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# Retrospective Study of Blood Transfusion Complications in the Capital Region of Denmark from 1999-2017: Characteristics of Potentially "Dangerous" Blood Donors?

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## Abstract

**Objectives:** We hypothesized that the blood donors most frequently involved in complications would induce more and severe immunologic transfusion complications compared to other donors, i.e. potentially "dangerous". Secondary aims were differences in demographic variables.

**Background:** Donor-related mechanisms may contribute to allogeneic blood transfusion complications and may represent a dangerous treatment adverse event.

**Materials and Methods:** By analyzing transfusion data from the Capital Region of Denmark from January 1, 1999 to December 31, 2017; 2,574,646 blood transfusions and 9,779 transfusion complications from 194,432 blood donors were included in our dataset. We divided donors into three groups based on the number of complications and complication frequency (potentially "dangerous" *vs*. two differently defined control groups i.e. control 1 and control 2), and compared the nature of transfusion complications and demographic variables by statistical analysis.

**Results:** There were no differences in the proportion of complication types between the potentially "dangerous" donors and control donors, and no difference in the proportion of complications from RBCs, plasma or platelets according to ABO and RhD blood types. However, more potentially "dangerous" donors were female and had ABO blood type B compared to control donors ($p<0.001$ and $p<0.01$, respectively). The potentially "dangerous" donors were younger compared to control donors (40.36 years *vs*. 45.24 years and 42.84 years, $p<0.001$).

**Conclusion:** The potentially "dangerous" did not display more/severe immunologic transfusion complications compared to control donors. However, they differed in regards to gender, age and blood type. Further research regarding the differences in complication frequency per donor and demographic variety is warranted.

**Keywords:** Blood donors; Transfusion reaction; Blood transfusion; Transfusion medicine

## Introduction

The safety of allogeneic blood transfusions has been significantly improved over the past decades, but blood transfusion still remain associated with adverse events i.e. transfusion complications [1]. Many transfusion complications are today considered "immunologic" due to the involvement of donor and/or recipient immune cells, antibodies, inflammatory signaling molecules etc. in the reaction [2-4]. It is highly debated whether some blood donors are "potentially "dangerous" i.e., prone to induce more immunologic adverse events in the recipient than what would be expected [5-7]. Donor-related mechanisms contributing to complications and pathophysiologic reactions associated with transfusion of allogeneic blood components represent a dangerous treatment adverse event which is potentially avoidable.

The literature on "dangerous" donors is sparse and previous attempts to find clear evidence on donor characteristics that influence transfusion outcome have not been compelling. Non-infectious donor characteristics have been proposed to have an impact on mortality outcome, with quality of evidence rated low to very-low [8]. Donor characteristics such as gender and age have also been suggested to influence recipient outcome, though this remain debated [8-10]. In contrast, it is evident that antibodies in donor blood may induce transfusion complications in recipients [11,12]. Male only-strategies for platelet and plasma transfusions significantly reduce the likelihood of Transfusion-Related Acute Lung Injury (TRALI) in multiple studies [13-15], which is explained by females having the highest antibody titers and the highest risk of immunization with subsequent antibody production due to pregnancies [16,17]. Only one case-study has identified a specifically "dangerous" donor,




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which resulted in multiple complications in 36% of the recipients, including a fatal case of TRALI [18]. This study demonstrated the role of leukocyte antibodies in TRALI but despite this, attempts to predict TRALI from antibody detection in donors have so far been unsuccessful [19,20]. Leukodepletion and male-only transfusions are considered essential for the reduction of transfusion complications [21,22], but multiple studies are now focusing on individual donor specific factors as predictors for outcome [23,24].

In Denmark, a well-established system of reporting transfusion complications is operative on a regional and national basis and all blood components used in Denmark are traceable from donor to recipient. Based on previous studies of donor related transfusion outcomes, the aim of the present study was to investigate a hypothesis of the existence of "immunologically dangerous" blood donors. This was done by retrospectively analyzing and categorizing transfusions and transfusion complications in the Capital Region of Denmark in the period of 1999-2017. Specifically, we compared the frequency of different types of transfusion complications, hypothesizing that blood donors with a history of a high frequency of transfusion complications would induce a higher number and more severe immunologic transfusion complications compared to controls.

## Materials and Methods

### Study design and database

The study was approved by the Danish Data Protection Agency (VD-2018-186, I-Suite no. 6428) and the Danish Health Authorities, Agency for Patient Safety (case no. 3-3013-2555/1).

This is a retrospective study based on prospectively collected data from the blood bank and transfusion database "Blodflödet", comprising data on all blood donations, blood production, and blood distribution and transfusion complications from March 1st 1996 onward from hospitals in the Capital Region of Denmark. The present study covered data from January 1st 1999 to December 31st 2017. The extracted data comprised information of both blood donors and recipients, anonymized with unique transfusion-IDs, as well as ABO and RhD blood type (recipients and donors), unique donation ID, date of donation, donor and recipient birth data and gender, date and time of the delivery of blood components for transfusion, type of blood component (Red Blood Cells (RBCs), plasma or platelets), ordering hospital and department and various processing data of the components. We focused on the most common blood components: RBCs (irradiated and non-irradiated), plasma (apheresis, whole blood derived, cryodepleted, cryoprecipitate pool) and platelets (pooled non-irradiated, pooled irradiated, apheresis non-irradiated, apheresis irradiated, all platelet components are leukoreduced). All RBCs were leukoreduced by leukofiltration from 2009, so the non-irradiated RBC components contain both leukoreduced and non-leukoreduced components until 2009 and leukoreduced components from 2009. Male-only strategies for plasma transfusions were introduced in 1999. Female plasma were only transfused in shortage of male plasma, and otherwise used for medicinal production.

