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## Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion (Review)

Simancas-Racines D, Osorio D, Martí-Carvajal AJ, Arevalo-Rodriguez I

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[Intervention Review]

# Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion

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## ABSTRACT

### Background

A blood transfusion is an acute intervention, implemented to solve life and health-threatening conditions on a short-term basis. However, blood transfusions have adverse events, some of them potentially related to immune modulation or to a direct transmission of infectious agents (e.g. cytomegalovirus). Leukoreduction is a process in which the white blood cells are intentionally reduced in packed red blood cells (PRBCs) in order to reduce the risk of adverse reactions. The potential benefits of leukoreduced PRBCs in all types of transfused patients for decreasing infectious and non-infectious complications remain unclear.

### Objectives

To determine the clinical effectiveness of leukoreduction of packed red blood cells for preventing adverse reactions following allogeneic blood transfusion.

### Search methods

We ran the most recent search on 10th November 2015. We searched the Cochrane Injuries Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE (OvidSP), Embase(OvidSP), CINAHL Plus (EBSCO), LILACS (BIREME), and clinical trials registers. In addition, we checked the reference lists of all relevant trials and reviews identified in the literature searches.

### Selection criteria

Randomised clinical trials including patients of all ages requiring PRBC allogeneic transfusion. Any study was eligible for inclusion, regardless of the length of participant follow-up or country where the study was performed. The primary outcome was transfusion-related acute lung injury (TRALI). Secondary outcomes were death from any cause, infection from any cause, non-infectious complications and any other adverse event.

### Data collection and analysis

At least two review authors independently performed study selection, 'Risk of bias' assessments and data extraction. We estimated pooled relative risk for dichotomous outcomes, and we measured statistical heterogeneity using  $I^2$  statistic. The random-effects model was used to synthesise results. We conducted a trial sequential analysis to assess the risk of random errors in cumulative meta-analyses.

## Main results

Thirteen studies, most including adult patients, met the eligibility criteria. We found no clear evidence of an effect of leukoreduced PRBC versus non-leukoreduced PRBC in patients that were randomised to receive transfusion for the following outcomes:

**TRALI:** RR 0.96, 95% CI 0.67 to 1.36,  $P = 0.80$  from one trial reporting data on 1864 trauma patients. The accrued information of 1864 participants constituted only 28.5% of the diversity-adjusted required information size (DARIS) of 6548 participants. The quality of evidence was low.

**Death from any cause:** RR 0.81, 95% CI 0.58 to 1.12,  $I^2$  statistic = 63%,  $P = 0.20$  from nine trials reporting data on 6485 cardiovascular surgical patients, gastro-oncology surgical patients, trauma patients and HIV infected patients. The accrued information of 6485 participants constituted only 55.3% of the DARIS of 11,735 participants. The quality of evidence was very low.

**Infection from any cause:** RR 0.80, 95% CI 0.62 to 1.03,  $I^2$  statistic = 84%,  $P = 0.08$  from 10 trials reporting data on 6709 cardiovascular surgical patients, gastro-oncology surgical patients, trauma patients and HIV infected patients. The accrued information of 6709 participants constituted only 60.6% of the DARIS of 11,062 participants. The quality of evidence was very low.

**Adverse events:** The only adverse event reported as an adverse event was fever (RR 0.81, 95% CI 0.64 to 1.02;  $I^2$  statistic = 0%,  $P = 0.07$ ). Fever was reported in two trials on 634 cardiovascular surgical and gastro-oncology surgical patients. The accrued information of 634 participants constituted only 84.4% of the DARIS of 751 participants. The quality of evidence was low.

**Incidence of other non-infectious complications:** This outcome was not assessed in any included trial.

## Authors' conclusions

There is no clear evidence for supporting or rejecting the routine use of leukoreduction in all patients requiring PRBC transfusion for preventing TRALI, death, infection, non-infectious complications and other adverse events. As the quality of evidence is very low to low, more evidence is needed before a definitive conclusion can be drawn.

## PLAIN LANGUAGE SUMMARY

### White blood cells reduction in packed red blood cell transfusions for preventing adverse reactions

#### Background

A blood transfusion is when blood is taken from one person and given to another person. Blood transfusions are given to solve life and health-threatening medical conditions on a short-term basis. However, blood transfusions have adverse events, some of them potentially related to an immune system response or due to the transmission of infectious agents (e.g. Human Immunodeficiency Virus). Leukoreduction is a process in which the white blood cells are intentionally removed from donated blood in order to reduce the risk of adverse reactions in people receiving the blood transfusion. The benefits of removing white blood cells with the intent of reducing infectious and non-infectious complications in all types of transfused patients remains unclear. Removing white blood cells is costly. The USA and UK spend tens of millions each year on the procedure. In the USA, the procedure costs approximately USD \$30 for each unit of blood product. It may not be worth spending so much money if there is no clear benefit to patients.

#### Clinical question

What are the benefits and harms of removing white blood cells from donated blood for people receiving a blood transfusion?

#### Study characteristics

We searched medical journals for reports of clinical trials which examined the effects of removing white blood cells from donated blood. We were interested in finding out whether the removal of white blood cells from donated blood resulted in patients receiving a blood transfusion having few complications such as transfusion-related acute lung injury, death, infectious and non-infectious complications, or any other adverse event. We included people of any age or sex, who received a blood transfusion for any reason. The evidence is based on studies retrieved up to 05 December 2014.

#### Main results

We found 13 studies which included people who received a blood transfusion during heart or cancer surgery, or because they were injured, had cancer, HIV or sepsis.

We found no clear evidence showing either benefits or harms for removing white blood cells from donated blood. For all of the outcomes examined (transfusion-related acute lung injury, death from any cause, infection from any cause, non-infectious complication or any other adverse event), there was no sign of benefit or harm.

#### Quality of evidence

The overall quality of evidence of the included studies ranges from very low to low. None of the studies included enough people to give a definitive answer about the usefulness of removing white blood cells from donated blood. New high-quality studies, involving a few thousand people, are needed to enable us to know the true benefits and harms of this procedure.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Leukoreduced PRBCs versus non-leukoreduced PRBCs for preventing adverse reaction from allogeneic blood transfusion

#### Leukoreduced PRBCs versus non-leukoreduced PRBCs for preventing adverse reaction from allogeneic blood transfusion

**Patient or population:** Patients receiving RBC transfusion

**Settings:** Any

**Intervention:** Leukoreduced PRBCs

**Comparison:** Non-leukoreduced PRBCs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-leukoreduced packed RBCs	Leukoreduced packed RBCs				
<b>TRALI</b> Follow-up: mean 28 days	<b>Study population</b>		<b>RR 0.96</b> (0.67 to 1.36)	1864 (1 study)	⊕⊕⊕⊕ <b>low</b> <sup>1</sup>	TSA yielded an inconclusive result.
	<b>63 per 1000</b>	<b>61 per 1000</b> (42 to 86)				
<b>Death due to any cause</b> Follow-up: median 2.5 months	<b>Study population</b>		<b>RR 0.81</b> (0.58 to 1.12)	6485 (9 studies)	⊕⊕⊕⊕ <b>very low</b> <sup>2</sup>	TSA yielded an inconclusive result.
	<b>93 per 1000</b>	<b>76 per 1000</b> (54 to 104)				
<b>Infection from any cause</b> Follow-up: mean 2.5 months	<b>Study population</b>		<b>RR 0.80</b> (0.62 to 1.03)	6709 (10 studies)	⊕⊕⊕⊕ <b>very low</b> <sup>3</sup>	TSA yielded an inconclusive result.
	<b>204 per 1000</b>	<b>163 per 1000</b> (127 to 210)				
<b>Adverse events</b> Follow-up: mean 3 months	<b>Study population</b>		<b>RR 0.81</b> (0.64 to 1.02)	634 (2 studies)	⊕⊕⊕⊕ <b>low</b> <sup>4</sup>	TSA yielded an inconclusive result.
	<b>387 per 1000</b>	<b>314 per 1000</b> (248 to 395)				
<b>Non-infectious complication</b>	<b>Study population</b>		Not estimable	—	—	No trial assessed this outcome.
	Not estimable	Not estimable				

\*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio; **TRALI:** Transfusion-related acute lung injury; **RBC:** Red blood cell; **PRBC:** Packed red blood cell; **DARIS:** Diversity-adjusted required information size.

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GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

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<sup>1</sup>Downgraded by two due to imprecision: small sample size as compared with the calculated DARIS and the wide CI overlapping zones of no effect, as well as potential harm or benefit, or both. Few events reported.

<sup>2</sup>Downgraded due to: high risk of bias (Six of nine included studies have high or unclear risk of bias, -1); important heterogeneity ( $I^2$  statistic: 63%, -1); and imprecision as reflected in the wide CI and an insufficient accrued information size compared with the DARIS (-1).

<sup>3</sup>Downgraded due to: high risk of bias (Seven of 10 included studies were at high or unclear risk of bias, -1); important heterogeneity ( $I^2$  statistic: 84%, -2); and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1)

<sup>4</sup>Downgraded due to: high risk of bias (All included studies evaluated were at high risk of bias, -1) and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1).

## BACKGROUND

### Description of the condition

Blood transfusion is the infusion of both soluble and cell-associated forms (red blood cells (RBCs), white blood cells (WBCs) and platelets) into a recipient (Vamvakas 2001). A blood transfusion is an acute intervention, implemented to solve life and health-threatening conditions on a short-term basis; and in general, its long-term effects tend to be of secondary importance (Tsai 2010).

However, blood transfusion is associated with an increasing risk of infectious and non-infectious adverse events (Wagner 2004; Hendrickson 2009; Sachs 2010). The incidence of non-infectious transfusion reactions is greater than that of infectious complications (Lavoie 2011). Mortality associated with non-infectious risks is also significantly higher and accounts for 87% to 100% of fatal complications of transfusions (Lavoie 2011).

The main non-infectious adverse events to the patient are transfusion-related acute lung injury (TRALI), which is considered the most severe non-infectious complication (Renaudier 2009; Triulzi 2009; Vamvakas 2009); non-haemolytic febrile transfusion reaction (NHFT) (King 2004; Blajchman 2006; Hoffman 2008) and allergic reactions (Tenorio 2007). Less frequent are transfusion-associated graft-versus-host disease (TA-GVHD) (Dwyre 2008; Hoffman 2008; Rühl 2009) and transfusion-related with an immunomodulation effect (TRIM) (Vamvakas 2006).

Several approaches have been considered to prevent adverse reactions related to transfusion (Martí-Carvajal 2010; Lavoie 2011; Lindholm 2011; Tobian 2011). Transfusion of leukocyte-reduced RBC concentrates is one of those approaches (Blajchman 2010; Blumberg 2010; Mukagatare 2010). Leukocytes (WBCs) in blood components can mediate febrile transfusion reactions, stimulate human leukocyte antigen (HLA) alloimmunization in transfusion recipients, and transmit some cell-associated pathogens such as cytomegalovirus (CMV). Therefore, it is desirable to remove WBCs from transfusable blood components (Galel 2009).

Appendix 1 shows non-infectious transfusion reaction definitions related to WBCs.

### Description of the intervention

Leukoreduction is a process in which the WBCs are intentionally reduced by almost 99.99% in RBC concentrates (Shapiro 2004). There are many methods to conduct this approach; however, this process is currently performed using selective leukoreduction filters (Galel 2009). According to the U.S. Food and Drug Administration (FDA), leukocyte-reduced RBC concentrates contain fewer than  $5 \times 10^6$  WBCs/unit and at least 85% of the original RBCs (Galel 2009), and according to the Council of Europe  $< 1 \times 10^6$  total WBC/unit. Usually, most RBC leukofiltration is performed by blood collection centres within the first few days after collection (Galel 2009).

### Leukoreduction in trauma patients

Safe transfusion products are a necessity for the successful treatment of trauma patients (Tien 2007; Theusinger 2009). It is unclear if leukoreduction of RBC concentrates is the best method of providing blood products for trauma patients (Nathens 2006; Phelan 2007; Watkins 2008). Retrospective studies have shown a

reduction of infectious complications in injured patients treated with leukoreduced AlloBT; this effect appears more pronounced in patients receiving massive transfusion ( $> 6$  units of PRBC) (Friese 2008).

### Leukoreduction in surgery

Several studies have focused on the advantages of leukoreduced PRBC cells for transfusion in cardiac surgery (van de Wattering 1998; Dzik 2002; Wallis 2002; Bilgin 2004; van Hilten 2004; Connery 2005); colorectal surgery (Jensen 1992; Houbiers 1994; Jensen 1996; Titlestad 2001; Dzik 2002; Skånberg 2007); gastrointestinal surgery (Tartter 1998; Dzik 2002; van Hilten 2004); and renal transplantation (Sanfilippo 1985; Opelz 1997; Hiesse 2001). However, some of the findings of these published trials are considered controversial. Furthermore, this approach has been used in patients with AIDS; but, is unclear if this alternative method is beneficial in this population (Collier 2001).

### How the intervention might work

Leukoreduction works through multiple mechanisms for preventing adverse reactions:

1. To prevent TRALI: avoiding the transfer of leukocytes and reducing the cellular antibody interaction complexes that damage the endothelium of the lung (Triulzi 2009; Sachs 2011).
2. To avoid post-transfusion infections through reducing some cell-associated pathogens, such as CMV (Bilgin 2004; Blajchman 2004; van Hilten 2004; Connery 2005; Friese 2008).
3. To prevent immunomodulation: donor WBCs may suppress the recipient's immune system by interacting with it, producing susceptibility to many pathological conditions including cancer recurrence and other malignancies (Blajchman 2002; Dellinger 2004; Flohé 2007).

### Why it is important to do this review

This Cochrane review is important for the following reasons:

Firstly, leukoreduction is expensive. About EUR 29 million/year are spent on implementing leukoreduction (AETSA 2007). Other studies reported costs ranging from CAD \$26 million to 46 million annually (CCOHTA 1998). One study estimated the total cost of implementing leukoreduction was about USD 600 million dollars per year in USA (Shapiro 2004). It has also been reported that leukoreduction results in an increase of approximately USD 30/unit of blood product (Phelan 2007). More recently, Tsantes 2014 reported an incremental cost-effectiveness ratio (ICER) of EUR 6916 to prevent one case of febrile non-haemolytic transfusion reactions (FNHTR). Secondly, the potential role of leukoreduction for decreasing mortality and infection is controversial (AETSA 2007; Mukagatare 2010). Thirdly, several studies and meta-analyses did not report conclusive results about leukoreduction, and showed methodological inconsistencies (Vamvakas 1996; Blumberg 1998; Jensen 1998; Fergusson 2004; Blumberg 2007; Vamvakas 2007). Therefore, it is important to conduct this Cochrane review to determine the potential benefits of leukoreduction procedure in patients requiring RBC concentrates, focused on the prevention of adverse reaction.



## OBJECTIVES

To determine the clinical effectiveness of leukoreduction of packed red blood cells for preventing adverse reactions following allogeneic blood transfusion.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs).

#### Types of participants

Patients requiring allogeneic packed RBC (PRBC) transfusion. Patients could be of any age.

#### Types of interventions

##### Intervention

- Leukoreduced PRBCs.

##### Comparison

- Non-leukoreduced PRBCs.

We applied no limitations to the leukoreduction procedures used.

#### Types of outcome measures

##### Primary outcomes

1. Incidence of TRALI.

##### Secondary outcomes

1. Death due to any cause.
2. Infection from any cause (number of patients out of the total randomised).
3. Non-infectious complications ([Appendix 1](#)).
4. Any other adverse event: "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" ([Nebeker 2004](#)).

We took the information size for the primary outcome of this Cochrane review from the relative risk reported in [Nathens 2006](#). This study included trauma patients. A total sample size of 8781 participants was defined to assess a relative risk reduction on TRALI events of 25%, from a baseline incidence in the control of 6.31% (alpha level of 5% and power of 90%).

### Search methods for identification of studies

In order to reduce publication and retrieval bias we did not restrict our search by language, date or publication status.

#### Electronic searches

The Cochrane Injuries Group Trials Search Co-ordinator searched the following:

1. Cochrane Injuries Group Specialised Register (10/11/2015)
2. Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (issue 10 of 12, 2015)

3. MEDLINE (OvidSP) (1950 to November week 1, 2015)
4. Embase + Embase Classic (OvidSP) (1947 to 10/11/2015)
5. LILACS (BIREME) (1982 to 10/11/2015)
6. CINAHL Plus (EBSCO) (1937 to 10/11/2015)
7. Clinicaltrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) (10/1/2015)
8. WHO International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>) (10/11/2015)

We have reported the search strategies in [Appendix 2](#). We adapted the MEDLINE search strategy as necessary for the other databases. To the MEDLINE search strategy we added the Cochrane Highly Sensitive Search Strategy for identifying RCTs. To the EMBASE strategy we added the terms of the search strategy and study design terms as used by the UK Cochrane Centre ([Lefebvre 2011](#)).

#### Searching other resources

We also searched the following websites (25 November 2014):

1. US FDA (<http://www.fda.gov>).
2. European Medicines Agency (<http://www.emea.europa.eu>).
3. Scirus ([www.scirus.com](http://www.scirus.com)).
4. American Association of Blood Banks (AABB) (<http://www.aabb.org>).
5. Transfusion Evidence Library (<http://transfusionguidelines.org>).

In addition, we checked the reference lists of all relevant trials and reviews identified.

### Data collection and analysis

We summarised data according to standard Cochrane methodologies, including the *Cochrane Handbook of Systematic Reviews for Interventions* ([Higgins 2011](#)) and the Methodological Expectations for Cochrane Intervention Reviews (MECIR) ([Chandler 2013](#)).

#### Selection of studies

Two review authors, Daniel Simancas-Racines (DSR) and Ingrid Arévalo-Rodríguez (IAR), independently assessed for inclusion all the potential studies identified from the literature searches. We consulted a third review author, Arturo Martí-Carvajal (AMC) for any disagreements, which were resolved through discussion and consensus.

#### Data extraction and management

Two review authors, DSR and IAR, independently extracted data from the included trials. We consulted AMC and Dimelza Osorio (DO) in the event of any disagreements, which we resolved through discussion and consensus. Data were recorded for: eligibility criteria, demographics (age, gender and country), type of surgery, setting of the patients (i.e. cardiac surgery, intensive care unit (ICU)) outcomes. DSR recorded the data into a database. IAR and DO checked the data entered.

We contacted the trial author when a full-text article was unavailable (see [Appendix 3](#) for details).

#### Assessment of risk of bias in included studies

Two review authors, DSR and IAR, independently assessed the quality of each trial using a simple form following the domain-



based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We compared the assessments and discussed any discrepancies between the review authors. We consulted a third review author (AMC) to resolve any disagreement and to reach consensus.

For each included trial, we assessed risk of bias (as low, high or unclear) for each of the following domains:

- Generation of random sequence (selection bias).
- Concealment of treatment allocation (selection bias).
- Blinding of participants and personnel (person delivering treatment) to treatment allocation (performance bias).
- Blinding of outcome assessors to treatment allocation (detection bias).
- Completeness of the outcome data (including checks for possible attrition bias through withdrawals, loss to follow-up and protocol violations). For the incomplete outcome data domain, we considered as a high risk of bias RCTs that losses participants after transfusion intervention. Additionally, we considered high risk of bias (design bias) as those studies in which the patients were not transfused because inconsistency to determine inclusion criteria adequately or when a premature randomisation was done.
- Selective reporting of outcomes (reporting bias).
- Other sources of bias (other bias).

#### Measures of treatment effect

All outcomes in this Cochrane review were binary outcomes. We calculated the treatment effect with risk ratios (RRs) with 95% confidence intervals (CI).

#### Unit of analysis issues

The unit of analysis was the patient. We collected and analysed a single measurement for each outcome from each patient.

#### Dealing with missing data

We assessed the percentages of the overall dropouts for each included trial and per each randomisation arm, and we evaluated whether an intention-to-treat (ITT) analysis had been performed or could be performed with the available published information. We defined these dropouts as the percentage of lost patients who received an effective transfusion, over the total of transfused patients reported for each arm of the included studies.

