	2	4	Sending 2 days supply as no fresher units	4
	Weekly	12	12	16		16
	Annually	624	624	832		832

9.4 Appendix 4: Making every drop count: reducing wastage of a novel blood component for transfusion of trauma patients

Open access Quality improvement report

BMJ Open Quality

Making every drop count: reducing wastage of a novel blood component for transfusion of trauma patients

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To cite: McCullagh J, Proudlove N, Tucker H, *et al*. Making every drop count: reducing wastage of a novel blood component for transfusion of trauma patients. *BMJ Open Quality* 2021;**10**:e001396. doi:10.1136/bmjoq-2021-001396

Received 8 February 2021
Accepted 19 June 2021

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ABSTRACT

Recent research demonstrates that transfusing whole blood (WB=red blood cells (RBC)+plasma+platelets) rather than just RBC (which is current National Health Service (NHS) practice) may improve outcomes for major trauma patients. As part of a programme to investigate provision of WB, NHS Blood and Transplant undertook a 2-year feasibility study to supply the Royal London Hospital (RLH) with (group O negative, 'O neg') leucodepleted red cell and plasma (LD-RCP) for transfusion of trauma patients with major haemorrhage in prehospital settings.

Incidents requiring such prehospital transfusion occur randomly, with very high variation. Availability is critical, but O neg LD-RCP is a scarce resource and has a limited shelf life (14 days) after which it must be disposed of. The consequences of wastage are the opportunity cost of loss of overall treatment capacity across the NHS and reputational damage.

The context was this feasibility study, set up to assess deliverability to RLH and subsequent wastage levels. Within this, we conducted a quality improvement project, which aimed to reduce the wastage of LD-RCP to no more than 8% (ie, 1 of the 12 units delivered per week).

Over this 2-year period, we reduced wastage from a weekly average of 70%–27%. This was achieved over four improvement cycles. The largest improvement came from moving near-expiry LD-RCP to the emergency department (ED) for use with their trauma patients, with subsequent improvements from embedding use in ED as routine practice, introducing a dedicated LD-RCP delivery schedule (which increased the units ≤2 days old at delivery from 42% to 83%) and aligning this delivery schedule to cover two cycles of peak demand (Fridays and Saturdays).

PROBLEM

There is evidence that transfusing whole blood (WB) for resuscitation of bleeding patients associated with trauma may be better than red blood cell (RBC) transfusion. However, manufacturing WB in the UK is technically difficult, the product has a shorter shelf life than RBC (14 vs 35 days) and the raw material (donated O negative (O neg) blood) is in short supply.

The Royal London Hospital (RLH) is part of Barts Health National Health Service (NHS) Trust. The hospital is one of the four major trauma centres (MTCs) in London and hosts the base for London's Air Ambulance (LAA) service. LAA operates the Helicopter Emergency Medical Service (HEMS), which provides prehospital advanced-trauma care across the whole region covered by the London MTCs. Their helicopters and rapid-response cars carry blood in Golden Hour boxes for transfusion. Over the last 4 years, they have administered a mean of 7.28 units of RBC per week (SD 2.60 units).

As part of the WB Feasibility Programme, in November 2018, NHS Blood and Transplant (NHSBT) started supplying RLH with (type O neg) leucodepleted red cell and plasma (LD-RCP) for use in the prehospital setting to treat major traumatic haemorrhage. In conjunction with this, RLH and HEMS made a clinical decision to change standard treatment from RBC to LD-RCP for the management of prehospital trauma patients who are bleeding.

By its nature, the availability of blood for prehospital transfusion is critical for patient outcomes,[1] and the demand for it is highly variable (our baseline prehospital weekly demand data have a coefficient of variation of 57%, which is higher than the benchmark for randomness represented by a Poisson distribution with the same mean).

There is a fine balance between supply and demand: ensuring that we have enough LD-RCP (or, potentially, eventually WB) for all prehospital trauma patients while minimising wastage. This product is manufactured from group O neg blood donations in particular short supply, and has a relatively short shelf life (14 days, after which it must be disposed of), and as part of the study, it was targeted at a limited group of patients. Wastage could therefore be high and result in significant loss to the NHS: financial and in treatment capacity. Minimising LD-RCP wastage would

be crucial in deciding the feasibility of introducing a WB component nationally.

During set-up agreements for the feasibility study, supply of LD-RCP to RLH was agreed at 12 units per week. This being a new product, with short shelf life and targeted use, we had only been able to speculate about the potential level of wastage and what should be considered acceptable. The initial prestudy target wastage level was set (optimistically) at 8% on average. Higher wastage then could trigger reassessment of the WB Programme. The aim of the quality improvement (QI) work described in this paper was to achieve this low wastage rate by the end of the 24-month feasibility study. We used the Model for Improvement[2] as a guiding framework. Later sections detail the metrics and change ideas. We used Plan–Do–Study–Act (PDSA) cycles of learning and improvement to test, adapt and implement our change ideas, with run and Statistical Process Control (SPC) charts to investigate system performance and demonstrate impacts.

Once the project started, we found that initial (baseline) wastage was very high (70%) and that many units had limited shelf life remaining at delivery (only 42% were age ≤2 days old and so having at least 12 days of opportunity for use). It became evident, therefore, that very considerable improvements were necessary.

BACKGROUND

There are four components of WB of importance in this paper: RBC, white blood cells (WBC or leucocytes), plasma and platelets, in the following combinations:

- RBC+plasma+platelets+WBC: WB, as donated blood.
- RBC (leucodepleted, LD): currently supplied to front-line NHS units for transfusion.
- RBC+plasma (LD): LD-RCP, as supplied in the feasibility study context here.
- RBC+plasma+platelets (LD): LD-WB, ideal WB component in development.

In the UK, all blood components are manufactured by NHSBT, who supply RBC, platelets and plasma for blood transfusion throughout the NHS.

Over the last decade, research has advanced our understanding of how the ratios of blood components transfused affect outcomes in trauma patients. Clinical trials have demonstrated that early and continuous resuscitation with RBC+fresh frozen plasma+platelets (in a 1:1:1 ratio, resembling WB) reduces mortality.[1 3] Therefore, in the UK, there is currently great interest in reintroducing a WB component for resuscitation of patients with traumatic major bleeding, particularly those presenting in prehospital settings.

To reduce the risk of variant CJD (Creutzfeldt-Jakob Disease) transmission, NHSBT removes WBC (leucocytes) from WB through LD filters. The LD filter currently used by NHSBT also removes platelets. So, in addition to the individual components (RBC, platelets and plasma), NHSBT can produce LD-RCP (RBC+plasma in the same bag). NHSBT is currently assessing platelet-sparing LD filters to enable manufacture of safe WB (LD-WB).[4]

However, both LD-RCP and LD-WB have a much shorter shelf life than RBC: 14 days compared with 35 days. In the USA, unused WB is reprocessed after 10 days to produce RBC,[5] avoiding blood component wastage. However, this is not possible in the UK due to regulatory constraints on hospital blood banks and hospital blood establishments, so in the NHS, there is risk of wastage.

Group O RhD Negative ('O neg') is considered the safest group to transfuse to patients with unknown blood groups. In addition to LD-RCP, O neg donations are also required for the manufacture of O neg RBC used for the transfusion of group O neg patients and for neonatal and for emergency transfusion of patients with acute bleeding requiring urgent resuscitation. In the UK, 12% of the demand for RBC is for O neg, but this group makes up only 8% of the population,[6] so there is a shortage of donors and so of supply of this group[6]; donated O neg blood is a precious resource for the NHS.

MEASUREMENT

The global metric (or key performance indicator, KPI) was the wastage of LD-RCP (ie, the number of units that had to be disposed of at expiry of their shelf life) in units per week (and equivalently this as a percentage of the 12 units delivered per week). We realised an important internal (or process) metric was the age of LD-RCP units at delivery. We agreed a benchmark with NHSBT of 2 days old based on pre-existing logistical processes, so the metric was percentage with age ≤2 days old at delivery.

Data were collected retrospectively from the laboratory information management system at RLH, *WinPath*. These data were analysed on a 1-week cycle and presented in the form of a dashboard including run and SPC charts.[2 7]

In the first phase of this QI programme, we established the current condition[8] of this new process: mapping[9] the LD-RCP flow (figure 1) and establishing baseline performance[2] on the metrics (figure 2 and table 1). In the SPC plot of the weekly blood wastage (the upper graph in figure 2), the first 14 datapoints are the preintervention period (14 weeks), which gives us the baseline performance: a mean wastage of 8.36 units per week (70% of the 12 delivered each week). Though the system is stable, this mean wastage was much higher than we had expected.

Later in the project, we also targeted the age of LD-RCP at delivery to RLH (shown in the lower graph in figure 2). This is dependent on the NHSBT supplier and was unaffected by our first set of interventions (PDSAs A1 and A2, which only changed the flow of blood downstream in the process (as shown in figure 1)). Therefore, we could use a longer period to establish the preintervention (pre PDSAs B1 and B2) performance, though since (as the performance is stable (as shown in figure 2)) using the 58 weeks to estimate this, rather than the 14-week baseline period used for wastage, makes little difference. We found

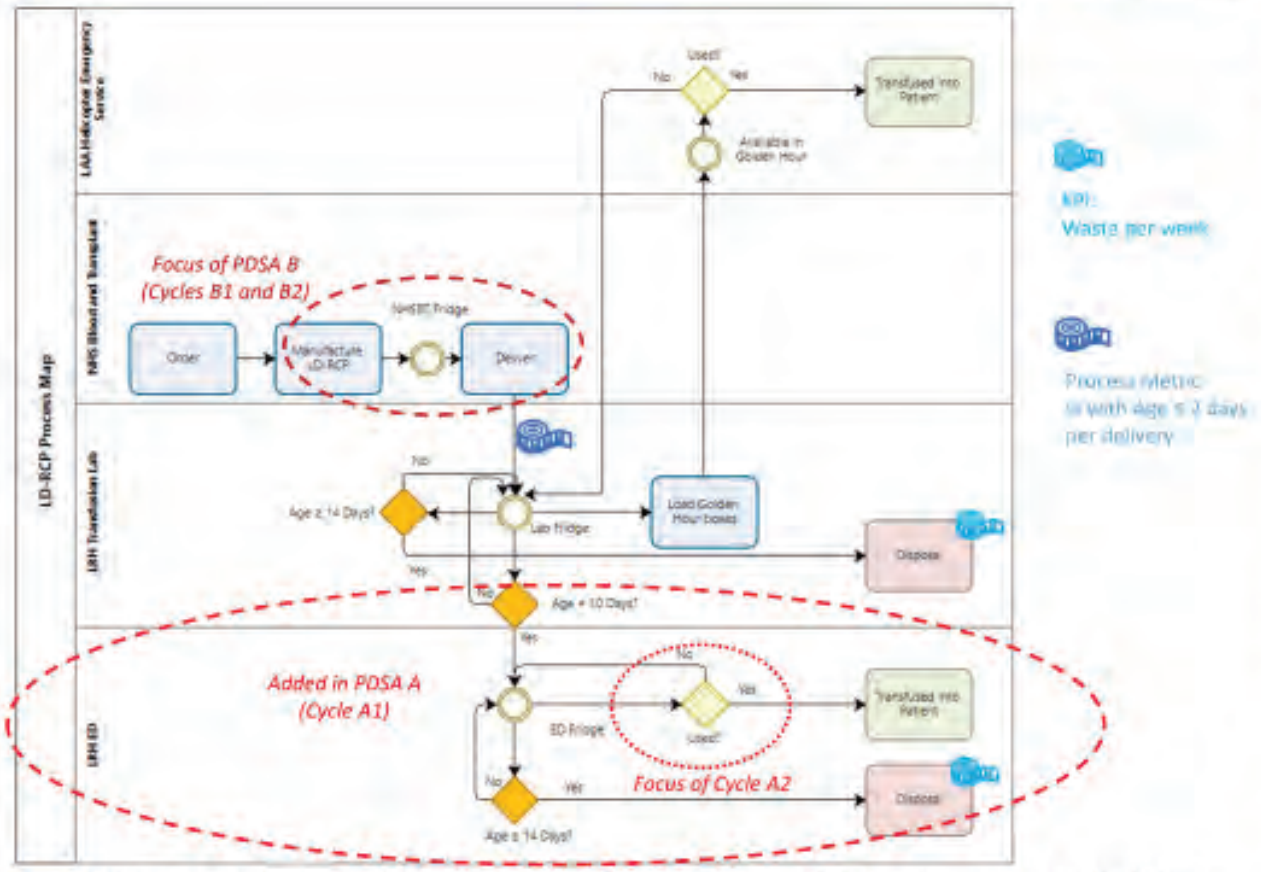

Figure 1 Process map. Royal London Hospital (RLH) ED, emergency department; KPI, key performance indicator; LAA, London's Air Ambulance; LD-RCP, leucodepleted red cell and plasma; NHS, National Health Service; NHSBT, NHS Blood and Transplant; PDSA, Plan–Do–Study–Act.