### Registration of transfusion complications

When a transfusion complication is suspected by clinicians, a formula is filled out and delivered to the Blood Bank for registration of the transfusion complication in Blodflödet together with a specific code for the most likely transfusion complication. Imputability (i.e. the probability that the recipient's symptoms are associated with the complication) is not assessed by clinicians. More than 30 possible transfusion complications are classified based on international consensus from the International Society of Blood Transfusion [25] (Supplementary 1). According to Danish legislation, transfusion complications are also reported to the Danish Registration of Transfusion Risks (Dansk Registering af Transfusionsrisici, DART), the Danish Patient Safety Database (Dansk Patientsikkerheds Database, DPSD) and/or the Danish Patient Safety Authority (Styrelsen for Patientsikkerhed, STPS) for national hemovigilance depending on severity. We classified the transfusion complications into following groups: i) Acute mild immunological complications, ii) Acute severe immunological, iii) Unknown acute immunological, iv) Delayed immunological complications, v) Non-immune mediated complications and vi) Respiratory complications, (Table 1 for classification of complications). The severity of transfusion complications (acute mild *vs.* acute severe immunological) was based on whether the complication was life threating or potential life-threatening based on a clinical assessment by the authors. Since this is a retrospective study, TRALI and TACO was not classified according to the newer definitions from 2019 [2,26].

### Data processing

In the original dataset, there were 2,910,010 component transfusions and 13,433 transfusion complications. After data processing (Figure 1), the dataset was reduced to 2,574,646 transfusions, where 9,779 resulted in a transfusion complication. 194,432 donors were included in the dataset. The data processing is described in detail in Supplementary 2.

### Statistical analysis

The open-source statistical software R version 3.2.3 and R studio Version 1.0.53 was used for data analysis, tidying data, graphical illustrations and statistical tests (R-code available upon request). The donor groups were compared as categorical variables by chi-squared test or Fisher's exact test. Non-normally distributed continuous variables were compared by Mann Whitney U-test (Wilcoxon rank-sum test). P-values less than 0.05 were considered significant.

### Subjects studied

The primary aim was to investigate blood donors with the highest frequency of transfusion complications and compare this group of donors with the rest of the donors with transfusion complications in our database, to either confirm or reject the hypothesis of the existence of "immunologically dangerous" donors. To do this, we defined potentially "dangerous" donors as: i) donors with ≥two blood donations, and ii) involved in ≥two transfusion complications and iii) having a frequency of transfusion complications above the upper quartile of transfusion complication frequencies (equivalent to ≥6.1% of donations resulting in transfusion complications) (Figure 2). Control groups 1 was defined by i) ≥two blood donations and ii) ≥two complications, but with having a frequency of transfusion complications below the upper quartile of transfusion complication frequencies (<6.1%). Control group 2 contained the remaining donors involved in a transfusion complication.

**Table 1:** Table showing demographic variables for donors and recipients (sex, blood type, number of donations and received transfusions), components, types of transfusion complications and subdivision of complications.

| | Donor | | | Recipient | | |
|---|---|---|---|---|---|---|
| **Sex** | **n donors** | **n donations** | **% donations** | **n recipients** | **n transfusions** | **% transfusions** |
| Female | 104,594 | 1,369,827 | (41.16) | 130,465 | 1,164,156 | (45.22) |
| Male | 89,307 | 1,957,194 | (58.82) | 109,715 | 1,410,490 | (54.78) |
| **Blood type** | | | | | | |
| O Rh negative | 15,456 | 307,403 | (9.24) | 15,977 | 172,405 | (6.7) |
| O Rh positive | 68,561 | 1,166,579 | (35.06) | 83,399 | 893,232 | (34.69) |
| A Rh negative | 14,832 | 273,129 | (8.21) | 16,788 | 182,058 | (7.07) |
| A Rh positive | 68,704 | 1,169,839 | (35.15) | 87,424 | 933,147 | (36.24) |
| AB Rh negative | 1,834 | 25,490 | (0.77) | 1,650 | 17,490 | (0.68) |
| AB Rh positive | 7,565 | 88,343 | (2.65) | 8,902 | 93,442 | (3.63) |
| B Rh negative | 4,070 | 57,245 | (1.72) | 3,976 | 42,071 | (1.63) |
| B Rh positive | 18,761 | 239,643 | (7.2) | 21,978 | 235,037 | (9.13) |
| XX | - | - | - | 86 | 7,764 | (0.22) |
| | **mean** | **(SD)** | | **mean** | **(SD)** | |
| **Age** | 40.19 | (12.39) | | 61.69 | 20.28 | |
| **Component** | **n transfusions** | | | **(%)** | | |
| **RBC** | **1,890,107** | | | **(73.41)** | | |
| Irradiated (leukoreduced) | 66,585 | | | | | |
| Non-irradiated (leukoreduced) | 976,678 | | | | | |
| Non-irradiated (non-leukoreduced) | 846,844 | | | | | |
| **Plasma** | **428,340** | | | **(16.64)** | | |
| Apheresis | 3,822 | | | | | |
| Cryodepleted | 9,025 | | | | | |
| Cryoprecipitate pool | 3,282 | | | | | |
| Whole blood derived | 412,211 | | | | | |
| **Platelets** | **256,199** | | | **(9.95)** | | |
| Apheresis (leukoreduced, irradiated) | 2,892 | | | | | |
| Apheresis (leukoreduced, non-irradiated) | 5,151 | | | | | |
| Pooled (leukoreduced, irradiated) | 59,087 | | | | | |
| Pooled (leukoreduced, non-irradiated) | 189,069 | | | | | |
| **Transfusion complications stratified according to type** | **n complications** | | | **(%)** | | |
| **Acute mild immunological** | **6001** | | | **(61.37)** | | |
| Febrile non-hemolytic transfusion reaction (FNHTR) | 5,055 | | | (84.24) | | |
| Allergic | 804 | | | (13.4) | | |
| Shivering, temp. <1° | 142 | | | (2.36) | | |
| **Unknown acute immunological** | **3124** | | | **(31.95)** | | |
| Unclassified | 3,101 | | | (99.26) | | |
| Other Acute Immunological | 23 | | | (0.74) | | |
| **Acute severe immunological** | **79** | | | **(0.81)** | | |
| Hypotensive transfusion reaction | 47 | | | (48.45) | | |
| Anaphylaxis | 32 | | | (32.99) | | |
| Acute Hemolytic Transfusion Reaction (AHTR) | 18 | | | (18.56) | | |
| **Delayed immunological** | **164** | | | **(1.68)** | | |

