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Research Article

Rate of Alloimmunisation to D, E, C Antigens in Rh-Negative Individuals Transfused with O RhD Positive Red Blood Cells in Emergency Situations: A Systematic Review and Meta-Analysis

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ABSTRACT

The limited supply of the universal blood, O RhD negative, has led to the implementation of transfusion policies regarding the standard use of O RhD positive blood in adult male and women of non-childbearing age in emergency situations. However, there are concerns over associated Rh alloimmunization risks, as Rh antigens have the potential to cause Hemolytic Transfusion Reaction (HTR) and Hemolytic Disease of the Fetus and Newborn (HDFN). Therefore, we thought to determine the rate of anti-D, anti-E and anti-C antibodies formation when this policy is applied. PubMed, Embase and SCOPUS were searched from inception date to August 2023 for eligible alloimmunisation studies with anti-D, anti-C and/or anti-E specific data. Meta-analyses were performed using Open Meta-Analyst software.

Twelve studies were included in the RhD alloimmunisation meta-analysis. The relative risk of RhD alloimmunisation of Rh-negative patients receiving O RhD positive RBCS in emergency situations was determined to be 24.2% (95% CI, 16.5%-32.9%, $p<0.001$). Four of these studies also reported anti-E and anti-C antibodies formation. The meta-analyses performed did not yield statistically significant results but suggests the risk of anti-E and anti-C seroconversion to be around 8% and 5% respectively.

Given the relatively low rate of RhD alloimmunisation observed and the low prevalence of RhD negative individuals in the general population the use of group O RhD positive RBCs in the emergency situations may be justified. However, further prospective studies are needed to confidently establish the rate of alloimmunisation to Rh antigens in this scenario.

Keywords: Rh alloimmunisation; Emergency transfusion; O RhD positive RBCs; Anti-D; Anti-E; Anti-C

INTRODUCTION

The Rh blood group system is the second most clinically significant blood group system in transfusion after the ABO group. The main antigens in this system (D, C, E, c, e) are very immunogenic and have the potential to cause Haemolytic Transfusion Reactions (HTR) and Haemolytic Disease of the Foetus and Newborn (HDFN). The D antigen is of particular concern as it is highly immunogenic, and RhD alloimmunisation is associated with severe cases of HTR and HDFN. In fact, before the prophylactic use of RhD immunoglobulin, antibodies to the D antigen were the main cause of HDFN and a frequent cause of foetal death [1].

With this in mind, transfusion practices worldwide involve routine RhD typing and provision of ABO and RhD matched red blood cells (RBCs) [2]. In emergency situations, however, transfusion of RBCs units may be required before pre-transfusion testing can be performed and the patient's ABO and RhD phenotype determined. In this situation, best practice involves the use of O RhD negative blood to avoid transfusion reactions due to possible anti-A, anti-B or anti-D antibodies, and to prevent RhD alloimmunisation of RhD negative recipients.

As 85% of Caucasians, 92% of Blacks and 99% of Asians are RhD positive, the indiscriminate use of O RhD negative blood in emergency situations and massive transfusions contribute to the shortage of this precious resource. Therefore, transfusion policies and protocols must be in place to optimise the use of O RhD negative RBCs units and conserve it for vulnerable populations, such as women of childbearing age with unknown blood type and RhD negative individuals.

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For this reason, the emergency use of O RhD positive blood in adult males and women beyond childbearing age of unknown blood type is standard practice in many countries, such as the United States of America, Canada and the United Kingdom [3]. Although this approach is deemed safe and recommended by leading professional organisations, such as the Association for the Advancement of Blood and Biotherapies, this strategy is not without risks. Rh alloimmunisation of RhD negative patients being one of the worst possible outcomes [2,3].

Rh alloimmunisation

Alloimmunisation occurs when exposure to foreign antigens through blood transfusion, pregnancy or transplant triggers an immune response. Exposure to as little as 0.1 ml of RhD positive RBCs can stimulate an immune system in a person that lacks the D antigen and result in the production of anti-D antibodies [2]. Subsequent exposure to RhD positive red blood cells results in sensitisation of these cells by anti-D antibodies and their subsequent destruction [4].