#### Assessment of heterogeneity

We quantified statistical heterogeneity using the  $I^2$  statistic. The  $I^2$  statistic describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We considered  $I^2$  statistic between 50% and 74% as a moderate statistical heterogeneity, whereas a value of  $\geq 75\%$  represents high heterogeneity. We explored heterogeneity using a sensitivity analysis.

#### Assessment of reporting biases

We created a funnel plot to assess reporting bias for each outcome (Sterne 2011) where there were data from at least 10 trials (Higgins 2011).

#### Data synthesis

We summarized sufficiently comparable trials using the random-effects model to accommodate the high heterogeneity, and used a fixed-effect model for the sensitivity analysis. We carried out the main analysis based on the number of randomised participants, using an ITT analysis. All the analyses were carried out using RevMan 2014.

#### Subgroup analysis and investigation of heterogeneity

No data were available to perform the following subgroup analyses for the primary outcome (incidence of TRALI):

1. By type of post-transfusion complication.
2. By technique or type of material used.
3. Immunosuppressed patient versus non-immunosuppressed patient.
4. Massive transfusion (> 6 units PRBCs) versus less.

#### Sensitivity analysis

We performed the following sensitivity analysis for the primary outcome:

1. To assess the robustness of estimates, we used both fixed-effect and random-effects models for all outcomes and compared results.
2. We conducted a sensitivity analysis comparing trials with low risk of bias, with those at unclear or high risk of bias, according to attrition bias (Higgins 2011).
3. We also conducted a sensitivity analysis based on transfused patients to explore the high heterogeneity.

#### Trial sequential analysis

We carried out a trial sequential analysis (TSA) for every dichotomous outcome evaluated in this systematic review: TRALI, death from any cause, infection from any cause, and adverse events/fever.

TSA is a type of statistical power analysis that can be used to further investigate the relevance of results ("strength of evidence") yielded by a meta-analysis (Wetterslev 2008). It is the counterpart of a sample size calculation as part of a conventional study design. TSA allows researchers to differentiate between "spurious" significant findings caused by random error in a data-set with only small numbers of participants and trials and a "truly" significant result with sufficient statistical power. Thereby, TSA also accounts for repeated significance testing. The optimal information size and O'Brien-Fleming alpha-spending boundaries indicating the "real" significance threshold are constructed by providing the numbers for alpha level, power, control group risk and inter-study heterogeneity (Thorlund 2011). TSA can be performed only if the information size (number of participants) is large enough as compared with the optimal information size, and only if the outcome is dichotomous. Further details can be found in the "User Manual for Trial Sequential Analysis (TSA)", provided by the Centre for Clinical Intervention Research of the Copenhagen Trial Unit (Thorlund 2011).

#### 'Summary of findings' tables

We used the GRADE approach (Guyatt 2011b) to assess the overall quality of evidence. The GRADE approach appraises the quality of a

body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias (Balslem 2011; Brozek 2011; Guyatt 2011a; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h). We created a 'Summary of Findings' table using GRADEpro GDT Guideline Development Tool ([www.gradepro.org](http://www.gradepro.org)). We have presented the body of evidence in [Summary of findings for the main comparison](#).

## RESULTS

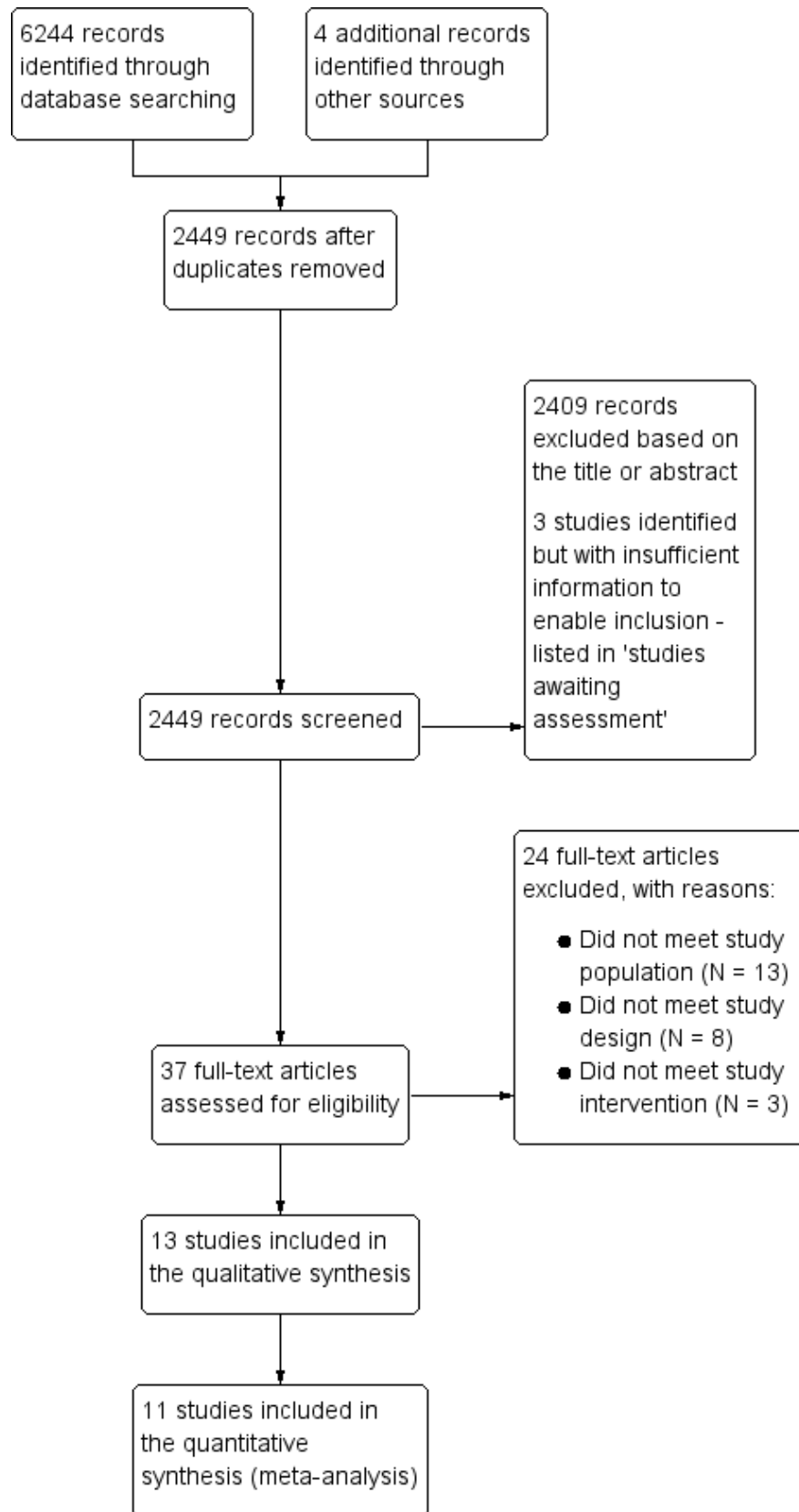
### Description of studies

See the [Included studies](#) section.

### Results of the search

We identified 6244 references. Thirteen RCTs met our inclusion criteria (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Boshkov 2006; Nathens 2006; Lapierre 2007; Donati 2014). See [Figure 1](#).

**Figure 1. Study flow diagram.**



We did not find any ongoing trials. Three studies were classified as awaiting assessment (Zhao 2004; NCT00810810; Waghmare 2012). There is insufficient information available about these studies to enable us to decide whether or not they should be included in the review. See [Characteristics of studies awaiting classification](#).

## Included studies

### Methodology characteristics

Trials were published between 1985 and 2014. They were conducted in various countries: five in the USA (Sanfilippo 1985; Tartter 1998; Collier 2001; Boshkov 2006; Nathens 2006), three in the Netherlands (van de Watering 1998; Bilgin 2004; van Hilten 2004), two in Denmark (Jensen 1996; Titlestad 2001), one in France (Lapierre 2007), one in the UK (Wallis 2002) and one in Italy (Donati 2014).

All trials had a parallel study design; 11 comparing two groups and two trials comparing three groups (van de Watering 1998; Wallis 2002). The number of trial participants ranged from 20 (Donati 2014) to 1864 (Nathens 2006), with a median of 531 participants.

In three trials participants were monitored for one month or less (Jensen 1996; Nathens 2006; Donati 2014). In 10 trials participants were monitored for between two and 15 months. In 11 trials there was an a priori sample size estimation, and one trial did not report how the sample size was derived (Sanfilippo 1985). In one trial the data used were taken from the report's abstract, and there was no information about the sample size calculation (Boshkov 2006). All trials used patients as the randomisation unit and unit of analysis. All trials reported inclusion criteria. Exclusion criteria were not reported in the Boshkov 2006 study abstract.

### Patient characteristics

All 13 included trials were conducted in adults, but two trials also included patients under 18 years of age: Collier 2001 ( $\geq 14$  years) and Nathens 2006 ( $\geq 17$  years). Twelve trials reported the gender of the participants; almost 60% of the included participants were men. Five trials involved cardiac surgery patients (van de Watering 1998; Wallis 2002; Bilgin 2004; van Hilten 2004; Boshkov 2006), four trials involved gastro-oncology surgery patients (Jensen 1996; Titlestad 2001; van Hilten 2004; Lapierre 2007), one trial involved non-surgical oncology patients (Lapierre 2007), one trial involved trauma patients (Nathens 2006), one trial included HIV infected patients (Collier 2001) and one trial involved patients with sepsis, severe sepsis or septic shock requiring ICU care (Donati 2014).

### Interventions

#### Leukoreduction definition

The extent of leukoreduction differed across the studies: two studies obtained 0.1 to  $0.3 \times 10^6$  per unit (Bilgin 2004; Titlestad 2001). Three trials reported  $5 \times 10^6$  leukocytes per unit of blood after leukoreduction (Collier 2001; Wallis 2002; Nathens 2006). Jensen 1996 reported  $1.2 \times 10^9$  per unit; van de Watering 1998 reported  $1.2 \pm 1.4 \times 10^6$  per unit; Tartter 1998 reported  $2 \times 10^5$  per unit; and Lapierre 2007 less than  $2 \times 10^4$  per unit. Four studies did not report definitions for leukoreduction (Sanfilippo 1985; van Hilten 2004; Boshkov 2006; Donati 2014).

### Type of filters

Trials were conducted using different types of filters. Two trials used "Cellselect Optima" filters (Bilgin 2004; van de Watering 1998). Four trials used "BPF4" filters for blood leukoreduction (Tartter 1998; Titlestad 2001; Wallis 2002; Nathens 2006). Jensen 1996 used "RC 100" filters and two trials used "Sepacell RZ-200B1" filters (Lapierre 2007; Donati 2014). Four trials did not report the type of filter used (Sanfilippo 1985; Collier 2001; van Hilten 2004; Boshkov 2006).

### Control groups

Trials were conducted using different types of comparator groups. Five trials used "Buffy coat depleted packed cells (PCs)" as a comparison group (Jensen 1996; van de Watering 1998; Wallis 2002; Bilgin 2004; van Hilten 2004). Eight trials used "unmodified RBC transfusion" or standard RBCs as a comparison group (Sanfilippo 1985; Tartter 1998; Collier 2001; Titlestad 2001; Boshkov 2006; Nathens 2006; Lapierre 2007; Donati 2014). One trial also used "Red blood cells concentrate with plasma reduction" as a third non-leukoreduced arm (Wallis 2002).

### Cointervention

Three studies described the use of platelets as co-intervention (Collier 2001; Bilgin 2004; Nathens 2006). Bilgin 2004 reported that platelets were all leukocyte-depleted by filtration; Collier 2001 did not describe the platelet leukoreduction process, and Nathens 2006 reported that all patients received apheresis platelets when platelets were required. Lapierre 2007 reported that none of the patients received platelets concentrate.

### Outcomes

One trial reported on TRALI (Nathens 2006).

Nine trials reported on death from any cause (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). Boshkov 2006 reported death only for the transfused patients group.

Ten trials reported on infection from any cause (Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007) the infections reported were: respiratory tract infections in six studies (Jensen 1996; van de Watering 1998; Titlestad 2001; Bilgin 2004; Nathens 2006; Lapierre 2007); urinary tract infections in five studies (Jensen 1996; van de Watering 1998; Bilgin 2004; Nathens 2006; Lapierre 2007); wound infections or surgical site infections in seven studies (Jensen 1996; Tartter 1998; van de Watering 1998; Titlestad 2001; Bilgin 2004; Nathens 2006; Lapierre 2007); bacteraemia or septicaemia in seven studies (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Bilgin 2004; Nathens 2006; Lapierre 2007); abdominal infection in three studies (Jensen 1996; Titlestad 2001; Nathens 2006). Collier 2001 included persons infected with HIV and CMV.

Three trials reported adverse events (Collier 2001; Wallis 2002; Lapierre 2007). One trial, Collier 2001, analysed fever episodes per transfusion, but not per study participant, thus it was not included in the meta-analysis.

Donati 2014 and Sanfilippo 1985 reported only physiological outcomes. There were no relevant data to include in the analyses.

**Excluded studies**

We excluded 24 studies (see [Characteristics of excluded studies](#)) for the following reasons:

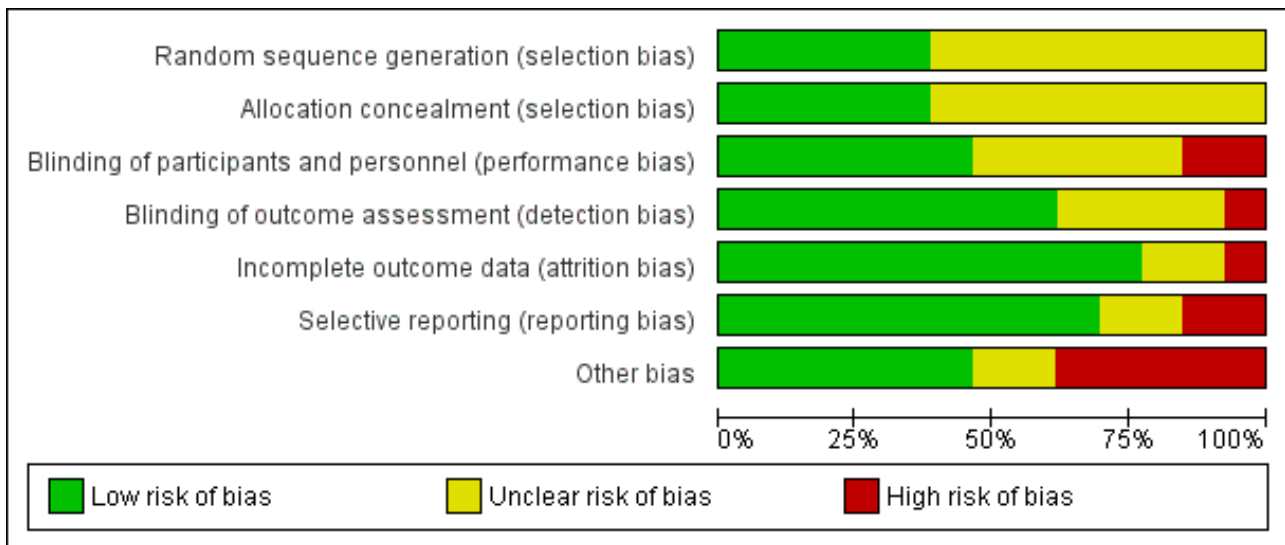
- Use of other blood products in the intervention groups (Gilbert 1989; Jensen 1992; Houbiers 1994; Bowden 1995; Kao 1995; Gu 1996; Nielsen 1999; Hayashi 2000; Dzik 2002; Efstathiou 2003; Connery 2005; Gu 2009).

- No transfusion in one of the study groups (Opelz 1997; de Vries 2004; Koskenkari 2005; Leal-Noval 2005; Salamonsen 2005; So-Osman 2010).
- Non-randomised clinical trial (Bracey 2002; de Vries 2003; Llewelyn 2004; Skånberg 2007), or a review article (van de Watering 2004; Vamvakas 2007).

**Risk of bias in included studies**

We have summarised the risk of bias in the included studies in [Figure 2](#) and [Figure 3](#).

**Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.**



**Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bilgin 2004	+	+	+	+	+	+	+
Boshkov 2006	?	?	?	+	?	?	-
Collier 2001	+	+	+	+	+	+	+
Donati 2014	?	+	+	+	+	+	+
Jensen 1996	?	?	?	+	+	+	?
Lapierre 2007	+	?	-	-	+	?	?
Nathens 2006	+	+	+	+	+	+	+
Sanfilippo 1985	?	?	?	?	?	-	-
Tartter 1998	?	?	?	?	+	-	-
Titlestad 2001	?	?	+	+	+	+	-
van de Watering 1998	?	?	?	?	+	+	+
van Hilten 2004	+	+	+	?	-	+	-
Wallis 2002	?	?	-	+	+	+	+



## Allocation

### Random sequence generation

In five trials there was low risk of bias related to the sequence generation method (Collier 2001; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). Eight trials had unclear risk of bias (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Titlestad 2001; Wallis 2002; Boshkov 2006; Donati 2014).

### Allocation concealment

In five trials there was low risk of bias related to the method of allocation concealment (Collier 2001; Bilgin 2004; van Hilten 2004; Nathens 2006; Donati 2014). Eight trials had unclear risk of bias (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Titlestad 2001; Wallis 2002; Boshkov 2006; Lapierre 2007).

## Blinding

### Blinding of participants and personnel

The risk of bias arising from the lack of blinding was rated as low in six trials (Collier 2001; Titlestad 2001; Bilgin 2004; van Hilten 2004; Nathens 2006; Donati 2014). The risk of bias from blinding was unclear in five trials (Sanfilippo 1985; Jensen 1996; Tartter 1998; van de Watering 1998; Boshkov 2006) and high in two studies (Wallis 2002; Lapierre 2007).

### Blinding outcome assessment

Eight trials had a low risk of bias arising from the method of blinding outcome assessment (Jensen 1996; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; Boshkov 2006; Nathens 2006; Donati 2014). Four studies were at unclear risk (Sanfilippo 1985; Tartter 1998; van de Watering 1998; van Hilten 2004) and one trial was at high risk of bias (Lapierre 2007).

## Incomplete outcome data

Ten trials were judged to be at low risk of bias from incomplete outcome data (Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; Nathens 2006; Lapierre 2007; Donati 2014). There was unclear risk of bias in two trials (Sanfilippo 1985; Boshkov 2006), and high risk of bias in one trial (van Hilten 2004).

## Selective reporting

We judged nine trials as at low risk of reporting bias (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Donati 2014). Two trials were at unclear risk of bias (Boshkov 2006; Lapierre 2007), and two trials were at high risk of bias (Sanfilippo 1985; Tartter 1998).

## Other potential sources of bias

Six trials appeared free of other potential sources of bias and we judged these trials to be at low risk of bias (van de Watering 1998; Collier 2001; Wallis 2002; Bilgin 2004; Nathens 2006; Donati 2014). Seven trials had design bias of different kinds: inconsistency in adequately determining inclusion criteria, premature randomisation (Sanfilippo 1985; Tartter 1998; van de Watering 1998; Titlestad 2001; van Hilten 2004; Boshkov 2006) or sample size bias (Lapierre 2007).

## Effects of interventions

See: [Summary of findings for the main comparison Leukoreduced PRBCs versus non-leukoreduced PRBCs for preventing adverse reaction from allogeneic blood transfusion](#)

## Leukoreduced PRBC versus non-leukoreduced PRBC

### 1. Primary outcomes

#### TRALI (analysis based on total randomised patients)

##### Overall analysis

One trial including 1864 participants showed no difference between treatment groups on TRALI (6.02% versus 6.31%) (RR 0.96, 95% CI 0.67 to 1.36;  $P = 0.80$ ) (Nathens 2006). See [Analysis 1.1](#).

