An international investigation into O red blood cell unit administration in hospitals: The GRoup O Utilization Patterns (GROUP) study

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Abstract (250 Words)

Background: Transfusion of group O blood to non-O recipients, or transfusion of RhD negative blood to RhD positive recipients, can result in shortages of group O or RhD negative blood, respectively. This study investigated RBC utilization patterns at hospitals around the world, and explored the context and policies that guide ABO blood group and RhD type selection practices.

Methods: This was a retrospective study on transfusion data from the 2013 calendar year. This study included a survey component that asked about hospital RBC selection and transfusion practices, and a data collection component where participants submitted information on RBC unit disposition including blood group and RhD type of unit and recipient. Units administered to recipients of unknown ABO or Rh group were excluded.

Results: Thirty-eight hospitals in 11 countries responded to the survey, 30 of which provided specific RBC unit disposition data. Overall, 11.1% (21,235/191,397) of group O units were transfused to non-O recipients; 22.6% (8,777/38,911) of group O RhD negative RBC units were transfused to O RhD positive recipients, and 43.2% (16,800/38,911) of group O RhD negative RBC units were transfused to recipients that were not group O RhD negative. Disposition of units and hospital transfusion policy varied within and across hospitals of different sizes, with transfusion of group O RhD negative units to non-group O RhD negative patients ranging from 0 to 33%.

Conclusion: A significant proportion of group O and RhD negative RBC units were transfused to compatible, non-identical recipients, though frequency of this practice varied across sites.
Introduction

Group O red blood cells (RBC), especially those that are also RhD negative, are a precious resource that are often in short supply. Recent data demonstrates a marked decline in the number of RBC units distributed by blood centers around the world over the past five years; however, despite this decline, the distribution of group O RBC units has increased as a proportion of the total number of distributed units. The reasons for the disproportionate increase in group O RBC unit distribution might include their preferred use in emergency settings when ABO/RhD of the recipient is unknown, exclusive use in the neonatal intensive care unit (NICU), use in patients with alloantibodies or who require antigen negative, phenotyped units to prevent alloimmunization, and to streamline hospital inventory management by maintaining only units that will be ABO compatible with any recipient. Thus, in addition to supplying the needs of group O recipients, there are additional pressures on group O RBC inventory unique to this blood group.

The number of group O RhD negative units that are transfused in many jurisdictions is greater than the percentage of group O RhD negative individuals in the population. For example, the national blood supplier to England and North Wales, the National Health Services Blood & Transplant Organization, requests hospitals maintain use of group O RhD negative RBCs to below 10.5% of total RBC requests to manage disproportionate supply and demand. This is because, in England 7.8% of individuals are group O RhD negative, while usage of group O RhD negative blood is higher. There are no evidence-based practice guidelines or established standards to serve as a benchmark for an acceptable frequency for the transfusion of group O and RhD negative RBC units to compatible, but non-identical recipients.

Given the importance of maintaining a stable and sufficient inventory of group O and RhD negative RBC units, this study investigated the RBC utilization patterns, specifically use of group O RBC units, at a variety of hospitals around the world, and explored the context and policies that guide their ABO/RhD selection practices when issuing RBC units for transfusion.
Study Design/Methods

This study was performed in two phases: A survey component that asked about hospital RBC selection and transfusion practices; and, a data collection component where the participants submitted information on their hospital’s group O RBC issuing practices.

Part 1: Survey on RBC transfusion practices and selection of RBC units

The survey was conducted in English under the auspices of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative, and was designed by a working group of international BEST members. The survey was then piloted with other BEST members from around the world to ensure its clarity and comprehensibility. A link to the final version of the survey was distributed via email to all members of the BEST Collaborative who were encouraged to both complete the survey and forward the link to other colleagues at different institutions. Thus, the total number of hospitals that received the link to the survey is not known. Hospitals of any size could participate and there was no minimum number of RBC transfusions required to participate.