| | | |
|---|---|---|
| Delayed Serologic Transfusion Reaction (DSTR) | 140 | (85.37) |
| Delayed Hemolytic Transfusion Reaction (DHTR) | 22 | (13.41) |
| Other delayed immunological | 2 | (1.22) |
| Transfusion-associated graft vs. host disease | 0 | 0 |
| Post transfusion purpura | 0 | 0 |
| **Respiratory** | **377** | **(3.86)** |
| Transfusion-Associated Dyspnea (TAD) | 310 | (82.23) |
| Possible Transfusion-Related Acute Lung Injury (TRALI) | 28 | 93.98) |
| Transfusion-Associated Circulatory Overload (TACO) | 24 | (6.37) |
| Transfusion-Related Acute Lung Injury (TRALI) | 15 | (7.42) |
| **Non immunological** | **34** | **(0.35)** |
| Other biochemical/physiological | 30 | (88.24) |
| Transfusion-Transmitted Infection (TTI) | 4 | (11.76) |

## Results

### The dataset

The present study analyzed data on blood donations, transfusions and transfusion complications in the Capital Region of Denmark from January 1, 1999 to December 31, 2017, containing data on more than 3.3 million blood donations, more than 2.5 million transfused blood components stratified into about 1.8 million units of RBC, 0.4 million units of plasma and 0.3 million units of platelets (Table 1). In the study period there were 9,779 transfusion complications corresponding to a frequency of 1 per 263.28 transfusions or 0.38%. Time trend in use of blood components from 1999-2017 are displayed in Supplementary Figure 1.

### Time trend in the frequency of transfusion complications from 1999-2017

In the period 1999-2017, the total annual number of transfusion complications decreased from 415 in 1999 (complication frequency of 0.35%) to 316 in 2017 (complication frequency of 0.32%). The frequency of transfusion complications for RBCs, plasma and platelets are displayed in Figure 3A. Throughout our study period, the most common type of transfusion complication was acute mild immunological complications, which accounted for 61.37% of all complications, followed by unknown acute immunological (31.95%) and respiratory complications (3.86%). The annual numbers of complication types stratified according to component type are illustrated in Figure 3B, 3D and 3F. The frequency of the different transfusion complications are described for the entire period in Table 1 including the total number of transfusions stratified according to blood component, which is also illustrated in Figure 3C, 3E and 3G. As previously reported [27,28] the leukoreduction of RBCs in 2009 significantly reduced the frequency of RBC transfusion complications, from 4612 (0.46%) in the period from 1999-2007 to 3120 (0.40%) in the period from 2009-2017 ($p < 0.001$), reflecting significantly fewer acute mild immunological complications (n=3026 *vs.* n=1779, $p < 0.001$) and delayed immunological complications (n=121 *vs.* n=42, $p < 0.001$) but relatively more acute severe immunological complications (n=11 *vs.* n=27, $p \leq 0.001$) and unknown acute immunological complications (n= 1296 *vs.* 1139, $p < 0.010$) (Supplementary Figure 2).

### Potentially "dangerous" donors

**Selection of potentially "dangerous" donors and control groups for comparison:** The number of transfusion complications per donor in the study period varied from 0 to 5 per donor. Of the 626 donors per year being implicated in transfusion complications, some donors had a significantly increased proportion of their donations resulting in a complication. In total, 10 donors per year i.e. a total of 195 donors met the criteria for potentially "dangerous" donors, equivalent to 0.10% of the total number of donors. (Figure 2 for the selection process for the potentially "dangerous" donors and the control groups).