The rate of RhD alloimmunisation once exposure has occurred varies greatly between different patient populations and appears to be related to the patient's immune status at the time of transfusion [2]. Early studies using healthy RhD negative volunteers suggested that the probability of RhD alloimmunisation is around 80% [5-7]. More recent studies demonstrated that a much lower incidence of alloimmunisation is observed in the clinical setting [5,8,9]. The probability of developing anti-D is estimated to be between 20 and 30 percent in immunocompetent hospitalized patients, while the incidence in immunocompromised patients is reported to be less than 10% [8,9].

Although not as immunogenic as the D antigen, other Rh antigens, such as the C and E antigens, are also among the most common causes of alloimmunisation [10-12]. The rate of anti-E and anti-c seroconversion is reported to be around 7% and 3% respectively. Anti-C antibodies are usually seen in conjunction with anti-D, which occurs in about 30% of RhD alloimmunisation cases [2]. Development of multiple antibodies to Rh antigens is not uncommon and therefore extended Rh phenotype is recommended in the chronically transfused [13].

Rh alloimmunisation following transfusion of O RhD positive RBCs in emergency situations

The rate of Rh alloimmunisation due to transfusion of O RhD positive RBCs in emergency situations is just now being properly documented in the literature [2]. A commonly referred paper by transfusion guidelines, Selleng et al. 2017, reported the risk for RhD alloimmunisation to be around 4%. This low seroconversion rate is explained by the great majority of the eligible participants in this study being RhD positive and therefore not capable of producing anti-D antibodies. The rate of anti-D seroconversion only including RhD negative participants is much higher at around 45%. Selleng et al research, as numerous others, do not report the rate of alloimmunisation to other clinically significant Rh antigens [14-18].

Many other related studies also have low numbers of RhD negative participants due to the low incidence RhD negative individuals in the general population and the studies' limiting inclusion criteria [5,14,18-20]. Therefore, there is a need to collate all the evidence available in the literature to better understand the risk of Rh alloimmunisation due to the provision of O RhD positive blood in emergency situations.

This systematic review and meta-analysis aim to determine the rate of RhD alloimmunisation in RhD negative patients that received O RhD positive blood transfusions as standard practice in emergency situations. Furthermore, as the predominant RhD negative haplotype is d c e, we also aim to determine the rate of anti-E and anti-C formation in this scenario, which hasn't been properly highlighted in the literature. Ultimately, providing supportive data to medical centres and professionals regarding expected Rh seroconversion outcomes when applying this transfusion strategy.

We hypothesise that the data will show significant variability due to the differing number of participants and patient populations in studies; nonetheless, we believe the median anti-D seroconversion rate after RhD-incompatible transfusions will fall within the expected range of 20%-30%. We also hypothesise that in addition to anti-D antibody formation, anti-E and anti-C antibodies will be observed in this population.

METHODOLOGY

This systematic review and meta-analysis followed the protocol outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). In addition, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was applied to assess the quality of the articles selected [21].

Search strategy

In order to identify appropriate studies for this meta-analysis, we systematically searched the PubMed, Embase and SCOPUS databases from inception date to August 2023 [22]. The search terms used included a combination of the following keywords: "Rh alloimmunisation", "Rh negative", "emergency transfusion", "uncross-matched transfusion", "O RhD positive red blood cells", "anti-D", "anti-C" and "anti-E". Manual search was also performed in the reference lists of the relevant literature and one additional eligible study was identified.

Study selection and eligibility

The title and abstract of the records retrieved by our search strategy were screened for their relevance to this review's aims. Articles that reported the incidence of anti-D, anti-C and/or anti-E formation after transfusion of O RhD positive RBCs as standard practice in emergency situations were deemed suitable. Identified articles were rejected based on the following exclusion criteria: (a) meta-analysis, conference abstracts and case reports; (b) not originally written in English; (c) full-text unavailable on the RMIT library or a public website; (d) duplicate data; (e) not relevant to research question. Eligible studies must also be composed of primarily non-oncology or non-immune compromised patients as these patient populations are known to have lower alloimmunisation rates than the general population.

Data extraction

following relevant data were extracted from eligible studies and tabulated: Primary author, publication year, and study design, study period, country of origin, inclusion criteria, patient population, median age, follow-up, and number of O RhD positive RBCs units transfused [5]. The number of Rh-negative recipients of mismatched transfusion and the number and rate of anti-D formation observed in this population. In addition, data relating to Rh combination antibodies and the number of anti-E and anti-C antibodies formed in this scenario were also recorded on this table.