The survey was based on the 2013 calendar year and it requested information on hospital demographics including hospital type, clinical services offered, hospital size, and distance from blood supplier. The survey was sent out at the end of the 2014 calendar year. Information on hospital transfusion practices and policies was also collected: the average daily RBC unit inventory levels, the average number of RBC units transfused, use of group O RBC units exclusivity for specific patient populations, maintaining group O RBC units in refrigerators outside the blood bank and their location, uncrossmatched RBC transfusion practices and hospital definition of childbearing age vis-à-vis female recipients.

Part 2: Data Collection on RBC utilization

Upon completion of the survey in Part 1, participants were emailed electronic data collection forms. Upon completion, these forms were returned electronically to McMaster University where they were archived and analyzed. The following data were collected in this part of the study: the number and ABO/Rh of the transfused RBC units, ABO/Rh of recipients, the service or hospital location to where the RBC units were issued, the total number of RBC units of all ABO groups issued to each hospital service area, and the total number of group O units issued to non-O
recipients by service area. Participants were asked to provide the indication for group O RBC units issued to non-O recipients. The forms were completed locally at each center for the calendar year 2013 with either monthly or quarterly RBC transfusion data, depending upon the participant’s reporting capability from their laboratory information system.

This study protocol was approved by the Hamilton Integrated Research Ethics Board, and all participants obtained the necessary ethics approvals at their institutions.

Statistical analysis
All data analyses were performed by a biostatistician at the McMaster Centre for Transfusion Research using SAS 9.3(SAS Institute, Cary, NC) software. Sub-analyses stratifying these percentages by hospital size and distance from blood supplier were also performed. The percentage of transfused group O RBC daily inventory was compared across hospital size and distance from blood supplier using the Kruskal-Wallis test and the Wilcoxon rank-sum test. Wilcoxon rank-sum test was also used to compare mean percentages of RBC transfusions by ABO/RhD of donor and recipient across varying sizes of hospital (large >1000 beds; medium 250-999 beds; small <250 beds). Univariate generalized linear models using beta distribution were performed to investigate the association of various factors with the percentage of group-O RBC units transfused to non-O recipients, which was a continuous variable between zero and one. The factors included were hospital size, services offered, distance from blood supplier, inventory management and hospital RBC transfusion policies. A p value of <0.05 was considered significant for all statistical tests.

Due to the significantly lower rate of RhD negative RBC units and recipients the Japanese contribution to the study was highlighted. Not all hospitals answered each question in the survey or provided complete information on hospital transfusion patterns by location or indication. Denominator values were adjusted accordingly.
Results

Part 1: Survey on hospital RBC unit selection practices

Hospital demographics

Thirty-eight hospitals in 11 countries responded to the survey. Responses were received from Australia, Brazil, Canada, Denmark, Germany, Japan, Netherlands, Norway, Poland, United Kingdom and the United States. At these hospitals a total of 540,883 RBC units were transfused during the 2013 calendar year. The demographics of the participating hospitals are summarized in Table 1. The clinical services offered at these hospitals were variable (Table 1).

RBC Inventory

Though not statistically significant, larger hospitals tended to transfuse a larger proportion of their daily inventory of group O RBC units, as compared to small and medium hospitals (Figure 1). In terms of the group O RhD negative inventory, large, medium and small hospitals transfused daily 24.3% (n=6), 9.9% (n=16) and 17.5% (n=8) of their total inventory, respectively (p =0.21; five hospitals did not provide inventory information and 3 hospitals did not carry group O RhD negative RBC inventory, all from Japan). In terms of group O RhD positive inventory, large hospitals transfused daily 36.8% (n=8) of their total inventory compared to 20.1% (n=17) and 21.8% (n=8) at medium and small hospitals, respectively (p=0.26; 5 hospitals did not supply inventory information) (Figure 1).

No statistically significant difference was found between the mean percentages of group O Rh D negative daily inventory transfused at hospitals located more than 50 km (14.0%, n=9) versus less than 50 km (15.6%, n=20) from their blood supplier (p=0.75). Two hospitals did not provide distance information.

