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Age of blood and adverse outcomes in a maternity population

Running head: Age of blood in a maternity population

Authors:

Jillian A Patterson[1]; David O Irving[2]; James P Isbister[3]; Jonathan M Morris[1]; Eleni Mayson[1]; Christine L Roberts[1]; Jane B Ford[1]

[1] Clinical and Population Perinatal Health, Kolling Institute, University of Sydney

[2] Research and Development, Australian Red Cross Blood Service

[3] Northern Clinical School, University of Sydney

Corresponding Author for manuscript and reprints: Jillian Patterson

Postal address: Clinical & Population Perinatal Health Research

c/- University Dept of O&G, Building 52, Royal North Shore Hospital

St Leonards NSW 2065 Australia

Phone: +61 2 9462 9815 Fax:+61 2 9906 6742 Email: jillian.patterson@sydney.edu.au

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BACKGROUND

In recent times there has been debate around whether longer storage time of blood is associated with increased rates of adverse outcomes following transfusion. It is unclear whether results focused on cardiac or critically ill patients apply to a maternity population. This study investigates whether older blood is associated with increased morbidity and readmission in women undergoing obstetric transfusion.

STUDY DESIGN AND METHODS

Women giving birth in hospitals in New South Wales, Australia between July 2006-December 2010 were included in the study population if they had received between 1-4 red cell units during the birth admission. Information on women's characteristics, transfusions and outcomes were obtained from 5 routinely collected datasets including blood collection, birth and hospitalisation data. Generalised propensity score methods were used to determine the effect of age of blood on rates of severe morbidity and readmission, independent of confounding factors.

RESULTS

Transfusion data were available for 2990 women, with a median age of blood transfused of 20 days (interquartile range 14,27 days). There were no differences in the age of blood transfused between women with and without severe morbidity (21 (14,28) vs 22 (15,30) days), and in women readmitted or not (22 (14,28) vs 22 (16,30) days). After considering potential confounding factors, no relationship was found between the age of blood transfused and rates of severe morbidity and readmission.

CONCLUSION

Among women receiving low volume transfusions during a birth admission, there was no evidence of increased rates of adverse outcomes following transfusion with older blood.

Keywords: Red Blood Cell Transfusion; Obstetrics; Blood Preservation; Storage Lesion

Introduction

In recent times there has been growing concern that harms may be caused by transfusion of 'older' blood, that is, blood close to the end of its 'shelf life'.[1-3] Results of observational studies across cardiac, surgical and critically ill patients have not consistently demonstrated an association between the age of red blood cells (RBC) and adverse outcome. [4,5] A meta-analysis of observational and randomized controlled trials suggested an increase in mortality with transfusion of older compared with fresher blood,[6] however a randomized trial in premature, very low birthweight neonates found no evidence of a difference in outcomes between those receiving fresher blood compared with those receiving standard issue.[7] Another randomized trial in adult cardiac surgery patients found no difference in multiple organ dysfunction between those receiving fresh (≤10 day old) and older (≥21 day) blood. [8] Two large randomized controlled trials have commenced to address this issue in critically ill patients[9,10] however findings have not been published to date. The implications of significant findings from these studies on blood bank management and clinical practice would be large. [11]

Observational studies can provide important information where randomized trials are not practical or not yet available. Observational studies are typically faster, less expensive, larger, and able to cover a more diverse range of patients than included in randomized controlled trials. As such, a number of observational studies of age of blood have been conducted although none to date have used linked routinely collected data nor investigated this in a maternity population. The results of these studies have differed by country, medical specialty, and population.[2,12,13] The results of these studies and trials may not be generalisable to a maternity population as these patients differ considerably from a critically ill or surgical population, in that they are usually otherwise healthy, younger women with normal marrow function capable of rapidly replenishing haemoglobin. In these women bleeding is often unexpected, but is generally well compensated for due to good pre-existing cardiopulmonary reserve and occurrence in clinical settings where rapid resuscitation facilities are

available. Severe outcomes such as mortality are rare. Although representing a small proportion of overall transfusions [14-16], the incidence of transfusion in the maternity population is increasing.[17]