##### Quality of evidence (TSA and GRADE)

The accrued information of 1864 participants constituted only 28.5% of the diversity-adjusted required information size (DARIS) of 6548 participants. We calculated DARIS based on a diversity of 4%; a proportion with the TRALI events of 6.3% in the control group; a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). With the inclusion of data from one trial, the Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. The TSA-adjusted 95% CI overlapped with no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.46 and RR 1.98, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was low (imprecision as reflected in the wide CI and only one trial with a small sample size as compared with the DARIS (-2)).

In the analysis including "only transfused patients", compared to all patients results were similar (RR 0.98, 95% CI 0.74 to 1.29;  $P = 0.87$ ; [Analysis 2.1](#)). We were unable to conduct other subgroup and sensitivity analyses because only one study measured this outcome. In this study, Nathens 2006, leukoreduction was performed pre-storage.

### 2. Secondary outcomes

#### Death due to any cause

##### Overall analysis (total randomised patients)

The meta-analysis of nine trials including 6485 participants showed no difference between treatment groups in the risk of death from any cause (8.54% versus 9.34%; RR 0.81, 95% CI 0.58 to 1.12,  $I^2$  statistic = 63%,  $P = 0.20$ ) (Jensen 1996; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). See [Analysis 1.2](#).

##### Sensitivity analysis

We conducted three sensitivity analyses; none of which were statistically significant. The RRs using the fixed-effect model were similar to that of the random effect model.

1. Including three studies with low risk of bias (Collier 2001; Bilgin 2004; Nathens 2006), compared to six studies at unclear or high risk of bias (RR 1.03, 95% CI 0.89 to 1.20;  $I^2$  statistic = 38%,  $P = 0.66$ ).
2. Including "only transfused patients", compared to all patients (RR 0.80, 95% CI 0.60 to 1.07,  $I^2$  statistic: 60%,  $P = 0.13$ , [Analysis 2.2](#)).



3. Post-storage leukoreduction, compared with pre-storage leukoreduction (RR 0.74, 95% CI 0.53 to 1.04,  $I^2$  statistic: 70%,  $P = 0.09$ ).

**Reporting bias**

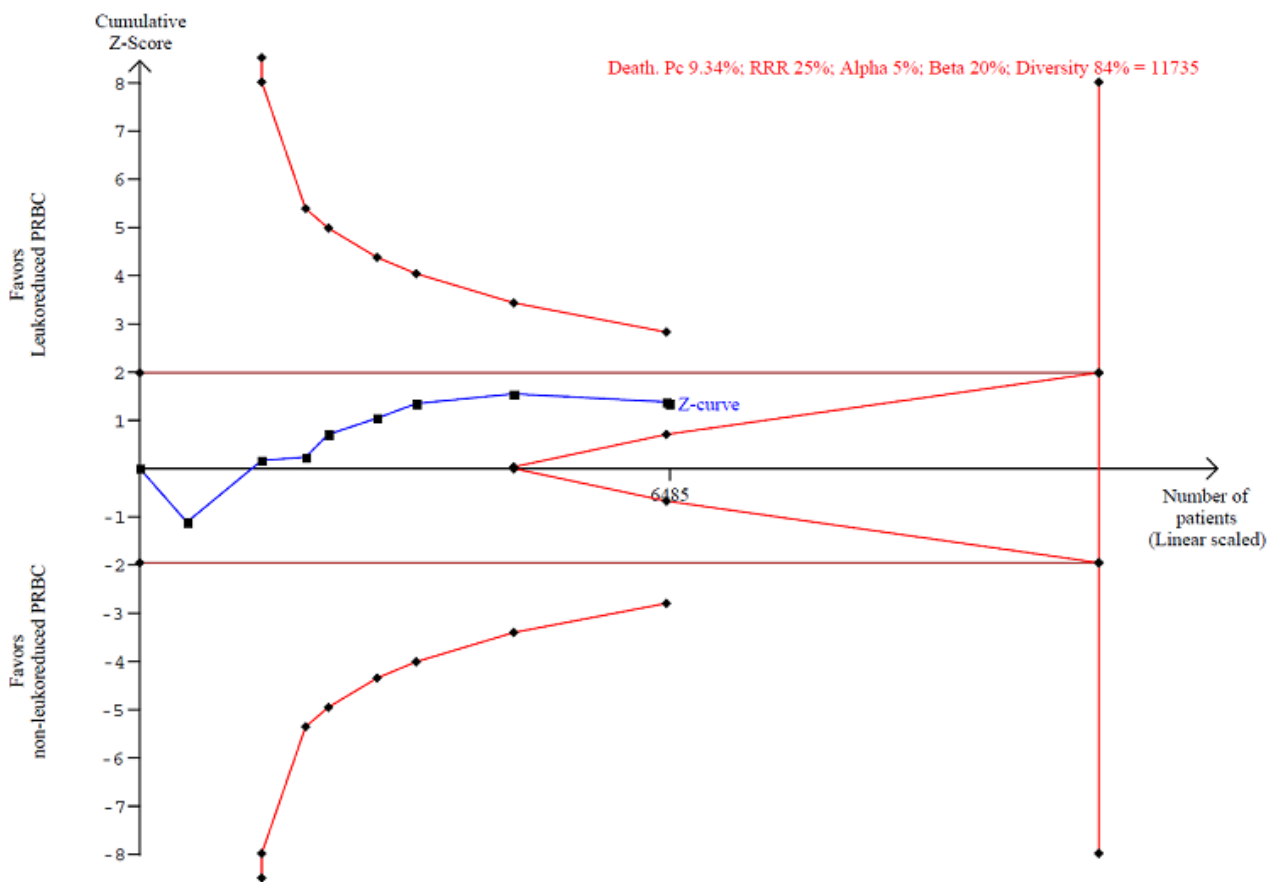
We did not explore reporting biases since the meta-analysis included fewer than 10 studies (Higgins 2011).

**Quality of evidence (TSA and GRADE)**

The accrued information of 6485 participants constituted only 55.2% of the DARIS of 11,735 participants. DARIS was calculated based on a diversity of 84%; a proportion of death from any cause

of 9.34% in the control group (median proportion of deaths in the control group); a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. The TSA did not indicate futility, as the cumulative Z-curve did not cross the futility wedge (Figure 4). The TSA-adjusted 95% CI overlapped with no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.51 and RR 1.27, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was very low (high risk of bias (-1); important heterogeneity (-1); and imprecision as reflected in the wide CI and an insufficient accrued information size compared with the DARIS (-1)).

**Figure 4. TSA calculated to reliably detect a 25% relative change in the incidence of death from any cause, assuming a control group event rate of 9.34% with a power of 80% at an alpha of 5%**



**Infection from any cause**

**Overall analysis (total randomised patients)**

The meta-analysis of 10 trials involving 6709 participants showed no difference between treatment groups in the risk of infection from any cause (17.7% versus 20.4%; RR 0.80, 95% CI 0.62 to 1.03;  $I^2$  statistic = 84%,  $P = 0.08$ ) (Jensen 1996; Tartter 1998; van de Watering 1998; Collier 2001; Titlestad 2001; Wallis 2002; Bilgin 2004; van Hilten 2004; Nathens 2006; Lapierre 2007). See Analysis 1.3.

**Sensitivity analysis**

The RR was different when we used the fixed-effect model (RR 0.85, 95% CI 0.77 to 0.93;  $I^2$  statistic = 84%,  $P = 0.0006$ ); however, the results of TSA indicate this statistically significant result may be a spurious finding.

We performed three other sensitivity analyses, which showed no statistically significant differences:

1. Including three studies with low risk of bias (Collier 2001; Bilgin 2004; Nathens 2006), compared with seven studies at unclear or

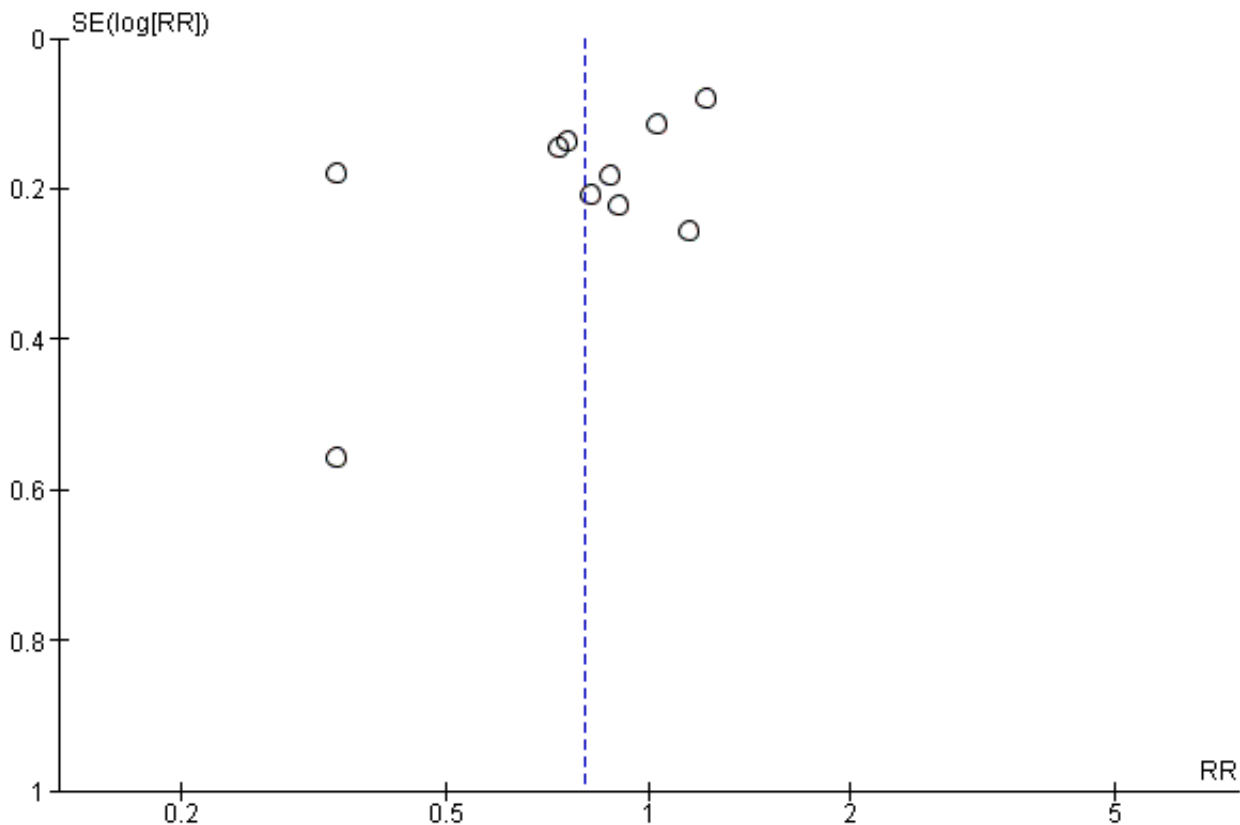
- high risk of bias (RR 0.92, 95% CI 0.63 to 1.34;  $I^2$  statistic = 83%,  $P = 0.67$ ).
- Including "only transfused patients", compared with all randomised patients (RR 0.76, 95% CI 0.58 to 1.00;  $I^2$  statistic = 87%,  $P = 0.05$ , [Analysis 2.3](#)), and the heterogeneity remained high.

- Post-storage leukoreduction, compared with pre-storage leukoreduction (RR 0.91, 95% CI 0.76 to 1.09;  $I^2$  statistic = 65%,  $P = 0.32$ ).

**Reporting bias**

After visual assessment of the funnel plot ([Figure 5](#)) and a formal assessment of the funnel plot asymmetry, applying the Egger's test ( $P = 0.09$ ), we found no sign of reporting bias.

**Figure 5. Funnel plot of comparison: 1 Leukoreduced PRBC versus non-leukoreduced PRBC. Main Analysis (Randomised patients), outcome: 1.3 Infection. Number of events of the total of randomised patients reported.**

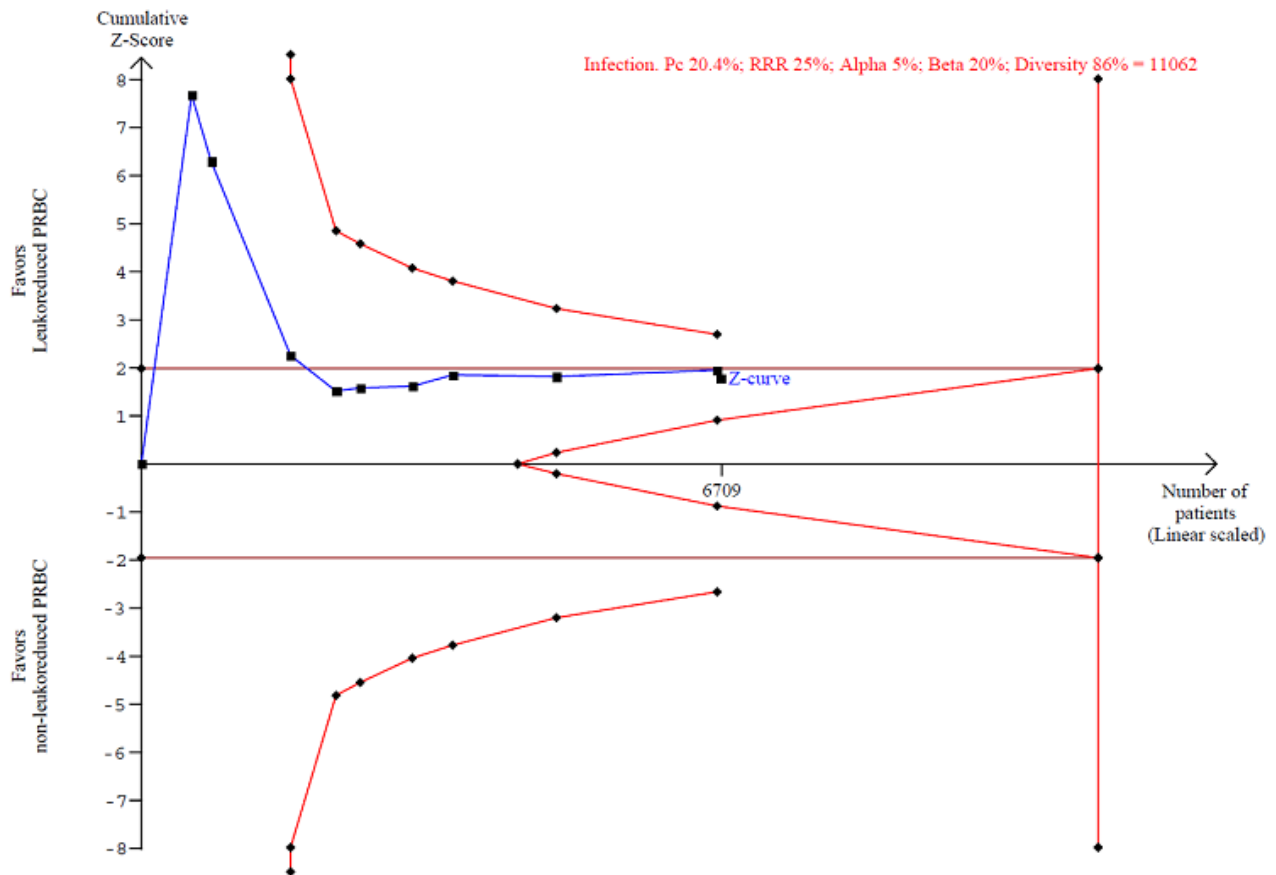


**Quality of evidence (TSA and GRADE)**

The accrued information of 6709 participants constituted only 60.6% of the DARIS of 11,062 participants. We calculated DARIS based on a diversity of 86%; a proportion of infection from any cause of 20.4% in the control group (median proportion in the control group); a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-

O'Brian-Fleming boundaries. TSA did not indicate futility, as the Z-curve did not cross the futility wedge ([Figure 6](#)). The TSA-adjusted 95% CI overlapped the zone of no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.57 and RR 1.12, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was very low (high risk of bias (-1); important heterogeneity (-2); and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1)).

**Figure 6. TSA calculated to reliably detect a 25% relative change in the incidence of infection from any cause, assuming a control group event rate of 20.4% with a power of 80% at an alpha of 5%.**



**Adverse events (fever)**

Three trials reported adverse events. However, we excluded one trial reporting fever as a temperature increase of at least 1°C per transfusion from the meta-analysis since fever was not analysed per study participant (Collier 2001).

**Overall analysis (total randomised patients)**

Two trials including 634 participants showed no difference between treatment groups in adverse events (31.9% versus 38.7%; RR 0.81, 95% CI 0.64 to 1.02; I<sup>2</sup> statistic = 0%, P = 0.07) (Wallis 2002). See Analysis 1.4.

**Sensitivity analysis**

In the sensitivity analysis comparing "transfused patients" with randomised patients, there was a statistically significant difference (RR 0.75, 95% CI 0.60 to 0.94, I<sup>2</sup> statistic = 0%, P = 0.01, Analysis 2.4); however, the results of TSA indicate this statistically significant result may be a spurious finding.

In a sensitivity analysis of data from one study, Wallis 2002, there was no difference when comparing post-storage with pre-storage leukoreduction (RR 0.81, 95% CI 0.64 to 1.04).

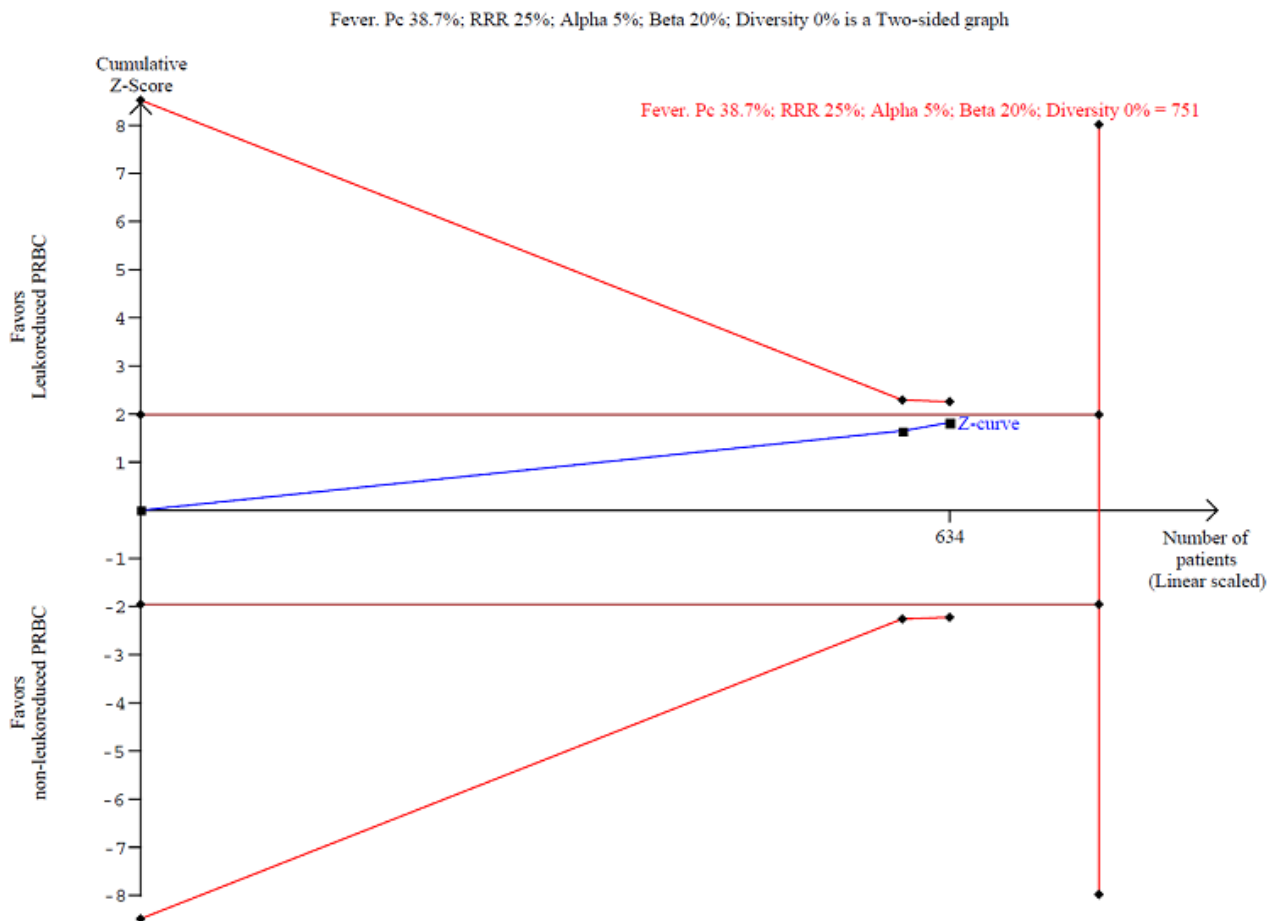
**Reporting bias**

We did not explore reporting biases since the meta-analysis included fewer than 10 studies (Higgins 2011).