baseline performance on this metric to be a median of only 42% with age ≤2 days (figure 2 lower graph).

DESIGN

Following analysis of the baseline data, we met to discuss the next steps. Though wastage was one of our main concerns prior to the start of the study, after reviewing the baseline data, it was clearly a bigger problem than we had expected.

The 'WB Programme Group' was established to evaluate new strategies to reduce the LD-RCP wastage, deal with other issues arising during the study and feed back results and progress to key stakeholders. This was a multidisciplinary team (MDT) consisting of the key feasibility study members (haematology consultants, emergency medicine and trauma consultants, transfusion scientists, a research fellow, blood component development scientists and blood component manufacturing specialists). As a group, we met every for 4 months to review the overall progress of the study and formulate new action plans. Key members directly involved in the management of LD-RCP delivery and stock management met more regularly to discuss compliance and review the data prior to the Group's main meetings.

The main idea was to widen access to the LD-RCP beyond the prehospital setting so that a unit approaching the end of its shelf life (and so becoming increasingly unlikely to be used for the targeted prehospital transfusion) could be used by other patients who could benefit. Although the LD-RCP component was developed mainly for use in the prehospital setting, as noted earlier (Background section), the rapid administration of this component (which is closer to WB than standard RBC) could produce improved outcomes for any major trauma patient. Therefore, a natural first target for any 'spare' LD-RCP was patients who present at the ED with trauma-induced major haemorrhage. For these patients, we expected ED staff to use any LD-RCP available in preference to RBC. If the wastage level was still above the 8% target, then a further strategy would be to transfuse LD-RCP at the end of its shelf life to other non-trauma patients who were bleeding and trauma patients in the operating theatre needing ongoing transfusion treatment with RBC and thawed plasma as part of routine care.

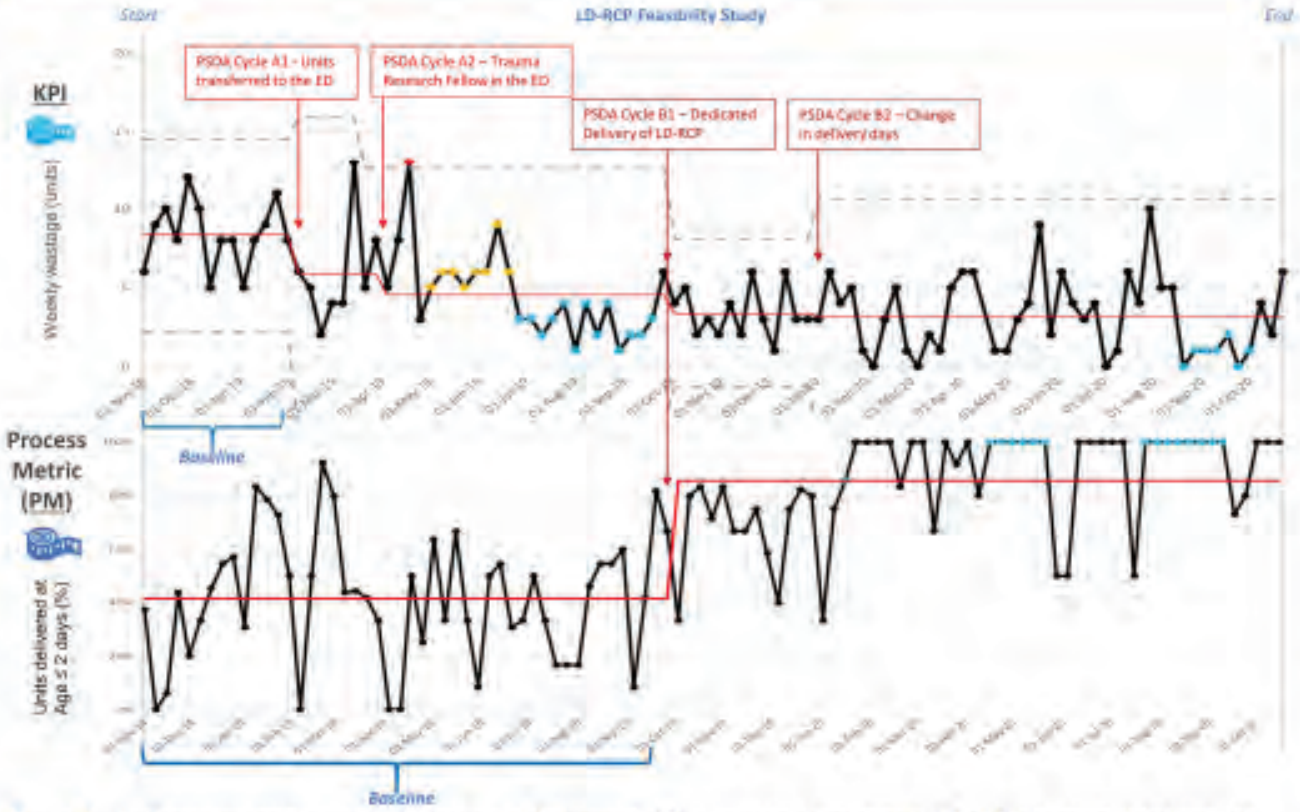

Figure 2 Performance metrics over the timeline of the project. ED, emergency department; LD-RCP, leucodepleted red cell and plasma; KPI, key performance indicator; PDSA, Plan–Do–Study–Act.

As the need for further improvement ideas became apparent, we also worked with NHSBT on delivery arrangements to increase the opportunity for use by increasing the proportion of units delivered at a 'young' age and coordinating the delivery day so the shelf-life window could span two peak-use periods (Fridays and Saturdays).

STRATEGY

We wanted to undertake three PDSA projects, but due to the COVID-19 pandemic, we were unable to implement the third PDSA (ie, transfusing LD-RCP to non-trauma patients with bleeding). In the end, we undertook two PDSA projects, each with two cycles. Each cycle was discussed in the WB Programme Group multidisciplinary meetings prior to commencement.

Table 1 summarises the progressive improvement cycles: aim, hypothesis, change idea, results and learning. The parts of the system changed or targeted are indicated on the process map in figure 1, and the results are shown on the graphs of the two metrics in figure 2.

The first project ('Project A') was to extend the LD-RCP pathway by moving remaining units down to the ED fridge at 10 days old (only 4 days of shelf life remaining). (Note: this never emptied the transfusion lab and HEMS stock as by age 10 days a subsequent delivery would have occurred, and units were used oldest first.) We pursued this change idea first, as it was within our span of control in the hospital so could be started immediately; the subsequent project ('Project B') required discussion with NHSBT about their manufacturing and delivery cycles.

The first PDSA cycle (A1) implemented this change and tested the impact. It achieved the first (modest and interim) target, but there was a long way to go. The study phase picked up that ED staff were not always using LD-RCP when it was available. A second cycle (A2) was therefore initiated, with the trauma research fellows (TRFs) working with ED staff with the aim of making preferential use of LD-RCP, when available, into routine practice. This cycle involved MDT education, targeted messaging at handovers, weekly focus on blood transfusion and targeted teaching at new staff induction.

Following this focus on a new pathway to ED use, the Group agreed that another reconsideration of the whole process was required to attempt to further substantially reduce the wastage. Our baseline data highlighted that LD-RCP was not being delivered to RLH as fresh as desirable: one unit was already 9 days old, so only having 5 days of shelf life left (and so, under the new pathway, only 1 day for prehospital use before transfer to the ED). Project B therefore focused on LD-RCP delivery to RLH to increase and adjust its window of availability for use (particularly for prehospital use). The weekly LD-RCP delivery had been alongside other NHSBT products. We conducted

Table 1 Improvement cycles

PDSA cycle	Plan/prediction	Do	Study	Act	Time required
Baseline	Establish current condition (map blood flow and analyse baseline performance)	'Go and see' analysis	KPI: mean weekly wastage=**8.36** units (**70**%) PM: median % age ≤2 days=42% per week(oldest=9 days)	Embark on cycles of improvement, aiming for mean weekly wastage less than or equal to one unit (8%) by November 2020	14 weeks
A1	Transfer near-expiry units to the ED Hypothesis: ED staff can make good use of LD-RCP for trauma patients First target: KPI: mean weekly wastage=six units (50%)	At age=10 days move LD-RCP to the ED fridge	KPI: mean weekly wastage=**5.88** units (**49%**) (PM: median % age ≤2 days=no change) Some ED patients eligible to receive LD-RCP had not, despite availability in the ED fridge	First target achieved but capability low (achieved in six out of the 8 weeks). Review highlighted that further work was required: conduct another cycle with modified plan and more ambitious target	8 weeks
A2	Encourage use by ED staff Hypothesis: trauma research fellows (TRFs) could establish LD-RCP use as routine practice for ED staff Second target: KPI: mean weekly wastage=four units (33%)	Existing TRFs work in the ED to assist with education, training and prompting use of LD-RCP	KPI: mean weekly wastage=**4.54** units (**38%**) (PM: median % age ≤2 days=no change)	SPC (figure 2) suggests effective after a time lag: four units achieved most weeks in second half but capability low (little safety margin). Further improvement ideas needed; tighten target a little	26 weeks
B1	Dedicated LD-RCP delivery slot Hypothesis: more LD-RCP received at age ≤2 if had dedicated delivery slots Third target: KPI: mean weekly wastage=three units (25%)	Work closely with NHSBT (supplier) using RLH metrics and data, agree dedicated delivery slot rather than the general delivery slots	KPI: mean weekly wastage=**3.38** units (28%) PM: median % age ≤2 days=83% per week	Big improvement in % age ≤2 days (process metric) but only small improvement in mean weekly wastage Further improvement ideas needed; tighten target a little	13 weeks
B2	Change LD-RCP delivery days Hypothesis: since prehospital trauma incidence highest on Fridays and Saturdays, delivery to cover 2 weekends would decrease wastage Fourth target: KPI: mean weekly wastage=three units (25%)	Change dedicated delivery days, Tue: two units, Wed: four units, Thu: two units, Fri: two units, Sat: two units	KPI: mean weekly wastage=**3.19** units (**27%**) (5 weeks with zero wastage) (PM: median % age ≤2 days: no change expected)	Ultimate target still not met, small further improvement in mean weekly wastage (large improvement since the start). Variation still high (% age ≤2 days appears to continue to improve)	17 weeks
C	Further extend the LD-RCP pathway to include non-trauma patients with major bleeding. Hypothesis: will further increase in demand for LD-RCP. Fifth target: KPI: mean weekly wastage=one unit (8%)	Units' age ≥10 days to be also used for non-trauma bleeding patients in hospital	Could not be implemented due to the COVID-19 pandemic		

ED, emergency department; KPI, key performance indicator; LD-RCP, leucodepleted red cell and plasma; NHSBT, NHS Blood and Transplant; PDSA, Plan–Do–Study–Act; PM, process metric; RLH, Royal London Hospital; SPC, Statistical Process Control.

an improvement cycle (B1) to work with NHSBT to coordinate manufacture and delivery, instituting a dedicated LD-RCP delivery. On further analysis and reflection, we realised that more trauma cases occurred (and therefore more blood was administered) on Friday and Saturday than any other days of the week. We therefore ran a further cycle (B2) to adjust the LD-RCP delivery schedule to allow more units' 14-day shelf life to span two Fridays and Saturdays.

