

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

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23     **Abstract**

24     The limited supply of universal plasma has resulted in transfusion of ABO incompatible plasma to  
25     patients. As the need to implement whole blood transfusion in pre-hospitals setting rises, the safest  
26     cut-off for anti-A/anti-B that does not cause haemolysis, remains unknown. In this first systematic  
27     review, we aimed to determine the lowest ABO titre and volume reported in the literature to cause  
28     haemolysis from ABO incompatible plasma transfusions (plasma, platelets and whole blood). We  
29     searched several databases from inception to October 2019, including all study types. Three  
30     independent reviewers extracted/reviewed the data. Primary outcome was clinical/laboratory  
31     haemolysis (as defined by studies) following ABO incompatible plasma transfusion. Results: We  
32     identified 4,034 citations, of which 40 studies were eligible, reporting a total of 48 cases (32 adults, 13  
33     children; 3 did not specify age). The methods for antibody measurement and antibody type (IgG or  
34     IgM) varied significantly between studies. Component's volumes were poorly reported. The most  
35     common component responsible for the haemolysis was apheresis platelets followed by pooled  
36     platelets and whole blood. Most haemolytic cases reported were due to anti-A. The lowest anti-A titre  
37     reported to cause haemolysis (children and adults) was 32 (IgG), while anti-B titre IgM was 4096  
38     (adults) and 16,384 (children). The lowest reported volume associated with haemolysis were 100 mL  
39     (adults) and 15 mL (children). Of the 48 cases, 7 (15%) died. Conclusion: The lowest titre reported to  
40     cause haemolysis was an anti-A of 32. ABO mismatch plasma transfusion is associated with significant  
41     mortality. There is a need to agree/standardise methods for ABO titration measurement  
42     internationally for plasma components and agree the safest anti-A/anti-B titre for transfusing ABO  
43     mismatched plasma.

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## 49    **1. Introduction**

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

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

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71    Most international blood services have accepted an anti-A and anti-B titre of <100 for IgM (saline) and  
72    <400 for IgG antibodies as a safe cut-off [5,8,9]. However, there is a great deal of variation in  
73    component titration methods, and it is therefore, difficult to establish a threshold for the critical high  
74    titre classification. Furthermore, the relationship between the titre and the risk of haemolysis is not

75 absolute and the severity of haemolysis from a transfusion of ABO incompatible plasma/platelets  
76 components can be affected by other factors, including, the isotype, volume transfused, age and  
77 weight of the recipient as well as underlying pathology[10]. A further consideration in determining an  
78 appropriate cut-off for high titre screening is drawing a balance between removing high titre  
79 donations and ensuring an adequate supply of components.

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

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

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### 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 reported in the literature that has resulted in a haemolytic transfusion reaction (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 haemolytic transfusion reaction?

## 2. Methods

### 2.1. Review Protocol

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

### 2.2. Eligibility Criteria

For this 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.

We defined “plasma containing component” as, fresh frozen plasma (FFP), thawed plasma, FFP24 (plasma frozen within 24hrs), 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 focused on animal or animal models. Haemolysis was defined as mentioned in each individual study and documented clearly.

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 (C.D) searched the following databases from their inception to 19 October 2019: MEDLINE (OvidSP) PubMed (pre-MEDLINE publications only), Embase (OvidSP), CENTRAL (The Cochrane Central Register of Controlled Trials) & CDSR, *The Cochrane Library* (Wiley interface, 2019, Issue 10), 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 (J.M, T.B and S.H) screened titles, abstracts and subsequently the full text manuscripts identified by the search assessing citations with reference to a priori criteria independently. J.M screened all the titles and T.B and S.H screened all the titles between them as second reviewers. Any disagreements were resolved by consensus.

### *2.5. Data extraction process*

A data-extraction form was developed by three reviewers (J.M. T.B. and S.H.) with input from SJB. The three reviewers (J.M, T.B and S.H) independently extracted the data, discussed the results, and

continuously updated the data-extraction form. A pilot of the data-extraction from 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, where available the volume of component transfused and where appropriate, study design details of assays used to measure anti-A and anti-B titre 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 was predominantly details of anti-A and anti-B titre measurements.