**Demography and blood types of potentially "dangerous" donors *vs.* control groups:** There were significant differences in the male-female proportions between the donor groups. More donors were female in the potential "dangerous" donor group and control group 2 (48.71% and 44.81% females, respectively) compared to control group 1 (30.82% female, $p<0.001$). The potentially "dangerous" donors were younger (mean age 40.36 years) compared to both control groups of donors (mean age for control group 1 = 45.24 years, mean age for control group 2 = 42.84 years, all $p<0.001$) (Figure 4A-6B). The distribution of ABO and RhD blood types among potentially "dangerous" donors did not differ compared to the other groups of donors, except for more potentially "dangerous" donors having blood type B (14.36%) compared to control group 1 (7.18%, $p \leq 0.01$) (Figure 4C-6G). When analyzing transfused blood components according to donor groups and blood types (ABO and RhD), more O RhD positive and A RhD positive RBCs from potentially "dangerous" donors were transfused ($p \leq 0.050$). Likewise, fewer O RhD positive, B RhD positive and A RhD positive and negative plasma transfusions were transfused from potentially "dangerous" donors ($p<0.05$, Supplementary Table 1).

**Components and types of transfusion complications from potentially "dangerous" donors *vs.* control groups:** Plasma apheresis tended to be associated with more plasma complications from the potentially "dangerous" donors compared to donors in both control group 1 ($p=0.060$) and control group 2 ($p=0.03$). Irradiated apheresis platelets from potentially "dangerous" donors were also associated with more platelets complications compared to donors in

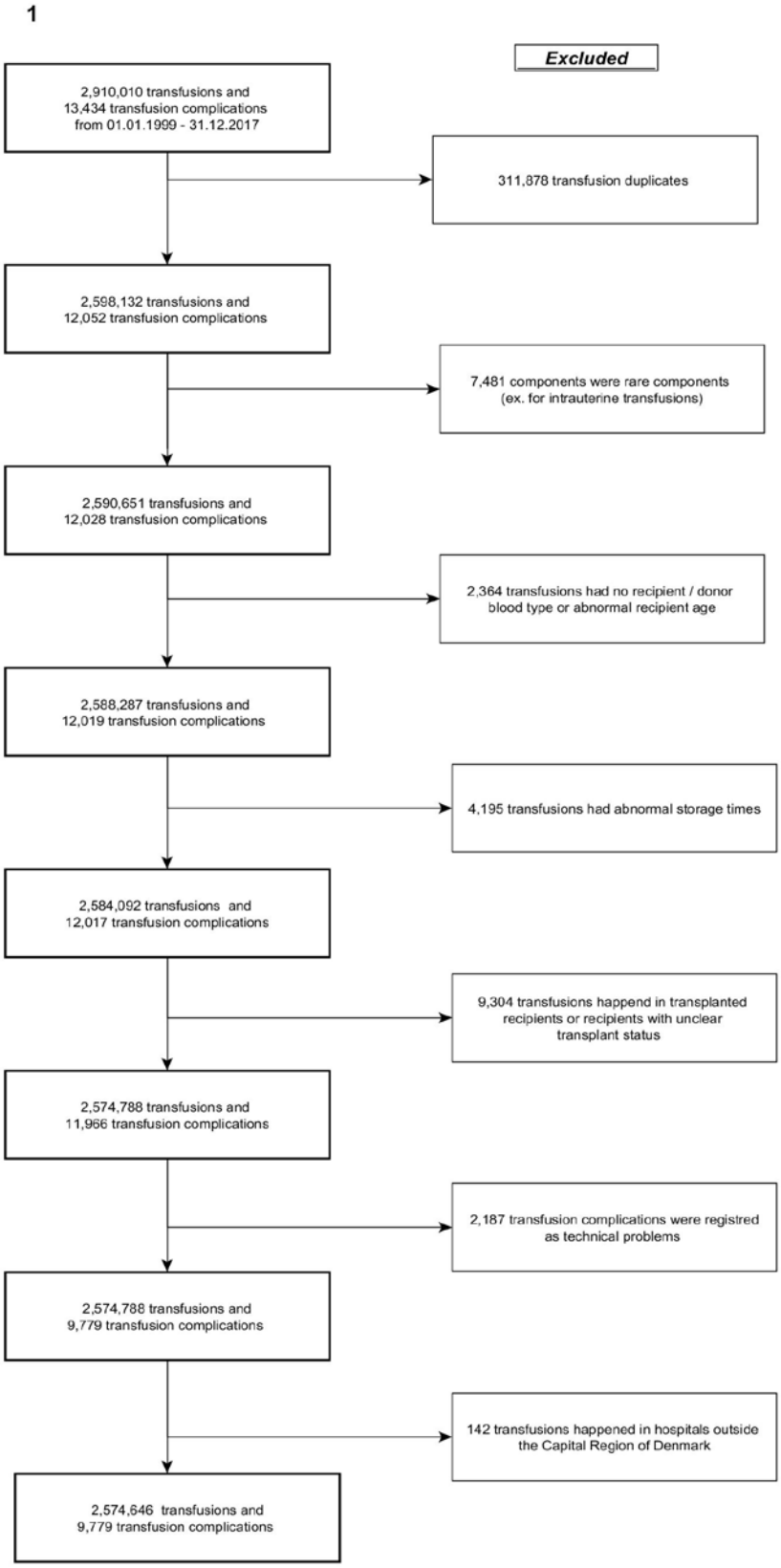


**Figure 1:** Flow diagram of data processing and data inclusion for analysis of transfusions and transfusion complications reported to Blodflödet, Capital Region of Denmark, 1999 to 2017.