Following the relative success of extending the LD-RCP pathway to include ED, we planned a final project ('Project C') to further extend the use of LD-RCP to non-trauma patients with major bleeding. This plan was approved in February 2020 by NHSBT and agreed by the WB Programme Group for implementation in April 2020. However, due to the COVID-19 pandemic, we were unable to complete this cycle due to lack of resources and rapidly changing staffing priorities within the NHS.

RESULTS

Our two main metrics of interest were total component wastage (KPI) and age of units on delivery (a process metric (PM)), measured on a weekly and monthly basis. Baseline data from the beginning of the study prior to any interventions demonstrated a stable baseline for measuring weekly component wastage.

As summarised in table 1 and shown in figure 2, over the four PDSA cycles, we reduced mean weekly wastage, from 8.36 units (70%) to 5.88 units per week (49%) and then 4.54 (38%); 3.38 (28%); and, finally, 3.19 units (27%).

A year after the study started, cycle B1 addressed the PM of percentage with age ≤2 days old through changes to the transport and delivery arrangements with NHSBT. We improved this metric from the baseline of 42%–83%. In the lower graph in figure 2, the number of datapoints above the new median suggests that performance is making further good progress towards an ultimate target of 100% of LD-RCP units being delivered at age ≤2 days.

Figure 2 demonstrates that the improvement was sustained for the remainder of the trial period (10 months after the final change). The results from this trial (including our design changes to reduce wastage) are now being used to plan the next stage of novel component supply trials.

Lessons and limitations

The aim of this project was to reduce the wastage level of LD-RCP. The two areas of focus were Project A, widening access to the blood product (and thus increasing demand), and Project B, maximising the useful availability of the product by adjusting the delivery schedule. The total wastage of LD-RCP component was reduced over the length of the study. However, although there were 17 individual weeks throughout this study period (of the total 103 weeks) in which we did manage to achieve the target wastage level of less than or equal to one unit, we never reached our overall target level of a mean of no more than 8%. However, we were unable to implement and test the impact of the last QI change idea (ie, transfusing LD-RCP to non-trauma patients in hospital who are bleeding).

One area not well investigated in advance was the actual demand for blood for major trauma in the prehospital setting. The agreement on a constant delivery level of 12 units per week was based on a quick analysis of HEMS Golden Hour box provision rather than a detailed analysis of historical demand (ie, past use of RBC). Such an analysis could have examined weekly demand levels and (importantly) its variation, together with any trend and longer-term cyclical patterns.

Similarly, prior analysis of within-week demand cycles might have prompted, in the setup, design of delivery cycles around this and then, in turn, fitting the manufacturing schedule to the delivery cycle. This was only addressed halfway (a year) through the study, with Project B. The widening demand work (Project A) had a big impact on wastage (as expected), so starting with this seems sensible. However, the length of time until delivery root causes were addressed is an example of the conflict between (i) very fast-cycle experimentation and improvement and (ii) disentangling the effects of a single change (or a single closely related bundle of changes) and being able to demonstrate its impacts (eg, with SPC).[2 8] This was compounded in this study by it being of a new product/service, so there was felt be no already-existing (historical) baseline performance data and that new datapoints accrued only once a week. The next phase of trials, currently being planned, will pick up on this and seek to make more effective use of data to predict demand.

In PDSA cycle A1, we unexpectedly found that ED staff did not use the new blood product (LD-RCP) whenever they could. EDs have many staff, with relatively high turnover. Cycle A2 took the remedial step of having TRFs working with them to educate and encourage take-up, a challenging task in a pressured environment. Our initiative benefitted from their ongoing educational input. Other trusts hosting prehospital trauma services generally have staff in similar roles; alternatively, this task could be taken on by dedicated education or transfusion practitioners, which all trusts should have.

The SPC chart highlights that there was a delay in the impact seen following the start of this cycle (A2). This lag in wastage reduction could demonstrate the time lapse between training/education and the application of the knowledge gained and in particular could be an example of how hard it is to change habits and to establish new routines, even with frequent practice and interaction with 'coaches'.[10]

Later, further analysis has established that not all LD-RCP wastage had occurred at the end of its shelf life: 14.1% of LD-RCP units were discarded due to failures in cold chain (these units were not kept at the appropriate temperature when stored). Furthermore, we also found that only 16.5% of transfers of units to the ED occurred at the intended 10 days old (and 36% were >12 days old)

representing opportunities for further improvement within the local system.

More detailed data analysis during the project might have picked this up and suggested additional PM. Cold-chain failures could have been another target for QI cycles, discovering root causes and reducing their incidence. Additional cycles of the 'Project A' work (transfer to the ED) might have targeted compliance with the 10-day action point, perhaps considering QI ideas like visual management cues, 5S workplace organisation and poka yoke mistake proofing.[11]

In future consideration of blood component flows, it would be very useful to institute routine analysis of wastage, perhaps with the sort of weekly datapoint SPC we have in this study, to monitor patterns (in close to real time) and to detect signals of things like changes in demand or ED staff practice.

CONCLUSION

Not all the PDSA cycles proved to be as effective in reducing the LD-RCP wastage as we expected, and the (ambitious) overall target of wastage of less than one unit per week (8%) was not achieved. Nevertheless, incremental reductions were demonstrated across the study period, reducing the weekly wastage from a mean of 8.36 units per week (70%) to 3.19 (27%) by the end of the study period.

The biggest impact on wastage was making the LD-RCP available to be used in the ED and thus increasing the demand through cascading what would likely have been surplus units to a secondary use. Potential prehospital demand for LD-RCP had been very roughly evaluated prior to the start of the study. More detailed analysis of historical transfusion demand in both prehospital and ED settings could have refined this (perhaps obviating the need for the B1 and B2 improvement cycles) and also stimulated explicit thinking about the trade-off between prehospital shortage of LD-RCP (requiring step-down to RBC) and prehospital surplus LD-RCP (allowing step-up from RBC in the ED and potential final wastage).

A recent review of modelling of perishable blood product inventory, in that case platelets, notes that many modelling methods have been attempted.[12] Our future work will concentrate on a deeper level of analysis and modelling for our situation. In particular:

- Analysis of demand:
  - To evaluate whether the weekly prehospital trauma demand can be forecast to a useful extent and with what lead time, as can be applied to some other emergency-care demand.[13 14]
  - To consider the use of surplus LD-RCP for other bleeding patients (outside of trauma).
- Analysis of supply:
  - *If* weekly demand is forecastable to a useful extent, to investigate whether it is feasible to institute a robust system to adjust supply and delivery accordingly.
- Development of a supply and demand model:
  - To analyse the trade-off between shortage and surplus of LD-RCP, considering both expected (long-run average) value and (one-off) risks. This type of problem, with uncertain demand and a perishable product, is one that has been investigated using operational research modelling,[12 15–17] an approach that could be useful here.

Acknowledgements JM concluded this work as part of the quality improvement unit of the Higher Specialist Scientist Training Programme, run by Alliance Manchester Business School of the University of Manchester and the Manchester Academy for Healthcare Scientist Education, on behalf of the National School of Healthcare Science, part of NHS Health Education England.

Contributors JM, HT, LG, AW, DE, JD, JL, AM and RD made substantial contributions to the design of the work. JM performed the collection, analysis and interpretation of data. JM and NP drafted the work with LG and HT. All authors reviewed the draft. JM is the guarantor of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study received approval from the NHS Health Research Authority for data collection (ref number 236783).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

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REFERENCES

1 Sperry JL, Guyette FX, Brown JB, *et al*. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. *N Engl J Med* 2018;379:315–26.
2 Provost LP, Murray SK. *The health care data guide: learning for data improvement*. San Francisco, CA: Jossey-Bass, 2011.
3 Holcomb JB, Tilley BC, Baraniuk S, *et al*. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015;313:471–82.
4 Huish S, Green L, Curnow E, *et al*. Effect of storage of plasma in the presence of red blood cells and platelets: re-evaluating the shelf life of whole blood. *Transfusion* 2019;59:3468–77.
5 Yazer MH, Jackson B, Sperry JL, *et al*. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. *J Trauma Acute Care Surg* 2016;81:21–6.
6 Foukaneli D, Bassey S, Bend M. Survey of group O D negative red cell use. 2018: NHS blood and transplant, 2018. Available: https://hospital.blood.co.uk/audits/national-comparative-audit/medical-audits/2018-survey-of-group-o-d-negative-red-cell-use [Accessed 21 Sept 2020].
7 Mohammed MA. Using statistical process control to improve the quality of health care. *Qual Saf Health Care* 2004;13:243–6.
8 Rother M. *Toyota kata: managing people for improvement, adaptiveness and superior results*. New York: McGraw-Hill, 2010.
9 NHS Institute for Innovation and Improvement. *Improvement leaders' guide: Process mapping, analysis and redesign*. NHSI: Coventry, 2005.

9.5 Appendix 5: Assessing the risks of haemolysis as an adverse reaction following the transfusion of ABO incompatible plasma-containing components – A scoping review

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

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Review

Assessing the risks of haemolysis as an adverse reaction following the transfusion of ABO incompatible plasma-containing components - A scoping review

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ARTICLE INFO

Keywords:
ABO incompatible
Plasma
Platelets
Titre
Volume
Anti-A
Anti-B
Haemolysis
Transfusion

ABSTRACT

Background

The limited supply of universal plasma has resulted in transfusion of ABO incompatible plasma to patients. As the need to implement whole blood transfusion in pre-hospitals setting rises, the lowest cut-off for anti-A/anti-B that does not cause haemolysis remains unknown. In this first scoping review, we aimed to determine the lowest ABO titre and volume reported in the literature to cause haemolysis from ABO incompatible plasma transfusions (plasma, platelets, cryoprecipitate, and whole blood).