Determining whether there is an independent risk of adverse outcomes following transfusion of older blood can be difficult. Although patients tend to receive the oldest matched RBC unit, the age of this unit depends on the individual blood type, number of transfusions expected, hospital and time of year.[1,11,18] These factors may also affect outcomes, and so need to be considered in any analysis. In addition, observational studies of the effect of age of blood on outcomes are prone to a number of confounding factors,[5,13] particularly confounding by indication and number of RBC units received. One method with the potential to reduce the effect of confounders on associations between outcomes and age of blood is the use of propensity scores.[19] Traditional propensity score methods only allow for a comparison of 'older' vs 'fresher' blood, requiring a dichotomisation of 'older blood' for which there is no widely accepted or intuitive cutpoint. More recently, propensity score methods have been extended which allow for the consideration of age of blood as a continuous factor.[20,21] These methods attempt to create a situation where, across the study population, patients with a similar propensity score are alike on all measured factors, except the age of blood they received. In this case differences in outcomes can be attributed to the age of blood received, rather than differences in patient characteristics.

This study aims to explore the relationship between age of blood and adverse outcomes in a maternity population, using propensity scores with age of blood as a continuous measure.

Materials and Methods:

This study included women giving birth in NSW public hospitals from July 2006 to December 2010 who received one to four RBC units during their birth admission. In NSW, maternity care is offered across a number of maternity hospitals with differing capability to manage complex cases, with the highest level of obstetric and neonatal care being offered at the metropolitan tertiary hospitals.

Women typically attend the closest public hospital, or can opt to receive treatment at a private hospital. Women with higher risk pregnancies may be treated at a tertiary facility, however these facilities also provide care for low risk women in their local area.

The birth admission was defined as the admission in which the delivery of the infant took place. Women with five or more units transfused were excluded due to: the difficulty in separating the indication for transfusion from adverse events following transfusion, the possibility that hospitals may have differing policies on age of blood used in massive transfusion protocols and because women with more transfusions are typically over-represented in the group receiving older blood.

Data on the women and blood transfusions were obtained from five administrative datasets. Pregnancy and birth information was obtained from the NSW Perinatal Data Collection ('birth data'), which records information on all livebirths and stillbirths of at least 400g or 20 weeks gestation in NSW. Data on maternal medical conditions was obtained from the Admitted Patients Data Collection ('hospital data'), a census of all hospital admissions in NSW, recording diagnoses and procedures coded according to the International Classification of Diseases – 10th Revision, Australian Modification, and the Australian Classification of Health Interventions. Information on blood transfusion was obtained from the Clinical Excellence Commission Bloodwatch Program Red Cell Utilisation database ('Red Cell data'). These data include data on each RBC unit issued to patients in NSW public hospitals from hospital pathology laboratories, however hospitals differed in the time at which they started contributing data to this program. Haemoglobin measures were available for some patients. Blood type and collection date were obtained for each RBC unit from the Australian Red Cross Blood Service ('Red Cross data'). Fact of death was obtained from the Registry of Births, Deaths and Marriages data ('deaths data').

The birth, hospital, deaths and red cell datasets were linked using probabilistic linkage based on personal identifiers, and the Red Cross data deterministically linked on RBC unit barcode, by the NSW Centre for Health Record Linkage (CHeReL). Only deidentified data were provided to

researchers. Transfusions were identified from the Red Cell data, and women with corresponding records across all four datasets (excluding 'deaths data') were retained for analysis.

This study was approved by the NSW Population and Health Services Research Ethics Committee.

Variable definitions

The primary outcomes for this study were *severe maternal morbidity* within 40 days of the birth *admission* and were ascertained from hospital data. Severe morbidity was measured using a composite indicator of one or more of sepsis, thromboembolic events, organ dysfunction, shock, cardiac arrest, cerebral oedema, coma, cerebral-vascular accident, assisted ventilation, dialysis, or death within 12 months. This indicator is based on a validated morbidity indicator,[22] but excludes events in the validated indicator likely to have occurred prior to the transfusion occurring. Readmission was defined as any subsequent readmission to the same or another facility within 6 weeks of discharge from the birth admission. Maternal demographic information, obstetric management and medical conditions were obtained from the birth and hospital data based on validation study reporting.[23,24]

Transfusion was identified from the Red Cell data, and age of blood calculated as the difference between collection date ('Red Cross data') and the date the unit was issued to the patient ('Red Cell data'). In the case of multiple transfusions, the age of blood was considered as the age of the oldest unit (maximum age of red cells). In NSW, units have a 42 day expiry and all RBC units have been leucodepleted since July 2008. Other studies have shown[13] that those patients receiving more transfusions are more likely to have received at least one unit of older blood, and so our analyses are adjusted for the number of transfusions received. Two sensitivity analyses were conducted. The first, considered the age of the youngest blood transfused. The second included only women where an increase in haemoglobin between pathology tests prior to and following issue of blood from the blood bank confirmed that a transfusion was received.