Hospital Policy for transfusing group O RBC units

Fourteen (36.8%) hospitals maintained one or more remote refrigerators containing a mean of 11.0 ±12.4 group O RhD negative RBC units and a mean of 14.0 ±22.2 group O RhD positive
RBC units. The locations of these refrigerators were in the operating room, emergency room, intensive care units (medical and surgical), oncology day service, air ambulance sites and satellite dispensing stations. At 24/38 (63.2%) hospitals, all patients in need of uncrossmatched RBC units were transfused with group O RhD negative RBC units. Alternative hospital policies for the selection of uncrossmatched RBC units included transfusing group O RhD negative RBC units: to women of any age (n=1); only to women of childbearing age and pediatrics patients (n=7); only to pediatric patients (n=1); only to women of childbearing age (n=4), and not further clarified (n=1). The upper threshold for women to be considered of childbearing age ranged from 45 - 55 years old depending upon the participating hospital’s policy. The upper threshold of childbearing age was specifically defined as age 50 at 5 hospitals in the USA, 2 in Germany and 2 in Norway, while one hospital in Canada and one in the USA uses age 45 and one hospital in the USA uses age 55. Of the hospitals who reported on neonatal transfusion practice policy, neonates received exclusively group O RBC units at 23/31 (74.2%) hospitals. Three respondents reported that group O RBC units are transfused in select ABO incompatible allogeneic stem cell transplant patients, and one reported that group O RBC units are transfused in allogeneic stem cell transplantation but did not elaborate further.

Part 2: Data collection on RBC transfusion practices

Six large hospitals, 17 medium hospitals and 7 small hospitals from 11 countries contributed data on the disposition of 415,696 RBC units that were transfused during the 2013 calendar year. Of those 415,696 units, 2,275 (0.6%) were transfused to recipients of unknown ABO/RhD; these units were excluded from the analysis, thus the total number of analyzable units was 413,421 (Table 2). A total of 144 (0.03% of analyzable RBC units) incompatible transfusions were reported; a comment was provided by 3 centres reporting incompatible transfusions stating that these were in the context of stem cell transplantation. These units have not been excluded from the analysis because they do not have a significant impact on the group O blood utilization. Of note, one hospital from Japan provided disposition data on 17,148 RBC units (4.1% of total analyzable RBC units).

Thirty participants contributed data to this part of the study. Overall, 11.1% (21,235/191,397) of the group O RBC units were transfused to non-O recipients. The mean percentage of group O
RBC units transfused to non-O recipients was similar in large, medium and small hospitals (7.6%, 12.2% and 13.1% respectively, p=0.29), although there was considerable variability surrounding these mean percentages (Figure 2 A).

For the 30 participants in this part of the study, of all the group O RhD negative RBC units, 22.6% (8,777/38,911) were transfused to group O RhD positive recipients; and 43.2% (16,800/38,911) of the group O RhD negative RBC units were transfused to non-O RhD negative recipients. The mean percentage of group O RhD negative RBC units transfused to non-O recipients varied by hospital size with 35.4%, 50.8% and 34.8% at large, medium and small hospitals, respectively (p=0.047, Figure 2 B). Group O RhD negative RBC units accounted for 9.4% (38,911/413,421) of total RBC units reported and group O RBC units accounted for 46.3% (191,397/413,421) of total RBC units reported.

**RBC transfusion patterns by hospital location**

Of the 30 hospitals that contributed to data on RBC transfusion patterns, 22 (73.3%) contributed to transfusion patterns by location and 21 (70%) to transfusion patterns by indications. The most common area of the hospital where group O RBCs were issued to non-O recipients was on the regular wards (Figure 3). Sixteen hospitals with a NICU contributed transfusion data by location; of these 9 (56%) provide exclusively group O RBC units to neonates; 4 (25%) dis not have this policy and 3 (19%) did not provide this information. The number of group O RBC units transfused to non-group O recipients in the NICU accounted for 480/12,637 (3.8%) of total group O RBC units transfused to non-group O recipients with 89/12,637 (0.70%) from the 4 hospitals where group O RBC units were not used exclusively for neonatal transfusion and 391/12,637 (3.09%) from the 9 hospitals where group O RBC units were transfused exclusively to neonates.