Methods

We searched several databases from inception to April 2022, including all study types. Three independent reviewers extracted and reviewed the data. Primary outcome was the anti-A and anti-B titre (measured by IgM or IgG) that resulted in measurable haemolysis following ABO incompatible plasma transfusion.

Results

We identified 5681 citations, of which 49 studies were eligible, reporting a total of 62 cases (34 adults, 14 children and 14 did not specify age). The methods for antibody measurement and antibody type (IgG or IgM) varied significantly between studies. Component volumes were poorly reported. The most common component responsible for the haemolysis was apheresis platelets followed by pooled platelets and whole blood. Most haemolytic cases reported were due to anti-A. The lowest anti-A titre reported to cause haemolysis (children and adults) was 32 (IgG), while for anti-B it was 512 (IgG and IgM) for adults, 16,384 for paediatrics (IgG and IgM) and 128 (IgM) in cases where the age was not specified. The lowest reported volume associated with haemolysis were 100 ml (adults) and 15 ml (children). Of the 62 15 (24%) died.

Conclusion

The lowest titre reported to cause haemolysis was an anti-A of 32. ABO mismatch plasma transfusion may be associated with significant mortality. There is a need to agree/standardise methods for ABO titration measurement internationally for plasma components and agree the lowest anti-A/anti-B titre for transfusing ABO mismatched plasma.

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https://doi.org/10.1016/j.blre.2022.101080

Available online 14 July 2022
0268-960X/

1. Introduction

The ABO blood group system remains the most important and clinically significant due to the naturally occurring presence of anti-A and anti-B in donors and recipients. These antibodies can result in immune red blood cell destruction (or haemolysis) resulting in significant morbidity and mortality for the recipient if ABO incompatible components are transfused. ABO incompatibility can be classified into two types: major incompatibility, where antibodies in the recipient bind to transfused red cells and minor incompatibility where antibodies in the transfused blood component bind to the recipients red cells [1].

Whilst the risk of haemolysis and serious harm is higher with the transfusion of ABO incompatible red cells than with ABO incompatible plasma components [2], there is still a risk of haemolytic transfusion reactions with components containing plasma. Currently national guidelines recommend that patients should receive ABO identical plasma and platelet components as a first choice [3–7] and for patients with an unknown blood group, group AB plasma/group A platelets are recommended . Additionally, it is not always possible to provide ABO-group identical platelets, even if a patient's blood group is known, due to limitations in supply. Therefore, several guidelines and blood services have protocols in place to reduce the risk of haemolysis due to the transfusion of non-ABO identical plasma/platelets. This includes a hierarchy of suitable ABO groups of the product based on the recipient's ABO group, and providing the components are confirmed to be 'high titre negative' for anti-A and anti-B. Not all blood providers routinely screen for high-titre anti-A/B and the cut-off level for what is defined as 'low titre' or 'high titre negative' remains unknown and lacks international consensus.

Most international blood services have accepted an anti-A and anti-B titre of <100 for IgM (saline) and <400 for IgG antibodies as a safe cut-off [3,6,8]. However, there is a great deal of variation in component titration methods, and it is therefore, difficult to establish a threshold for the critical high titre classification. Furthermore, the relationship between the titre and the risk of haemolysis is not absolute and the severity of haemolysis from a transfusion of ABO incompatible plasma/platelets components can be affected by other factors, including, the isotype, volume transfused, age and weight of the recipient as well as underlying pathology [9,10]. A further consideration in determining an appropriate cut-off for high titre screening is drawing a balance between removing high titre donations and ensuring an adequate supply of components.

There is now interest in transfusing whole blood (WB) components in emergency and pre-hospital settings, as this allows for the 1:1:1 resuscitation of bleeding patients with red cells, plasma, and platelet transfusion [11]. In such settings, if we are to transfuse WB in the early stage of bleeding, a group O WB component (that contains both anti-A and anti-B in the plasma) would be the most appropriate group to transfuse, as the patient's blood group is likely to be unknown. Therefore, for non-group O recipients there is a potential risk of a haemolytic transfusion reaction occurring due to the transfusion of ABO incompatible plasma. Thus, it is important to quantify this risk, particularly as these patients are likely to receive a high volume of plasma in the immediate resuscitation period.

This scoping review aims to assess the evidence on the impact of ABO incompatible plasma/platelets and determine the lowest observable anti-A or anti-B titre levels and the lowest volume that have resulted in haemolytic transfusion reactions (both laboratory and clinical). For this review, we have concentrated only on minor ABO incompatibility and therefore, restricted the review to the transfusion of ABO incompatible plasma-containing blood components (platelets, plasma, cryoprecipitate, and whole blood) and the risk of haemolysis associated with anti-A and anti-B in the transfused component only. Other adverse reactions associated with the transfusion of blood components were not considered.

1.1. Objectives

Objectives of this scoping review were to answer the following questions:

1) In individuals receiving ABO incompatible plasma containing components, what is the lowest observable anti-A and anti-B titre (measured by IgG or IgM) reported in the literature that has resulted in haemolysis (clinical or laboratory)?

2) In individuals receiving ABO incompatible plasma containing components, what is the lowest observable ABO incompatible plasma volume that has resulted in haemolysis?

2. Methods

2.1. Review protocol

Our protocol was written using the PRISMA extensions for Scoping Reviews.

2.2. Eligibility criteria

For this systematic review studies were eligible if they included patients of any age, who received a transfusion of an ABO incompatible plasma containing component where haemolysis was reported. Paediatric population was defined as ages 0–17 years.

We defined "plasma containing component" as, fresh frozen plasma (FFP), thawed plasma, FFP24 (plasma frozen within 24 h), lyophilised plasma, freeze dried plasma, cryoprecipitate, apheresis platelet, pooled platelet, or whole blood. We excluded studies addressing: ABO incompatible packed red cell transfusions; intravenous immunoglobulins; anti-D administration; haematopoietic stem cell transplants, and studies using animal models. Haemolysis was defined as described in each individual study.

Studies were included if they were randomised control trials (RCTs), cluster-RCTs with at least two intervention sites in each arm, non-RCTs, repeated measures studies, controlled before-and-after studies, case reports, case control studies, reports from hemovigilance schemes if published as a paper and any other study type that has assessed the risk of haemolysis with ABO incompatible plasma transfusion.

2.3. Information source and search strategies

An information specialist (CD) searched the following databases from their inception to 24 April 2022; MEDLINE (OvidSP), PubMed (pre-MEDLINE publications only), Embase (OvidSP), CENTRAL (The Cochrane Central Register of Controlled Trials) & CDSR, *The Cochrane Library* (Wiley interface, 2022, Issue 4), Transfusion Evidence Library (Evidentia Publishing), Web of Science (Thomson Reuters), Scopus (Elsevier), Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). There were no restrictions on publication date, language, publication status or study design (Appendix A).

2.4. Selection of sources and evidence

Search results were uploaded to Covidence, a web-based software platform, to facilitate the screening process. Three review authors (JM, TB and SH) independently screened abstracts and then the full text of potentially eligible studies., with one reviewer (JM) screening all abstracts and full text Any disagreements were resolved by consensus.

2.5. Data extraction process

A data-extraction form was developed by three reviewers (JM, TB and SH) with input from SJB. The three reviewers (JM, TB and SH)

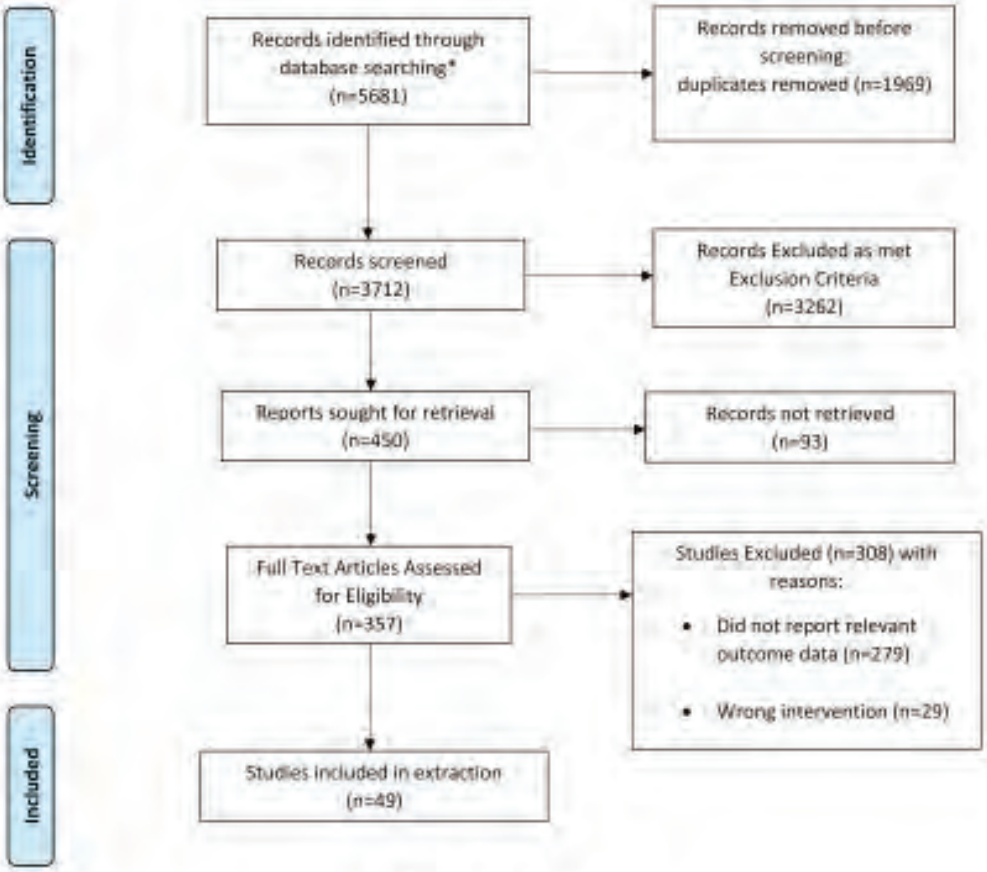


Fig. 1. Prisma flow chart.

independently extracted the data, discussed the results, and continuously updated the data-extraction form. A pilot of the data-extraction form was completed by all three reviewers prior to starting the extraction process.

2.6. Data items

The following parameters were collected: study ID, study setting and country, date of publication, study participant demographics, details of component transfused, the volume of component transfused, details of assays used to measure anti-A and anti-B titre, recipient and component blood type, and details of diagnostic tests used to measure haemolysis markers. We also collected data on clinical outcomes where available: mortality, morbidity and whether a haemolytic transfusion reaction was reported. Due to constraints on time, resources, and the age of some papers we did not contact the authors of the papers if missing data was identified or suspected. Missing data were predominantly details of methods used to measure anti-A and anti-B titres.

2.7. Synthesis of results

We summarised the extracted data in a table format, grouping studies by type and ABO blood group of the component transfused, age of patients, method of measuring the titre levels and volume of plasma component transfused. The primary outcome of this review was anti-A and anti-B titre (measured by IgM or IgG) that resulted in measurable haemolysis following ABO incompatible plasma transfusion The secondary outcome was assessing the association between volume of ABO incompatible plasma administered and haemolysis.

2.8. Statistics

As this is a scoping review, we have not statistically analysed the data rather we have reported the findings in tables and plots and commented narratively on the findings in the text. The focus of the reporting is the anti-A and anti-B titre, volume of ABO-incompatible plasma transfused, and patient outcome. Data for adult patients is reported separately from data for paediatric patients, as we considered that the volume and titre of anti-A/B that may causes haemolysis to be different.