Statistical methods

Generalised propensity score (GPS) methods [20,25] were used to take account of factors which might influence the age of blood received and also the occurrence of an adverse outcome. This is a two stage process. In the *first stage*, a linear regression model was built to model the relationship between covariates and age of blood received, with an emphasis on including factors likely associated with outcome. Factors considered were blood group, leucodepletion, month and year of transfusion, number of RBC transfusions received, hospital facilities and location, maternal age, bleeding or platelet disorders, as well as important pregnancy risk factors including parity, gestational age, postpartum haemorrhage (PPH), antepartum haemorrhage (APH), multiple gestation, mode of birth, pregnancy hypertension and gestational diabetes. From this model, each patient is assigned a series of propensity scores, reflecting the probability of that patient receiving blood of a certain age. To ensure valid inferences, women with extreme propensity scores were removed.[25] In the *second stage*, a regression model was built to model the effect of age of blood on maternal morbidity and readmission using the observed age of blood and adjusting for the corresponding propensity score for each subject. This was then used to develop the dose response curve, by calculating the curve for each age of blood, using the predicted propensity scores for each subject. [20]

Confidence intervals were obtained from 1000 bootstrap samples of the process including the generation of the GPS. Balance was assessed by comparing the significance of age of blood in predicting the covariate, with and without adjusting for the GPS. When the propensity score achieves balance across covariates, after adjusting for the GPS, the outcome can be considered to have occurred independent of probability of receiving blood of a given age. Results are presented as the rate of adverse outcomes for each age of blood, having removed the effect of other measured factors, and are presented graphically.

To facilitate comparison to previous studies, age of blood was also dichotomized into <14 days or ≥14 days, and a new propensity score model built to consider the propensity to receive fresh blood. Women receiving blood <14 days were matched to women receiving older blood, but having a similar propensity score. The odds of adverse outcome for receiving older compared with fresher blood was calculated. All analyses were performed in SAS 9.3 (Cary, NC).

Results

Between July 2006 and December 2010, there were 235,843 births in 54 NSW hospitals participating in data submission. Of these a total of 2990 women received 1-4 transfusions during the birth admission, and 416 women received 5 or more RBC units and were excluded. Of those receiving 1-4 units, almost three quarters were aged 20-34 years, just over half (53.6%) were in their first pregnancy and 9.5% had bleeding or platelet disorders. The majority of women (66.3%) received 1-2 RBC units (Table 1). Altogether 59.3% gave birth at tertiary facility. Overall the rate of severe maternal morbidity was 3.7% (N=111), and the overall rate of readmission was 4.6% (N=139).

The median age of blood transfused was 20 days (Interquartile range [IQR] 14,27), and the median number of units transfused was 2 (IQR 2,3). The median age of the oldest unit transfused was 22 days (IQR 15,30) (Figure 1), however this varied by number of units transfused. Women delivering in regional hospitals were more likely to be transfused with blood ≥14 days old than women delivering in tertiary hospitals (90.3% vs 78.0%) (Table 1).

Amongst those with severe maternal morbidity, the median age of blood transfused was 21 days (IQR 14,28), and amongst those without severe morbidity was 22 days (15,30), and for those readmitted was 22 days (14,28) vs 22 days (16,30). Without adjustment for maternal risk factors, or quantity transfused, the odds of severe morbidity for a one day increase in maximum age of blood

was 1.0 (95% CI: 0.97,1.01) and for readmission was 1.0 (0.97,1.00), indicating no univariate association between age of blood and morbidity in this sample.

After removal of patients with extreme propensity scores, 2957 (99%) patients were included in the final analysis, and the propensity score model balanced important covariates. Figure 2 and Figure 3 show the relationship between age of the oldest blood transfused, and maternal morbidity and readmission. There was no significant difference from the overall outcome rates for either morbidity or readmission rates for any age of blood. A sensitivity analysis considering the effect of the minimum age of blood transfused likewise found no significant difference in age of blood transfused and maternal morbidity or readmission rates.

Among the 1880 (63%) women with haemoglobin tests recorded both before and after transfusion indicating the transfusion was given, there was similarly no relationship between maximum age of blood received and adverse outcomes.

