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Packed red cells versus whole blood transfusion for severe paediatric anaemia, pregnancy-related anaemia and obstetric bleeding: an analysis of clinical practice guidelines from sub-Saharan Africa and evidence underpinning recommendations

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Abstract

Objective: Blood component transfusion is increasingly promoted in sub-Saharan Africa (SSA), but is resource-intensive so whole blood is often used. We examined SSA recommendations about whole blood and packed red cell transfusions for pregnancy-related bleeding or anaemia, and paediatric anaemia, and evaluated the evidence underpinning these recommendations.

Method: Relevant SSA guidelines were identified using five electronic databases, websites for SSA Ministries of Health, blood transfusion services and WHO. To facilitate comparisons, indications for transfusing packed red cells or whole blood within these guidelines and reasons given for these recommendations were recorded on a pre-designed matrix. The AGREE II tool was used to appraise guidelines that gave a reason for recommending either packed red cells or whole blood. We systematically searched MEDLINE, CINAHL, Global Health, Cochrane library and NHSBT Transfusion Evidence Library, using PRISMA guidelines, for clinical studies comparing whole blood with packed red cells or combined blood components in obstetric bleeding or anaemia, or paediatric anaemia. Characteristics and findings of included studies were extracted in a standardised format and narratively summarised.

Results: 32 English language guidelines from 15 SSA countries mentioned packed red cell or whole blood use for our conditions of interest. Only seven guidelines justified their recommendation for using packed red cells or whole blood. No recommendations or justifications had supporting citations to research evidence. 33 full-text papers, from 11,234 citations, were reviewed but only one study met our inclusion criteria. This was a single-centre study in post-partum haemorrhage.

Conclusion: Evidence comparing whole blood and packed red cell transfusion for common paediatric and maternal indications is virtually absent in SSA. Therefore, it is unclear whether policies promoting red cells over whole blood transfusion are clinically appropriate. Building a relevant evidence base will help develop effective policies promoting the most appropriate use of blood in African settings.

Keywords: Whole blood; packed red cells; Sub-Saharan Africa; systematic review; evidence-based medicine; AGREE II; clinical guideline quality; transfusion medicine; paediatric anaemia; obstetric haemorrhage; pregnancy-related anaemia

Introduction

In sub-Saharan Africa (SSA) and other low- and middle-income regions, the majority of blood transfusions are given as whole blood. High-income countries use preparations of red cell concentrates for transfusions rather than whole blood, which is in line with international recommendations. This involves removing the majority of plasma from donated whole blood by centrifugation and adding an additive solution (for example from the United Kingdom see https://www.transfusionguidelines.org/transfusion-handbook/3-providing-safe-blood/3-3-blood-products). Red cell preparations are being increasingly promoted in sub-Saharan Africa, but whether the exclusive use of packed red cell transfusions, which for the purposes of this study we define as any preparation of red blood cells derived from one unit of whole blood, is necessary or beneficial in SSA *versus* whole blood, is unclear. Understanding why packed red cells are recommended, and the evidence to support these recommendations, is important to ensure the most appropriate use of packed red cells and whole blood for clinical use in SSA.

Transfusion services in SSA experience chronic shortages of blood and have traditionally been hospital-based models in which relatives and friends donate blood for patients in the hospital. They also differ from those in high-income countries in terms of the demands for blood and patterns of blood use, and the technical, logistic and financial constraints that they face. In much of SSA, the majority of blood is given as whole blood for emergency transfusions. The most common reasons for transfusion are severe paediatric anaemia (1, 2) and obstetric-related anaemia and blood loss (3-5). By contrast, whole blood use in high-income settings is uncommon and almost all transfusions are packed red cells. The transfusion services are managed through partially or fully centralised collection, processing and distribution networks (6-8) and transfusions are generally planned and commonly used for chronic conditions in older patients, such as to support chemotherapy (9, 10).

The main role of transfusion services is to provide red blood cells for transfusion, whether in the form of whole blood or of packed red cell transfusions. The arguments that favour the use of packed red cells or whole blood include concerns around the risks of circulatory overload with whole blood or the loss of potentially beneficial clotting factors with packed cells. Separation of red cells from whole blood means that remaining plasma can be used for transfusion or fractionated into blood products. However, in low and middle-income countries (LMIC) the capacity to use plasma directly or as products, is limited and fractionation facilities are very scarce (11).