Statistical analysis

Meta-analyses were performed to calculate the rate of anti-D, anti-C and anti-E alloimmunisation with 95% confidence intervals using the Open Meta-Analyst software. One-armed proportion an analysis was performed using the arcsine transformed proportion method [23]. Binary random effects model with maximum likelihood parameters was selected. A p-value of less than 0.05 was considered statistically significant and heterogeneity was evaluated using I2 statistics.

RESULTS

Study selection

Our search strategy led to retrieval of 2957 citations from the electronic databases utilised (PubMed, Embase and SCOPE). 864 duplicates were identified and removed before title screening. 1982 citations were removed after title screening, as they were not relevant to our review's purpose. Similarly, 111 papers' abstracts were screened, and 74 studies were deemed irrelevant and excluded. 37 full-text articles were assessed for eligibility. After thoroughly examination of these articles, 26 papers was excluded based on our exclusion criteria and 11 were deemed eligible. The number of papers excluded based on each exclusion criteria is depicted on Figure 1. The reference list of the selected papers was examined, and one additional eligible paper was identified from this manual search. All 12 papers identified were included in this meta-analysis.

Study characteristics

The 12 studies included in this review and meta-analysis examined the incidence [5], of Rh alloimmunisation [8,9,15-17,24] or the safety of uncross matched transfusion with type O RhD positive red blood cells in emergency situations. As seen on Table 1, almost all of the studies had a retrospective design and were conducted in the USA or Germany (Table 1) [14,18-20]. Most of the studies were composed of trauma patients, either adult males or women at least 40 years old [15-20,25]. A few studies also included male teenagers [5,24,25], and two studies did not include patients older than 50 years [16,25].

Generally, the studies excluded patients with previous history of Rh antibodies, patients that died or patients that received Rh immune globulin (Rh-Ig) after mismatched transfusion. The length of serological follow-up varied greatly between studies and even within patients of the same study. The median serological follow-up for each study can be seen on Table 1.

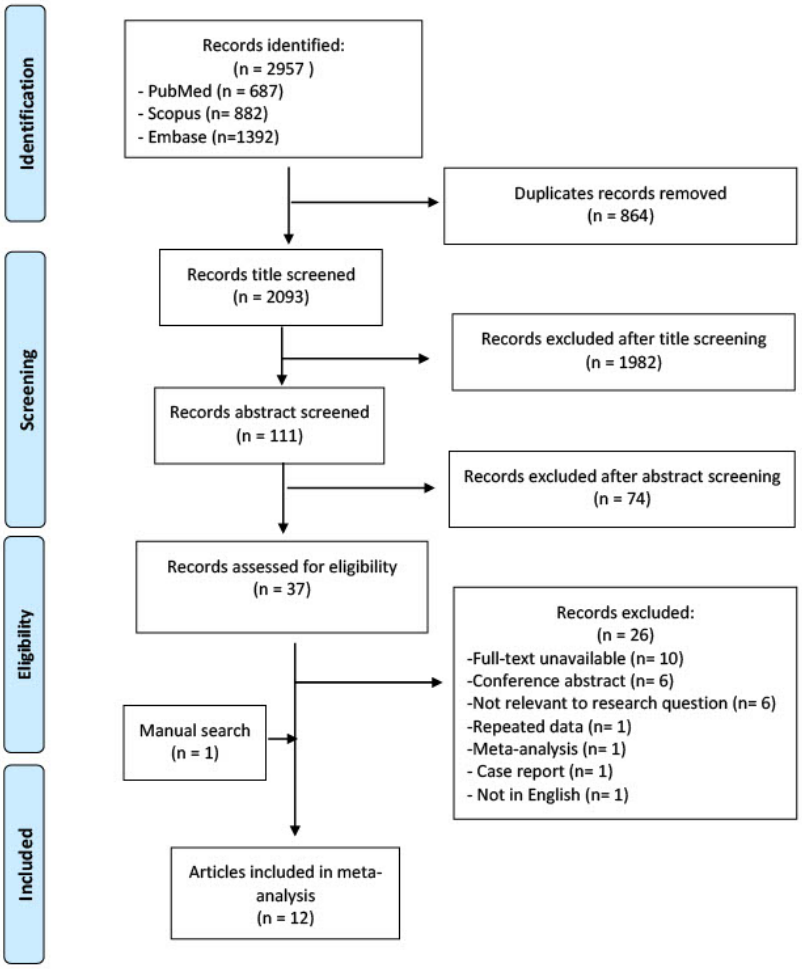

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart displaying the literature search and screening process for the selection of eligible studies on the rate of alloimmunisation to D, E, C antigens in Rh-negative individuals transfused with O RhD positive blood in emergency situations.