3. Results

3.1. Study selection

We identified 5681 citations (including 224 ongoing trials), which were reduced to 3712 citations after duplicates were removed (Fig. 1, Prisma Flow Chart). Three review authors (JM, TB and SH) excluded 3262 citations based on the abstract, leaving 450 full text articles for review. The full text of 93 records could not be found: thus, 357 full text articles were reviewed for eligibility. Of the 357 citations, 308 studies were excluded because; 279 did not report haemolysis and 29 reported haemolysis due to something other than ABO-incompatible transfusion. Of the 49 eligible papers, all were case reports/short case series. We identified no completed or ongoing RCTs.

3.2. Synthesis of results

A total of 49 papers, all case reports, published between 1946 and 2022, were included, of which eight reported more than one case of

Table 1
A table compiling all the papers reporting on adult cases.

Author	Year	Country	Component type	Volume	Component blood group	Patient blood group	Antibody	Method of measurement	Inferred antibody isotype	Antibody titre	Mortality (Y/N)
Haemolytic transfusion reactions due to anti-B											
Pierce et al	1985	–	Pooled Platelet	–	O	B	Anti-B	–	–	16,384	–
Reis et al	1989	Canada	Apheresis Platelet	–	O	B	Anti-B	IAT	IgG	4096	No
Sauer-Heilborn et al	2002	US	Apheresis Platelet	526 ml	O	B	Anti-B	DTT/Saline IAT	IgM/IgG	2048/4096	–
Daniel-Johnson et al	2008	USA	Apheresis Platelet	100 ml	A	B	Anti-B	IgG/Saline	IgG/IgM	16,384/ 163816384	No
Milkins et al	2017	UK	Apheresis Platelet		A	AB	Anti-B	–	–	512	–
Shachner et al	2018	US	Apheresis Platelet	135 ml	A	B	Anti-B	Saline Tube	IgM	512	No
Balbuena-Merle et al	2019	USA	Apheresis Platelet	367 ml	O	B	Anti-B	Tube IAT	IgG	512	Yes
Swain et al	2019	Australia	Apheresis Platelet	–	A	AB	Anti-B	IAT/Saline	IgG/IgM	32,000	No
Haemolytic transfusion reactions due to anti-A											
Ebert et al	1946	USA	Whole Blood	350 ml	O	A	Anti-A	–	–	2048	No
McLeod et al	1982	USA	Apheresis Platelet	100-200 ml*	O	A	Anti-A	IAT/Saline	IgG/IgM	10,240/640	No
Ferguson et al	1988	Canada	Apheresis Platelet	–	O	A	Anti-A	IAT/RT	IgG/IgM	4000/256	No
Murphy et al	1990	UK	Apheresis Platelet	255 ml	O	A	Anti-A	IAT/Saline	IgG/IgM	1024/256	–
Muir et al	1998	USA	Apheresis Platelet	225 ml	O	A	Anti-A	Saline	IgM	128	–
Williamson et al	1999	UK	Apheresis Platelet	–	O	A	Anti-A	–	–	–	–
Lawson et al	2000	USA	Apheresis Platelet	371 ml	O	A	Anti-A	Saline RT	IgM	16,384	No
Vaiboneni	2000	Italy	Apheresis Platelet	30-35 ml*	O	A	Anti-A	37 °C/RT	IgG/IgM	128/8000	–
Zubair et al	2004	USA	Apheresis Platelet	150 ml	O	A	Anti-A	37 °C/RT	IgG/IgM	2048/512	–
Sadani et al	2006	UK	Apheresis Platelet	–	O	A	Anti-A	IAT/DTT	IgG/IgM	640/1280	Yes
Rosen et al	2008	USA	Pooled Platelets	–	O, B	A	Anti-A	–	–	–	–
Losada et al	2010	USA	Apheresis Platelet	–	O	A	Anti-A	AHG	IgG	32	–
Fontaine et al	2012	USA	Apheresis Platelet	231 ml	O	A	Anti-A	Tube IgG/IgM	IgG/IgM	2048/512	Yes
Piskorski et al	2014	USA	Pooled Platelets	–	O	A	Anti-A	–	–	–	–
Kundrapu et al	2017	USA	Apheresis Platelet	–	O	A	Anti-A	IgG/IgM	IgG/IgM	1024/256	No
Cummings et al	2018	USA	Apheresis Platelet	–	O	A	Anti-A	–	–	–	–
Perdin et al	2018	US	Pooled Platelet	–	O	A	Anti-A	IgG/IS	IgG/IgM	2048/64	No
Basu et al	2019	India	Apheresis Platelet	–	O	A	Anti-A	IAT/Saline	IgG/IgM	1024/128	–
Gammon et al	2019	USA	Pooled Platelet	–	O	A	Anti-A	37 °C/IS	IgG/IgM	2048/256	No
Guerrero et al	2019	USA	Pooled Platelet	–	O	A	Anti-A	Saline	IgM	64	–
Moinuddin et al	2019	USA	Apheresis Platelet	280 ml	O	A	Anti-A	Saline RT	IgM	512	No
Hou et al	2019	Taiwan	Platelet	–	B	A	Anti-A	IgM/IgG	IgM/IgG	256/2048	–
Pasion et al	2021	USA	Apheresis Platelet	–	O	A	Anti-A	RT/IAT	IgM/IgG	32/256	–
Haemolytic transfusion reactions due to anti-A/anti-B											
Chow et al	1991	–	Pooled and Apheresis		O, A, B	AB	Anti-A/ Anti-B	–	–	1024	No
McManigal & Sims	1999	USA	Apheresis Platelets		O, A, B	AB	Anti-A/ Anti-B	–	–	–	No

The volumes recorded in the table are those of the whole component except for those highlighted * which report the plasma volume of the component. ^Multiple units of different blood group were transfused. IAT (Indirect Antihuman globulin Test), RT (Room Temperature) and IS (Immediate Spin). Data not reported in the cases is represented by (–)

haemolysis [12–19], thereby 62 cases of haemolysis provided the data for this review. 34 (53%) cases involved adult patients (Table 1), 14 (22%) [13–17,49–55] were paediatric patients (Table 2) and 14 (22%) [12,27] cases did not specify the age of the patient (Table 3).

The data we were able to extract are presented in Figs. 2 and 3 and discussed separately for adults and children below.

3.3. Adult cases

3.3.1. Component & blood group

The blood components responsible for the haemolysis reported in 34 adult cases were apheresis platelets (24,70%) [13,16,16, 21–28,31,33–37,39–41,44,52], pooled platelets (7, 20%) [15,17,45–52], both apheresis and pooled platelets (1, 3%) [53], whole blood component 1 (3%) [56] and platelet that was not further specified as apheresis or pooled 1 (3%) [55]. Of the components transfused, 26 (76%) were group O [13–25,28–31,33,36,37,39–44,52], 4 (13%) were group A [13,31,37,39] 1 was group B [55] and 3 (9%) were reported as multiple units transfused of different groups (O, A & B) [30,52,53].

3.3.2. Haemolysis and clinical outcomes

Of the 34 adult cases, 20 (59%) [13,16,20,22, 24,25,36,40,41,44,52,54,28–34] reported both clinical symptoms, DAT, and eluate results. 26 (72%) [13,15,16,20,30, 32,34,36–38,40–44,46–48,50–52,55,58–61], reported a positive DAT, 24 (70%) [13,16,20,22,24–26,28,29–34,36–40,18,41,44, 52,54], reported an eluate result and 29 (85%) [13,15,16,28–31, 33–37,39–42,44–46,48,49–52,54–56,61], reported clinical symptoms of haemolysis. Patient outcomes were reported in only 14 (41%) [13,19,23,24,27,28,32,34,36,37,39,41,42,44] cases and 3 (9%) [35,42,45] reported the death of the patient. These 3 cases were all following the transfusion of group O apheresis platelets, haemolysis resulting from anti-A in 2cases [35,45] and anti-B in 1 case [42], all with a titre of >500.

3.3.3. Antibody titre

Of all adult cases, 28 (82%) [13,16–19,21–24, 27–31,33–38,40,41,43,44,52,54,55] reported the antibody titre of the unit responsible for causing the haemolysis (Table 1), of which 19 [16,18,19,21–25,28–30,33,37,41,43,44,52,54] were due to anti-A, 8 were due to anti-B [13,17,31,34,36,37,39,42] and 1 was due to anti-A and anti-B [53]. However, only 24 (71%) cases reported the method of measurement, temperature or the isotype [13,16,18,19,21–25, 28,30,31,33–37,40,41,44,52,54].The antibody isotype (IgG or IgM) was only directly reported in 5 cases [13,45,46,51,55], the temperature (37 °C or room temperature (RT)) of the method was recorded in 6 cases [16,32,40,41,44,47,49] and the methods recorded in the papers were as follows; saline (11), Anti-Human Globulin (AHG)/IAT (10), immediate spin (1), 2 cases specifically reported that testing was carried out using the tube method and 2 cases reported the use of Dithiothreitol (DTT). The lowest antibody titre reported in the literature for adult patients was an anti-A titre of 32 measured by AHG [48] and an antibody titre of 32 measured at RT [41] and for anti-B it was 512 IgG and IgM [37,62].

3.3.4. Component volume

13 (41%) cases reported the volume of the component or the volume of plasma in the component[13,16,19,22,24,28,30,31,34,35,40,41,43,]. The lowest component volume transfused that was reported in the adult literature was 100 ml of a group A apheresis platelet unit transfused to a group B patient with an anti-B titre of 16,384 measured by IgG [13]. The transfusion reaction was characterised by dark brown urine and a grossly haemolysed sample with a positive DAT. The patient was reported to have made a full recovery.

3.4. Paediatric cases

3.4.1. Component & blood group

The blood components responsible for the haemolysis reported in the 14 paediatric cases were apheresis platelets (9) [13,14,16,17,21, 23,25,26], pooled platelets (1) [15], whole blood component (1) [23], cryoprecipitate (1) [24], pooled plasma (1) [20], and thawed plasma (1) [14]. Of the components transfused, 13 were group O [14–17,45–50,57] and 1 was group A [13].

3.4.2. Haemolysis

Of the 14 paediatric cases included in this review, 11 reported a positive DAT [13–16,20–22,24,25], 10 reported an eluate result [13–17,20,22,23,25] and 13 reported clinical symptoms of haemolysis [13–16,20–24,26,63]. A total of 6 cases reported clinical symptoms, DAT and eluate results [13,14,16,20,22,23]. Patient outcome was reported in 11 cases [13,14,16,17,20–22,25,26] and 4 cases reported the death of the patient [16,17,20,22].

3.4.3. Antibody titre

Of the 14 paediatric cases reported, 9 reported the antibody titre of the unit responsible for causing the haemolysis [13,16,17,20–23,25,26], of which 7 were due to anti-A [16,17,20–22,25,26] and only 2 were due to anti-B [13,47] (Table 2). However, only 2 cases reported the isotype measured [13,23]. The temperature of the method was recorded in 3 cases [16,21,26] and the method was reported in 3 cases (Saline and IAT/AHG) [13,25,26]. The lowest antibody titre reported in the literature for paediatric patients was an anti-A titre of 32, although no measurement method was provided from these cases; one of the transfusions resulted in the death of the patient [20]. For anti-B the lowest antibody titre reported to cause haemolysis was 16,384 as measured by saline [13].