## *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 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 commented narratively on the findings in the text. The focus of the reporting is the anti-A and anti-B titre as reported by each paper, haemolysis and volume of non-ABO plasma

transfused. Data from adult patients is reported separately from data from 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 4,034 citations (including 179 ongoing trials), which were reduced to 3,235 citations after duplicates were removed (Fig. 1, Prisma Flow Chart). Three review authors (J.M, T.B and S.H) excluded 2808 citations based on the abstract, leaving 427 full text articles for review. The full text of 92 records could not be found: thus, 335 full text articles were reviewed for eligibility. Of the 335 citations, 295 studies were excluded because 269 did not report haemolysis and 26 reported an incorrect intervention. Of the 40 eligible papers, all were case reports/studies. We identified no completed or ongoing RCTs.

#### 3.2. Synthesis of Results

A total of 40 papers all case reports, published between 1946 and 2019 were included for extraction, of which 6 reported more than one case of haemolysis[12–17], thereby 48 cases of haemolysis provided the data for this review. 32 (67%)[13,15-44,] cases involved adult patients (Table 1), 13 (27%)[13–17,45–50] were paediatric patients (Table 2) and 3 (6%)[12,51] cases did not specify the age of the patient.

#### 3.3. Adult cases

##### 3.3.1.Component & Blood Group

The blood components responsible for the haemolysis reported in adult cases were apheresis platelets 23 (72%)[13,16,18-20,23,24,27–35,37,39–43], pooled platelets 7 (22%)[15,17,25,26,36,38], both



apheresis and pooled platelets 1(3%)[44] and whole blood component 1 (3%)[52]. Of the components transfused, 25 (78%) were group O[15–31,34–37,39,40,43], 4 (13%) were group A[13,33,41,42] and 3 (9%) were reported as multiple units transfused of different groups (O, A & B)[32,38,44].

### *3.3.2.Haemolysis and clinical outcomes*

Of the 32 adult cases, 18 (56%)[13,16,19,20,23,26,28,30,31,34–40,42,] cases reported both clinical symptoms, DAT, and eluate results. 24 (75%)[13,15,16,19,20,23,24,26–28,30,32,34–43,53,] reported a positive DAT, 22 (69%)[13,16,18-20,23,24,26,28,30-32,34–40,42-44,] reported an eluate result and 27 (84%)[13,15,16,18–21,23,25–31,33–38,40–42,52,54,] reported clinical symptoms of haemolysis. The outcome of the patient was reported in only 14 (44%)[13,19,23,24,27,28,32,34,36,37,39,41,42,44] cases and 3 (9%)[19,24,39] 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 2[24,39] of the cases and anti-B in 1 case[19], all with a titre of >500.

### *3.3.3.Antibody titre*

Of all adult cases, 26 (78%)[13,16,17,19,20,22–25,27–30,33–37,39–44,53] reported the antibody titre of the unit responsible for causing the haemolysis (Table 1), of which 17[16,20,22–25,27–31,34–36,39,43] were due to anti-A, 8 were due to anti-B [13,17,19,33,37,40–42] and 1 was due to anti-A and anti-B[44]. However, only 22 (66%) cases reported the method of measurement, temperature or the isotype[13,16,19,20,23–25,27–29,30,31,34,36,37,39–43] and 14 (44%) studies reported more than one method to determine titration[13,16,20,23–25,27,31,35,36,39,40,42,43,]. The antibody isotype (IgG or IgM) was only reported in 4 cases[13,24,27,36], the temperature (37°C or room temperature) of the method was recorded in 5 cases[16,23,25,28,34,43] and the methods recorded in the papers were as follows; saline (11), Anti-Human Globulin (AHG)/IAT (9), 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 [29] and for anti-B it was 4096 measured by Saline IAT[40].

#### *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 100ml of a group A apheresis platelet unit transfused to a group B patient with an anti-B titre of 16384 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 13 paediatric cases were apheresis platelets (n = 8)[13,14,16,17,45,48,49], pooled platelets (n = 1)[15], whole blood component (n = 1)[46], cryoprecipitate (n = 1)[47], pooled plasma (n = 1)[50], and thawed plasma (n = 1)[14]. Of the components transfused 12 were group O[14–17,45–50] and 1 was group A[13].

#### *3.4.2.Haemolysis*

Of the 13 paediatric cases included in this review, 10 reported a positive DAT[13–16,45,47,48,50], 10 reported an eluate result[13–17,45,46,48,50] and 12 reported clinical symptoms of haemolysis [13–16,45–47,49,50,55]. A total of 6 cases reported clinical symptoms, DAT and eluate results[13,14,16,45,48,50]. The outcome of the patient was reported in 10 cases[13,14,16,17,45,48–50] and 4 cases reported the death of the patient[16,17,45,50].