The most common reasons for issuing group O RBC units to non-O recipients included emergency issued uncrossmatched units (33.1%), O units close to expiry (31.9%), units phenotyped for patients with known antibodies (21.1%) and use in stem cell transplant recipients (13.7%).

**Associations between utilization and hospital characteristics and policy**
Univariate analyses for the percentage of group O RBC units transfused to non-O recipients demonstrated no statistically significant associations with hospital characteristics or hospital transfusion policy (Figure 4). However, some trends were identified. Hospitals with cardiovascular, cancer/oncology, and obstetrics services reported transfusing a smaller percentage of group O RBC units to non-O recipients. Hospitals that provided exclusively group O RBC units to neonates had a higher rate of transfusing group O RBC units to non-O recipients.

Univariate analyses demonstrated a significant association between the rate of transfusing group O RhD negative RBC units to non-O RhD negative recipients (ie. recipients who are group A, B and AB RhD positive and negative and group O RhD positive) and hospital size: small and large hospitals had a lower percentage of transfusing group O RhD negative RBC units to non-O RhD negative recipients compared to medium sized hospitals (Figure 5). Likewise hospitals with cancer/oncology services were significantly associated with transfusing a lower percentage of group O RhD negative RBC units to non-O RhD negative recipients. Presence of a NICU service was associated with transfusing a significantly higher percentage of group O RhD negative RBC units to non-O RhD negative recipients.
Discussion

There are currently no evidence-based guidelines that indicate what would be an acceptable percentage of group O RBCs transfused to non-O recipients. This study provides detailed data from 38 hospitals in 11 countries on the size of the RBC inventory, hospital RBC transfusion policies, and RBC transfusion patterns that can contribute to development of evidence based guidelines. There is considerable variability across hospitals of similar size in terms of the frequency of transfusing ABO/RhD compatible but non-identical RBC units. While it is apparent that saving group O RBC units for transfusion to group O recipients and RhD negative units for transfusion to RhD negative recipients is most optimal, a benchmark to guide best practices for compatible, non-identical transfusion has not yet been established.

The hospitals included in this study varied in size, services offered, distance from the blood supplier and RBC transfusion policy. Hospitals with cardiovascular, cancer/oncology and obstetrics services demonstrated trends towards lower percentage of group O RBC units transfused to non-O recipients, perhaps as a result of increased demand and turnover in their inventory. That smaller hospitals had the highest but not significantly different percentage of transfusing group O RBC units to non-O recipients compared to medium and large hospitals is likely due to smaller hospitals stocking relatively more group O blood to avoid outdating non-O units if they are uncommonly transfused. Smaller hospitals may have the added concern about running out of stock from a major bleed prompting increased proportion of O stock. In addition, smaller hospitals with obstetrics services may stock increased proportions of O negative stock due to concerns of managing a severe postpartum hemorrhage.

This study demonstrates that 11.1% of group O RBC units were transfused to non-O recipients. In some circumstances, such as in bleeding emergencies when the recipient’s blood group is unknown, this practice is unavoidable, and this was the predominant indication provided for issuing group O RBC units to non-O recipients. The second most common reason for issuing group O RBC units to non-O recipients was because the units were close to expiry. This is an avoidable reason for issuing group O RBCs to non-O recipients and it relates more to inventory management than transfusion policy. Some retrospective studies question the safety of providing compatible, non-identical RBC transfusions. A recent review of 18,843 non-O inpatients showed increased in-hospital mortality amongst the group A patients who received non-identical
blood compared to patients who received group identical blood. Prospective, randomized studies comparing patient outcomes associated with receiving ABO compatible versus ABO identical RBC transfusion would be required to determine if this association is causal.