3.4.4. Component volume

A total of 8 paediatric cases reported the volume of the component or the volume of plasma in the component [13,14,16,20,22,24–26]. The lowest component volume transfused that was reported to have caused a haemolytic transfusion reaction (HTR) in the paediatric literature was 15ml of a unit of cryoprecipitate [24], no antibody titre was reported and the patient was reported to have made a full recovery.

3.5. Age not specified cases

3.5.1. Component & blood group

The blood components responsible for the haemolysis reported in the 14 cases where age was not specified were apheresis platelets (7) [12,19,64,65] and platelets that were not further specified into apheresis or pooled (7) [18]. Of the components transfused, 11 were group O [12,18,19,65], 2 were group A [13,18] and 1 group B [18].

3.5.2. Haemolysis

Of the 14 cases where age was not specified, 1 reported a positive DAT and eluate result [64] and 3 reported clinical symptoms of haemolysis [12,66]. A total of 8 cases reported patient outcome and 8 reported the death of the patient [18,65].

3.5.3. Antibody titre

Of the 14 cases where age was not specified,9 reported the antibody titre of the unit responsible for causing the haemolysis [12,18,65], of which 4 were due to anti-A [12,18] and only 2 were due to anti-B

Table 2
A table of the papers reporting on paediatric cases.

Author	Year	Country	Age	Weight	Component type	Volume	Component blood group	Patient blood group	Antibody	Method of measurement	Inferred antibody isotype	Antibody titre	Mortality (Y/N)
Haemolytic transfusion reactions due to anti-B													
Boulter et al	1995	USA	6 yrs		Whole Blood	-	O	B	Anti-B	IgG	-	>64,000	-
Daniels-Johnston et al	2008	USA	5 yrs	26 kg	Apheresis Platelets	37 ml	A	B	Anti-B	IgG/Saline	IgG/IgM	16,384/16384	No
Haemolytic transfusion reactions due to anti-A													
Wood et al	1967	US	9 yrs		Pooled Plasma	5700 ml	-	A	Anti-A	-	-	32	Yes
Bunnah et al	1973	UK	5 yrs		Cryoprecipitate	15 ml[a]	O	AB	Anti-A	-	-	-	No
Pierce et al	1985	-	2 yrs	25.5 kg	Apheresis Platelets	-	O	A	Anti-A	-	-	32,000	Yes
Dugaid et al	1999	UK	5wks		Apheresis Platelets	-	O	A	Anti-A	-	-	-	No
Dugaid et al	1999	UK	9dys		Apheresis Platelets	-	O	AB	Anti-A	-	-	-	No
Dugaid et al	1999	UK	4 m		Thawed Plasma	90ml[a]	O	A	Anti-A	-	-	-	No
Valbonesi	2000	Italy	16 yrs	-	Apheresis Platelets	-	O	A	Anti-A	37 °C/RT	IgG/IgM	128/8000	Yes
Argudillo et al	2004	USA	8 m	9 kg	Apheresis Platelets	107 ml[a]	O	A	Anti-A	-	-	128	Yes
Sagiuchiar et al	2005	US	2 yrs	12 kg	Apheresis Platelets	145 ml	O	A	Anti-A	IAT/Saline RT	IgG/IgM	16,384/1024	No
Harris et al	2007	USA	8 yrs	30 kg	Apheresis Platelets	300 ml	O	A	Anti-A	IAT	IgG	4096	No
Pisklenk et al	2014	USA	11 yrs		Pooled Platelets	-	O	AB	Anti-A	-	-	-	-
Augustine et al	2021	India	9 yrs	35 kg	Apheresis Platelets	-	O, B	AB	Anti-A	RT	IgM	128/32	No

The volumes recorded in the table are those of the whole component except for those highlighted * which report the plasma volume of the component. [a]Multiple units of different blood group were transfused. IAT (Indirect Antihuman globulin Test) and RT (Room Temperature). Data not reported in the cases is represented by (-).

[18,65] (Table 3). However, only 1 case reported the isotype measured [18]. The method was reported in 3 cases (Immediate spin and IAT/AHG) [13,25,28]. The lowest antibody titre reported in the literature for this group was an anti-A titre of 128 [12,18] and an anti-B titre of 128 as measured by immediate spin [65].

3.6. Relationship between volume and titre

There was a paucity of data reported on the volume of the components transfused in each of the cases identified, with only 43.8% reporting the volume of the component transfused or the volume of plasma in the component. The lowest volume that resulted in haemolysis for both the adult and paediatric populations were 100 mll and 15ml respectively. With this very limited sample, we saw no obvious relationship between volume and titre (Fig. 2).

4. Discussion

4.1. Summary of evidence

In this first systematic scoping review our objective was to determine a) the lowest observable anti-A and anti-B titre reported in the literature with ABO-incompatible plasma-containing components that resulted in a haemolytic transfusion reaction (based on clinical or laboratory definitions), and b) the relationship between titre and volume and lowest observable ABO incompatible plasma volume that has resulted in a haemolytic transfusion reaction.

Our findings identified 62 case reports (34 adults and 14 paediatric, with 14 cases not reporting age) where ABO incompatible plasma/platelet components have resulted in haemolysis. There was heterogeneity in the methods for reporting haemolysis and the ABO titration methods. The volume of the components transfused in each of the cases was poorly reported with only 19 (31%) providing this information. Antibody titre was also poorly reported with 47 (74%) of cases providing this information and only 23 (37%) reporting the titres for both IgG and IgM isotypes. Platelet components were the most reported components to result in haemolysis in both paediatrics and adults. The lowest anti-A titre reported to cause haemolysis was 32 (paediatrics and adult), while for anti-B it was 512 (IgG and IgM) for adults,16,384 for paediatrics (IgG and IgM) and 128 (IgM) in cases where the age was not specified. The lowest component volume transfused that was reported to have caused a haemolytic transfusion reaction was 100 ml in adults and 15ml in paediatric. Clinical outcomes were also poorly reported, but of the 34 (55%) cases that reported these, 15 (24%) cases reported that the patient had died.

4.2. Discussion of the results

In this first systematic review, we identified 62 case reports between 1946 and 2022 where ABO incompatible plasma/platelet components have resulted in haemolysis. There were no completed or ongoing randomised trials. As expected, platelet components were the most reported components to result in haemolysis in both the paediatrics and adults, as ABO-incompatible platelet transfusions are more often given compared ABO-incompatible plasma due to limitations in supply including HLA requirement. There were also two cases that reported haemolysis from a unit of whole blood (1 adult case with an anti-A titre of 2048 and 1 paediatric case with an anti-B titre of >64,000 IgG). These cases were reported in 1946 and 1995 [23,66] respectively, prior to more recent requirements to screen such donations for high titre anti-A/B. With increasing interest in the use of whole blood for resuscitation of trauma patients who are bleeding, it is very important to put these results into perspective. A systematic review conducted to assess the difference in safety outcomes with the transfusion of WB compared to blood components for any bleeding patient regardless of age or clinical condition identified six RCTs with a total of 618 participants, none of

Table 3
A table of the papers reporting on cases where age of the patient was not specified.

Author	Year	Country	Component type	Volume	Component blood group	Patient blood group	Antibody	Method of measurement	Inferred antibody isotype	Antibody titre	Mortality (Y/N)
Haemolytic transfusion reactions due to anti-B											
Ruby et al. 2021	2008	USA	platelet	–	O	B	Anti-B	–	–	–	Yes
Daniel-Johnson et al	2009	USA	Apheresis Platelet	–	A	B	Anti-B	–	–	–	–
Ruby et al. 2021	2015	USA	platelet	–	A	B	Anti-B	–	–	2048	Yes
Storch et al. 2021	2019	USA	Apheresis Platelet	–	O	B	Anti-B	IS/AHG	IgM/IgG	128/512	Yes
Malvik et al.	2020	USA	Apheresis Platelet	–	O	B	Anti-B	–	–	–	–
Haemolytic transfusion reactions due to anti-A											
Bachowski et al.	2010	Canada	Apheresis Platelet	–	O	A	Anti-A	IS/IAT	IgM/IgG	512/4096	–
Bachowski et al.	2010	Canada	Apheresis Platelet	–	O	A	Anti-A	IS/IAT	IgM/IgG	128/512	–
Ruby et al. 2021	2011	USA	platelet	–	O	A	Anti-A	IgM/IgG	IgM/IgG	512/2048	Yes
Ruby et al. 2021	2012	USA	platelet	–	O	A	Anti-A	–	–	–	Yes
Ruby et al. 2021	2014	USA	platelet	–	O	A	Anti-A	–	–	2048	Yes
Malvik et al	2020	USA	Apheresis Platelet	–	B	A	Anti-A	–	–	–	–
Haemolytic transfusion reactions due to anti-A/anti-B or no antibody specified											
Ruby et al. 2021	2014	USA	platelet	–	O	AB	anti-A and anti-B	–	–	128	Yes
Ruby et al. 2021	2018	USA	platelet	–	O	AB	–	–	–	32,000	Yes
Malvik et al	2020	USA	Apheresis Platelet	–	O	AB	–	–	–	128	–

IAT (Indirect Antihuman globulin Test) and RT (Room Temperature). Data not reported in the cases is represented by (–).

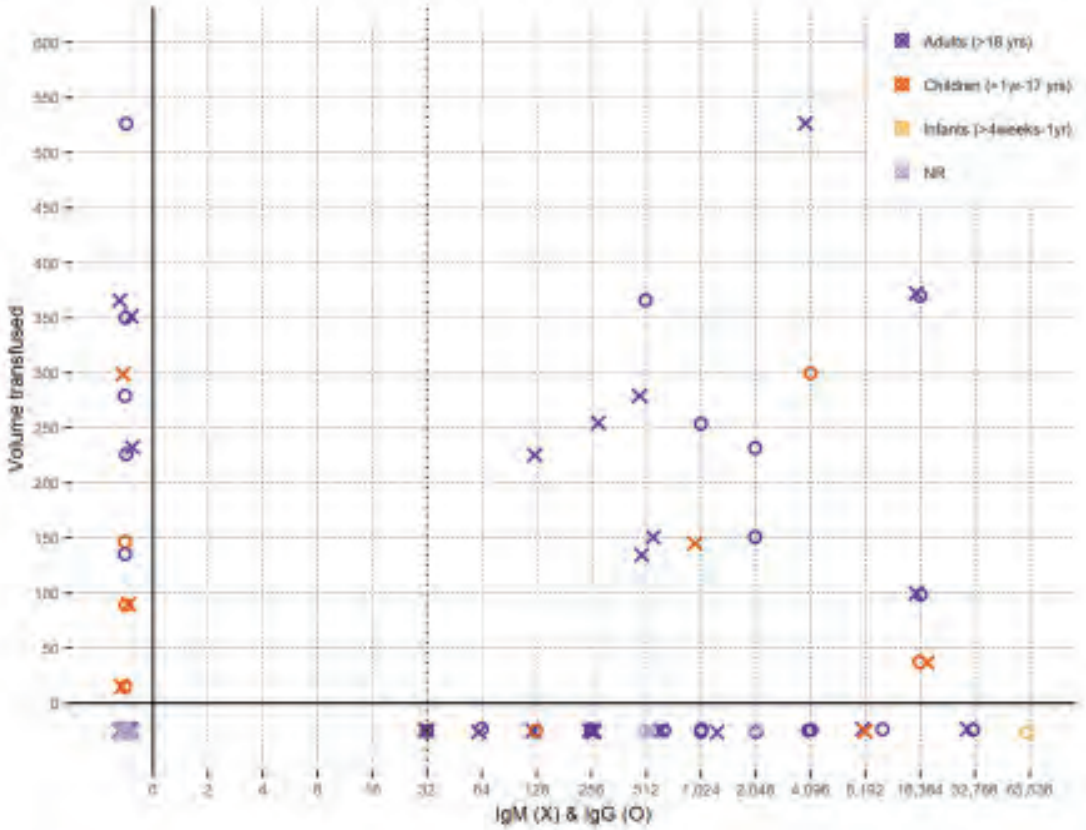
which were reported to have suffered from a haemolytic transfusion reaction [67]. Similar results have been reported in recent observational studies of whole blood transfusion in trauma patients [68]. It is important to acknowledge that during bleeding there is a significant blood volume loss and therefore it could be argued that risk of haemolysis in such patients could be lower compared to patients who are not bleeding. However, the scope of this review was not able to answer this important point. Furthermore, in an international survey on the use of group O whole blood for the resuscitation of civilian trauma patients in 2020, the definitions for 'low titre anti-A and anti-B' varied between <50 and <256 with the two main methods being Saline tube without anti-human globulin (AHG) or Saline tube with AHG [9].