**Quality of evidence (TSA and GRADE)**

The accrued information of 634 participants constituted only 84.4% of the DARIS of 751 participants. DARIS was calculated based on a diversity of 0%; a proportion of infection from any cause of 38.7% in the control group (median proportion in the control group); a relative risk reduction of 25%; an alpha of 5%; and a beta of 20% (power = 80%). The Z-value neither crossed the conventional statistical boundaries of 5% nor the Lan-DeMets-O'Brian-Fleming boundaries. TSA did not indicate futility, as the Z-curve did not cross the futility wedge (Figure 7). The TSA-adjusted 95% CI overlapped with the zone of no effect (RR 1.0) and is compatible with both a potential benefit and a potential harm (RR 0.68 and RR 1.05, respectively); thus, the TSA yielded an inconclusive result. The quality of evidence was low (high risk of bias (-1); and imprecision due to the CI crossing the threshold of meaningful effect and an insufficient sample size as compared with the DARIS (-1)).

**Figure 7. TSA calculated to reliably detect a 25% relative change in the incidence of fever, assuming a control group event rate of 38.7% with a power of 80% at an alpha of 5%.**



**Non-infectious complications**

The included trials did not assess this pre-defined outcome.

**DISCUSSION**

**Summary of main results**

In this systematic review we included 13 trials involving cardiovascular surgical, gastro-oncology surgery, trauma and HIV patients who were randomised to receive leukoreduced compared with non-leukoreduced PRBC transfusion. After analysis of the study data, we are unable to conclude whether or not leukoreduction of PRBC has an effect on preventing TRALI (one trial), death (nine trials), infection (10 trials) and other adverse events (fever, reported in two trials). The quality of evidence was low (TRALI and adverse events) to very low (death and infection) due to high heterogeneity, imprecision and high risk of bias. None of the included trials reported on other non-infectious complications. The sensitivity analyses of trials at low risk of bias showed neither a beneficial or harmful effect of leukoreduction of PRBC on the pooled data regarding death, infection and adverse events.

**Overall completeness and applicability of evidence**

**Overall completeness of evidence**

We analysed 13 controlled clinical trials that met our predefined inclusion criteria. Two trials reported only physiological results and we excluded them from the meta-analyses. Only one RCT evaluated the primary outcome (TRALI). However, we obtained data from 11 trials which contributed to the effect estimates of the secondary outcomes (death from any cause, infection from any cause and adverse events/fever). We found no trials evaluating non-infectious complications other than TRALI (e.g. FNHTR). Therefore, the pre-specified objectives and outcomes of our Cochrane review were partially addressed and the results are inconclusive. Consequently, the findings of this review should be interpreted with caution until more data are available.

**Applicability of evidence**

This Cochrane review is complex for a variety of reasons:

Firstly, regarding the population: the identified studies enrolled patients with different health problems, including trauma, cancer, cardiac disease and HIV-infected patients. Some important patient populations were not studied at all (e.g. paediatric or obstetric patients) or were insufficiently assessed (e.g. one RCT of trauma patients). In this context, external validity may be limited due

to a lack of studies analysing these populations. Furthermore, the effect of leukoreduction on some types of patients without a strong indication for leukoreduced PRBC has not been sufficiently evaluated: single-transfused patients, patients without history of FNHTR, patients who are not receiving long-term platelet transfusions and those who are not at risk of developing CMV disease.

Secondly, regarding the intervention, the included studies did not adequately report several aspects related to the transfusion of RBC that need to be considered when interpreting the results, namely: the use of leukoreduced or non-leukoreduced platelets as a co-intervention, the timing of leukoreduction (i.e. pre-storage or post-storage), the type of filter used (e.g. Cell select Optima, BPF4, RC 100, Sepacell RZ-200B1), leucocyte reduction definition (e.g. 0.1 to  $0.3 \times 10^6$  WBC/unit,  $5 \times 10^6$ ,  $2 \times 10^5$  per unit, etc.) and the type of transfusion (i.e. allogeneic or autologous).

Thirdly, regarding the outcomes: not all the included trials assessed relevant clinical outcomes. Relevant infections (e.g. CMV), non-infectious complications (e.g. TRALI, FNHTR) and any other adverse events were not sufficiently assessed or reported (Schulz 2010). The various follow-up intervals (28 days to 15 months) may represent another limitation for the assessment of outcomes.

Fourthly, regarding the costs: leukoreduction is widely implemented in clinical practice in many countries and some countries have established universal leukoreduction for blood transfusions (Laupacis 2001). However, the high costs related to this procedure deserve special attention. Even though the reintroduction of non-leukoreduced products probably provides no clinical impact, it does entail economic consequences. Changing the strategy from performing universal to selective leukoreduction would result in an important decrease in the costs (e.g. almost EUR 30 million per year in Spain (AETSA 2007)). Tsantes 2014 reported an incremental cost-effectiveness ratio (ICER) of EUR 6916 to prevent one case of FNHTR. Additionally, it is reasonable to consider other costs associated with maintaining dual inventories of leukoreduced PRBC and non-leukoreduced PRBC.

Finally, as leukoreduction of PRBC was shown to have no effect on preventing TRALI, death, infection and other adverse events reported by RCTs, these results have to be adequately interpreted within the context of current clinical practice which differs internationally and among populations. Other strategies might be more cost-effective than leukoreduction in terms of avoiding adverse events related to transfusion PRBC, such as the use of restrictive transfusion triggers (Carson 2012; Rohde 2014), that have shown effectiveness regardless of whether blood products are leukoreduced or not.

### Quality of the evidence

The body of evidence available to date does not allow a definitive conclusion to be drawn about the benefits and harms of leukoreduction. The included RCTs had important methodological limitations: 1. poor and incomplete reporting of inclusion and exclusion criteria; 2. important attrition bias due to the exclusion of many patients included, but not transfused; 3. incomplete information on allocation concealment; 4. inadequate reporting of other blood components as co-interventions; and 5. incomplete reporting of clinical outcomes of interest. Additionally, some of the

included trials showed important inconsistency in the estimates of effect.

### Potential biases in the review process

We applied Cochrane systematic review methodology to the search for and selection of studies for inclusion in the review. However, despite our effort to include all published studies evaluating leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion, it is possible that not all relevant data were identified. The small number of trials identified in our review raises concerns about publication bias. In order to identify this potential bias we performed a funnel plot. However, this visual method was possible only for one outcome (infection of any cause), since fewer than 10 studies assessed the other outcomes.

We contacted trial authors during the identification of trials (see Appendix 3) to clarify some questions related to the eligibility criteria, but not while we completed data extraction and analysis. We took into account only published data during these processes, considering the missing information as reporting bias.

In the review protocol we defined the main analysis based on the ITT approach (Simancas-Racines 2012). However, during the data extraction we identified an important number of patients included but not transfused. This may affect the precision of the effect estimations. In order to explore this scenario, we carried out a per-protocol analysis (only transfused patients) which did not reflect relevant differences in relation to the primary outcome (TRALI) and secondary outcomes death and infection from any cause, but the secondary outcome adverse events (fever) showed differences.

A limitation of the review was not considering the effect of buffy coat depletion in the estimations through a sensitivity analysis, because we had not planned such analysis in advance. Another limitation was not considering the subgroup analysis of the potential effect of different types of filters used in the included studies for all outcomes. We planned this analysis in the review protocol only for the primary outcome.

### Agreements and disagreements with other studies or reviews

Reviews and meta-analyses on postoperative infection and death related to the leukoreduction of blood products have been carried out previously. However, as far as we know, no systematic reviews focused on non-infectious complications, such as TRALI or FNHTR, have yet been published. In the overall analysis of death from any cause, the findings of other reviews are in accordance with our results. Nevertheless, one systematic review showed a 50% reduction in the probability of postoperative infection (Blumberg 2007) and another review analysing "only patients who received transfusion" found a statistically significant reduction of 40% in postoperative infection, but a non-significant reduction in mortality (Fergusson 2004).

These two reviews have several limitations. They included studies with other blood components apart from leukoreduced PRBC cells as interventions, as well as non-randomised studies. Moreover, heterogeneity between studies was not taken into account and the risk of bias of included studies was not appropriately assessed. Furthermore, some relevant studies were not included.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is no clear evidence for supporting or rejecting the routine use of leukoreduction in all patients requiring PRBC transfusion for preventing TRALI, death from any cause, infection from any cause, non-infectious complications and other adverse events. The quality of evidence is very low to low. Given that leukoreduction is a very expensive procedure, clinicians and policy makers may need to reconsider whether transfusing leukoreduced PRBC is suitable for all types of patients, especially for patients without a strong indication for leucocyte reduction. In countries where leukoreduction has not been universally implemented yet, selective leukoreduction is an option to be considered until better evidence on the effectiveness or harms of this procedure is available.

### Implications for research

Taking into account the inconclusive evidence found in this Cochrane review, further research is needed to assess the relative efficacy, safety and cost-effectiveness of leukoreduction in different clinical settings and for different conditions. Researchers should consider that premature randomisation is an important issue because it may cause attrition bias and affect the interpretation of the results; in this case, it may affect the true effect of leukoreduced PRBC. Further research should also consider aspects of the study design (Chan 2013), such as verifying the inclusion

and exclusion criteria before randomisation. Researchers should also improve the reporting of interventions and co-interventions (Schulz 2010), for example whether or not a blood transfusion includes other components or not (e.g. leukoreduced or non-leukoreduced platelets). Moreover, further studies should address all relevant outcomes (Gabriel 2012), such as death from any cause, infectious complications (e.g. risk of CMV transmission, or at least, evaluate the risk of CMV reactivation from transfused leukoreduced PRBC cells), non-infectious complications (e.g. TRALI, NHFRT) and any other adverse events related to the PRBC transfusion.

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Theusinger OM, Spahn DR, Ganter MT. Transfusion in trauma: why and how should we change our current practice?. *Current Opinion in Anaesthesiology* 2009;**22**(2):305-12. [PUBMED: 19390257]

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Thorlund K, Engström J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Version available from [www.ctu.dk/tsa](http://www.ctu.dk/tsa). Copenhagen, Denmark: Copenhagen Trial Unit: Centre for Clinical Intervention Research, 2011.

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cumulative meta-analysis. *Journal of Clinical Epidemiology* 2008;**61**(1):64-75. [PUBMED: 18083463]

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Bilgin 2004

Methods	Design: Parallel group RCT  Country: The Netherlands  Multicentre study: Yes (two university hospitals: Academic Medical Center and Leiden University Medical Center)  Setting: Hospital  Follow-up: 90 days  Unit of allocation: Patients  Unit of analysis: Patients
Participants	Inclusion criteria: Adults > 18 years undergoing valve surgery  Exclusion criteria: Those with a medical indication for leukocyte-depleted erythrocytes or who had received blood transfusions within the previous three months  Patients enrolled: 496  Patients randomised: 474  Buffy coat-depleted packed cells: 237  Leukocyte-depleted erythrocytes (LDs): 237  Patients transfused: not clearly reported  Patients considered for the analysis: 474  Main characteristics of patients:  Age: Buffy coat-depleted packed cells group = 66.6 ± 12.5 years; LD group = 65.3 ± 14.7 years  Percentage of men: Buffy coat-depleted packed cells group = 57%; LD group = 52%  Percentage of erythrocyte transfusions more or equal to four: Buffy coat-depleted packed cells group = 55.3%; LD group = 61.2%

**Bilgin 2004** (Continued)

Storage time of the units: Buffy coat-depleted packed cells group =  $19.7 \pm 5.4$  ; LD group =  $17.4 \pm 5$

Percentage of use of aprotinin: Buffy coat-depleted packed cells group = 37.1; LD group = 36.3

**Interventions**

1. Experimental: Leukocyte-depleted erythrocytes (LDs) (pre-storage leukoreduction).
2. Control: Buffy coat-depleted packed cells (PCs).

Co-intervention:

1. Quote: "Not all patients underwent induced hypothermia (29° to 33°C). In one hospital, aprotinin was used in some patients; this hospital had a medium-care ward. Prophylactic antibiotics were given to all patients for 48 hours." (Page 2756).
2. Quote: "Platelet concentrates were prepared from pooled buffy coats and were all leukocyte-depleted by filtration ( $< 1 \times 10^6$  leukocytes per product) before storage".

**Outcomes**

Primary:

1. Mortality at 90 days after surgery.

Secondary:

1. Incidence of in-hospital mortality.
2. Causes of death.
3. Incidence of multiple organ dysfunction syndrome.
4. Infections during the hospital stay.
5. Duration of ICU stay.
6. Hospitalization.

Quote: "An independent safety committee monitored the interim results of the primary end point." (Page 2757).

**Notes**

Trial registration: Not reported

Funding: This study was financially supported by the Netherlands Heart Foundation (grant 98.183) (Page 2760)

Rol of sponsor: Not reported

A priori sample size estimation: Yes

Conducted: Between June 1999 and May 2001

Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a straightforward randomizations was performed by using a fixed block size (n=24) to ensure a balance between the randomizations groups" (Page 2756).
Allocation concealment (selection bias)	Low risk	Quote: "...the technicians randomly assigned the patients by opening a sealed and numbered envelope." "In the hospital electronic information system, a code was used during the study period to hide the random assignment" (Page 2756).
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The patients, surgeons, anaesthesiologists, and the trial coordinators were blinded to the random assignment, as the technicians placed uniform study labels on the description on the erythrocyte bags" (Page 2756).



**Bilgin 2004** (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients, surgeons, anesthesiologists, and the trial coordinators were blinded to the random assignment, as the technicians placed uniform study labels on the description on the erythrocyte bags. In the hospital electronic information system, a code was used during the study period to hide the random assignment" (Page 2756).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss after transfusion: 0.4% (2/474)  Loss after transfusion in prestorage by filtration of LDs (LDs): 0.8% (2/237)  Loss after transfusion in Buffy coat-depleted packed cells (PCs): 0% (0/237)  Loss after transfusion. Imbalance between comparison groups: 0.8%
Selective reporting (reporting bias)	Low risk	Comment: The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Other bias	Low risk	The study appears to be free of other sources of bias.

**Boshkov 2006**

Methods	Design: Parallel group RCT  Country: USA  Multicentre study: Yes (three centre trial)  Setting: Hospital  Follow-up: 2 to 12 months  Unit of allocation: Patients  Unit of analysis: Patients
Participants	Inclusion criteria: <ul style="list-style-type: none"> <li>Undergoing coronary artery bypass grafting, cardiac valve replacement or a combination of the two.</li> </ul> Exclusion criteria: Not reported in the abstract <ul style="list-style-type: none"> <li>Patients enrolled: Not clearly reported in the abstract.</li> <li>Patients randomised: 1226.</li> </ul> Prestorage leukoreduced RBC (LR-RBCs): The number of patients is not clearly reported in the abstract.  Standard RBCs (S-RBCs): The number of patients is not clearly reported in the abstract. <ul style="list-style-type: none"> <li>Patients transfused: 562.</li> <li>Patients considered for the analysis: Not clearly reported in the abstract.</li> </ul> Main characteristics of patients:  "Groups were statistically equivalent demographically and by all Society of Thoracic Surgery risk criteria".
Interventions	1. Experimental: LR-RBCs (pre-storage leukoreduction).

**Boshkov 2006** (Continued)

2. Control: S-RBCs.

Co-intervention: not reported in the abstract

Outcomes	Primary:  1. Operative and postoperative mortality at 60 days after surgery.  Secondary: Not reported in the abstract.
Notes	Trial registration: Not reported in the abstract  Funding: Not reported in the abstract  Role of sponsor: Not reported in the abstract  A priori sample size estimation: Not reported in the abstract  Conducted: Not reported in the abstract  Declared conflicts of interest: "No relevant conflicts of interest to declare" (reported in the abstract)  Other relevant information: All study characteristics were obtained from the abstract. We tried to contact two trial authors by email, but no response has not yet been obtained

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients (undergoing coronary artery bypass grafting, cardiac valve replacement, or a combination of the two) were pre-operatively randomised to receive either LR- or S-RBCs (Abstract).  Insufficient information to permit judgement of 'low risk' or 'high risk'.
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients and clinicians were blinded as to product type" (Abstract).  The blinding methods are not clearly reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients and clinicians were blinded as to product type" (Abstract).  Comments: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"562 patients (45.8%) were transfused: 304 received LR-RBCs and 258 S-RBCs" (Abstract)  Loss after transfusion: Not reported in the abstract  Loss after transfusion LR group: Not reported in the abstract  Loss after transfusion Control group: Not reported in the abstract  Loss after transfusion. Imbalance between comparison groups: Not reported in the abstract.

**Boshkov 2006** (Continued)

		Comment: Insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided).
Selective reporting (re-reporting bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk' (Abstract data).
Other bias	High risk	Design bias: 1226 patients randomised; only 562 (45.8) were transfused.