In this study, 22.6% of group O RhD negative RBC units were transfused to group O RhD positive recipients, and 43.2% of group O RhD negative RBC units were transfused to non-O RhD negative recipients. This practice creates a challenge for blood suppliers. According to Canadian Blood Services data, only 7% of the Canadian population is group O RhD negative. The GROUP study findings are in accord with those in the Trends For Collection (TFC) study which showed an overall disproportionate increase in the number of group O RhD negative RBC units compared to the group B and AB positive units collected by eight national or provincial blood services and seven American blood centers from 2010 to 2014.

At 63.2% of hospitals included in this study, all patients in need of uncrossmatched RBC units were transfused with group O RhD negative RBC units regardless of sex. This is in contrast to the 2014 AABB recommendations for the Choosing Wisely Campaign that states as recommendation number 5: Don’t transfuse O negative blood except to O negative patients and in emergencies for women of childbearing potential with unknown blood group. This recommendation is supported as well by the United Kingdom National Health Service’s guidelines from 2009.

The majority (74.2%) of hospital respondents reported that group O RBC units are exclusively transfused to all neonates. This practice is often done to limit wastage by using aliquots of the same RBC unit for transfusion of multiple neonates, and also to reduce the risk of transfusing the wrong blood, given that obtaining samples in duplicate is a challenge, reverse testing for blood group is not possible and that the names of neonates often frequently change. This practice also helps to ensure that blood transfused to neonates is compatible with both mom and baby. Not surprisingly, having a policy of providing group O blood exclusively to the neonate population was associated with an increased probability of transfusing group O RBC units to non-O recipients, even though only 4% of group O RBC transfusions to non-O recipients were found to occur in the NICU according to 21 participants who reported on location where such transfusions were issued. However, not all participants who provided data on hospital policy contributed their data on the disposition of RBC units (part 2 of this study). The practice has been the focus of a
small number of retrospective studies with outcomes that varied from suggesting potential harm\textsuperscript{9} to showing no significant differences.\textsuperscript{10} A high quality prospective study might offer valuable insights into the safety of this common-place practice.

This study was limited by the sample size and by the retrospective study design. The majority of hospitals were academic centres. Even with 38 hospitals completing the survey and 30 of those contributing RBC transfusion data, the variability in size, populations served and services offered made it difficult to identify strong associations between RBC transfusion practices, hospital characteristics and transfusion policies. Our analysis did not include the group O units that were issued to recipients whose ABO group was unknown at the time that group O units were issued (as, in the emergency setting, often the ABO group was only identified later on) and this would have provided added insight. Twenty-one hospitals contributed to data on hospital transfusion patterns by location and 22 by indication, which limits applicability to all participating hospitals. The frequency of blood group O in each participant’s local population was not captured so it is unknown whether this contributed to variation in group O RBC utilization.

In summary, this is the first time that the ABO/RhD of the RBC units and that of their recipients have been investigated on an international scale. A significant proportion of group O and RhD negative RBC units were transfused to non-O, non-identical recipients, though the frequency of this practice varied across sites. The optimal frequency of providing ABO compatible but not identical RBC units has not yet been established, and might depend on factors such as the hospital’s policy for providing uncrossmatched emergency issue RBC units and their neonatal transfusion practices. The results of this study provide data and insights towards developing benchmarking for optimal compatible, non-identical ABO/Rh transfusion practices.