Table 1: Characteristics of eligible studies investigating the rate of alloimmunisation to D, E, C antigens in Rh-negative individuals transfused with O RhD positive blood in emergency situations.

Study	Study design	Study period	Country	Patient population	Median age	Inclusion criteria	Median follow-up	Median n of units
Dutton et al. 2005 [19]	Retrospective	1 year, 2000	USA	Trauma patients	Not specified	Recipients of uncrossmatched group O RBCs survival greater than 24 hours	72 days	1 responder
Flommersfeld et al. 2018 [18]	Retrospective	Jan 1 2010 - Dec 31 2014	Germany	Trauma patients in ER	Not specified	Recipients of RBCs in ER. Included patients who died or lost follow-up	Not specified	13*
Frohn et al. 2003 [8]	Retrospective	Nov 1997 - Jun 2002	Germany	42% abdominal surgery, 33% CV surgery, 14% trauma, 5% DIC, 6% miscellaneous	59* non-responders 62* responders	Rh-negative recipients of O RhD positive RBCs with no previous antibody history. Did not include patients with haematologic disorders.	174* days non-responders	11* non-responders 6* responders
Meyer et al. 2014 [5]	Retrospective	Jan 2001 - Aug 2011	USA	ER patients: 50% Trauma, 25% gastrointestinal and 25% vascular surgery	52 years old	ER patients that received emergency released RBCs. Survived past 7 days and had at least one follow-up antibody screen	103.5 days	10
Miraflor et al. 2012 [20]	Retrospective	Jul 2008 - Aug 2010.	USA	Trauma patients	Not specified	Recipients of emergency transfusion in the ER or operating room.	Not specified	4
Raval et al. 2021 [20]	Retrospective	Jan 1 2010 - Dec 31 2019	USA	Trauma patients with MTP activation	41 years old	Recipients of uncrossmatched group O RhD positive RBCs or LTOWB. ≥ 18 years old, follow-up ≥ 14 days	220 days non-responders 161.5 days responders	5
Seheult et al. 2022 [16]	Retrospective	Jan 1 2010 - Dec 31 2019	USA	Trauma patients	35 non-responders 32 responders	18–50 years of age RhD negative patients who received RhD positive RBC or LTOWB during their resuscitation and follow-up ≥ 14 days	♂ 197 non-responders ♂ 37 non-responders	5 non-responders 3 responders

Selleng et al. 2017 [16]	Prospective, observational study	Jan 1 2001 - Dec 31 2015	Germany	Hospitalised patients	65 years old	Patients with unknown blood type who received emergency transfusions of O RhD positive RBCs.	12 months	4
Tchakarov et al. 2014 [24]	Retrospective	Jan 2012 - Nov 2013	USA	57.7% trauma, 19.3% CV surgery, 11.6% other, 7.6% oncology, 3.8% Transplant	49* years old	Recipient of RhD positive RBCs, follow-up every 3 days during hospitalisation	67.6 days	4
Williams et al. 2019 [15]	Retrospective	Oct 2015 - Sep 2018	USA	Trauma patients with MTP activation	39.5 responders	RhD negative patients that received at least 1 unit of RhD-positive RBCs and a minimum follow-up of 6 months.	Not specified	3 responders
Yazar et al. 2007 [9]	Retrospective	Jan 1 2005 - Aug 15 2005	USA	Critically ill nononcology patients	72 non-responders 74 responders	RhD negative recipients of Rh-positive RBCs, no previous antibody history, and follow-up ≥ 10 days	182* days	3 non-responders 2.5 responders
Yazar et al. 2021 [25]	Retrospective	2000 – 2019	USA	Trauma patients	33 years old	13-50 years old RhD negative patients transfused with RhD positive RBCs or LTOWB during their resuscitation. Follow-up≥ 14 days	51 days non-responders 101 days responders	3

Note: * Mean

All the studies identified reported the incidence of RhD alloimmunisation, with four of these studies also reporting the incidence of anti-E and anti-C formation, as seen on Table 2 [5,9,15,24]. Two additional studies mentioned anti-C and anti-E seroconversion, but did not provide sufficient data for the rates of alloimmunisation to these antigens to be determined [8,18].