**Collier 2001**

Methods	Design: Parallel group RCT Country: USA Multicentre study: Yes (11 academic medical centres) Setting: Hospital Follow-up: 12 months Unit of allocation: Patients Unit of analysis: Patients
Participants	Inclusion criteria: Those 14 years of older, with confirmed HIV infection and documented CMV infection (by chart or antibody testing), Karnofsky performance score of $\geq 40$ , expected survival of more than 1 month, symptomatic anaemia requiring red blood concentrates transfusion and no received transfusions within 72 hours of enrolment. Exclusion criteria: Those with a surgical reason for transfusion, a priori history for transfusion, renal failure requiring dialysis, thrombocytopenic purpura, used intravenous immunoglobulin within 6 weeks of entry or those that had started new antiretroviral drugs or systematic immunomodulators within 2 weeks of entry. <ul style="list-style-type: none"> <li>• Patients enrolled: 531.</li> <li>• Patients randomised: 531.</li> </ul> Leukoreduced red blood concentrates transfusion: 265 Unmodified red blood concentrates transfusion: 266 <ul style="list-style-type: none"> <li>• Patients transfused: 521.</li> <li>• Patients considered for the analysis: 470.</li> </ul> Main characteristics of patients: Age: Leukoreduced group = $38.3 \pm 8.2$ years; Unmodified group = $38.4 \pm 8.3$ years Percentage of men: Leukoreduced group = 79%; Unmodified group = 79% Percentage of antiretroviral therapy-potent combination: Leukoreduced group = 27%; Unmodified group = 22% Karnofsky score: Leukoreduced group = $71.4 \pm 13.2$ ; Unmodified group = $70.9 \pm 12.8$ CD4 cells/ $\mu$ L, median: Leukoreduced group = 16 (3 to 71.5); Unmodified group = 12.5(4 to 76)

**Collier 2001** (Continued)

Interventions	1. Experimental: Leukoreduced RBC transfusion (pre-storage leukoreduction) 2. Control: Unmodified RBC transfusion.  Cointervention: Leukoreduced platelets if was required.
Outcomes	1. Primary (changed 3 months after beginning of study): a. Survival. "...additional resources were obtained to increase accrual to 640 and change the primary clinical end point to survival" (Page 1594). 2. Secondary: a. Time to death. b. First serious HIV-related complication (including specific AIDS-defining conditions and serious bacterial infections associated with median survival times of < 1 year or an acute mortality > 5%). c. Time to new or progressive CMV end organ disease. d. Plasma HIV RNA and CMV DNA levels. e. Lymphocyte subset markers. f. Change in cytokine and lymphocyte activation markers.
Notes	Trial registration: Not reported  Funding: This study was financially supported by Roche Molecular systems and National Heart, Lung and Blood Institute (contract RR00046) (Page 1600).  Role of sponsor: Reagents: Funding/Support: Reagents for detection and quantitation of CMVDNA by polymerase chain reaction were contributed by Roche Molecular Systems (Alameda, Calif). Support provided by National Heart was not detailed  A priori sample size estimation: Yes  Conducted: July 1995 through June 1999  Declared conflicts of interest: Trial authors received research funding from Roche

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study was a randomised, double blind, comparative study" (Page 1593).  Quote: "Treatment allocation was made centrally by the study coordinating center, using stratified permuted blocks with dynamic balancing within each center" (Page 1593).
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was made centrally by the study coordinating center, using stratified permuted blocks with dynamic balancing within each center" (Page 1593).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The participants, investigators, study coordinators, and persons having any contact with the patients were blinded to study treatment assignments. Blood bank technical staff who prepared the blood products were aware of the treatment assignments" (Page 1593).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The participants, investigators, study coordinators, and persons having any contact with the patients were blinded to study treatment assignments. Blood bank technical staff who prepared the blood products were aware of the treatment assignments" (Page 1593).
Incomplete outcome data (attrition bias)	Low risk	Loss after transfusion: 9.8% (51/521)

**Collier 2001** (Continued)

All outcomes

Loss after transfusion LR group: 10.8 (28/259)

Loss after transfusion Control group: 8.8% (23/262)

Imbalance between comparison groups: 2%

Selective reporting (reporting bias)	Low risk	Comment: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

**Donati 2014**

Methods	Design: Parallel group RCT Country: Italy Multicentre study: No Setting: Hospital Follow-up: Not clearly reported, outcomes were measured up to 1 hour after blood transfusion Unit of allocation: Patients Unit of analysis: Patients
Participants	Inclusion criteria: Adult patients admitted to ICU of the AOU Ospedali Riuniti of Ancona with sepsis, severe sepsis or septic shock as diagnosed according to standard criteria and requiring blood transfusion for haemoglobin (Hb) levels of less than 8 g/dL or as indicated by the attending physician in accordance with the local hospital guidelines. Exclusion criteria: Aged < 18 years, previous blood transfusions during ICU stay, previous history of coagulation disorders, cardiogenic or hemorrhagic shock, pregnancy and factors impeding the sublingual microcirculation evaluation (oral surgery and maxillofacial trauma) <ul style="list-style-type: none"> <li>• Patients enrolled: 20</li> <li>• Patients randomised: 20</li> </ul> Leukodepleted RBC transfusion: 10 Non-leukodepleted RBC transfusion: 10 <ul style="list-style-type: none"> <li>• Patients transfused: 20</li> <li>• Patients considered for the analysis: 20</li> </ul> Main characteristics of patients: Age: Non-leukodepleted group = 70 (65 to 72) years; leukodepleted group = 74 (64 to 79) years Percentage of men: Non-leukodepleted group = 50%; leukodepleted group = 70%
Interventions	<ol style="list-style-type: none"> <li>1. Experimental: Leukodepleted RBC transfusion: leukoreduction was performed by a blood bank physician using the filter Sepacell RZ-200 (Fenwal, Inc., Lake Zurich, IL, USA) within a maximum of 5 days after donor blood withdrawal (post-storage leukoreduction).</li> <li>2. Control: Non-leukodepleted RBC transfusion.</li> </ol> Cointervention: Related to sepsis treatment (fluid therapy, vasopressors and inotropic agents, antibiotics, etc.)

**Donati 2014** (Continued)

- Outcomes
1. Primary:
    - a. Microcirculatory Flow Index (MFI) before and after blood transfusion.
  2. Secondary:
    - a. Peripheral tissue oxygen saturation (StO<sub>2</sub>).
    - b. Tissue Hb index (THI).
    - c. Vascular lumen perfused boundary region (PBR).
    - d. Glycocalyx damage markers.

Notes

Trial Registration: NCT01584999

Funding: Not reported

Role of sponsor: Not reported

A priori sample size estimation: Yes

Conducted: February 2011 and 2012

Declared conflicts of interest: One trial author "CI is the inventor of Sidestream Dark Field imaging technology" technique used to measure the outcomes, this author "holds shares in MicroVision Medical and was a consultant for this company more than four years ago but has had no further contact with the company since then. He declares that he has no other competing interests in this field other than his commitment to promoting the importance of the microcirculation during patient care and no other relationships or activities that could appear to have influenced the submitted work. HV holds the position of chief scientific officer in GlycoCheck BV. The other authors declare that they have no competing interests".

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Low risk	"Blood product randomization was performed through sealed envelopes by a physician at the blood bank" (Page 2).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"a physician at the blood bank blindly provided the blood bags to the ICU; neither the attending physician nor the investigators nor the patients were aware of the type of RBCs transfused" (Page 2).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"a physician at the blood bank blindly provided the blood bags to the ICU; neither the attending physician nor the investigators nor the patients were aware of the type of RBCs transfused" (Page 2).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All patients transfused were analysed.  Patients lost to follow-up: None.
Selective reporting (reporting bias)	Low risk	Comment: The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Low risk	—

**Jensen 1996**

Methods	<p>Design: Parallel group RCT</p> <p>Country: Denmark</p> <p>Multicentre study: Yes (2 university departments of colorectal surgery; page 844).</p> <p>Setting: Hospital</p> <p>Follow-up: 30 days after surgery</p> <p>Unit of allocation: Patients</p> <p>Unit of analysis: Patients</p>
Participants	<p>Inclusion criteria: Patients admitted for elective colorectal surgery</p> <p>Exclusion criteria: &lt; 18 years of age, need for emergency surgery, or immunosuppressive treatment, except steroids</p> <ul style="list-style-type: none"> <li>• Patients enrolled: 589</li> <li>• Patients randomised: 589</li> </ul> <p>Leucocyte-depleted red cells group: 290</p> <p>Buffy-coat-poor red cells group: 299</p> <ul style="list-style-type: none"> <li>• Patients transfused: 260</li> <li>• Patients considered for the analysis: 586</li> </ul> <p>Main characteristics of patients:</p> <p>Age = Median (range): Leucocyte-depleted red cells group = 69 (35 to 89) years; Buffy-coat-poor red cells group = 68 (29 to 92) years</p> <p>Percentage of men: Leucocyte-depleted red cells group = 50%; buffy-coat-poor red cells group = 48%</p> <p>Number of procedures: Sigmoid resection: Leucocyte-depleted red cells group = 11; Buffy-coat-poor red cells group = 19</p> <p>Blood loss = Median (range): Leucocyte-depleted red cells group = 715 (50 to 3500) mL; Buffy-coat-poor red cells group = 805 (10 to 4300) mL.</p>
Interventions	<ol style="list-style-type: none"> <li>1. Leucocyte-depleted red cells group (the timing of leukoreduction is not reported).</li> <li>2. Buffy-coat-poor red cells group.</li> </ol> <p>Cointervention:</p> <p>Quote: "All patients received an intravenous dose of cefuroxime 3 g and metronidazole 1.5 g after induction of anaesthesia" (Page 842).</p>
Outcomes	<p>This RCT did not specify by primary or secondary outcomes.</p> <ol style="list-style-type: none"> <li>1. Abdominal wound infection: Accumulation of pus with spontaneous discharge or requiring surgical drainage.</li> <li>2. Deep surgical infection: Intraabdominal abscess or septicaemia.</li> <li>3. Pneumonia: Fever and infiltrate on chest radiography.</li> <li>4. Surgical complications: Anastomotic leakage, abdominal wound dehiscence, intra-abdominal bleeding and ileus.</li> <li>5. Operation-related mortality: Death during hospital stay or within 30 days after surgery.</li> </ol>
Notes	<p>Trial Registration: Not reported.</p> <p>Funding: Not reported.</p>



**Jensen 1996** (Continued)

Role of sponsor: Not stated.

A priori sample size estimation: Yes.

Conducted: Between January 1992 and January 1995.

Declared conflicts of interest: Not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly allocated using sealed envelopes to receive either..." (Page 841).  Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Allocation concealment (selection bias)	Unclear risk	Quote: "were randomly allocated using sealed envelopes to receive either..." (Page 841) Use of opaque envelopes is not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Physicians who were blinded to the transfusion protocol performed follow-up examinations..." (Page 842).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All patients transfused were analysed. (Page 842).
Selective reporting (reporting bias)	Low risk	Comment: The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Comment: Sample size estimation took into account loss to follow-up due to no transfusion.

**Lapierre 2007**

Methods	Design: Parallel group RCT
	Country: France
	Multicentre study: No
	Setting: Hospital
	Follow-up: 6 months
	Unit of allocation: Patients
	Unit of analysis: Patients

**Lapierre 2007** (Continued)

**Participants**

Inclusion criteria: "Patients included in the trial were more than 18 years of age and of both sexes and were to undergo surgery for cancer...with a transfusion-during-surgery (TdS) risk greater than 30 percent".

Exclusion criteria: "Patients were not eligible for inclusion if they presented contraindications to the use of UN-RBCs or presented any RBC antibodies and/or anti-HLA and/or antigranulocyte alloimmunization" (page 1692).

- Patients enrolled: 161
- Patients randomised: 37

Unmodified RBCs (UN-RBC): 19

Leukoreduced RBCs (LR-RBC): 18

- Patients transfused: 36
- Patients considered for the analysis: 35

Main characteristics of patients:

Age = Median (range): Unmodified RBCs group = 56 (40 to 73) years; Leukoreduced RBCs group= 54 (37 to 65) years

Percentage of men: Unmodified RBCs group = 33%; Leukoreduced RBCs group = 47%

Tumour location: Pelvis: Unmodified RBCs group = 11; Leukoreduced RBCs group = 8. Head and neck: Unmodified RBCs group = 6; Leukoreduced RBCs group = 7. Miscellaneous: Unmodified RBCs group = 1; Leukoreduced RBCs group = 2

Blood loss = Median (range): Unmodified RBCs group = 1500 (300 to 3650) mL; Leukoreduced RBCs group = 1325 (300 to 6800) mL

**Interventions**

1. Unmodified RBCs.
2. Leukoreduced RBCs (post-storage leukoreduction).

Cointervention: Two patients (11%) in the unmodified RBCs group and three patients (18%) received fresh-frozen plasma. None of the patients received platelet concentrate.

**Outcomes**

"The main endpoint of the study was to compare immune status in both treatment groups" (page 1692). This was measured through surrogate variables (i.e. microchimerism, peripheral blood cell counts and cytokine production capacity). However, other outcomes were described: "In addition to immune status, other factors compared between the two groups were survival and incidence of nosocomial infection" (page 1694).

**Notes**

Trial registration: ClinicalTrials database NCT00180869

Funding: "grants from the French Association for Cancer Research (L'Association pour la Recherche sur le Cancer [9653]) and the French Association for Blood Transfusion Research (L'Association pour la Recherche en Transfusion [081997])" (page 1691)

Role of sponsor: Not stated

A priori sample size estimation: Yes

Conducted: between 15 September 1997 and 28 February 1998

Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
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**Lapierre 2007** (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "The randomization was performed centrally by computer in the Gustave Roussy Cancer Institute Biostatistics Unit after the investigator had sent a fax indicating the minimization factors of the patient" (page 1693).
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients and surgeons were not blinded of the treatment allocation" (page 1693).
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients and surgeons were not blinded of the treatment allocation" (page 1693).
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 patients were transfused: 18 received unmodified RBCs (UN-RBC) and 18 received Leukoreduced RBCs (LR-RBC).  Loss after transfusion: 2.77% (1/36).  Loss after transfusion LR group: 1 died during surgery.  Loss after transfusion Control group: None.  Loss after transfusion. Imbalance between comparison groups: 5%.
Selective reporting (reporting bias)	Unclear risk	Survival after perioperative transfusion is reported in Figure 2. However, number of death is not clearly reported.
Other bias	Unclear risk	Comment: Sample size estimate was calculated based on Th2 polarization. It is unclear what dropout rate was considered in the sample size estimation of 75 participants.

**Nathens 2006**

Methods	Design: Parallel group RCT  Country: USA  Multicentre study: No  Setting: Hospital  Follow-up: 28 days after randomisation  Unit of allocation: Patients  Unit of analysis: Patients
Participants	Inclusion criteria: Age of above 17 years and red cell transfusion within 24 hours of injury  Exclusion criteria: Those with an anticipated survival of less than 48 hours, active infection at presentation, receipt of blood products for the current injury before randomisation, individuals with blood group AB Rh negative or B Rh negative, patients with clinically significant red cell alloantibodies requiring an antiglobulin crossmatch, recipients with prior requirements for irradiation, leukoreduction, or CMV protection, subjects enrolled in a concurrent study of pre-hospital hypertonic saline resuscitation or incarcerated subjects.

**Nathens 2006** (Continued)

- Patients enrolled: 1864
- Patients randomised: 1864

Standard transfusion: 935

Leukoreduced transfusion: 929

- Patients transfused: 515
- Patients considered for the analysis: 324

Main characteristics of patients included in full analysis.

Age: Standard group = 42.1 ± 18 years; Leukoreduced group = 42.3 ± 19 years

Percentage of men: Standard group = 69%; Leukoreduced group = 66%

Percentage of penetrating injury mechanism: Standard group = 18%; Leukoreduced group = 19%

Injury Severity Score: Standard group = 25.5 ± 11; Leukoreduced group = 23.9 ± 11

**Interventions**

1. Leukoreduced transfusion: Prestorage-Leucoreduced RBC (pre-storage leukoreduction).
2. Standard transfusion: Non Prestorage-Leucoreduced RBC (standard units).

Cointerventions: "All patients received apheresis platelets when platelets were required" (Page 343).

**Outcomes**

1. Primary:
  - a. Infection within 28 days of randomisation.
2. Secondary:
  - a. Resource use: ventilator days, lengths of hospital stay and length of ICU.
  - b. Degree of multiple organ dysfunction.
  - c. Mortality.

Note: TRALI was assessed by [Watkins 2008](#) as a secondary analysis.

**Notes**

Trial registration: [www.clinicaltrials.gov](http://www.clinicaltrials.gov), August 23, 2005. Registration No.: NCT00135291

Funding: National Institutes of Health (NIH)

Role of sponsor: The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review or approval of the manuscript.

A priori sample size estimation: Yes

Conducted: Between 3 February 2003 and 30 August 2004.

Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The hospital-based transfusion support service performed the randomization in a 1:1 ratio, using a permuted block scheme (block size of six)" (Page 344).
Allocation concealment (selection bias)	Low risk	Quote: "Using preprinted sealed opaque envelopes containing the study identification number and randomization arm (listed as arm 1 or arm 2) to conceal allocation" (Page 344).
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Before unit issue, the transfusion service added a Food and Drug Administration approved study label to blind the leukoreduction process; the transfusion report accompanying the red cell unit was also blinded" (Page 343).

**Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion (Review)**

**Nathens 2006** (Continued)

## All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Before unit issue, the transfusion service added a Food and Drug Administration approved study label to blind the leukoreduction process; the transfusion report accompanying the red cell unit was also blinded" (Page 343).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss after transfusion: 5% (16/324).  Loss after transfusion LR group: 7% (11/156).  Loss after transfusion Control group: 3% (5/168).  Imbalance between comparison groups: 4%.
Selective reporting (reporting bias)	Low risk	Comments: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

**Sanfilippo 1985**

Methods	Design: Parallel group RCT  Country: USA  Multicentre study: No  Setting: Hospital  Follow-up: 1 year  Unit of allocation: Patients  Unit of analysis: Patients
Participants	Inclusion criteria: All potential cadaver renal allograft recipients  Exclusion criteria: Not clearly reported <ul style="list-style-type: none"> <li>• Patients enrolled: 126</li> <li>• Patients randomised: 107</li> </ul> PRBCs group: 42  Leukocyte poor red cells group: 45  Mixed group: 20 <ul style="list-style-type: none"> <li>• Patients transfused: 107</li> <li>• Patients considered for the analysis: 107</li> </ul> Main characteristics of patients included in full analysis were not fully stated:  Quote: "there were no significant differences between transfusion groups in terms of demographic factors, including number of transfusions, age, race, sex, degree of HLA match, number of diabetics or the use of ATG posttransplant" (Page 117).
Interventions	1. PRBCs group: PRBCs. 2. Leukocyte poor red cells group: Leukocyte poor red cell (the timing of leukoreduction is not reported).

**Sanfilippo 1985** (Continued)

Cointerventions: "All transplant recipients received conventional maintenance immunosuppressive therapy with azathioprine and prednisone, and antithymocyte globulin (ATG) and/or bolus methylprednisolone was used for the treatment of rejection episodes" (Page 117).

Outcomes	This RCT did not specify by primary or secondary outcomes.  1. Panel reactive antibody (PRA) levels: percent of panel cells showing at least 20% lysis with patients' serum, regardless of serum dilution, as determined by the antiglobulin modification. 2. Allograft and patient survival.
Notes	Trial registration: Not reported.  Funding: National Kidney Foundation of North Carolina  Role of sponsor: Not stated  A priori sample size estimation: No  Conducted: Between September 1980 and June 1982  Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...after obtaining informed consent, patients were randomly assigned to receive" (Page 116).  Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Allocation concealment (selection bias)	Unclear risk	Quote: "...after obtaining informed consent, patients were randomly assigned to receive..." (Page 116).  Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Selective reporting (reporting bias)	High risk	Comment: The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Other bias	High risk	Design bias.

## Tartter 1998

Methods	<p>Design: Parallel group RCT</p> <p>Country: USA</p> <p>Multicentre study: No</p> <p>Setting: Hospital</p> <p>Follow-up: Unclear. Quote: "Patients were followed up daily in the hospital until discharge (...) and contacted by phone following discharge to elicit possible symptoms of infection".</p> <p>Unit of allocation: Patients</p> <p>Unit of analysis: Patients</p>
Participants	<p>Inclusion criteria: Those scheduled for inpatient gastrointestinal surgery under general anaesthesia</p> <p>Exclusion criteria: Not clearly reported</p> <ul style="list-style-type: none"> <li>• Patients enrolled: 224</li> <li>• Patients randomised: 224</li> </ul> <p>Filtered group: 106</p> <p>Unfiltered group: 118</p> <ul style="list-style-type: none"> <li>• Patients transfused: 59</li> <li>• Patients considered for the analysis: 221</li> </ul> <p>Main characteristics of patients:</p> <p>Age (Unclear if median or mean): Filtered group = 54 years; Unfiltered group = 50 years</p> <p>Percentage of men: Filtered group = 49%; Unfiltered group = 50%</p> <p>Hematocrit (Unclear if median or mean): Filtered group = 38; Unfiltered group = 37</p> <p>Percentage of hypertension: Filtered group = 14%; Unfiltered group = 10%</p> <p>Percentage of diagnosis of malignancy: Filtered group = 38%; Unfiltered group = 38%</p>
Interventions	<ol style="list-style-type: none"> <li>1. Filtered group: Leukocyte-filtered RBCs (the timing of leukoreduction is not reported).</li> <li>2. Unfiltered group: PRBCs.</li> </ol> <p>Cointerventions: "Preoperative preparation included intravenous antibiotics for all patients and bowel cleansing with Golytely for patients in whom transection of the colon or rectum was anticipated" (Page 463)</p>
Outcomes	<p>This RCT did not specify by primary or secondary outcomes.</p> <ol style="list-style-type: none"> <li>1. Postoperative infectious complications: abdominal wound infections, urinary tract infections, Pneumonia, intra-abdominal collections.</li> <li>2. Length of stay</li> <li>3. Hospital charges.</li> </ol>
Notes	<p>Trial Registration: Not reported.</p> <p>Funding: Pall Corporation, Gel Cove, NY</p> <p>Role of sponsor: Not stated.</p> <p>A priori sample size estimation: Unclear. Trial authors reported the criteria for sample size calculation, including a 60% of dropout rate ("40% of gastrointestinal surgery patients at our institution receive</p>



**Tartter 1998** (Continued)

blood transfusions"). The software or method for sample size calculation is not reported. Using the ARCSINUS approximation, and using the same criteria reported by authors, 174 subjects are necessary in first group and 174 in the second to find as statistically significant a proportion difference, expected to be of 0.2 in group 1 and 0.05 in group 2, with an anticipated drop-out rate of 60%. The study included 224 participants (118 and 106 patients in each group), 59 were transfused (26%) and 50 participants received allogeneic RBC transfusions.