Separation of donated whole blood to give red cell concentrates for transfusion is being strongly promoted in SSA (12), but the extent to which this recommendation is evidenced by Africa-relevant clinical research is unclear. Given the differences in blood demands, supply and transfusion service organisation in SSA compared to high resource regions, there is a need to clarify the benefit of using packed red cells instead of whole blood in SSA. Evaluating the evidence for transfusing packed red cells rather than whole blood for common clinical indications in SSA will help to ensure clinical guidelines and funding priorities for strengthening African transfusion capacity are based on sound evidence. More research in this area was recognised as a priority at a meeting to discuss transfusion research priorities in SSA in 2015 (13).

The purpose of this study was to synthesize recommendations from national transfusion guidelines from SSA concerning the use of packed red cells or whole blood and to conduct a systematic scoping review to evaluate the available evidence relevant for the African context, underpinning these recommendations. The review focused on the use of packed red cells or whole blood for the most common indications for transfusion in SSA – namely severe paediatric anaemia, pregnancy-related anaemia and obstetric haemorrhage.

Methods

Our overall approach to this study was to identify guidelines from SSA covering a range of clinical specialities and conditions (i.e. in general medicine, obstetric, paediatric, neonatal, transfusion and malaria) that included recommendations regarding the use of packed red cells and whole blood. This yielded information about which conditions packed red cells and whole blood transfusions were recommended for and why. For guidelines that gave a justification for their recommendations we used the AGREEII appraisal tool to assess the quality of the guidelines. We then performed a literature search for clinical studies comparing packed red cells with whole blood for obstetric haemorrhage, pregnancy-related anaemia and paediatric anaemia, which are the commonest indications for transfusion in SSA settings. The evidence obtained from the literature search was compared to the justifications for recommendations within the guidelines and an assessment made of the extent to which policy recommendations were supported by scientific evidence.

Identification and Appraisal of Sub-Saharan African Guidelines Mentioning Whole Blood or Packed Red Cell Use

We searched for SSA guidelines from general medicine, obstetrics, paediatrics, neonatal medicine, malaria and transfusion that mentioned whole blood or packed red cell use in order to synthesize the recommendations and the evidence used to make the recommendations. Information was sought on the following three questions: For what conditions were packed red cells and whole blood recommended? What explanations did the guidelines give for using either blood whole blood or packed red cells in specific clinical settings? To what extent were these recommendations based on an appraisal of the clinical evidence?

One author (NK) searched for national and regional guidelines from SSA that contained recommendations regarding packed red cell and whole blood use in five databases: WHO IRIS, WHO AFROLIB, WHO AIM, Google Scholar and Pubmed. NK also performed grey literature searches using national Ministry of Health and blood transfusion service websites from SSA countries, and the WHO website, using combinations of word searches in Google, for relevant guidelines, including national standard treatment guidelines, maternal, neonatal and paediatric guidelines, malaria guidelines and clinical transfusion guidelines.

Inclusion criteria for publications were guidelines that described the use of whole blood or packed red cell transfusions rather than simply "blood", were in English, were available on the internet, and were intended for use within SSA. Where multiple editions of the same guideline were available, only the most recent one was used. No publication date restriction was applied and there was no restriction on age or other characteristics of transfusion recipients. Besides including guidelines that made recommendations regarding packed red cell or whole blood use for specific paediatric or obstetric indications, we also included guidelines that made a general preferential statement regarding packed red cell or whole blood, use irrespective of indication or patient group, if it was deemed to be written in a way that was relevant to paediatric or obstetric practice.

Information from relevant guidelines was recorded onto a pre-piloted data extraction form. This included information on the country of origin and scope of the guideline, year of publication, indications given within the guideline for transfusing packed red cells or whole blood and reasons given in the guideline for using either blood component in these situations. Guidelines differed in the level of detail with which they defined specific indications for transfusion. Therefore attempts to generalise these indications for transfusion into simple categories such as "obstetric anaemia" and "obstetric haemorrhage" would mask a lot of this detail and reduce the specificity of our conclusions. Thus, information on indications for transfusing packed red cells or whole blood within

identified guidelines and the reasons given for these recommendations were tabulated into broad categories of indications that allowed guidelines to be compared while maintaining as much detail as possible.

For guidelines whose recommendations for whole blood and packed red cell use were based on references to scientific literature, or which gave some other justification for using either component, three reviewers (SB, SJ and NK) independently assessed the methodological rigour and transparency of guideline development using the Appraisal of Guidelines for Research and Evaluation II tool (AGREE II). This is a validated tool to appraise the quality of practice guidelines and comprises 23 key items embedded within six domains: scope and purpose, stakeholder Involvement, rigour of development, clarity of presentation, applicability and editorial independence (14). Each item in each guideline was scored from one to seven by each of the appraisers, with seven being the highest score. R data analysis software version 3.4.0 was used to calculate the mean and standard deviation of scores for each domain. Scaled domain scores were also calculated using a formula recommended by AGREEII (14), which is shown below.

$$\text{Scaled domain score (\%)} = \frac{\text{(Obtained score – minimum possible score)}}{\text{(Maximum possible score – minimum possible score)}}$$

The scaled score represented the percentage of the total possible score for each domain that was achieved by each guideline.