Quality assessment of included studies

The quality of the 12 studies included in this meta-analysis was assessed using the STROBE checklist with the most relevant criteria summarised in Table 3. Most criteria were fulfilled by the eligible studies with exception of addressing bias and discussing potential limitations [22]. Only 2 out of the 12 studies [14,15,17], acknowledged potential sources of bias and 5 of these studies also failed to discuss their studies limitations [8,9,18,24]. However, efforts were made to reduce bias such as excluding patients with Rh antibody history. It should be noted that one paper showed a lower quality than others. Williams et al. failed most criteria as it is a published "letter to editor" where the authors discuss another paper in addition to their own findings [15]. Therefore, there is a lack in the structure of the paper and incomplete information. Nonetheless, it contains all relevant data to determine RhD alloimmunisation rates and was included in this meta-analysis.

Table 2: Results of eligible studies investigating the rate of alloimmunisation to D, E, C antigens in Rh-negative individuals transfused with O RhD positive blood in emergency situations.

Study	No of eligible RhD negative patients	No of anti-D formers	Anti-D rate	Rh combination antibodies	Total Anti-E	Total Anti-C
Dutton et al. 2005 [19]	10	1	10%	-	-	-
Flommersfeld et al. 2018 [18]	18	9	50%	Not specified	Not specified	Not specified
Frohn et al. 2003 [8]	78	16	20.50%	Not specified	Not specified	Not specified
Meyer et al. 2014 [5]	8	1	12.50%	1 anti-D, C, E	2	1
Miraflor et al. 2012 [20]	3	1	33%	-	-	-
Raval et al. 2021 [17]	129	10	7.80%	-	-	-
Seheult et al. 2022 [16]	235	77	32.70%	-	-	-
Selleng et al. 2017 [14]	31	14	45%	-	-	-
Tchakarov et al. 2014 [24]	26	3	11%	2 anti-D,E	2	0
Williams et al. 2019 [15]	59	10	17%	1 anti-D, C, E 1 anti-D, E 2 anti-D, C	2	3
Yazar et al. 2007 [9]	98	22	22%	3 anti-D,C,E 7 anti D, E 2 anti-D, C	11	5
Yazar et al. 2021 [25]	96	41	42.70%	-	-	-

Note: Not specified- The study mentions anti-E and anti-C seroconversion but does not specify how many out its total patient population developed these antibodies

Table 3: Quality assessment of the studies included in this meta-analysis using the STROBE checklist.

	Dutton et al. 2005 [19]	Flommers-feld et al. 2018 [18]	Frohn et al. 2003 [8]	Meyer et al. 2014 [5]	Miraflor et al. 2012 [20]	Raval et al. 2021[17]	Seheult et al. 2022 [16]	Selleng et al. 2017 [14]	Tchakarov et al. 2014 [14]	Williams et al. 2019 [15]	Yazar et al. 2007 [9]	Yazar et al. 2021[25]
Title and abstract												
Clear title and abstract	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Introduction												
Explains scientific background and state objectives	Y	Na	Y	Y	Y	Y	Y	Y	Y	Na	Y	Y
Methods												
Describe setting, relevant dates, exposure, follow-up	Y	Y	Y	Y	Yb	Y	Y	Y	Yc	Y	Y	Y

Describe eligibility criteria and methods of selecting participants	Nd	Nd	Y	Y	Y	Y	Y	Y	Y	Nd	Y	Y
Describe statistical methods	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y
Address bias	N	N	N	N	N	Y	N	Y	N	N	N	N
Results												
Give characteristics of study participants	N	Ne	Y	Y	Ne	Y	Y	Y	Y	Nf	Y	Y
Explain missing data and give reason for non-participation	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Report number of outcome events	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion												
Summarise, interpretate key results, compare with related studies	Y	Y	Ng	Y	Y	Y	Y	Y	Y	Ng	Y	Y
Discuss potential limitations	Y	N	N	Y	Y	Y	Y	Y	N	N	N	Y