Group O was the most common blood group to cause haemolysis and many clinical guidelines indeed advise against the use of group O plasma containing components for non-group O patients [4,6] unless a significant amount of plasma has been removed for example by suspending platelets in platelet additive solution. Anti-A was the antibody responsible for most cases of haemolysis, which supports the existing knowledge base that anti-A is more immunogenic than anti-B. Group A was responsible for 7 (4 adult, 1 paediatric and 2 age not specified) cases of haemolysis, all reported within the last 12 years from the transfusion of apheresis platelets. All these cases had an anti-B titre above the level considered 'safe' by most international blood services with the lowest titre to result in haemolysis reported as 512 measured by saline tube [37].

There was huge heterogeneity in the way that ABO titration methods were reported, with some papers only reporting the temperature and others reporting the isotype of the antibody being measured. Some papers reported two methods and titre levels however, there was often no explicit reference to the isotype measured although this could be inferred from the data. Further, the methods for reporting haemolysis varied between papers. Some papers reported serological haemolysis with DAT and an eluate being the most common laboratory tests, others reported only clinical haemolysis, and some reported both laboratory and clinical haemolysis. The details on clinical recovery were not provided for all cases, and where it was provided (34 cases), a full recovery was reported in 19 cases, and of the 62 cases, 15 patients (3 adult, 4 paediatric and 8 no age specified) died due to haemolysis, highlighting the need for caution when transfusing ABO incompatible plasma components and the importance of establishing safe ABO titres.

Our findings showed that 88% of cases reported the titre of the ABO antibody responsible for haemolysis and the lowest titre reported to cause haemolysis in both the paediatric and adult cases was an anti-A IgG titre of 32. Based on the current evidence and taking into considerations the limitations mentioned above, we can conclude that an anti-A titre of <32 could be considered the lowest cut-off to almost eliminate the risk of haemolysis associated with ABO incompatible plasma transfusion. A recent international forum that assessed the policies for the transfusion of ABO or RhD non-identical platelets, reported the current methods and cut offs for measuring high titre anti-A and anti-B from eight different respondents. The majority of respondents routinely test for IgM only, with all having a cut off between 64 and 128 equivalent to saline tube agglutination method. These cut offs are at a level chosen to be a pragmatic balance between reducing risk as far as possible on the one hand, whilst maintaining and adequate supply of components on the other [5].

The findings from this review suggest that in order to fully mitigate the risk of haemolysis from ABO compatible plasma transfusion, that a



Reported titres (IgM and IgG) plotted against reported volume with missing values replaced by negative numbers so that a volume with no reported titre will be plotted to the left of the y-axis and a titre with no reported volume will be plotted below the x-axis.

The x-axis is on a log scale to make lower titre values more readable. The points on the plot have been jittered because some of the pairs of values are repeated in the dataset.

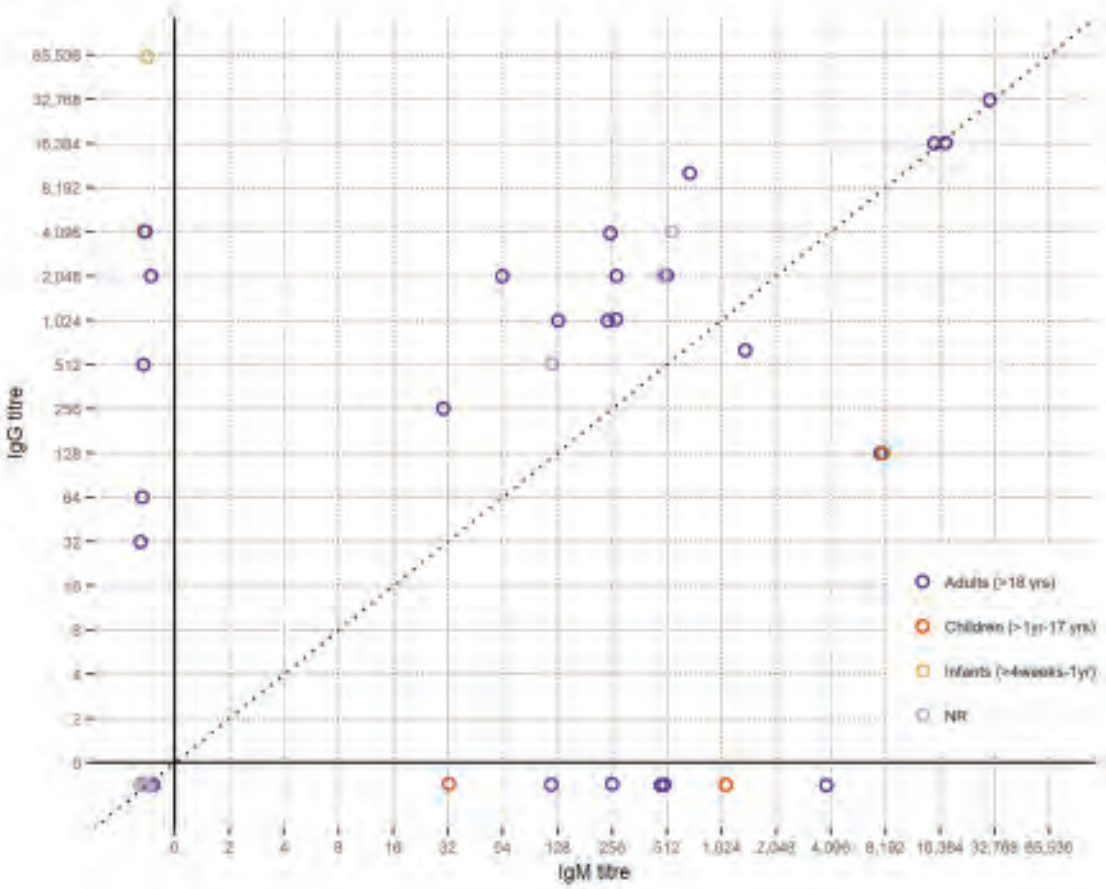
Excludes one very high volume (5,700ml) with no reported titres.

Fig. 2. A graph showing the relationship between volume of component transfused and IgM/IgG titre.

lower cut off of 32 may be required. This could theoretically be achieved through more selective screening of donations, but this may result in too many donations being unable to be used due to the likely limited proportion of the donor population with values below 32, especially for group O donors. Although the lowest titre of anti-A that was implicated in a HTR was as low as 1/32 IgG, reports at this level are rare, most being associated with higher titres. Therefore, there needs to be a balanced consideration between the titre at which risk reduction for HTR is likely to be maximised and the ability to have sufficient donations to make such products from. The case reports within this review are too few to draw conclusions on the relationship between IgG and IgM in blood donors, and whether there is a need to review policies for whether IgG as well as IgM should be screened for. In fact, large data sets on this aspect are lacking. Alternatively, another way of addressing this issue is to consider methods to further dilute or remove anti-A/B from plasma-rich blood components.

We cannot draw any strong conclusions about the importance of volume, or the relationship between volume and titre, with respect to risk of haemolysis due to limited data provided in the case reports. We considered that it is likely that not only the titre of anti-A/B in the component that is important, but also the volume of the component transfused i.e. the dose of antibody transfused. Additionally, factors such as avidity of the antibodies and recipient factors would also likely be important in determining whether a reaction would occur. Defining a critical cut off is challenging, in part because as this review suggest, and others have postulated, there is no definitive relationship between titre and risk of HTR [60]. Although volume and titre of incompatible plasma transfused are related to risk, this relationship is not absolute and recipient factors such ABO zygosity and complement regulatory deficiencies are thought to play a role in determining the likelihood of a HTR occurring [70,71]. Further, adsorption of anti-A and B through soluble A and B and A and B antigens on the endothelium of patients of mis-matched ABO group are thought to contribute to the low level of HTR observed. We note that there are several points on the plot in Fig. 2 which correspond to fairly low titres transfused in fairly low volume and so it is clear that there is a risk even when volume*titre is relatively small. We cannot reliably quantify that risk. Our sample consists largely of case reports, less than half of which reported both volume and titre(s), and there will be some bias inherent in the decision to publish a case report at all. Very high volumes transfused imply very sick recipients and it is possible that haemolysis is less likely to be considered a notable outcome worth publishing for this group, especially when weighed against the ability to obtain large quantities of blood products in an emergency. Conversely, very high titres ordered or supplied in error, or because the risk was perceived to be small for low volume transfusions, might be less likely to be published because the motivation of case reports is often an interesting or unexpected outcome, and not a confession of clinical error.

The non-random sample of cases reported in the literature means that we cannot conclude that the relatively high proportion of deaths



IgM plotted against IgG with missing values replaced by negative numbers so that an IgG titre with no corresponding IgM titre will be plotted to the left of the y-axis and an IgM titre with no corresponding IgG titre will be plotted below the x-axis.

The axes are on a log scale to make lower titre values more readable; each square on the plot represents a doubling. The points on the plot have been jittered because some of the pairs of values are repeated in the dataset.

Fig. 3. A graph showing IgM and IgG titres that were reported in literature.

(15%) in this review is at all representative of the true underlying risk from ABO-incompatible transfusions.

4.3. *Limitations*

This scoping review has some limitations. Firstly, to make our review more feasible, we were only able to include papers that were written in English and secondly, we only included papers that were available online. Thirdly, we did not approach authors for incomplete data due to large number of abstracts and papers we had to screen and review and because most of the missing data will not exist due to the nature of case reports and the age of many of these papers. We cannot reliably quantify the impact of these limitations to the overall findings of the review. Moreover, we need to recognise that the rate of under recognition and/or under reporting of this complication is probably significant [72], and therefore would not have been captured by this review.