### 3.4.3. Antibody titre

Of the 13 paediatric cases reported, 8 reported the antibody titre of the unit responsible for causing the haemolysis [13,16,17,45,46,48–50], of which 6 were due to anti-A[16,17,45,48–50] and only 2 were due to anti-B[13,46] (Table 2). However, only 2 cases reported the isotype measured[13,46]. The temperature of the method was recorded in 2 cases[16,49] and the method was report in 3 cases (Saline and IAT/AHG)[13,48,49]. 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 this case: this transfusion resulted in the death of the patient[50]. 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 ( what is the %) paediatric cases reported the volume of the component or the volume of plasma in the component[13,14,16,45,47–50]. The lowest component volume transfused that was reported to have caused a HTR in the paediatric literature was 15mls of a unit of cryoprecipitate[47], no antibody titre was reported and the patient was reported to have made a full recovery.

There was a paucity of data reported on the volume of the components transfused in each of the cases, 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 100ml and 15mls respectively. With this very limited sample, we saw no obvious relationship between volume and titre (Figure 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

has resulted in a haemolytic transfusion reaction (clinical or laboratory), and b) the lowest observable ABO incompatible plasma volume that has resulted in a haemolytic transfusion reaction.

Our findings identified 48 case reports (32 adults and 13 paediatric, with 3 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 44% providing this information. Platelet components were the most reported components to result in haemolysis in both paediatrics and adults. Based on the current evidence and taking into considerations above limitations, the lowest anti-A titre reported to cause haemolysis was 32 (paediatrics and adult), while for anti-B it was 4096 for adults and 16,384 for paediatrics (both measured by Saline IAT). 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 26 cases that reported these, 7 cases died.

#### *4.2 Discussion of the results*

In this first systematic review, we identified 48 cases reported between 1946 and 2019 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 >64000). These cases were reported in 1946 and 1995[46,56] 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. 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 5 (4 adult and 1 paediatric) 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[41].

There was huge heterogeneity in the way that ABO titrations 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 (25 cases), a full recovery was reported in 18 cases, and of the 48 cases, 7 patients (3 adult and 4 paediatric) 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 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 a safe cut-off for 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 cut off of 32 may be required. This could theoretically be achieved through more selective screening of donations, bearing in mind the likely limited proportion of the donor population with values below 32, or methods to dilute or remove anti-A/B to this level.

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. We note that there are several points on the plot in Figure 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. However, our sample consists largely of case reports, less than half of which reported both volume and titre(s) and there may be some bias inherent to the kinds of case reports clinicians have chosen

to submit. 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 mea culpa.

#### *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 abstract and paper we had to screen and review. We don't know 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[57], 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 100ml in adults and 15mls in

379 paediatric. Of the 48 cases reported, 15% of cases died, highlighting the clinical importance of the risk  
380 of harm due to haemolysis associated with ABO mismatch plasma containing components.

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

#### 385 **Research Agenda**

- 386 • Agreeing and standardising methods for measuring ABO titres internationally
- 387 • Determine and agree a safe cut-off for defining low titre ABO antibodies for plasma containing  
388 components.

#### 390 **Practice Points**

- 391 • Based on the current evidence there has been no clinical or laboratory haemolysis reported  
392 from the transfusion of ABO incompatible plasma components with an anti-A titre of <32 as  
393 measured by AHG.
- 394 • The lowest reported ABO incompatible plasma volume transfusion to have been associated  
395 with haemolysis were 100 ml in adults and 15ml in paediatric.

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404     **Declarations of Interest**

405     All authors declare no conflict of interests.

406

407     **Contribution to authorship:**

408     JM, LG, SJB, LE and RC designed the study. CD conducted the search for eligible studies. JM, TB and

409     SH extracted the papers and JM, TB, SH and JS analysed the data. All authors contributed to the

410     writing of the article.