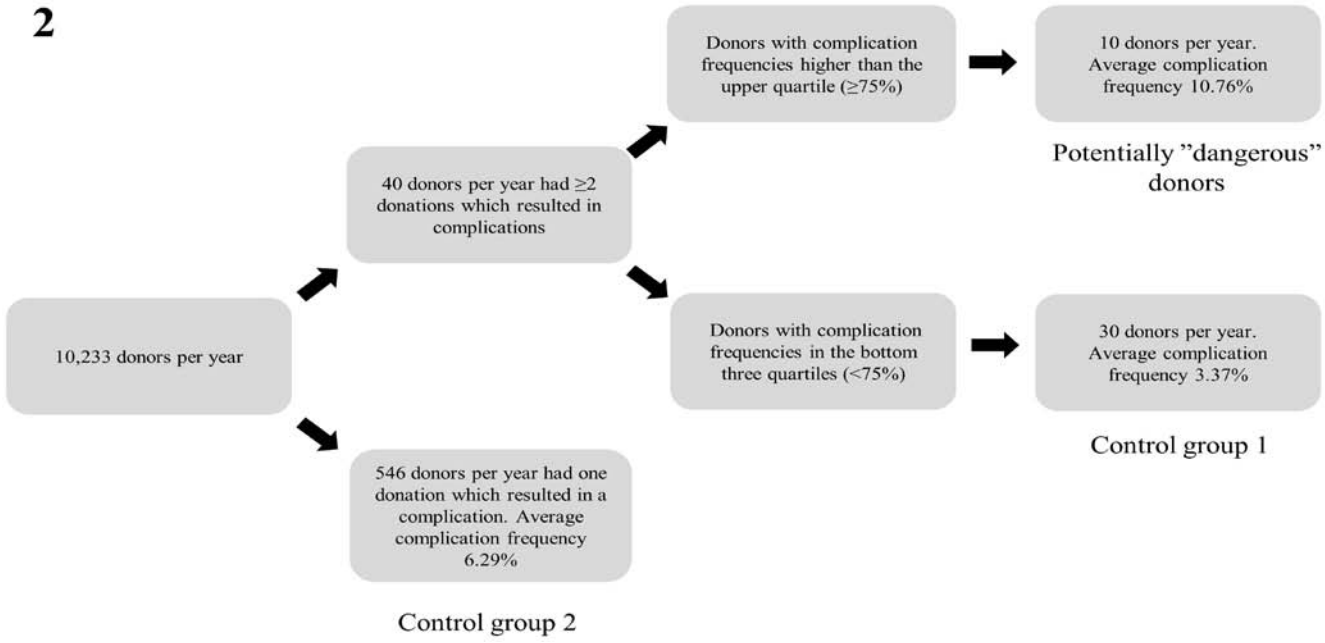


**Figure 2:** Flow diagram of the selection of potentially "dangerous" blood donors and control groups based on transfusions and transfusion complications reported to Blodflödet, Capital Region of Denmark, 1999 to 2017. Donors with ≥2 complications were subdivided according to frequency of transfusion complications, with the upper quartile of donors with the highest frequencies chosen as potentially "dangerous" (≥75% quantile; frequency 6.1%- 50%, 95% confidence interval [CI] 9.88; 11.64). The donors with ≥2 complications in the bottom three quartiles (complication frequency 1.4-6.0 %, 95% confidence interval [CI] 3.27; 3.46) were appointed "control group 1". Donors who had one donation resulting in a complication were appointed "control group 2" (complication frequency 0.6%-100%, 95% confidence interval [CI] 6.09; 6.49).