5. Conclusions and future directions

In summary, our review showed significant heterogeneity in the methods for reporting clinical and laboratory haemolysis and the ABO titration methods. The information on volumes transfused and clinical recovery were also poorly reported. Platelet components were the most reported components to result in haemolysis in both paediatrics and adults. The lowest titre reported to cause haemolysis in both paediatrics and adults was an anti-A titre of 32, and the lowest component volume transfused that was reported to have caused a haemolytic transfusion reaction was 100 ml in adults and 15mls in paediatric cases. Of the 48 cases reported, 15% of cases died, highlighting the clinical importance of the risk of harm due to haemolysis associated with ABO-incompatible plasma-containing components, although we cannot provide any meaningful estimate of the true risk of death in these cases.

Based on this evidence, we can conclude that an anti-A titre below 32 is unlikely to cause a haemolytic reaction. However, further research is needed to a) standardise the methods for the measurement of ABO titrations and b) agree the lowest cut-off levels for high titre negative components internationally.

Research agenda

- Agreeing and standardising methods for measuring ABO titres internationally
- Determine and agree the lowest cut-off for defining low titre ABO antibodies for plasma containing components.

Practice points

- Based on the current evidence there has been no clinical or laboratory haemolysis reported from the transfusion of ABO incompatible plasma components with an anti-A titre of <32 as measured by AHG.

- The lowest reported ABO incompatible plasma volume transfusion to have been associated with haemolysis were 100 ml in adults and 15 ml in paediatric.

Funding

This review was funded by NIHR (National Institute for Health Research) Invention for Innovation (Ref Nr: II-LA-0417-20003) awarded to Dr. Rebecca Cardigan and Dr. Laura Green. The views expressed in this publication are those of the author(s), and not necessarily those of the NIHR. The funders had no role in the study design, data collection/ analysis or preparation of this article. The views expressed in this article are those of the authors and not necessarily of the funders.

Contribution to authorship

JM, LG, SJB, LE and RC designed the study. CD conducted the search for eligible studies. JM, TB and SH extracted the papers and JM, TB, SH and JS analysed the data. All authors contributed to the writing of the article.

Declaration of Competing Interest

All authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2022.100999.

References

[1] Daniels G, Bromilow I, editors. Essential guide to blood groups. Oxford: John Wiley & Sons; 2013. https://doi.org/10.1002/9781118688915.
[2] Bolton-Maggs P, editor. Poles D et al. Serious Hazards of Transfusion (SHOT) Steering Group Chair Professor Steering Group (SG) during 2017; 2018.
[3] Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. Br J Haematol 2017;176:365–94. https://doi.org/10.1111/bjh.14423.
[4] Green L, Bolton-Maggs P, Beattie C, Cardigan R, Kallis Y, Stanworth SJ, et al. British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding. Br J Haematol 2018;181:54–67. https://doi.org/10.1111/bjh.15167.
[5] Cardigan R, New HV, Estcourt L, Zhiburt E, Dubey R, Bengtsson J, et al. International Forum on Policies and Practice for Transfusion of ABO and RhD Non-Identical Platelets: Summary. Vox Sang. 2021. p. 1–9. https://doi.org/10.1111/vox.13129.
[6] The Australian and New Zealand Society of Blood Transfusion. Guidelines for Transfusion and Immunohaematology Laboratory Practice. 1st ed. Australian and New Zealand Society of Blood Transfusion Ltd; 2020.
[7] Nahirniak S, Slichter SJ, Tanael S, Rebulla P, Pavenski K, Vassallo R, et al. Guidance on platelet transfusion for patients with Hypoproliferative thrombocytopenia. Transfus Med Rev 2015;29:3–13. https://doi.org/10.1016/j.tmrv.2014.11.004.
[8] Berséus O, Boman K, Nessen SC, Westerberg LA. Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma. Transfusion 2013;53. https://doi.org/10.1111/trf.12095.
[9] Yazer MH, Spinella PC. An international survey on the use of low titer group O whole blood for the resuscitation of civilian trauma patients in 2020. Transfusion 2020;60:S176–9. https://doi.org/10.1111/trf.15601.
[10] Yazer MH, Cap AP, Spinella PC, Alarcon L, Triulzi DJ. How do I implement a whole blood program for massively bleeding patients? Transfusion 2018;58:622–8. https://doi.org/10.1111/trf.14474.
[11] Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma. JAMA 2015;313:471. https://doi.org/10.1001/jama.2015.12.
[12] Bachowski G, Mair DC, Lose R, Skeate RC. Determination of anti-A and anti-B titers in random donors and donors involved in hemolytic reactions from platelets. Transfusion 2010;2:160A–1A. https://doi.org/10.1111/j.1537-2995.2010.02824-1.x.
[13] Daniel-Johnson J, Leitman S, Klein H, Pusey J, Schelbert P, Alter H, et al. Probiotic-associated high-titer anti-B in a group A platelet donor as a cause of severe hemolytic transfusion reactions. Transfusion 2008;48:260A.
[14] Duguid JK, Minards J, Bolton-Maggs PH. Lesson of the week: incompatible plasma transfusions and haemolysis in children. BMJ 1999;318:176–7.
[15] Pakorski A, Sweeney J. Intravascular hemolysis from prepooled platelets. Transfusion 2014;2:142A. https://doi.org/10.1111/trf.12849.
[16] Valbonesi M, De Luigi MC, Lercari G, Florio G, Bruni R, Van Lint MT, et al. Acute intravascular hemolysis in two patients transfused with dry-platelet units obtained from the same ABO incompatible donor. Int J Artif Organs 2000;23:642–6.
[17] Pierce RN, Reich LM, Mayer K. Hemolysis following platelet transfusions from ABO-incompatible donors. Transfusion 1985;25:60–2.
[18] Ruby KN, Harm SK, Dunbar NM. Risk of ABO-incompatible plasma from non-ABO-identical components. Transfus Med Rev 2021;35:118–22. https://doi.org/10.1016/j.tmrv.2021.06.006.
[19] Mahrik N, Leon J, Schlueter AJ, Wu C, Knudson CM. ABO-incompatible platelets are associated with increased transfusion reaction rates. Transfusion 2020;60:285–93. https://doi.org/10.1111/trf.15655.
[20] Wood M, Pratt WB, Childers D. A hidden danger of pooled plasma. Am J Surg 1967;114:629–35.
[21] Augustine M, Murugesan M, Gopakumar KG, Jithin TK. Case report and strategies to mitigate passive hemolysis with platelet transfusions in children. Asian J Transfus Sci 2021;15:229–32. https://doi.org/10.4103/ajts.ajts_25_21.
[22] Angiolillo A, Luban NL. Hemolysis following an out-of-group platelet transfusion in an 8-month-old with Langerhans cell histiocytosis. J Pediatr Hematol Oncol 2004;26:267–9.
[23] Beattie G, Bradley MR, Pow M, Robinson J, Haley R. Acute haemolysis due to passively transfused high-titre anti-B causing spontaneous in vitro agglutination. Immunohematology 1995;11:43–5.
[24] Burnaie D, Hudson AE, Wood CB, Bruton M. Acute anaphylaxis, pulmonary oedema, and intravascular haemolysis due to cryoprecipitate. Arch Dis Child 1973;48:483–6.
[25] Harris SB, Josephson CD, Kost CB, Hillyer CD. Nonfatal intravascular hemolysis in a pediatric patient after transfusion of a platelet unit with high-titer anti-A. Transfusion 2007;47:1412–7.
[26] Sapatnekar S, Sharma G, Downes KA, Wiersma S, McGrath C, Yomtovian R, et al. Acute hemolytic transfusion reaction in a pediatric patient following transfusion of apheresis platelets. J Clin Apher 2005;20:225–9. https://doi.org/10.1002/jca.20072.
[27] Daniel-Johnson JA, Sheldon S, Lee-Stroka H, Tran MT, Quillen K. Universal platelet screening for high-titer Anti-A and Anti-B in a hospital-based donor center detects a significant prevalence of high titer group O and A units. Transfusion 2009;3:116A.
[28] Blair E, Benson K. Evaluation of changes in hemoglobin levels associated with ABO-incompatible plasma in apheresis platelets. Transfusion 1998;38:51–5.
[29] McLeod BC, Sassetti RJ, Weens JH, Vaithianathan T. Haemolytic transfusion reaction due to ABO incompatible plasma in a platelet concentrate. Scand J Haematol 1982;28:193–6.
[30] McManigal S, Sims KL. Intravascular hemolysis secondary to ABO incompatible platelet products. An underrecognized transfusion reaction. Am J Clin Pathol 1999;111:202–6.
[31] Milkins C, Ball J, Poles D, Bark J, Bolton-Maggs P. Risk and impact of haemolytic transfusion reaction due to passive ABO antibodies as evidenced by serious hazards of transfusion data. Br J Haematol 2017;176(Suppl):21–2. https://doi.org/10.1111/bjh.14613.
[32] Moinuddin IA, Millward P, Fletcher CH. Acute intravascular hemolysis following an ABO non-identical platelet transfusion: a case report and literature review. Am J Case Rep 2019;20:1075–9. https://doi.org/10.12659/AJCR.915521.
[33] Murphy MF, Hook S, Waters AH, Sinclair J, Whelan J, Bown C, et al. Acute haemolysis after ABO-incompatible platelet transfusions. Lancet 1990;335:974–5.
[34] Ross MB, Conradie AS. Transfusion of ABO-incompatible platelets causing severe haemolytic reaction. Clin Lab Haematol 1989;11:233–40.
[35] Sadani DT, Urbaniak SJ, Bruce M, Tighe JE. Repeat ABO-incompatible platelet transfusions leading to haemolytic transfusion reaction. Transfus Med 2006;16:375–9. https://doi.org/10.1111/j.1365-3148.2006.00684.x.
[36] Sauer-Heilborn A, Kadidlo D, Rosen L, Scofield T, Nulke KE. Passive antibody-triggered hemolysis: an ABO-incompatible platelet transfusion. Transfusion 2002;42:112S.
[37] Shachner TR, Clark CT. Acute hemolytic transfusion reaction in group B recipient associated with group a apheresis platelet donor: case report and literature review. Case Rep Med 2018;2018:8259531. https://doi.org/10.1155/2018/8259531.
[38] Williamson LM, Lowe S, Love EM, Cohen H, Soldan K, McClelland DB, et al. Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. BMJ 1999;319:16–9.
[39] Swain F, Daly J, Baidya S, Wilson B, Morrison J, Liew YW, et al. Acute haemolytic reaction secondary to an ABO minor mismatched platelet transfusion from a group A blood donor. Transfus Med 2019;29:133–5. https://doi.org/10.1111/tme.12591.
[40] Zahir A, Grant R, Black N, Birchall M, Roy A, Roy V. Severe acute hemolytic transfusion reaction following ABO mismatched platelet transfusion: should ABO mismatched platelet transfusion policy be evaluated. Blood 2004;104:1108.
[41] Pusan JO, Nagy LH, McCaskey BK, Shine L, Bryant A, McGann HL, et al. When O blood finds unrecognized acute hemolytic reaction from out-of-group PL A-compatible platelet transfusion. Ann Clin Lab Sci 2021;51:267–70.
[42] Balbuena-Merle R, West FB, Tormey CA, Hendrickson JE. Fatal acute hemolytic transfusion reaction due to anti-B from a platelet apheresis unit stored in platelet additive solution. Transfusion 2019;59:1911–5. https://doi.org/10.1111/trf.15240.
[43] Basu D, Basu S, Roy J, Reddy M, Chandy M, Bhoumik J. Incompatible crossmatch: first sign of a hemolytic transfusion reaction due to out-of-group platelet