## Appendix A.

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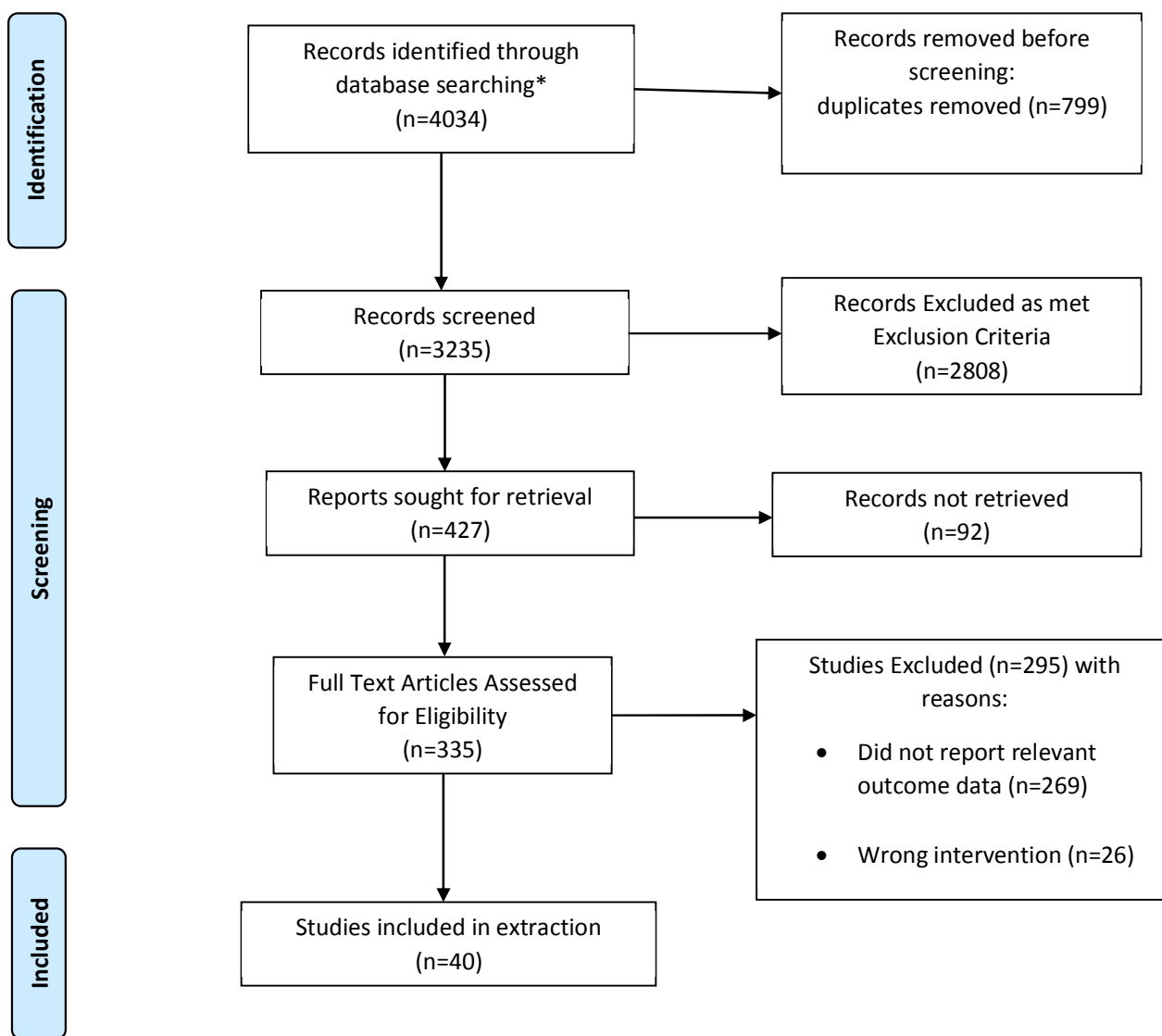