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References


Table 1. Characteristics of the 38 hospitals that participated in the survey

<table>
<thead>
<tr>
<th>Hospital demographics</th>
<th>Number of Hospitals</th>
<th>Percentage of all respondents (n=38)</th>
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</thead>
<tbody>
<tr>
<td>Size of hospital</td>
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<tr>
<td>&lt;250 beds (small)</td>
<td>9</td>
<td>23.7</td>
</tr>
<tr>
<td>250-999 beds (medium)</td>
<td>21</td>
<td>55.3</td>
</tr>
<tr>
<td>&gt;=1000 beds (large)</td>
<td>8</td>
<td>21.1</td>
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<tr>
<td>Distance from blood supplier (km)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50km*</td>
<td>27</td>
<td>76.3</td>
</tr>
<tr>
<td>50-99km</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>&gt;=100km</td>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>Not provided</td>
<td>2</td>
<td>5.3</td>
</tr>
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<td>Transfusion Volumes</td>
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<tr>
<td>Hospitals transfusing &lt;10,000 RBC units/year</td>
<td>17</td>
<td>44.7</td>
</tr>
<tr>
<td>Hospitals transfusing 10,000-70,000 RBC units/year</td>
<td>21</td>
<td>55.3</td>
</tr>
<tr>
<td>Hospital Type</td>
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<td></td>
</tr>
<tr>
<td>Non-teaching hospital</td>
<td>6</td>
<td>15.8</td>
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<tr>
<td>Teaching hospital</td>
<td>32</td>
<td>84.2</td>
</tr>
<tr>
<td>Services offered</td>
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<td></td>
</tr>
<tr>
<td>Oncology/Cancer</td>
<td>32</td>
<td>84.2</td>
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<tr>
<td>Cardiovascular</td>
<td>33</td>
<td>86.8</td>
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<tr>
<td>Obstetrics</td>
<td>30</td>
<td>78.9</td>
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<tr>
<td>Trauma</td>
<td>32</td>
<td>84.2</td>
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*50km = approximately 30 miles
Table 2. Distribution of transfused RBC units by blood group and Rh ABO/RhD.

<table>
<thead>
<tr>
<th>Recipients</th>
<th>Group O</th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhD neg</td>
<td>22,111</td>
<td>2,122</td>
<td>12</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>RhD pos</td>
<td>8,777</td>
<td>137,152</td>
<td>1</td>
<td>15</td>
<td>0</td>
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<tr>
<td>RhD neg</td>
<td>1,565</td>
<td>142</td>
<td>21,918</td>
<td>1,523</td>
<td>0</td>
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<tr>
<td>RhD pos</td>
<td>3,125</td>
<td>6,307</td>
<td>5,128</td>
<td>128,235</td>
<td>0</td>
</tr>
<tr>
<td>RhD neg</td>
<td>1,283</td>
<td>81</td>
<td>0</td>
<td>0</td>
<td>4,680</td>
</tr>
<tr>
<td>RhD pos</td>
<td>1,513</td>
<td>5,875</td>
<td>0</td>
<td>3</td>
<td>2,450</td>
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<tr>
<td>RhD neg</td>
<td>177</td>
<td>12</td>
<td>698</td>
<td>11</td>
<td>165</td>
</tr>
<tr>
<td>RhD pos</td>
<td>360</td>
<td>795</td>
<td>272</td>
<td>2,543</td>
<td>141</td>
</tr>
<tr>
<td>Total*</td>
<td>38,911</td>
<td>152,486</td>
<td>28,029</td>
<td>132,372</td>
<td>7,436</td>
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</table>

*Excluding 2,275 units transfused to recipients of unknown ABO/RhD
Figure 1. Average percentage of units transfused from daily inventory across hospitals of varying size (Large: ≥1000 beds; Medium: 250-999 beds; Small: <250 beds).
Figure 2. A. Percentage of group O RBC units transfused to non-O recipients by hospital size. B. Percentage of group O RhD negative RBC units transfused to non-O RhD negative recipients by hospital size. See text for statistical analysis.
Figure 3. Disposition of group O RBC units transfused to non-O recipients by hospital location.
Figure 4: Univariate analyses for the percentage of group O RBC units transfused to non-O recipients
Figure 5. Univariate analyses for the percentage of group O RhD negative RBC units transfused to group O RhD positive recipients (95% CI)
Figure 1 legend:

95% confidence interval of the average percentage for each hospital size group

Figure 2 legend:
Legend: + mean; - median; box: Inter Quartile Range (IQR); dashed line: minimum and maximum values; o: outliers