Considering women who received older (≥14 day) blood compared with women receiving fresher blood, 510 (95%) women receiving fresh blood were matched to women receiving older blood (N=1020). The odds of severe morbidity was 1.05 (0.58,1.91) for those receiving older vs fresher blood, and for readmission was 0.73 (0.42,1.27).

Discussion

This study found no relationship between age of blood transfused and either severe morbidity or readmission rates among women requiring a low volume blood transfusion during a birth admission. This finding was unchanged when age of blood was considered as <14 vs ≥14 days. Consistent with other studies, we found women receiving more RBC units tended to receive older blood,[13] however once the effect of number of units received, and other factors associated with age of blood transfused were taken into account, there were no apparent trends in increased morbidity or readmission with older blood.

The median storage time of blood was 20 days, which is consistent with other studies reporting average or median age of blood between 14[26] and 28[27] days, despite differences in shelf life between countries.[2] The median age of blood however was longer than the estimated average of blood transfused in US hospitals, 16.4 days. [5] A large number of observational studies to date have been single centre studies, and generalizability of these studies may be limited as it has been acknowledged that different hospital types may differ in median age of blood used.[5] We found some difference in the age of blood transfused between regional and urban hospitals, reflective of the centralized processing of blood in NSW. Reassuringly for these contexts, the age of blood was not associated with increased adverse outcomes.

This study considered rates of severe maternal morbidity and readmission, which differ from outcomes considered in other studies. Other studies have focused on mortality, sepsis or infection, organ failure, requirement for mechanical ventilation, intensive care admission, deep vein thrombosis, renal failure and length of stay. [26-32] The typically younger and healthier nature of maternity patients mean these outcomes, although serious, are rare, and more common outcomes, such as readmission are also important to consider. Such outcomes are not commonly considered in other specialties. In addition to examining readmission, we considered a composite measure of severe morbidity which contained many of the outcomes considered in other studies (excluding

intensive care admission and length of stay). This allowed us to consider some of the severe outcomes that occur too rarely in maternity populations for individual associations with age of blood to be estimated. Use of a composite indicator also increases ascertainment of severe morbidity from routinely collected data, where individual aspects of morbidity may be under-reported, and composite measures are less susceptible to random fluctuations due to rare events.[22] In women with massive haemorrhage, the ability to determine the age of blood effects is hampered by the volume and therefore different ages of blood given.[13,33] By limiting the study population to women receiving 1-4 units of blood, and adjusting for number of units transfused, we reduce the confounding introduced by quantity transfused. The characteristics of the study population confirm transfusions were not occurring in the context of massive haemorrhage, with two-thirds of women receiving 1-2 units. Such transfusions are more likely to be given to correct symptomatic anaemia postnatally or where the risk of rebleeding is considered high, rather than in the context of active bleeding. The high proportion of women receiving two units of red cells (58.6%) compared with a single unit (7.7%) reflects current practice, however recent guidelines promote transfusion of a single unit, followed by reassessment in stable, non-bleeding patients. [34]

Our finding of no relationship between adverse outcomes and age of blood transfused amongst low-risk maternity patients is consistent with findings among other low risk groups. Vamvakas and Carven examined length of stay after transfusion of an average of 4.1 units of blood following CABG surgery, which they considered a 'lower risk' population, and found no effect of age of blood after adjustment (which included number of units transfused).[35] Similarly, in pediatric cardiac surgery patients, Manlhoit et al found no relationship between outcomes and age of blood in patients receiving 4 or fewer units, but found an increase in adverse outcomes in patients receiving higher volumes of blood.[36] A study by Weinberg et al found an increase in mortality with transfusion of older blood in less severely injured trauma patients, however in this study, some patients received up to 104 units of blood, and it is difficult to distinguish the effects of the number of units and age of blood transfused.[37] Such studies have suggested that there may be a dose effect, where a single unit

of older blood may not be sufficient to contribute to adverse outcomes. [35] Others have proposed that patients who are already compromised may not cope as well with the additional insult of older blood (the two-hit hypothesis),[38] and that patients with better physiological reserves may be better able to compensate for any sub-optimal characteristics of transfused blood and as transfusion not as time critical, the body may have time to wait for reversal of some aspects of the storage lesion.[39,40]