Conducted: Between 1 August 1993 and 31 January 1994

Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated by the study personnel in the blood bank" (Page 463).  Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all patients transfused were analysed (Page 842).
Selective reporting (reporting bias)	High risk	This RCT did not report mortality.  Comment: The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Other bias	High risk	Design bias.  Sample size bias. Trial authors reported the criteria for sample size calculation, including a 60% of dropout rate ("40% of gastrointestinal surgery patients at our institution receive blood transfusions"). The software or method for sample size calculation is not reported. Using the ARCSINUS approximation, and using the same criteria reported by the study authors, 174 subjects are necessary in first group and 174 in the second to find as statistically significant a proportion difference, expected to be of 0.2 in group 1 and 0.05 in group 2, with an anticipated drop-out rate of 60%. The study included 224 participants (118 and 106 patients respectively), 59 were transfused (26%) and 50 participants received allogeneic RBC transfusions.

**Titlestad 2001**

Methods                      Design: Parallel group RCT

**Leukoreduction for the prevention of adverse reactions from allogeneic blood transfusion (Review)**

**Titlestad 2001** (Continued)

Country: Denmark  
 Multicentre study: No  
 Setting: Hospital  
 Follow-up: 30 days  
 Unit of allocation: Patients  
 Unit of analysis: Patients

**Participants**

Inclusion criteria: Patients admitted —acute and elective— to the Department of Colorectal surgery, undergoing open colorectal surgery

Exclusion criteria: Those receiving blood transfusions within the final 3 months prior to surgery and those below 18 years

- Patients enrolled: 279
- Patients randomised: 279

Leukocyte-depleted erythrocyte suspensions group (LD-SAGM): 139 patients

Buffycoat-depleted group: 140 patients

- Patients transfused: 125 (112 to the allocated group)
- Patients considered for the analysis: 279

Main characteristics of patients:

Age: Median/range: Leukocyte-depleted erythrocyte group = 71 (66 to 77) years; Leukocyte-depleted erythrocyte = 73 (62 to 79) years

Percentage of men: LD-SAGM group = 51%; Non-leukocyte-depleted erythrocyte suspensions (SAGM) group = 60%

Number of malignant colorectal disease: LD-SAGM group = 37; SAGM group = 56

Hemoglobin: Median/range: LD-SAGM group = 12.6 (10.6 to 14.2) g/dL; SAGM group = 12.4 (11.1 to 13.9) g/dL

**Interventions**

1. Experimental: LD-SAGM (pre-storage leukoreduction).
2. Control: SAGM.

Cointervention: "all patients received perioperative prophylactic antibiotics intravenously (3 g ampicillin or 3 g cefuroxim and 1.5 g metronidazol)" (Page 149).

Platelet transfusion as co-intervention was not reported

**Outcomes**

This RCT did not specify by primary or secondary outcomes.

1. Postoperative infectious complications: Abdominal wound infection, intra-abdominal abscess, septicaemia, pneumonia.
2. Non-infectious surgical complications: Anastomosis leakage, wound rupture, intra-abdominal bleeding, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, cerebral ischaemic stroke, death.

**Notes**

Trial registration: Not reported

Funding: Not reported

Role of sponsor: Not reported

A priori sample size estimation: Yes (but not fulfilled)

**Titlestad 2001** (Continued)

Conducted: Between May 1997 and November 1999

Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were allocated in the blood bank to receive either..." Page 148.  Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The blood units were supplied by the blood bank, and all units were blinded. White labels were placed on the unit product code numbers, but bar code labels were intact, ensuring safe handling" (Page 149).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Surgeons who were blinded to the transfusion protocol performed the follow-up examinations" (Page 149).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss after transfusion: 10.4% (13/125).  Loss after transfusion LR group: 12.7 % (7/55).  Loss after transfusion Control group: 8.5% (6/70).  Imbalance between comparison groups: 4.2%.
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	High risk	Sample size bias. "Discontinued study due to large exclusions than expected, as well as higher rates of infection, insufficient sample size" (Page 149).  The estimation of sample size bias considered 10% of random error and did not reported it.  Design bias.  Industry bias: Unclear.

**van de Watering 1998**

Methods	Design: Parallel group RCT
	Country: The Netherlands
	Multicentre study: No
	Setting: Hospital
	Follow-up: 60 days after surgery
	Unit of allocation: Patients

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van de Watering 1998 (Continued)

Unit of analysis: Patients

Participants	<p>Inclusion criteria: Adults patients undergoing Coronary Artery Bypass grafting (CAGB) surgery, cardiac valve surgery or a combination of both, who had not received blood within the last 6 months.</p> <p>Exclusion criteria: None clearly reported</p> <ul style="list-style-type: none"> <li>• Patients enrolled: 944</li> <li>• Patients randomised: 914</li> </ul> <p>Packed cells without buffy coat: 306</p> <p>Fresh-filtered units: 305</p> <p>Stored-filtered units: 303</p> <ul style="list-style-type: none"> <li>• Patients transfused: 866</li> <li>• Patients considered for the analysis: 914</li> </ul> <p>Main characteristics of patients:</p> <p>Age: Standard packed cells without buffy coat group = 64.4 ± 9.5 years; Fresh-filtered units group = 62.9 ± 9.8 years. Stored-filtered units group = 63.3 ± 9.1 years</p> <p>Percentage of men: Standard packed cells without buffy coat group = 72%; Fresh-filtered units group = 74%. SF group = 68%</p> <p>Percentage of history of myocardial infarction: Standard packed cells without buffy coat group = 50.3%; Fresh-filtered units group = 44.6%. Stored-filtered units group = 46.4%</p> <p>Preoperative Hb: Standard packed cells without buffy coat group = 8.8 ± 0.9 mmol/L; Fresh-filtered units group = 8.9 ± 0.9 mmol/L. Stored-filtered units group = 8.8 ± 0.9 mmol/L</p> <p>Postoperative Hb: Standard packed cells without buffy coat group = 6.6 ± 0.7 mmol/L; Fresh-filtered units group = 6.6 ± 0.7 mmol/L. Stored-filtered units group = 6.5 ± 0.7 mmol/L</p>
Interventions	<ol style="list-style-type: none"> <li>1. PC trial arm: Standard packed cells without buffy coat.</li> <li>2. FF trial arm: Fresh-filtered units (pre-storage leukoreduction).</li> <li>3. SF trial arm: Stored-filtered units (post-storage leukoreduction).</li> </ol> <p>Cointervention: Quote: "Antibiotic prophylaxis was given for 24 hours with CABG and for 48 hours with valve or combined surgery" (Page 563).</p>
Outcomes	<ol style="list-style-type: none"> <li>1. Primary:             <ol style="list-style-type: none"> <li>a. Incidence of postoperative infections.</li> <li>b. HLA antibody formation.</li> </ol> </li> <li>2. Secondary:             <ol style="list-style-type: none"> <li>a. Duration of hospitalisations.</li> <li>b. Postoperative mortality within 60 days.</li> <li>c. Other postoperative complications.</li> </ol> </li> </ol>
Notes	<p>Trial registration: Not reported</p> <p>Funding: NPBI bv, Emmer-Compascuum, The Netherlands</p> <p>Role of sponsor: Not reported</p> <p>A priori sample size estimation: unclear. Trial authors reported the only two criteria for sample size calculation (the proportion expected in each group). The dropout rate expected is not reported.</p> <p>Conducted: Between March 1992 and August 1994</p>

**van de Watering 1998** (Continued)

Declared conflicts of interest: Not reported

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were, by means of a randomizations list at the hospital transfusion service, randomly allocated..." (Page 563).
Allocation concealment (selection bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'low risk' or 'high risk'.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The surgeons and anesthetists were blind to the randomizations result" (Page 563).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The surgeons and anesthetists were blind to the randomization result" (Page 563).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All patients transfused were analysed (Page 567).
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	Low risk	

**van Hilten 2004**

Methods	<p>Design: Parallel group RCT</p> <p>Country: The Netherlands</p> <p>Multicentre: Yes, 19 hospitals (3 university, 10 clinical, 6 general)</p> <p>Setting: Hospital</p> <p>Follow-up: 15 months</p> <p>Unit of allocation: Patients</p> <p>Unit of analysis: Patients</p>
Participants	<p>Inclusion criteria: Patients with ruptured aortic aneurysm elective non-ruptured AA surgery or gastrointestinal oncology)</p> <p>Exclusion criteria: Those aged under 18 years, had received transfusions in the three month before the date of randomisation, or had a previous adverse reaction to blood transfusions or had a specific indications for filtered products.</p> <ul style="list-style-type: none"> <li>• Patients enrolled: 1200</li> <li>• Patients randomised: 1200</li> </ul> <p>Non-filtered products: 605</p> <p>Filtered products: 595</p>

**van Hilten 2004** (Continued)

- Patients transfused: 494
- Patients considered for the analysis: 1051

Main characteristics of patients allocated to groups (transfused+non-transfused):

Age: Non-filtered group = 67 ± 11 years; Filtered group = 66 ± 11.5 years

Percentage of men: Non-filtered group = 69%; Filtered group = 68%

Percentage of patients transfused: Non-filtered group = 53%; Filtered group = 51%

Duration of surgery: Non-filtered group = 210 min; Filtered group = 205 min

Interventions	1. Experimental group: Filtered RBC transfusions (pre-storage leukoreduction). 2. Control group: Non-filtered RBC transfusions. (buffy coat removed and were plasma reduced).
Outcomes	Primary: 1. Mortality and duration of stay in intensive care.  Secondary: 1. Multi-organ failure. 2. Infections. 3. Length of hospital stay.
Notes	Trial registration: <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a> , 23 August 2005. Registration No.: NCT00135291  Funding: Health insurance Board, the Netherlands, The National Sanquin Blood banks.  Role of sponsor: Not reported  A priori sample size estimation: Yes  Conducted: Since June 2000 until December 2001  Declared conflicts of interest: Yes  Note: 22 patients because of administrative and logistic errors. The intake of patients in the study had to be stopped at the end of 2001 because of the implementation of universal leucocyte depletion of RBCs in The Netherlands. This measure was taken by the Dutch Ministry of Health in an effort to reduce the risk of possible transmission of variant Creutzfeldt-Jacob disease in non-filtered transfusions.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed either by telephone (central registration of randomisation) or by opening numbered and sealed envelopes at the hospital blood transfusion services. The transfusion service ensured that the released RBCs appeared identical" (Page 2).
Allocation concealment (selection bias)	Low risk	Quote: "randomisation was performed either by telephone (central registration of randomisation) or by opening numbered and sealed envelopes at the hospital blood transfusion services. The transfusion service ensured that the released RBCs appeared identical" (Page 2).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the identity of the patient nor the randomisation group was stored in the main database. The actual randomisation was provided to the statistician only at the final analysis. (Page 2).

**van Hilten 2004** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "During the study, protocol violations were reported monthly to the national trial office. Patients who received products in violation of randomisation remained in the assigned arm for intention to treat analysis." (Page 2).
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Loss after transfusion: 9.35% (51/545).</p> <p>Loss after transfusion filtered RBC transfusions: 11% (30/267).</p> <p>Loss after transfusion non-filtered RBC transfusions: 7.5% (21/278).</p> <p>Imbalance between comparison groups: 3.5%.</p> <p>Comment: Missing outcome data are balanced in numbers across study groups. However, reasons for missing outcome data are likely to be related to true outcome (Protocol violations).</p>
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.
Other bias	High risk	Design bias.

**Wallis 2002**

Methods	Design: Parallel group RCT Country: UK Multicentre study: No Setting: Hospital Follow-up: 3 months after discharge Unit of allocation: Patients Unit of analysis: Patients
Participants	Inclusion criteria: Patients admitted for elective coronary artery bypass grafting or aortic or mitral valve replacement, either singly or in combination Exclusion criteria: Those with a history of recurrent infections, had a current blood disorder, were taking steroid or other immunosuppressive drugs or received transfusions within the past 12 months <ul style="list-style-type: none"> <li>• Patients enrolled: 597</li> <li>• Patients randomised: 597</li> </ul> Plasma reduced group: 198 patients Buffy coat-depleted group: 204 patients WBC filtered group: 195 patients <ul style="list-style-type: none"> <li>• Patients transfused: 509</li> <li>• Patients considered for the analysis: 597</li> </ul> Main characteristics of patients (included non-transfused): Age: Plasma reduced group = 62.2 ± 9.1 years; Buffy coat-depleted group = 62.4 ± 8.1 years. WBC filtered group = 61.7 ± 8.6 years



**Wallis 2002** (Continued)

Gender ratio (men to women): Plasma reduced group = 2.9; Buffy coat-depleted group = 2.6; WBC filtered group = 2.9

Preoperative Hb in g/dL: Plasma reduced group =  $14.2 \pm 1.2$ ; Buffy coat-depleted group =  $14.1 \pm 1.2$ . WBC filtered group =  $14.2 \pm 1.2$

Discharge Hb in g/dL: Plasma reduced group =  $11.3 \pm 0.9$ ; Buffy coat-depleted group =  $11.3 \pm 1$ . WBC filtered group =  $11.1 \pm 0.9$

Interventions	<ol style="list-style-type: none"> <li>1. Plasma reduced.</li> <li>2. Buffy coat-depleted.</li> <li>3. WBC filtered (pre-storage leukoreduction).</li> </ol>
Outcomes	<p>Primary</p> <ol style="list-style-type: none"> <li>1. Events coded as hospital acquired infection.</li> </ol> <p>Secondary:</p> <ol style="list-style-type: none"> <li>a. Length of hospital stay.</li> <li>b. Postoperative fever.</li> <li>c. Use of antibiotics in hospital.</li> <li>d. Evidence of infection after discharge from hospital.</li> </ol>
Notes	<p>Trial registration: Not reported</p> <p>Funding: This study was supported in part by a grant from the Northern and Yorkshire R &amp; D directorate of the National Health Service</p> <p>Role of sponsor: Not reported</p> <p>A priori sample size estimation: Yes</p> <p>Conducted: Not reported</p> <p>Declared conflicts of interest: Not reported</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive, in the event of a transfusion, PR, BCD, or WCF blood" (Page 1128).
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization by sealed envelopes was carried out in the hospital blood transfusion department at the time of the admission clinic" (Page 1128). Use of opaque envelopes is not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The surgical staff were not blinded as to the blood component given, but were unaware of the randomization when the first decision to transfuse was made" (Page 1128).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: Collection and review of data to determine postoperative infections and other variables were carried out without knowledge of the randomization or type of blood given" (Page 1128).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All patients transfused were analysed.

**Wallis 2002** (Continued)

Selective reporting (reporting bias)	Low risk	The study protocol is unavailable but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Other bias	Low risk	Comment: The study appears to be free of other sources of bias.

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
<a href="#">Bowden 1995</a>	The study population received other blood components along with or different from PRBC transfusion.
<a href="#">Bracey 2002</a>	Non-randomised clinical trial.
<a href="#">Connery 2005</a>	Study protocol included patients with no indication of RBCs. Intervention poorly specified.
<a href="#">de Vries 2003</a>	No control group.
<a href="#">de Vries 2004</a>	No transfusion intervention.
<a href="#">Dzik 2002</a>	Study protocol included patients with no indication of RBCs.
<a href="#">Efstathiou 2003</a>	Autologous transfusion as intervention.
<a href="#">Gilbert 1989</a>	The study population received other blood components along with or different from PRBC transfusion.
<a href="#">Gu 1996</a>	The study population received other blood components along with or different from PRBC transfusion.
<a href="#">Gu 2009</a>	Autologous transfusion as intervention.
<a href="#">Hayashi 2000</a>	Autologous transfusion as intervention.
<a href="#">Houbiers 1994</a>	Study protocol included patients with no indication of RBCs.
<a href="#">Jensen 1992</a>	The study population received other blood components along with or different from PRBC transfusion.
<a href="#">Kao 1995</a>	The study population received other blood components along with or different from PRBC transfusion (platelets intervention).
<a href="#">Koskenkari 2005</a>	No transfusion intervention.
<a href="#">Leal-Noval 2005</a>	No transfusion intervention.
<a href="#">Llewelyn 2004</a>	Non-randomised clinical trial.
<a href="#">Nielsen 1999</a>	Study protocol included patients with no indication of RBCs.
<a href="#">Opelz 1997</a>	Control group did not receive transfusion.
<a href="#">Salamonsen 2005</a>	No transfusion intervention.

Study	Reason for exclusion
Skånberg 2007	Non-randomised clinical trial.
So-Osman 2010	Did not report a control group.
Vamvakas 2007	Meta-analysis.
van de Watering 2004	Narrative review.

### Characteristics of studies awaiting assessment [ordered by study ID]

#### NCT00810810

Methods	Study design: Parallel group RCT Allocation: Randomized Endpoint classification: Efficacy study Intervention model: Parallel assignment Masking: Single blind (Investigator) Primary purpose: Prevention
Participants	Inclusion criteria: <ul style="list-style-type: none"> <li>At least 18 years of age.</li> <li>Scheduled for open heart surgery of cardiopulmonary bypass that involves: CABG, CABG with valve, aneurysm repair.</li> <li>Urgent or elective surgery.</li> </ul> Exclusion criteria: <ul style="list-style-type: none"> <li>Scheduled for open heart surgery of cardiopulmonary bypass that involves: placement of a ventricular assist device, cardiac transplantation, aortic dissection repair.</li> <li>Emergent surgery.</li> <li>Participation in other clinical research studies within 30 days of randomisation.</li> <li>Immunosuppressive treatment.</li> <li>Refuse blood transfusion.</li> <li>Disease or condition placing subject at undue risk or decision of attending doctor.</li> </ul> Condition requiring high volume transfusion therapy.
Interventions	Active comparator 1: Standard blood components Transfusion, if ordered by physician, with unfiltered RBCs and apheresis platelets Experimental 2: Leukoreduced blood components Transfusion, if ordered by a physician, of leukoreduced RBCs and apheresis platelets Experimental: 3 Leukoreduced and irradiated

**NCT00810810** (Continued)

	Transfusion, if ordered by physician, of gamma irradiated leukoreduced RBCs and gamma irradiated apheresis platelets
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> <li>• Production, de novo, of antibody to HLA antigens (Time frame: 0 to 5 weeks after surgery).</li> </ul> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> <li>• Changes in number or cytokine profile of CD4 T regulatory cells or NKT cells.</li> </ul> <p>(Time frame: 0 to 5 weeks after surgery)</p>
Notes	<p>This study has been completed, but we did not find any publication related to it in the search.</p> <p>Inclusion or exclusion decision cannot be made because sufficient information is not currently available.</p>

**Waghmare 2012**

Methods	<p>Study Design: RCT</p> <p>Allocation: Randomized</p> <p>Endpoint classification: Efficacy study</p> <p>Intervention model: Parallel assignment</p> <p>Masking: Open labeled</p> <p>Primary purpose: Prevention</p>
Participants	Sixty-four consecutive ICU. All had severe falciparum malaria and required blood transfusion. Pregnant women and patients with previous blood transfusion were excluded.
Interventions	<p>Filtered group: Leukodepleted blood transfusion using bedside leukodepletion filter versus regular</p> <p>Control group: non-leukodepleted blood transfusion</p>
Outcomes	<p>Death from all causes at 28 days, incidence of Acute Respiratory Distress Syndrome and sepsis, severity of multiple organ dysfunction, and length of ICU stay in the two treatment groups.</p> <p>Patients were studied over 16 months.</p>
Notes	<p>Registration number: Unknown</p> <p>Inclusion or exclusion decision cannot be made because sufficient information is not currently available.</p>

**Zhao 2004**

Methods	<p>Study design: RCT</p> <p>Allocation: Randomized</p> <p>Endpoint classification: Efficacy study</p> <p>Intervention model: Parallel assignment</p>
---------	--

**Zhao 2004** (Continued)

Masking: Unknown

Primary purpose: Prevention

Participants	One hundred patients with cirrhosis of liver, gastric ulcer and cancer were selected to receive RBC concentrates with leukocyte filtration. Another group of 50 patients with liver necrosis, gastric ulcer and cancer were selected to receive non-filtered RBC concentrates. Two hundred and forty patients with acute or chronic leukaemia, aplastic anaemia, multiple myeloma, thrombocytopenia purpura, diabetes mellitus, cirrhosis of liver, upper gastrointestinal haemorrhage, severe hepatitis, burn and cancer post radioactive or chemical treatment were divided into 2 groups with 120 patients in each one and selected randomly to receive platelet concentrates.
Interventions	RBC concentrates with leukocyte filtration versus non-filtered RBC concentrates.
Outcomes	incidence rates of febrile nonhaemolytic transfusion reactions (FNHTR).
Notes	Registration number: Unknown.  Inclusion or exclusion decision cannot be made because sufficient information is not currently available.