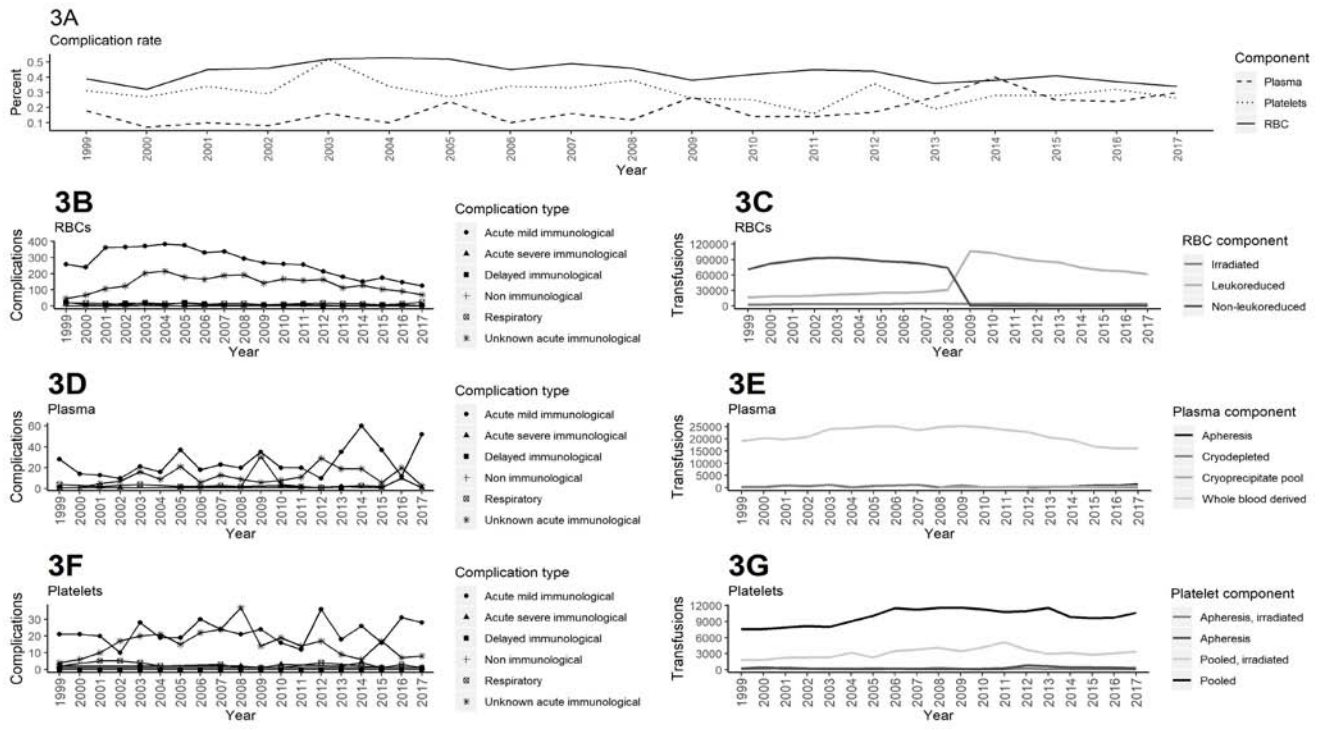


**Figure 3:** A) Frequency of transfusion complications for RBCs, plasma and platelets per year in the Capital Region of Denmark, 1999 to 2017. Types of transfusion complications in absolute counts per year from RBC components B), plasma components D) and platelet components F). Absolute counts of RBC transfusions C), plasma transfusions E) and platelet transfusions G), subdivided by components per year.

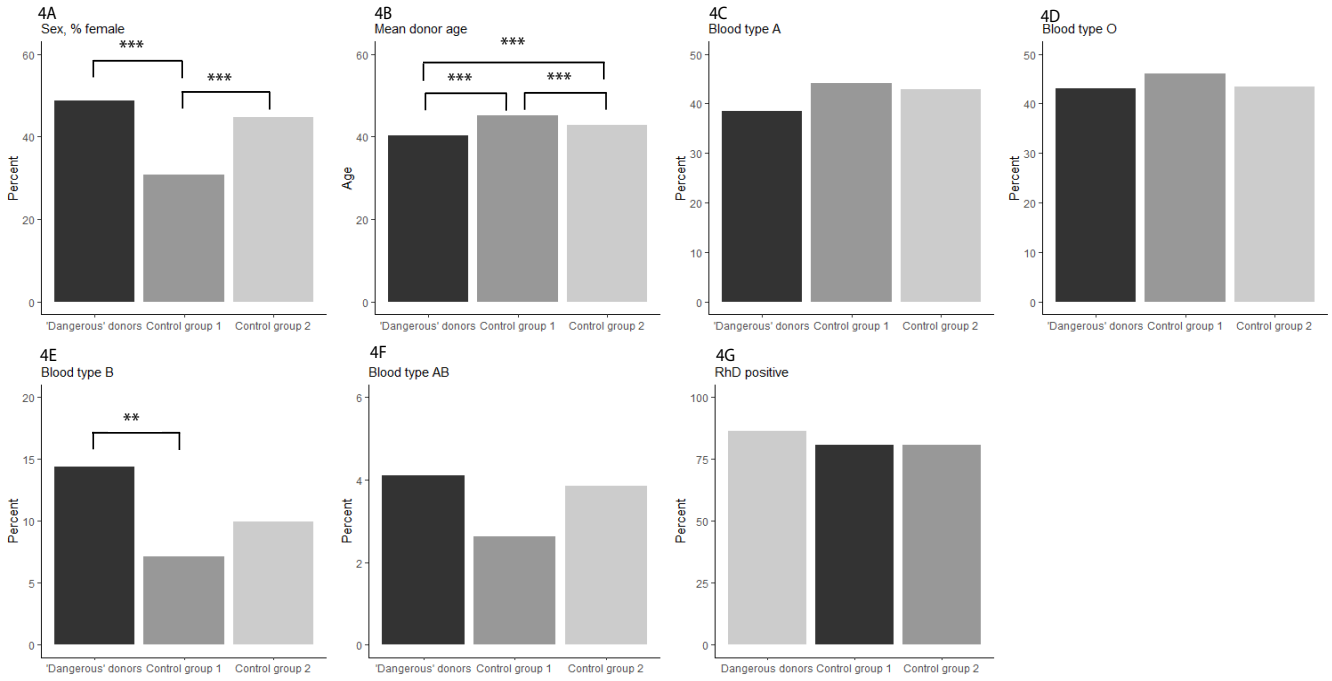


**Figure 4:** Histogram showing demographic variables between potentially "dangerous" donors, control group 1 and control group 2 based on transfusions and transfusion complications reported to Blodflödet, Capital Region of Denmark, 1999 to 2017. A) Percentage of female donors, B) Mean donor age, C-G) Percentage of ABO and RhD donor blood types. **P≤0.01, ***P≤0.001.