Similarly, studies involving transfusion of fresh or old blood into healthy volunteers have found that although transfusion of older blood was associated with some compositional changes in the RBCs and physiological responses, these did not translate into adverse events. Hod et al found higher serum total bilirubin levels after transfusion of 40-42 day old blood, indicating increased haemolysis due to cell damage. They also found higher transferrin saturation after transfusion, but that the haemoglobin rise was the same in fresh and old blood. There was no difference in the inflammatory markers C-reactive protein or interleukin-6 between fresh and older blood. Although in vitro studies showed proliferation of *Escherichia coli*, there were no cases of sepsis resulting from the older blood. [41] Other studies in healthy volunteers have found that there were minimal effects on microcirculation and tissue oxygenation after transfusion of older (42 day) blood compared with fresh (7 day) blood,[42] and that transfusion of both fresh and older (24 day) blood caused impaired oxygen exchange. [43]

The results of animal and laboratory studies have been more conclusive. A canine study by Solomon and colleagues of large volume (exchange) transfusion in canines with pneumonia found that animals transfused with older blood had higher mortality than those receiving fresher blood. [44] Other studies have described the “storage lesion”- the accumulation of changes in red cell structure and deformability, oxygen affinity, 2,3-diphosphoglycerate and adenosine triphosphate concentrations which occur with increased storage of blood, as well as changes in the storage medium. [40] Although these are progressive changes, effects are seen after as little as 14 days, however changes in 2,3-diphospoglycerate are reversed within 72 hours of transfusion.

The blood supply chain implications of changes to the maximum storage life of blood are considerable. [11,45] Some observational studies have suggested that patients in some disciplines may benefit from transfusion of fresher blood, [26,30,46-48] however early results of randomized trials suggest this may not be the case. If, following further trials, policies of giving fresher blood to these patients are introduced, blood banks will need to implement new procedures to maintain blood stock levels, and prevent excessive outdating of stock.

Strengths and limitations

This study is the first observational study to look at age of blood in a maternity population, and includes a large population of almost 3000 transfused women. It makes use of linked administrative data collected at the time of blood collection (blood packs), through to following birth (birth and hospital discharge data). Generalized propensity scores were used to avoid the need to dichotomize age of blood. A large number of well reported potential confounders were considered, and were balanced across age of blood transfused, meaning any effect of age of blood was not due to differences in observable patient characteristics. While this analysis was able to consider a range of confounders, unmeasured differences in patient characteristics may remain. In particular, we were not able to consider patient blood group, only blood group transfused and whether the patient received more than one type of blood.

While population data are ideal for investigating rare outcomes such as maternal morbidity, the timing of morbidity in relation to the birth event are unknown. While haemorrhage-related morbidities that are likely to have preceded transfusion were removed from the composite measure of maternal morbidity it is possible some of the complications may have occurred prior to transfusion. Results for readmission are not subject to the same consideration. The composite outcome was used to enhance ascertainment of severe outcomes,[22] and increase detection of

adverse events, however the rate of adverse outcomes remained low. While this is reassuring, it means that with just under 3000 women in this study, there was limited power to detect small changes in adverse outcome rates. It is also encouraging that a similar lack of association was found with readmission.

While not all blood issued to patients may have been given, the sensitivity analysis restricting to women with haemoglobin values that increased (indicating receipt of a transfusion) reassuringly showed no effect of age of blood on adverse outcomes.

Conclusions

This study found no evidence that adverse outcomes are increased with transfusion of older blood in maternity patients receiving up to four units of blood. The demonstrated lack of an association between age of blood and adverse outcomes in the obstetric setting is reassuring in the context of conflicting findings in other specialties.

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Table 1: Women transfused in selected NSW public hospitals between July 2006 and December 2010, by age of oldest blood transfused.

		Total (col %)	**Maximum Age of blood <14 days (row %)**	**Maximum Age of blood ≥14 days (row %)**
Total		2990 (100.0)	539 (18.0)	2451 (82.0)
Maternal Age	Under 20	161 (5.4)	26 (16.1)	135 (83.9)
	20-34	2175 (72.7)	380 (17.5)	1795 (82.5)
	35+	654 (21.9)	133 (20.3)	521 (79.7)
Private Patient		434 (14.5)	71 (16.4)	363 (83.6)
Multiple birth		127 (4.2)	23 (18.1)	104 (81.9)
Primiparous		1603 (53.6)	291 (18.2)	1312 (81.8)
Bleeding/Platelet disorder		283 (9.5)	62 (21.9)	221 (78.1)
Antepartum haemorrhage		180 (6.0)	34 (18.9)	146 (81.1)
Placenta Praevia		206 (6.9)	44 (21.4)	162 (78.6)
Caesarean Section		1040 (34.8)	197 (18.9)	843 (81.1)
Instrumental Delivery		597 (20.0)	111 (18.6)	486 (81.4)
Induction		1024 (34.2)	183 (17.9)	841 (82.1)
Small for gestational age		207 (6.9)	45 (21.7)	162 (78.3)