Note: Y= yes, criteria fulfilled; N= no, criteria not fulfilled; a Objectives not stated; b Follow-up period stated on results section; c Dates stated on results section; d Not clearly stated; e Characteristics of the eligible RhD negative participants not provided; f Only characteristics of alloimmunised participants were given; g Doesn't compare results with other similar studies

RhD alloimmunisation meta-analysis

meta-analysis and forest plot was performed on the rate of RhD alloimmunisation in the proposed scenario (Figure 2A). Across the 12 studies included in this meta-analysis, 205 RhD negative patients developed an anti-D antibody out of 791. Therefore, the overall rate of RhD alloimmunisation of Rh-negative patients receiving O RhD positive RBCS in emergency situations was determined to be 24.2% (95% CI, 16.5%–32.9%, p<0.001). This result is highly statistically significant with a p-value of less than 0.001. However, the included studies were shown to have a high degree of heterogeneity (I2=82.71%, p<0.001).

Anti-E seroconversion meta-analysis

meta-analysis and forest plot was performed on the rate anti-E seroconversion in the proposed scenario, as seen on Figure 2B. Only 4 of the 12 studies reported the incidence of anti-E formation in quantitative form [5,9,15,24]. The overall rate of anti-E seroconversion was determined to be 8.3% (95% CI, 4.2%–13.5%). However, this finding was not deemed statistically significant as a p-value greater than 0.05 was obtained (p=0.146). The heterogeneity among the studies was found to be low (I2=19.83%, p=0.146).

Anti-C seroconversion meta-analysis

A meta-analysis and forest plot was conducted on the rate anti-C seroconversion in the proposed scenario, as seen on Figure 2C. Only 4 of the 12 studies reported the incidence of anti-C formation in quantitative form [5,9,15,24]. The overall rate of anti-C seroconversion was determined to be 4.8% (95% CI, 2.2%–8.2%). However, this finding was not deemed statistically significant as a p-value greater than 0.05 was obtained (p=0.699). An I2 value of 0% was obtained, suggesting the studies are homogeneous and the differences observed between their data are more likely due to random sampling error (Figure 2).