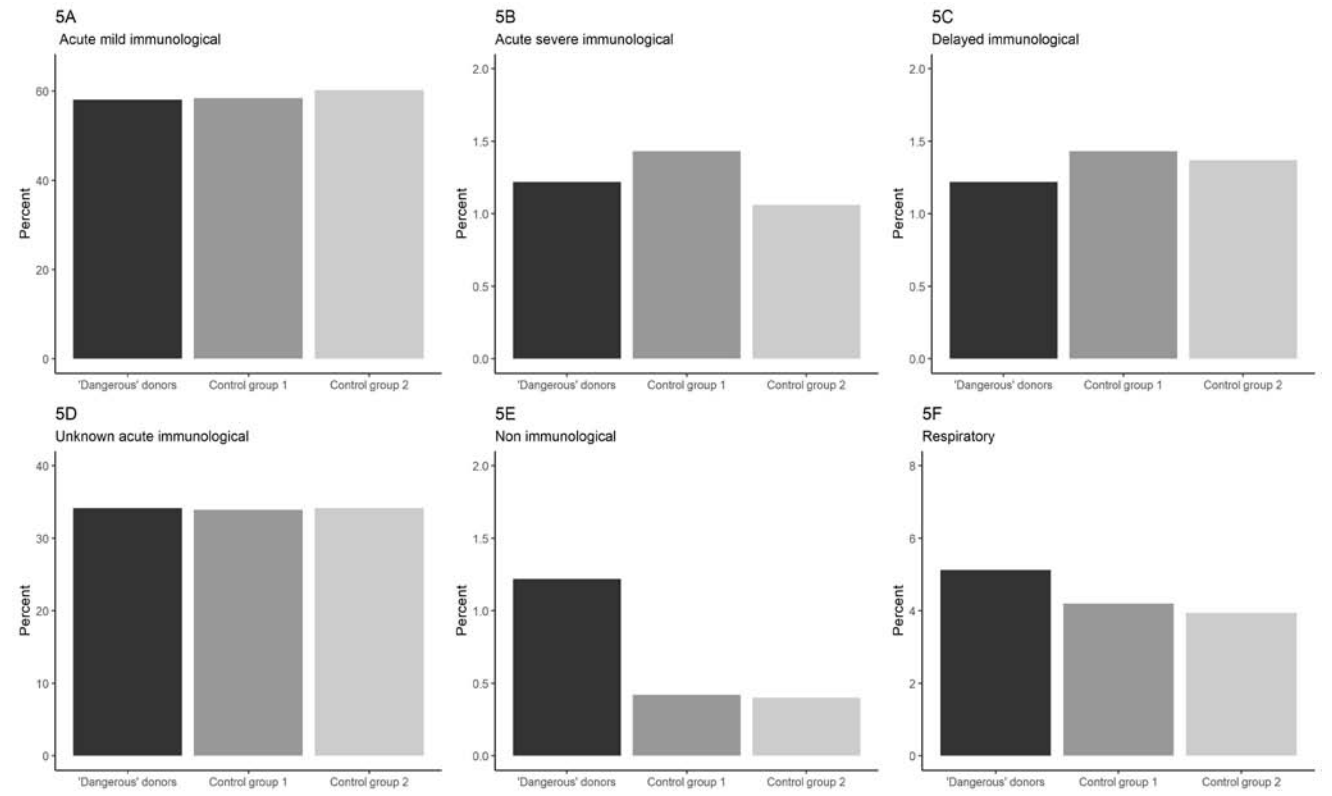


**Figure 5:** Histogram showing complications in percentage between potentially "dangerous" donors, control group 1 and control group 2 based on transfusion complications reported to Blodflödet, Capital Region of Denmark, 1999 to 2017. Y-axis shows the percentage of total complications from the donor groups. A) Acute mild immunological complications, B) Acute severe immunological complications, C) Delayed immunological complications, D) Unknown acute immunological complications, E) Non immunological complications, F) Respiratory complications. There are no significance differences between the groups.

control group 2 (p=0.050), (Supplementary Table 2 for significances of complication frequencies between the groups in regard to transfused components). No significant differences were observed in the proportion of complications from the potentially "dangerous" donors according to ABO and RhD blood types compared to the control groups for RBCs, plasma or platelets. However we observed differences between control group 1 and 2, with more complications from control 1 donors with B RhD positive and A RhD negative plasma ($p \leq 0.05$ and $p \leq 0.001$).

The most common type of transfusion complication from the potentially "dangerous" donors was acute mild immunological complications with 5,186 complications per 100,000 transfusions (accounting for 58.00% of all complications *vs.* 58.5% and 60.3% in control group 1 and 2) followed by unknown acute immunological complications with 3,051 complications per 100,000 transfusions (34.20 % *vs.* 34.0% and 32.9% in control group 1 and 2). Next was respiratory complications with 458 complications per 100,000 transfusions (5.12 % *vs.* 4.21% and 3.94% in control group 1 and 2), acute severe immunological with 109 per 100,000 transfusions (1.22% *vs.* 1.43% and 1.06% in control group 1 and 2), delayed immunological complications with 109 per 100,000 transfusions (1.22% *vs.* 1.43% and 1.37% in control group 1 and 2) and non-immunological with 21.80 per 100,000 transfusions (0.24% *vs.* 0.42% and 0.41% in control group 1 and 2). There were no differences in the proportion of the complication types between potentially "dangerous" donors and the control groups (Figure 5A-5F). The hypothesis that blood donors with high-frequency transfusion complications having more and severe immunologic transfusion complications was not supported by these data.

## Discussion

We hypothesized that some donors were potentially more "dangerous" than others based on the large differences in complication frequencies per donor, and stratified donors into three different groups based on their complication frequencies. The potentially "dangerous" donors did not differ compared to other donors with regards to types of complications experienced by the recipients. Except for extremely high numbers of complications per 100,000 transfusions, the hypothesis that these donors were prone to induce more and severe immunological complications in the recipients was rejected. Furthermore, potentially "dangerous" donors did not induce either more respiratory complications or non-immunological complications. Therefore, the potentially "dangerous" high frequency donors seemed to result in similar types of transfusion complications compared to other donors, despite the demographic variables and components being involved in complications.