Large for gestational age		446 (14.9)	68 (15.2)	378 (84.8)
Hospital type	Tertiary	1772 (59.3)	390 (22.0)	1382 (78.0)
	Regional	658 (22.0)	64 (9.7)	594 (90.3)
	Urban/other	560 (18.7)	85 (15.2)	475 (84.8)
Year	2006	195 (6.5)	68 (34.9)	127 (65.1)
	2007	547 (18.3)	83 (15.2)	464 (84.8)
	2008	614 (20.5)	157 (25.6)	457 (74.4)
	2009	704 (23.5)	55 (7.8)	649 (92.2)
	2010	930 (31.1)	176 (18.9)	754 (81.1)
Number of transfusions	1	229 (7.7)	60 (26.2)	169 (73.8)
	2	1752 (58.6)	340 (19.4)	1412 (80.6)
	3	589 (19.7)	93 (15.8)	496 (84.2)
	4	420 (14.0)	46 (11.0)	374 (89.0)

Figure Legends

Figure 1: Maximum age of blood transfused in birth admission

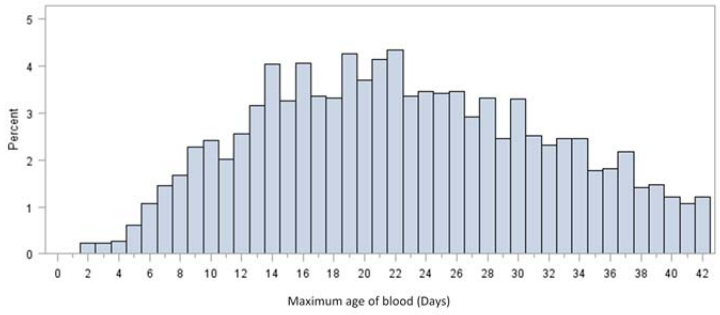


Figure 2: Dose response curve for age of blood and severe maternal morbidity

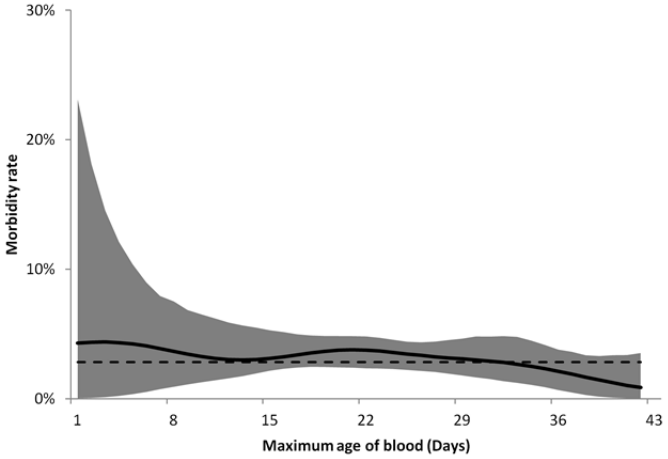
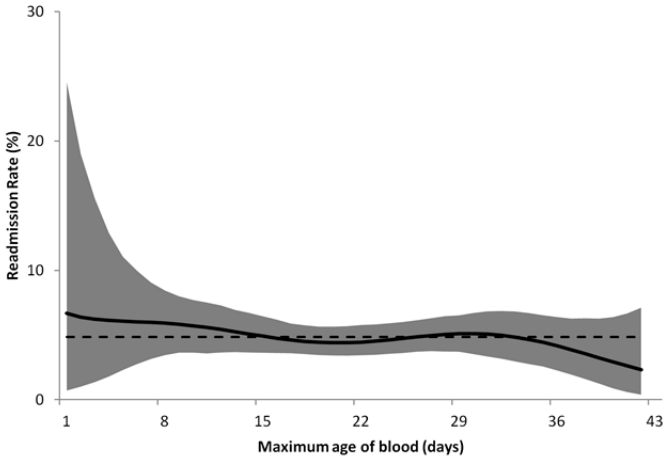


Figure 3: Dose response curve for age of blood and readmission rates



Appendix 1: Flowchart showing derivation of study population