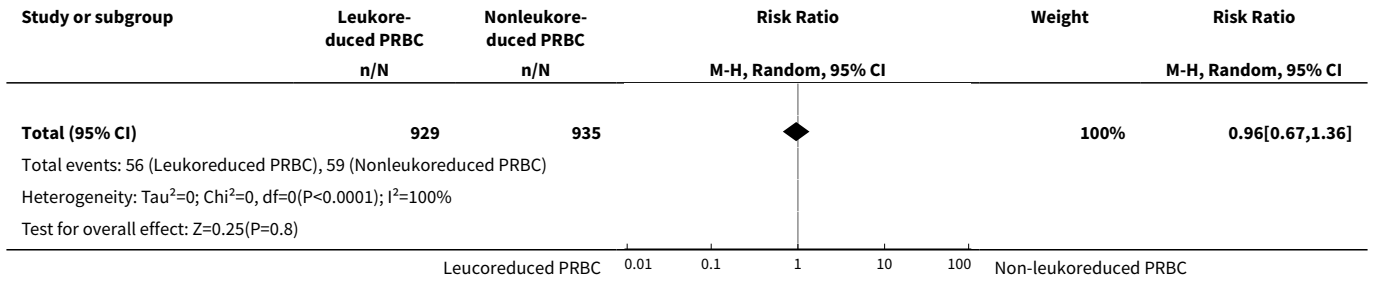
**DATA AND ANALYSES**

**Comparison 1. Leukoreduced PRBC versus non-leukoreduced PRBC. Main analysis (randomised patients)**

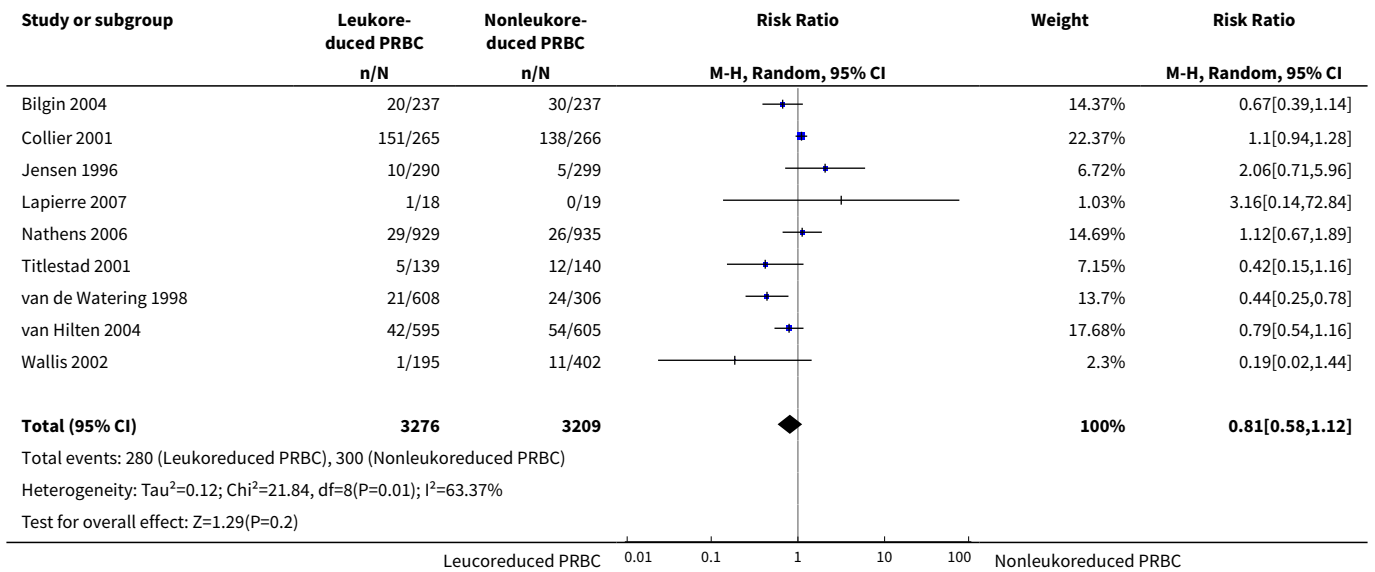
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TRALI. Number of events of the total of randomised patients reported	1	1864	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.67, 1.36]
2 Death. Number of events of the total of randomised patients reported	9	6485	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.12]
3 Infection. Number of events of the total of randomised patients reported	10	6709	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.03]
4 Adverse events. Number of events of the total of randomised patients reported	2	634	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.02]
4.1 Fever	2	634	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.64, 1.02]

**Analysis 1.1. Comparison 1 Leukoreduced PRBC versus non-leukoreduced PRBC. Main analysis (randomised patients), Outcome 1 TRALI. Number of events of the total of randomised patients reported.**

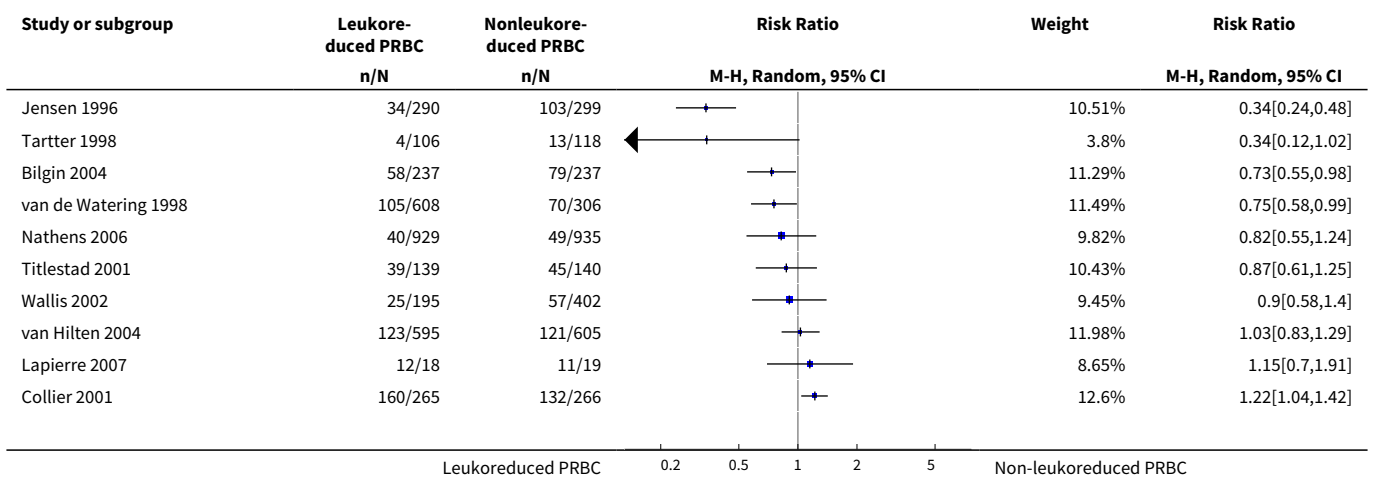
Study or subgroup	Leukoreduced PRBC	Nonleukoreduced PRBC	Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI			M-H, Random, 95% CI
Nathens 2006	56/929	59/935			100%	0.96[0.67,1.36]
			Leukoreduced PRBC		Non-leukoreduced PRBC	

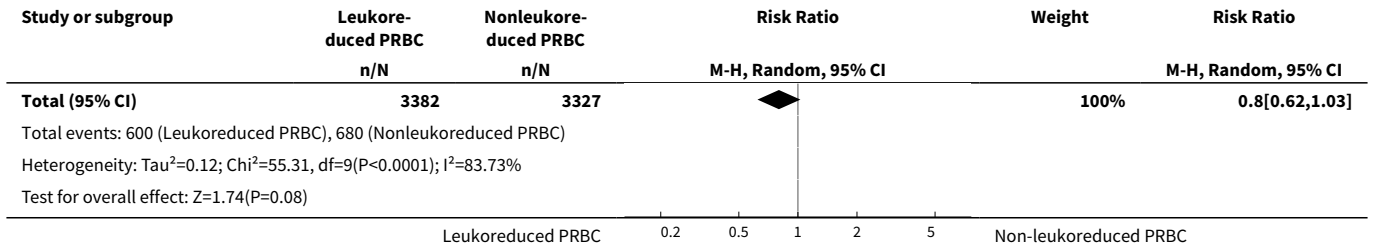


**Analysis 1.2. Comparison 1 Leukoreduced PRBC versus non-leukoreduced PRBC. Main analysis (randomised patients), Outcome 2 Death. Number of events of the total of randomised patients reported.**

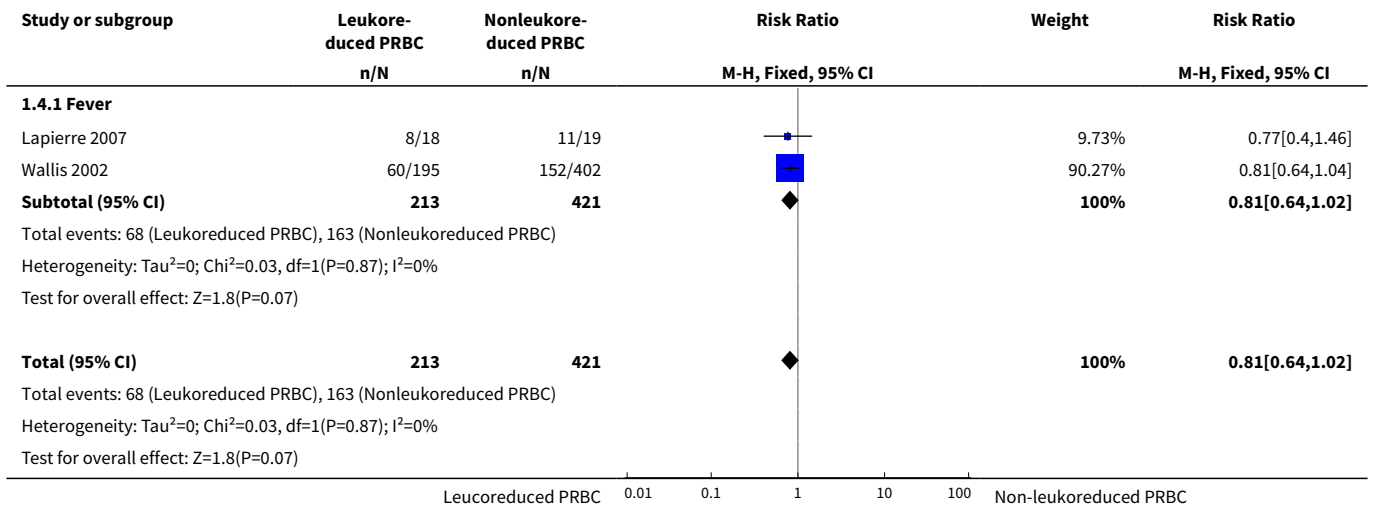


**Analysis 1.3. Comparison 1 Leukoreduced PRBC versus non-leukoreduced PRBC. Main analysis (randomised patients), Outcome 3 Infection. Number of events of the total of randomised patients reported.**





**Analysis 1.4. Comparison 1 Leukoreduced PRBC versus non-leukoreduced PRBC. Main analysis (randomised patients), Outcome 4 Adverse events. Number of events of the total of randomised patients reported.**

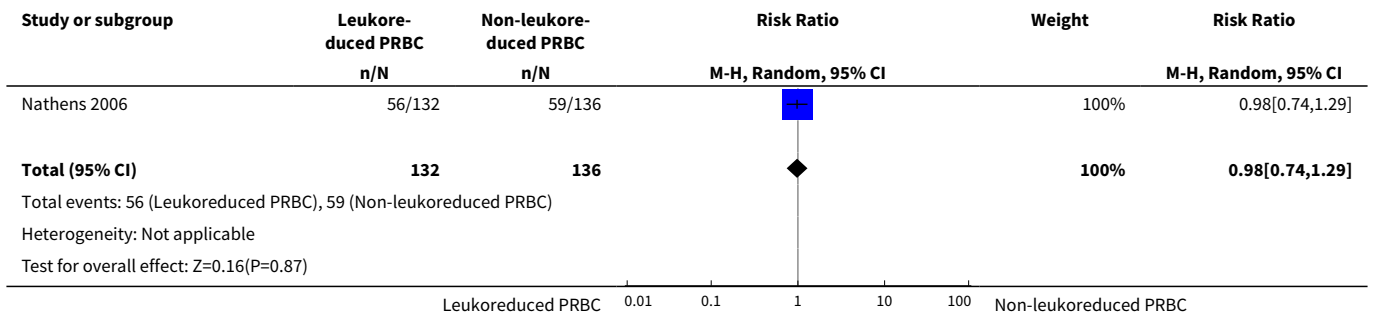


**Comparison 2. Leukoreduced PRBC versus non-leukoreduced PRBC. Secondary analysis (transfused patients)**

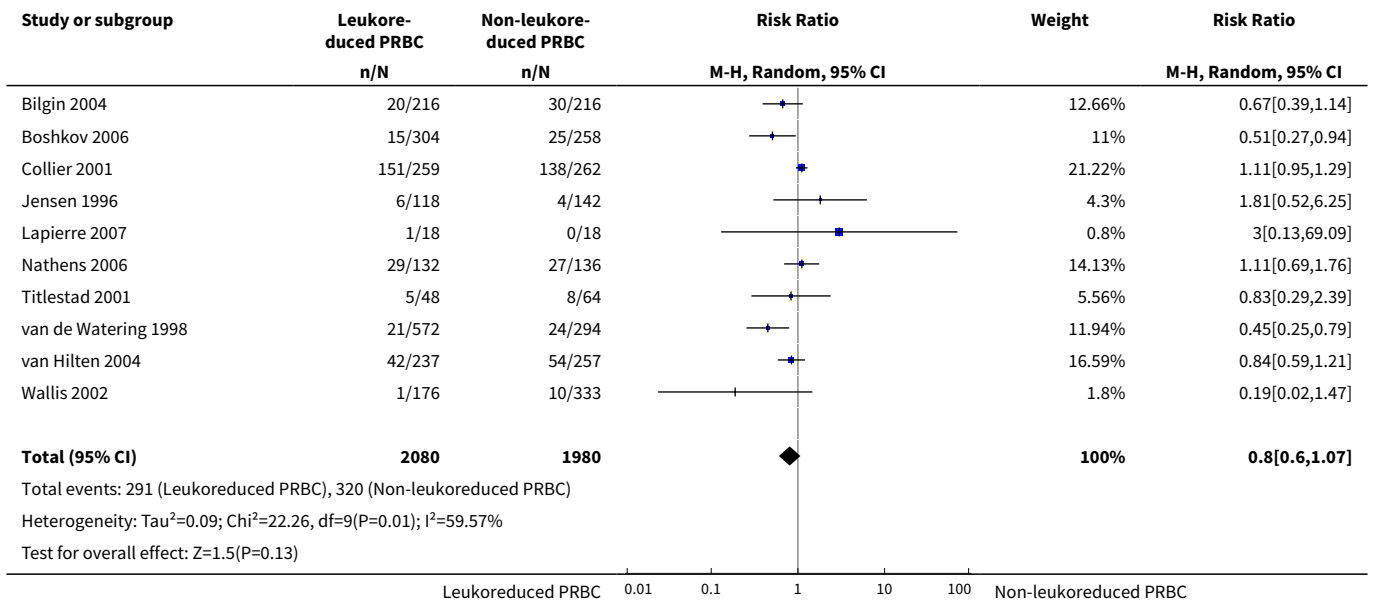
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TRALI. Number of events of the total of transfused patients reported	1	268	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.29]
2 Death. Number of events of the total of transfused patients reported	10	4060	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.60, 1.07]
3 Infection. Number of events of the total of transfused patients reported	10	3557	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
4 Adverse events. Number of events of the total of transfused patients reported	2	544	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.94]
4.1 Fever	2	544	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.94]



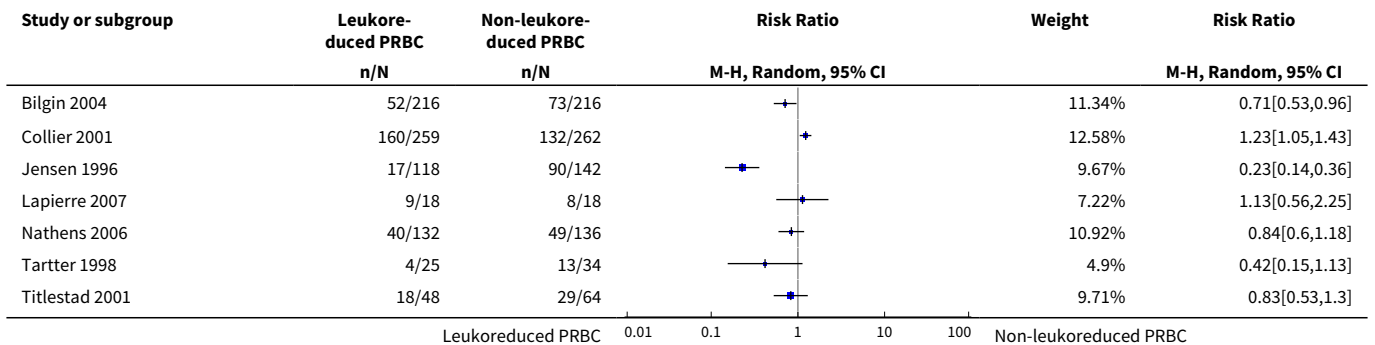
**Analysis 2.1. Comparison 2 Leukoreduced PRBC versus non-leukoreduced PRBC. Secondary analysis (transfused patients), Outcome 1 TRALI. Number of events of the total of transfused patients reported.**