The potentially "dangerous" donors were younger with a higher proportion of females. It is unclear whether this could be related to hormones, iron-status or more circulating antibodies/previous pregnancies as debated by previous studies [16,17,30]. Historically, female plasma has been linked to increased complication frequencies, but since male-only plasma has been enforced since 1999, female plasma is not considered a confounding factor in plasma components, though female plasma in platelets and RBCs could still contribute to more transfusion complications. In terms of blood types, more potentially "dangerous" donors had blood type B. More O RhD positive and A RhD positive RBC transfusions originated from potentially "dangerous" donors whereas there were fewer O RhD positive, B RhD positive and A RhD positive and negative plasma transfusions. Notably, potentially "dangerous" donors had more apheresis plasma and platelets transfusions compared to the control groups, indicating that individual blood components from potentially "dangerous" donors may have resulted in higher transfusion complications. However, no difference was observed for the proportions of complications from the potentially "dangerous" donors according to their ABO and RhD blood types for RBCs, plasma or platelets.

Overall, the frequency of transfusion complications in the Capital Region of Denmark has remained unchanged from 1999-2017 and matches international reports [29]. The leukoreduction of RBCs significantly reduced the frequency of transfusion complications though we observed a slightly higher frequency of acute severe and unknown acute immunological complications. However, this is considered to have little clinical impact due to the low number of events per year.

## Strengths and Limitations of the Study

Identifying multiple donors "complications records" based on extensive data of millions of transfusions is only possible due to the Blood Bank tracking system, which is based on prospectively collected data. The retrospective study has several strengths: all donations have systematically been noted and all recipients and donors are labeled with a specific id number, making tracking of donors and recipients possible. All donations have a donation number unique to the specific donations; ensuring possible tracking if a concern occurs regarding a donation (ex. suspicion of contamination, blood borne diseases, complications etc.). Danish Registry of Transfusion Risks (DART) reports the Danish annual results of adverse events and complications associated with transfusion of blood components to IHNs hemovigilance Database (ISTARE), based on direct reporting to DART supported by data from Blodflödet.

It is noteworthy that the second most common complications we observed were unclassified transfusion complications. The high number of complications in this category suggests that the clinical picture during a transfusion complication can be very ambiguous and difficult for clinicians to interpret. It also calls for more education and training for the detection and diagnosis for the medical staff, as well as clear and easy guidelines for the reporting of complications. Since nomenclatures and definitions of transfusion complications change over time, we did not use the newer definitions of TRALI and TACO [2,26]. To our knowledge the nomenclature of complications otherwise has not change in the time period of our study in the Capital Region of Denmark. If a recipient received multiple transfusions and subsequent developed a transfusion reaction, all transfused component suspected were labeled as origin of complication, which is a bias in the study. Under-reporting is an unfortunate and a frequent problem in transfusion medicine and has been described in prior studies [29,31,32]. We expect large unreported numbers in our study as well, which is a limitation of our study. To counter this problem we have planned a quality-assured based study, where Electronic Health Reports (EHR) from patients with transfusion complications in the Capital Region are reviewed for correct identification and registration,

as well as correct reporting of eventual transfusion complications, in accordance with previous studies [32,33]. Furthermore, use of artificial intelligence specifically text data mining may also be a tool to assess this issue by obtaining high-quality information about transfusion complications from EHR. We did not investigate the shelf life of blood products and the impact of transfusion complications due to the extent of the study, which may be a possible confounder. The issue of recipient confounding was not assessed, however patients who have received multiple transfusions might be more prone to minor incompatibility. To counter this problem, we have planned a study to investigate this further by statistical permutation analysis.

### Classification of "dangerous" donors and control groups

We proposed a model of classification of the donors in our dataset, which allowed us to compare the donors based on the number of transfusions complications and complications frequency. These conditions were an attempt to quantify and subdivide donors, and may have been done differently by other researchers.

### Clinical implications and future research

Further research into donor-related transfusion complications in the recipient is highly warranted. Even though the groups of donors did not differ in proportion types of complications, the observed differences in complication frequencies per donor remain unexplained. If the immunopathology contributing to this difference is described and validated in other studies, this could reduce the risk of potentially harmful transfusion complications for recipients by for example identifying and excluding these donors permanently for blood donation. Also, it could create a platform for future databases and laboratory studies of the potential mechanisms contributing to transfusion complications from donors, potentially paving the way for personalized transfusion medicine.

## Conclusion

We introduced the concept of potentially "dangerous" donors based on the differences in transfusion complication frequencies observed for donors in our study. These potentially "dangerous" donors differed from the other donors associated with transfusion complications in terms of male-female ratio, age, blood types and components involved in transfusion complications, but not in terms of complication types. The high frequency donors were not associated with more/severe immunologic transfusion complications, and the hypothesis of "immunologically dangerous" blood donors is therefore rejected. However, we did find a demographic profile for general "dangerous" high frequency donors. Further research regarding the differences in complication frequency per donor is highly warranted.

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SBH contributed to the conception and design of the work, acquisition, analysis and interpretation of data, drafted the manuscript and approved the final version to be published. CEH contributed to the acquisition, analysis and interpretation of data, revised the work critically and approved the final version to be published. JHVS, MHD and MBH contributed to interpretation of data, revised the work critically and approved the final version to be published. SRO contributed to the conception and design of the work and analysis and interpretation of data, revised the work critically and approved the final version to be published.

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