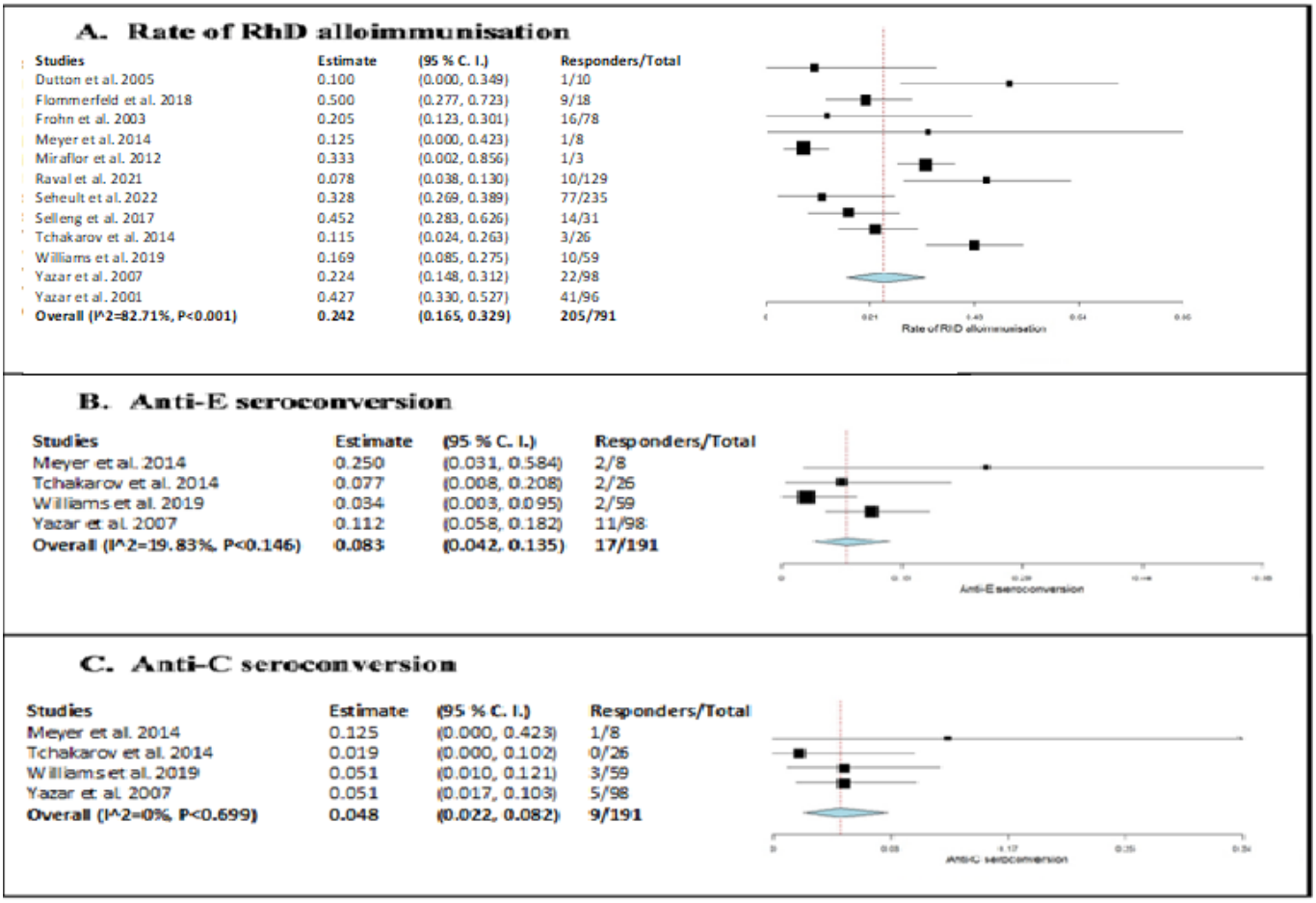

Figure 2: Forest plots of meta-analysis on the (A) rate of RhD alloimmunisation; (B) anti-E; (C) anti-C seroconversion in Rh-negative individuals transfused with O RhD positive RBCs in emergency situations.

DISCUSSION

In emergency situations, the prompt transfusion of RBCs can be a necessary and lifesaving procedure, however, it can also pose a significant risk to patients as pre-transfusion testing to determine the patient blood group and unit compatibility cannot always be performed in time. The use of O RhD negative blood is deemed the safest approach in this scenario, however, this altruistic and scarce resource. To balance the need to conserve the universal blood supply, it is standard practice in some countries to use O RhD positive blood in adult males and women of non-childbearing age in emergency situations. This is a controversial policy as the risks associated with this approach are not yet well known, with reported RhD alloimmunisation rates varying greatly [2].

The 12 studies analysed in this meta-analysis reported RhD alloimmunisation rates ranging from 7.8% to 50% in the proposed scenario. However, our findings reveal an overall rate of 24.2% (95% CI, 16.5%–32.9%, p<0.001), which is within the expected range of 20%-30% previously reported in the clinical setting.

Aside from the small size of some of our studies, many other factors may have contributed to the variance in RhD alloimmunisation rates among studies and consequently the high heterogeneity found in this meta-analysis [5,18-20]. A possible reason for this is the differences in the studies' patient populations, such as type and extend of injury. For example, Rava et al. Study population comprised of patients with severe traumatic injury requiring MTP activation and reported the lowest RhD alloimmunisation rates seen in this meta-analysis (7.8%) [17]. This lower rate may be related to immunomodulatory effect and stress-related immune suppression caused by severe traumatic injury.

Age differences between studies populations may also have played a role, due the impaired immune function associated with old age [26-28]. This may be one of the reasons why Yazar et al.[25], study, which only looked at patients up to 50 years old, reported one of the highest RhD alloimmunisation rates (42.7%) seen in this meta-analysis [25,29].

Other factors that contribute to the highly variable rates reported may relate to differences in studies characteristics and methodology, such as inclusion and exclusion criteria. For example, some of the studies excluded patients that developed an anti-D antibody within 14 days after exposure, as any reactivity seen was deemed to be due to an anamnestic response, while most of the other studies recognised these patients' anti-D formation as a primary antibody response to RhD [16,17,22]. This may have possibly led to under-reporting by some studies if patients developed a brisk primary immune response in less than 14 days or over-reporting if studies without such exclusion criteria did not interpret anamnestic signs cautiously.