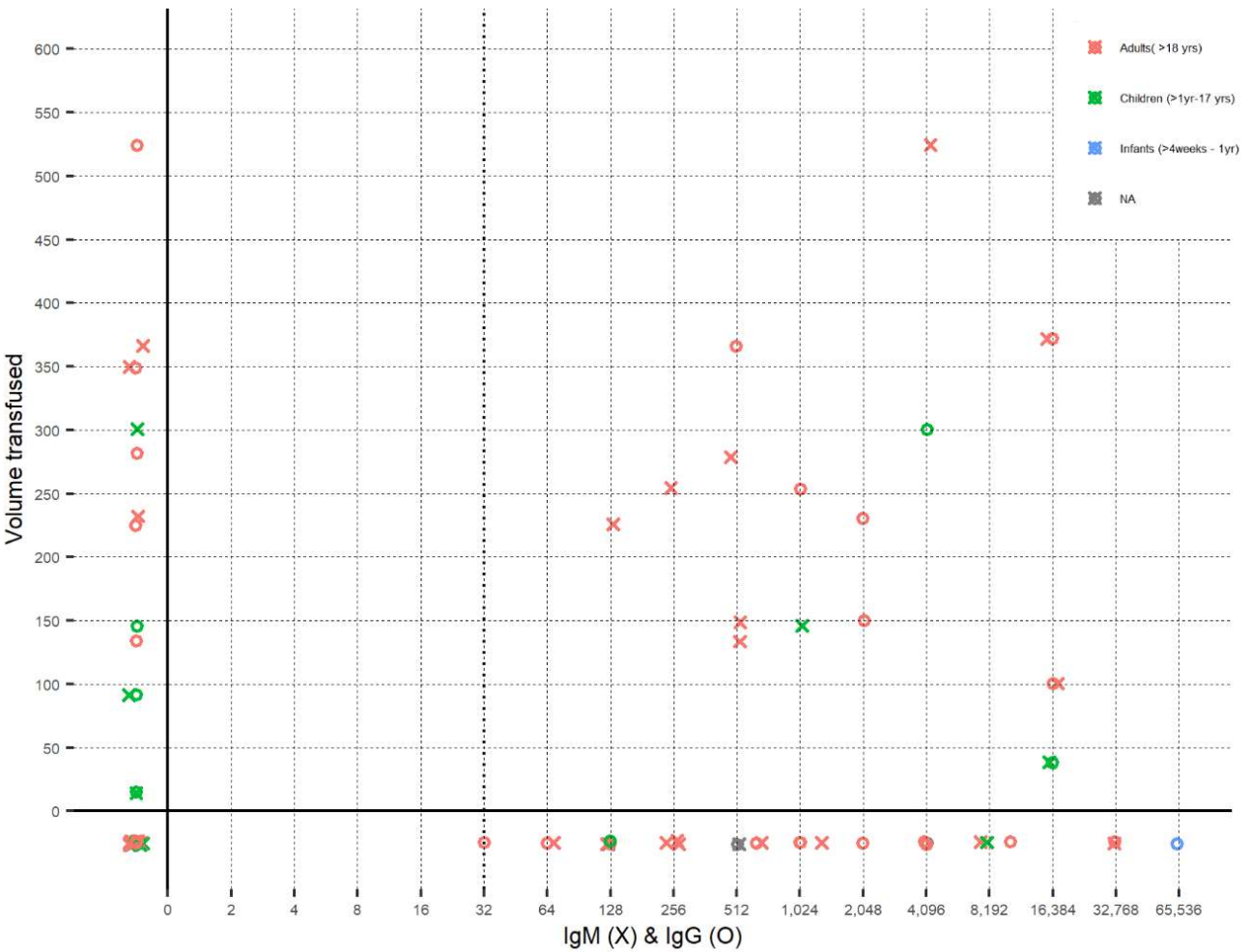
**Figure 1. Prisma Flow Chart**