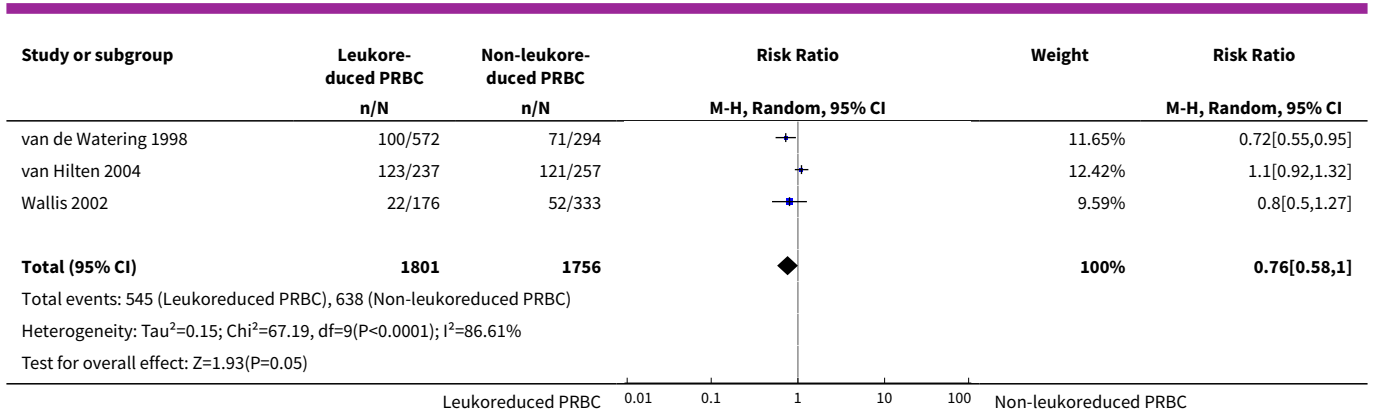


**Analysis 2.2. Comparison 2 Leukoreduced PRBC versus non-leukoreduced PRBC. Secondary analysis (transfused patients), Outcome 2 Death. Number of events of the total of transfused patients reported.**

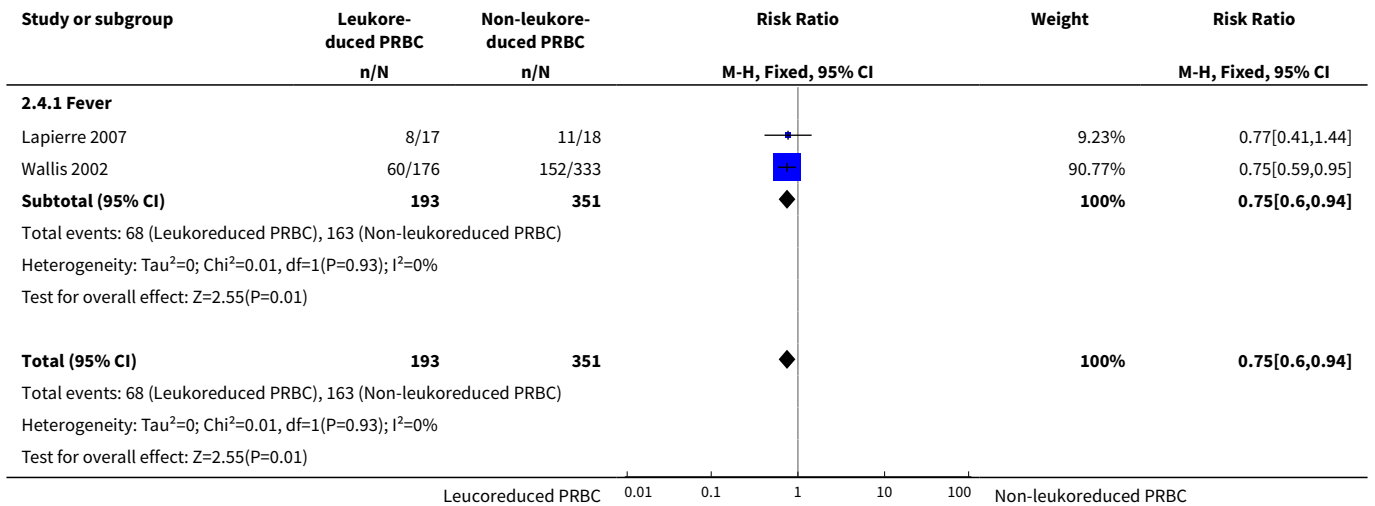


**Analysis 2.3. Comparison 2 Leukoreduced PRBC versus non-leukoreduced PRBC. Secondary analysis (transfused patients), Outcome 3 Infection. Number of events of the total of transfused patients reported.**





**Analysis 2.4. Comparison 2 Leukoreduced PRBC versus non-leukoreduced PRBC. Secondary analysis (transfused patients), Outcome 4 Adverse events. Number of events of the total of transfused patients reported.**



**APPENDICES**

**Appendix 1. Non-infectious adverse reactions**

Term	Definition	Reference
<b>Allergic reactions</b>	<p>Allergic reactions are probably the most frequent, occurring in 1% to 2% of all transfusion reactions. The symptoms range from local or diffuse pruritus, urticaria, erythema and cutaneous flushing to anaphylactic allergic reactions occurring within minutes of the transfusion. Anaphylactoid reactions fall in between the two ends of the spectrum.</p> <p>Uncomplicated allergic reactions are associated with increased histamine (increased during storage), cytokines, mast cell activators (i.e. leukotrienes), and other vasoactive substances (C3a and C5a) produced by donor leukocytes during storage.</p>	Tenorio 2007

(Continued)

<b>Febrile non-haemolytic transfusion reactions (FNHTR)</b>	FNHTR are defined as a temperature rise of at least 1°C in association with a transfusion or up to 4h after that may be accompanied by chills or rigors. Such reactions are due to acquired antibodies to donor leukocyte antigens or pyrogenic cytokines (IL-1, IL-6, IL-8 and TNF-D) elaborated by leukocytes present in the blood components or products.	Tenorio 2007
<b>Transfusion-related acute lung injury (TRALI) (clinical definition)</b>	The earliest definition of TRALI included all patients who developed acute respiratory distress, moderate to severe hypoxaemia (PaO <sub>2</sub> 30 to 50 mmHg), rapid onset of pulmonary edema, mild to moderate hypotension, and fever (defined as a 18°C to 28°C rise in body temperature from pre-transfusion baseline) within 6 hours of receiving a plasma-containing blood transfusion. The definition excluded patients if they had underlying cardiac or respiratory disease.	Goldman 2005; Toy 2005
<b>TRALI (histopathological definition)</b>	As evidenced by interstitial lung leak and lung histology that showed septal thickening, with inflammatory infiltrate consisting mainly of granulocytes was observed in mice transfused with large amounts (4.5 mg/kg) of a murine IgG subclass II.	Looney 2006
<b>Non-hemolytic febrile transfusion reaction (NHFTTR)</b>	Leukocyte apoptosis or monocyte activation, or both, may cause cytokines to accumulate in the blood products during storage. Symptoms/signs: fever, chills.	Heddle 1999; King 2004; Hoffman 2008
<b>Transfusion-associated graft-versus-host disease (TA-GVHD)</b>	When viable immunological T cells present in blood products are introduced into an immuno-incompetent host who cannot destroy the donor lymphocytes. Symptoms/signs: nausea, vomiting, anorexia, fever, watery diarrhoea, liver function abnormality, bone marrow aplasia, skin rash, icterus and renal failure.	Hoffman 2008; Rühl 2009

## Appendix 2. Search strategies

### Cochrane Injuries Group Specialised Register

"blood transfusion" AND (leuk\* OR leuc\* OR plasmapheresis OR cytappheres OR apheresis)

### Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library)

```
#1MeSH descriptor Blood Component Removal explode all trees
#2MeSH descriptor Leukocyte Reduction Procedures explode all trees
#3MeSH descriptor Cytapheresis explode all trees
#4(plasmapheresis or cytappheres* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucapheresis)
#5(Leukoreduc* or leukodeplet* or leukofilt* or leukocyte-reduc* or leucoreduc* or leucodeplet* or leucofilt* or desleucotizat*)
#6buffy coat-depleted
#7leukocyte count or leukocyte free or leucocyte count or leucocyte free
#8((Blood or white blood cell* or WBC or plasma) NEAR/3 (reduc* or deplet* or replete* or remov* or filtrat* or filter* or cytappheresis))
#9((leukocyte* or leucocyte*) NEAR/3 (reduc* or deplet* or replete* or remov* or filtrat* or filter*))
#10(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11MeSH descriptor Blood Transfusion explode all trees
#12((allogenic or allogeneic) NEAR/3 blood transfusion*)
#13(blood component* NEAR/3 transfusion*)
#14((erythrocyte* or leukocyte* or platelet* or RBC or red blood cell* or WBC or white blood cell* or thrombocyte* or blood) NEAR/3 Transfusion*)
#15(#11 OR #12 OR #13 OR #14)
#16(#10 AND #15)
```

### Medline (OvidSP)

```
1.exp Blood Component Removal/
2.exp Leukocyte Reduction Procedures/
3.exp cytappheresis/
```

- 4.(plasmapheresis or cytapheres\* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucapheresis).ab,ti.
- 5.(Leukoreduc\* or leukodeplet\* or leukofilt\* or leukocyte-reduc\* or leucoreduc\* or leucodeplet\* or leucofilt\* or desleucotizat\*).mp.
- 6.buffy coat-depleted.ab,ti.
- 7.(leukocyte count or leukocyte free or leucocyte count or leucocyte free).ab,ti.
- 8.((Blood or white blood cell\* or WBC or plasma) adj3 (reduc\* or deplet\* or replete\* or remov\* or filtrat\* or filter\* or cytapheresis)).ab,ti.
- 9.((leukocyte\* or leucocyte\*) adj3 (reduc\* or deplet\* or replete\* or remov\* or filtrat\* or filter\*)).ab,ti.
- 10.or/1-9
- 11.exp Blood Transfusion/
- 12.((allogenic or allogeneic) adj3 blood transfusion\*).ab,ti.
- 13.(blood component\* adj3 transfusion\*).ab,ti.
- 14.((erythrocyte\* or leukocyte\* or platelet\* or RBC or red blood cell\* or WBC or white blood cell\* or thrombocyte\* or blood) adj3 Transfusion\*).ab,ti.
- 15.or/11-14
- 16.10 and 15
- 17.randomi?ed.ab,ti.
- 18.randomized controlled trial.pt.
- 19.controlled clinical trial.pt.
- 20.placebo.ab.
- 21.clinical trials as topic.sh.
- 22.randomly.ab.
- 23.trial.ti.
- 24.17 or 18 or 19 or 20 or 21 or 22 or 23
- 25.(animals not (humans and animals)).sh.
- 26.24 not 25
- 27.26 and 16

#### Embase + Embase Classic (OvidSP)

1. exp Blood Component Removal/
2. exp Leukocyte Reduction Procedures/
3. exp cytapheresis/
4. (plasmapheresis or cytapheres\* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucapheresis).ti,ab.
5. (Leukoreduc\* or leukodeplet\* or leukofilt\* or leukocyte-reduc\* or leucoreduc\* or leucodeplet\* or leucofilt\* or desleucotizat\*).ti,ab.
6. buffy coat-depleted.ti,ab.
7. (leukocyte count or leukocyte free or leucocyte count or leucocyte free).ti,ab.
8. ((Blood or white blood cell\* or WBC or plasma) adj3 (reduc\* or deplet\* or replete\* or remov\* or filtrat\* or filter\* or cytapheresis)).ti,ab.
9. ((leukocyte\* or leucocyte\*) adj3 (reduc\* or deplet\* or replete\* or remov\* or filtrat\* or filter\*)).ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp blood transfusion/
12. ((allogenic or allogeneic) adj3 blood transfusion\*).ti,ab.
13. (blood component\* adj3 transfusion\*).ti,ab.
14. ((erythrocyte\* or leukocyte\* or platelet\* or RBC or red blood cell\* or WBC or white blood cell\* or thrombocyte\* or blood) adj3 Transfusion\*).ti,ab.
15. 11 or 12 or 13 or 14
16. 10 and 15
17. exp Randomized Controlled Trial/
18. exp controlled clinical trial/
19. placebo.ab.
20. randomi?ed.ti,ab.
21. \*Clinical Trial/
22. randomly.ab.
23. trial.ti.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp animal/ not (exp human/ and exp animal/)
26. 24 not 25
27. 16 and 26

#### CINAHL Plus (EBSCO)

- S1 (MH "Blood Component Removal+")  
 S2 (MH "Cytapheresis+")

S3 TX plasmapheresis or cytapheres\* or apheresis or plateletpheresis or pheresis or phereses or aphereses or leukapheresis or leucapheresis  
 S4 TX Leukoreduc\* or leukodeplet\* or leukofilt\* or leukocyte-reduc\* or leucoreduc\* or leucodeplet\* or leucofilt\* or desleucotizat  
 S5 TX buffy coat-depleted  
 S6 TX leukocyte count or leukocyte free or leucocyte count or leucocyte free  
 S7 TX (Blood or white blood cell\* or WBC or plasma) N3 (reduc\* or deplet\* or replete\* or remov\* or filtrat\* or filter\* or cytapheresis)  
 S8 TX (leukocyte\* or leucocyte\*) N3 (reduc\* or deplet\* or replete\* or remov\* or filtrat\* or filter\*)  
 S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8  
 S10(MH "Blood Transfusion+")  
 S11 TX (allogenic or allogeneic) N3 blood transfusion\*  
 S12 TX blood component\* N3 transfusion\*  
 S13 TX (erythrocyte\* or leukocyte\* or platelet\* or RBC or red blood cell\* or WBC or white blood cell\* or thrombocyte\* or blood) N3 Transfusion\*  
 S14 S10 or S11 or S12 or S13  
 S15 S9 and S14  
 S16 (MH "Clinical Trials")  
 S17 PT clinical trial\*  
 S18 TX clinical N3 trial\*  
 S19 TI ( (singl\* N3 blind\*) or (doubl\* N3 blind\*) or (trebl\* N3 blind\*) or (tripl\* N3 blind\*) ) or TI ( (singl\* N3 mask\*) or (doubl\* N3 mask\*) or (trebl\* N3 mask\*) or (tripl\* N3 mask\*) ) or AB ( (singl\* N3 blind\*) or (doubl\* N3 blind\*) or (trebl\* N3 blind\*) ) or AB ( (singl\* N3 mask\*) or (doubl\* N3 mask\*) or (trebl\* N3 mask\*) or (tripl\* N3 mask\*) )  
 S20 TX randomi?ed N3 control\* N3 trial\*  
 S21 (MH "Placebos")  
 S22 TX placebo\*  
 S23(MH "Random Assignment")  
 S24 TX random\* N3 allocat\* -  
 S25 MH quantitative studies -  
 S26 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 -  
 S27 S15 and S26 Limiters - Exclude MEDLINE records

#### LILACS

((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535\$ OR (Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) OR ((Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw tripl\$) AND (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) OR Mh placebos OR Tw placebo\$ OR (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337\$ OR Mh follow-up studies OR Mh prospective studies OR Tw control\$ OR Tw prospectiv\$ OR Tw volunt\$ OR Tw volunteer\$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) AND (Medicina Transfusional or la transfusión or As transfusões or blood transfusion or Transfusión Sanguínea)

#### Clinicaltrials.gov

( leuk\* OR leuc\* OR plasmapheresis OR cytapheres OR apheresis ) [DISEASE] AND transfusion [TREATMENT]

#### WHO Clinical Trials Registry Platform Search Portal (<http://apps.who.int/trialsearch/>)

Condition: leuk\* OR leuc\* OR plasmapheresis OR cytapheres OR apheresis

Recruitment status: ALL

#### Appendix 3. Study authors contacted

Trial author	Date of contact	Reply
Dr. Boshkov and Dr and Dr. Van Winkle (donna.vanwinkle@med.va.gov; vog.av.dem@elkniwnav.annod)	08 October 2014	None yet
Study: "Prestorage Leukoreduction of Transfused Red Cells Is Associated with Significant Ongoing 2-12 Month Survival Benefit in Cardiac Surgery Patients".		

(Continued)

Dr Morris (morrisc@ohsu.edu) and Dr. Van Winkle (donna.vanwin- kle@med.va.gov; vog.av.dem@elkniwnav.annod)	08 October 2014	None yet
Study: "Prestorage Leukoreduction of Transfused Red Cells Is Associated with Significant Ongoing 2–12 Month Survival Benefit in Cardiac Surgery Pa- tients" (Blood journal as one of the abstracts from the ASH Annual Meeting (2006 108: Abstract 578). Study included ( <a href="#">Boshkov 2006</a> ). Data extraction from abstract only.		
Dr. Nelson (knelson@psbc.org) and Dr. Aldea (aldea@u.washington.edu).	04 December 2014	None yet
Study: "Immunomodulation Following Transfusion" (ClinicalTrials.gov NCT00810810)		
Dr. van de Watering (l.vandewatering@sanquin.nl, l.m.g.van_de_Water- ing@lumc.nl)	22 May 2015	The author provided more details about fol- low-up
Study: <a href="#">van de Watering 1998</a>		
Dr. van Hilten (j.vanhilten@sanquin.nl)	22 May 2015	The author clarified the relation between two references
Poster "Characterization of the effects of leukocyte-filtered red blood cell transfusions in major surgery" related to the study <a href="#">van Hilten 2004</a>		
Dr. Waghmare and Dr. Desai (no email found, we contacted through Research- Gate)	23 May 2015	None yet
Poster: "Open Labeled, Randomized, Controlled Trial Comparing Leukode- pleted (Filtered) Blood Transfusion and Non-Leukodepleted (Unfiltered) Blood Transfusion in Cases of Severe Falciparum Malaria." Published in Chest 10/2012; 142(4_MeetingAbstracts):232A.		
Dr. Zhao (shumingzhao@yahoo.com and through ResearchGate)	25 July 2015	None yet
Study: "Clinical assessment of preventing febrile nonhaemolytic transfusion reaction by leukocyte-depleted blood transfusion". And the poster "Preven- tion and reduction of febrile nonhaemolytic transfusion reaction by leukocyte filtration blood transfusion"		

## CONTRIBUTIONS OF AUTHORS

All review authors contributed to the conception and design of this Cochrane review. Doctors Simancas-Racines, Arevalo-Rodriguez and Osorio contributed to the analysis and interpretation of data, and drafted the manuscript. All review authors contributed by commenting on the review critically for intellectual content and gave final approval of the document to be published.

## DECLARATIONS OF INTEREST

IA-R: None known.

AM-C: None known.

DO: None known.

DS-R: None known.

## SOURCES OF SUPPORT

### Internal sources

- Universidad Tecnológica Equinoccial, Ecuador.  
Academic
- Fundación Universitaria de Ciencias de la Salud, Bogotá D.C., Colombia.

### External sources

- Iberoamerican Cochrane Center, Spain.  
Academic

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In order to improve the quality of this Cochrane review, we made the following changes from the original protocol ([Simancas-Racines 2012](#)):

1. Data synthesis included a second meta-analysis: 'only transfused patients' as a sensitivity analysis. We performed this analysis due to the important number of patients not transfused as reported in most of the included studies. This analysis complements the main analysis planned in the review protocol: events reported among the total number of randomised patients.
2. We carried out a sensitivity analysis "excluding post-storage leukoreduction studies" to explore the effect of this variable on the effect estimate.
3. We conducted a TSA to assess the risk of random errors in the cumulative meta-analyses.
4. We changed our criteria for assessing the statistical heterogeneity in the meta-analyses. In the protocol it was classified an  $I^2$  statistic value of 40 to 60% as moderate, and 75% and above as high. In the review, we have now defined moderate heterogeneity as an  $I^2$  statistic of 50 to 74%, and high as 75% or above.

## NOTES

In future versions of this review we will also include, for all outcomes:

- a subgroup analysis by medical condition
- a subgroup analysis by type of filter
- a sensitivity analysis by buffy coat

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Leukocyte Reduction Procedures; Cause of Death; Erythrocyte Transfusion [\*adverse effects]; Infections [etiology]; Randomized Controlled Trials as Topic

### MeSH check words

Adolescent; Adult; Female; Humans; Male