Finally, the significant differences in serologic follow-up length between studies and even between patients of the same study may have contributed to the discrepancies in the incidence of RhD alloimmunisation observed. As it may take several months for antibodies to be detected, the short follow-up periods of some studies or patients may have been insufficient to capture all recipients who might eventually become alloimmunised [30]. This may have led to under-reporting and help explain the low RhD alloimmunisation rates

observed by Meyer, Dutton and Tchakarov et al. On the other hand, the significant longer serological follow-up of all patients in Selleng et al. study may help explain the higher alloimmunisation observed [5,14,19,24].

Risk of alloimmunisation to other Rh antigens

In addition to RhD alloimmunisation, RhD negative patients that receive Rh-positive blood are at risk of developing antibodies to other Rh antigens, more specifically the E and C antigens, as the great majority of RhD negative individuals also lack these antigens [2]. On a related study, Gonzalez et al. reported that 50% of the patients that became RhD alloimmunised after Rh incompatible RBCs transfusion developed a further antibody to another Rh antigen (anti-E and/or anti-C) [31]. This highlights the importance of considering anti-E and anti-C antibody formation when analysing the alloimmunisation risks associated with the transfusion of O RhD positive RBCs in Rh negative individuals in emergency situations.

However, only 4 of the 12 studies included in this meta-analysis specified if anti-E and anti-C formation was observed in this scenario. Our findings suggest the risk of anti-E and anti-C seroconversion to be 8.3% (95% CI, 4.2%–13.5%) and 4.8% (95% CI, 2.2%–8.2%) respectively. Although these findings have no statistical significance, they are still clinically significant, as a considerable number of patients did develop anti-E and anti-C as we hypothesised.

Perhaps some of the reasons why no statistically significant data was obtained from our anti-E and anti-C seroconversion meta-analyses were the small number of studies included and the small sample size of some of the studies, which could have affected the precision of the results obtained. Furthermore, only 1 out of the 4 studies included actually aimed to determine the incidence of anti-E and anti-C formation in the proposed scenario [9]. The other 3 studies mentioned the presence of these antibodies as additional findings observed during their research. This may have led to under-reporting by these studies as the focus of their research was not to identify and determine the incidence of anti-E and anti-C seroconversion.

It is important to note that as the studies reported patients having anti-D and anti-C combinations, the presence of an anti-G antibody should have been considered and disproved. The G antigen is present on most D positive and all C positive RBCs, and therefore anti-G antibodies appears as a combination of anti-D and anti-C in initial antibody identification testing. Adsorption and elution studies are necessary to determine if indeed a patient with this picture have formed anti-D and anti-C antibodies, or an anti-G is present in addition to or instead of one or both of these antibodies [2].

Limitations and future steps

The main limitation of this systematic review and meta-analysis is the retrospective nature of almost all the studies included. In addition to potentially introducing report bias, this resulted in the lack of consistent and serial serologic follow-ups. As the studies' participants were not monitored for an appropriate length of time to capture all alloimmunisation events, the true rate of RhD alloimmunisation may have been underestimated. Furthermore, most of the included studies have a small sample size which may limit the effect of generalisability. Lastly, only a small number of studies with incomplete information were able retrieved from the literature regarding anti-E and anti-C formation in the proposed scenario.

On this basis, further large prospective studies are needed to confidently establish the rate of RhD alloimmunisation in Rh-negative individuals transfused with O RhD positive red blood cells in emergency situations. This should allow for more complete and lengthier follow-up of participants and better gathering of relevant information, such as participants' complete transfusion, alloimmunisation, and pregnancy histories as well as the extend Rh phenotype of patients and the units transfused. Future research should also aim to identify antibodies to other Rh antigens, specifically E and C, so the risk of alloimmunisation in this scenario is better understood and can be properly determined.

CONCLUSION

Given the relatively low rate of RhD alloimmunisation observed in this meta-analysis along with the very low prevalence of RhD negative individuals in the general population, the use of O RhD positive blood in the emergency situations may be justified. The emergency transfusion of O RhD positive blood in males and women of non-childbearing as standard practice, should be considered by institutions experiencing significant shortage of O RhD negative blood. However, as more and more institutions implement this approach, further prospective studies should be conducted so the alloimmunisation risks associated with this practice can be better understood and the alloimmunisation rates to Rh antigens can be established.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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