Figure 2: Scatter plot of volume transfused and reported antibody titres



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.

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	-	-	16384	-
Reis et al	1989	Canada	Apheresis Platelet	-	Opos	Bpos	Anti-B	IAT	IgG	4096	No
Sauer-Heilbom et al	2002	US	Apheresis Platelet	526ml	Opos	Bpos	Anti-B	DTT/Saline IAT		2048/4096	-
Daniel-Johnson et al	2008	USA	Apheresis Platelet	100ml	A	Bpos	Anti-B	IgG/Saline	IgG/IgM	16384/16384	No
Milkins et al	2017	UK	Apheresis Platelet		A	AB	Anti-B	-	-	512	-
Shachner et al	2018	US	Apheresis Platelet	135ml	Apos	Bpos	Anti-B	Saline Tube	IgM	512	No
Balbuena-Merle et al	2019	USA	Apheresis Platelet	367ml	O	B	Anti-B	Tube IAT	IgG	512	Yes
Swain et al	2019	Australia	Apheresis Platelet	-	Apos	ABpos	Anti-B	IAT/Saline	IgG/IgM	32000	No
Haemolytic transfusion reactions due to anti-A											
Ebert et al	1946	USA	Whole Blood	350ml	O	Apos	Anti-A	-	-	2048	No
McLeod et al	1982	USA	Apheresis Platelet	100-200ml*	O	Apos	Anti-A	IAT/Saline	IgG/IgM	10240/640	No
Ferguson et al	1988	Canada	Apheresis Platelet	-	O	Aneg	Anti-A	IAT/RT	IgG/IgM	4000/256	No
Murphy et al	1990	UK	Apheresis Platelet	255ml	O	Aneg	Anti-A	IAT/Saline	IgG/IgM	1024/256	-
Mair et al	1998	USA	Apheresis Platelet	225ml	O	A	Anti-A	Saline	IgM	128	-
Williamson et al	1999	UK	Apheresis Platelet	-	O	A	Anti-A	-	-	-	-
Larsson et al	2000	USA	Apheresis Platelet	371ml	O	A	Anti-A	Saline RT	IgM	16384	No
Valbonesi	2000	Italy	Apheresis Platelet	30-35ml*	Opos	Apos	Anti-A	37°C/RT	IgG/IgM	128/8000	-
Zubair et al	2004	USA	Apheresis Platelet	150ml	O	A	Anti-A	37°C/RT	IgG/IgM	2048/512	-
Sadani et al	2006	UK	Apheresis Platelet	-	Opos	Apos	Anti-A	IAT/DTT		640/1280	Yes
Rosen et al	2008	USA	Pooled Platelets	-	O, B	A	Anti-A	-	-	-	-
Losada et al	2010	USA	Apheresis Platelet	-	O	Apos	Anti-A	AHG	IgG	32	-
Fontaine et al	2012	USA	Apheresis Platelet	231ml	O	Apos	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	-	Opos	Apos	Anti-A	IgG/IgM	IgG/IgM	1024/256	No
Cummings et al	2018	USA	Apheresis Platelet	-	O	A	Anti-A	-	-	-	-
Peedin et al	2018	US	Pooled Platelet	-	O	A	Anti-A	IgG/IS	IgG/IgM	2048/64	No
Basu et al	2019	India	Apheresis Platelet	-	Opos	Apos	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
Guerente et al	2019	USA	Pooled Platelet	-	Opos	Apos	Anti-A	Saline	IgM	64	-
Moinuddin et al	2019	USA	Apheresis Platelet	280ml	O	A	Anti-A	Saline RT	IgM	512	No
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



**Table 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. IAT (Indirect Antihuman globulin Test), RT (Room Temperature) and IS (Immediate Spin). Data not reported in the cases is represented by (–).

Author	Year	Country	Component Type	Volume	Component Blood Group	Patient Blood Group	Antibody	Method of Measurement	Inferred Antibody Isotype	Antibody Titre	Mortality (Y/N)
<b>Haemolytic transfusion reactions due to anti-B</b>											
Boothe et al	1995	USA	Whole Blood	–	Oneg	B	Anti-B	IgG	–	>64000	–
Daniel-Johnson et al	2008	USA	Apheresis Platelet	37ml	A	B	Anti-B	IgG/Saline	IgG/IgM	16384/16384	No
<b>Haemolytic transfusion reactions due to anti-A</b>											
Wood et al	1967	US	Pooled Plasma	5700ml	–	Apos	Anti-A	–	–	32	Yes
Burman et al	1973	UK	Cryoprecipitate	15ml*	O	AB neg	Anti-A	–	–	–	No
Pierce et al	1985	–	Apheresis Platelet	–	O	A	Anti-A	–	–	32000	Yes
Duguid et al	1999	UK	Apheresis Platelet	–	O	Apos	Anti-A	–	–	–	No
Duguid et al	1999	UK	Apheresis Platelet	–	O	ABpos	Anti-A	–	–	–	No
Duguid et al	1999	UK	Thawed Plasma	90mls*	O	Apos	Anti-A	–	–	–	No
Valbonesi	2000	Italy	Apheresis Platelet	–	Opos	Apos	Anti-A	37°C/RT	IgG/IgM	128/8000	Yes
Angiolillo et al	2004	USA	Apheresis Platelet	107ml*	Opos	Apos	Anti-A	–	–	128	Yes
Sapatnekar et al	2005	US	Apheresis Platelet	145ml	Opos	Apos	Anti-A-	IAT/Saline RT	IgG/IgM	16384/1024	No
Harris et al	2007	USA	Apheresis Platelet	300ml	O	A	Anti-A	IAT	IgG	4096	No
Piskorski et al	2014	USA	Pooled Platelets	–	O	AB	Anti-A	–	–	–	–

**Table 2:** A table of the papers reporting on paediatric cases which also reported the titre responsible for the haemolysis. The volumes recorded in the table are those of the whole component except for those highlighted \* which report the plasma volume of the component. IAT (Indirect Antihuman globulin Test) and RT (Room Temperature). Data not reported in the cases is represented by (–)

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