Identification of Evidence Comparing Packed Red Cells or Whole Blood for Clinical Use

We followed the five-step Joanna Briggs Institute Guidelines for conducting a systematic scoping review, to evaluate the evidence comparing packed red cells with whole blood for severe paediatric anaemia, obstetric haemorrhage and pregnancy-related anaemia (15). This type of review aims to "rapidly map the evidence available for a research area, for instance when the range and type of evidence is heterogeneous or complex" (16), or to cover a broad range of concepts. We selected this method in order to be able to cover evidence related to a range of conditions, population groups (children of different ages, pregnant and post-partum women) and different geographic regions. Evaluating the extent to which packed red cells and whole blood have been compared in the research literature required interrogation of a range of study designs, including both retrospective and prospective studies. We were interested in the extent to which any clinical outcomes were reported in the published literature, including mortality, morbidity related to transfusions or to the underlying bleeding condition, and comparisons made regarding the amount of blood transfused. We did not publish a study protocol beforehand.

We focused on three conditions - severe paediatric anaemia, pregnancy-related anaemia and post-partum bleeding - because these groups are the major recipients of blood transfusion in Africa. In SSA severe anaemia is often multi-factorial so for each of these three conditions our search strategy encompassed haemoglobinopathies, malaria, malnutrition and undifferentiated presentations with severe anaemia (1, 2) (Appendix 1). Combining these different search terms allowed a wider range of potentially relevant studies to be captured. This approach has also been used in a systematic review evaluating the effect of routine blood transfusion in patients with malaria and severe anaemia, which also incorporated haemoglobinopathies into its search strategy as these are also an important cause of anaemia in many malaria-affected regions (17). Search results were reported according to PRISMA guidelines (18).

The search strategy was built using word variations of key terms, incorporated into MeSH headings and keyword searches. Keywords were also extracted from articles retrieved during the search and incorporated into the search strategy. Five online databases were searched: MEDLINE (Ebscohost, 1946 to March 2017), CINAHL, Global Health databases, and Cochrane library and NHSBT Transfusion Evidence Library (1950 to March 2017) with all searches completed by March 2017. Results were imported into an online platform, Rayyan QCRI (19) for duplicate extraction.

Two independent reviewers screened citations and abstracts from retrieved studies for full-text review and according to pre-specified inclusion criteria which were studies in English, on human subjects, and that compared whole blood with packed red cells, or whole blood with combined blood components, for paediatric and pregnancy-related anaemia, or conditions relevant to these patient groups, or obstetric haemorrhage. For the purpose of this study, packed red cells were defined as any preparation of red blood cells derived from one unit of whole blood. No publication date or geographic restrictions were applied. A third reviewer independently resolved discrepancies that emerged during selection of publications for full review.

Studies were excluded if we were unable to obtain the English language full text despite extensive efforts including through the British Library repository. Studies of autologous transfusion, and studies where blood was not transfused directly from a blood bag into a recipients' vein (such as exchange transfusion, intra-uterine transfusion and cardio-pulmonary bypass), were excluded. One author (NK) screened the full texts of short-listed studies for subsequent inclusion, and extracted information about study characteristics, key findings and major limitations for the included studies, into a pre-designed matrix.

Results

Sub-Saharan African Guidelines on the Use of Whole Blood or Packed Red Cells

32 English-language guidelines from 15 countries were identified that specifically mentioned packed red cell or whole blood use. After excluding earlier editions of the same guideline, there were 14 national Standard Treatment Guidelines, six malaria guidelines, five clinical transfusion guidelines, four paediatric guidelines, two maternal health guidelines and one neonatal health guideline included in the final analysis (Figure 1 and Table 1). The publication dates of included guidelines ranged from 2004 to 2015.

Guidelines frequently differed in their recommendations – three guidelines recommended packed red cells RC for haemorrhage, one recommended fresh whole blood and five suggested either packed red cells or whole blood could be used (Figure 2). One guideline recommended packed red cells for obstetric haemorrhage; another recommended whole blood. Seven guidelines recommended packed red cells for decompensated anaemia, whereas two suggested that packed red cells and whole blood were interchangeable. Three separate guidelines from two countries recommended packed red cells for decompensated paediatric anaemia; two guidelines from two countries suggested that packed red cells and whole blood were interchangeable (Figure 2).

Only 7 of the 32 (22%) guidelines stated a rationale for recommending packed red cells or whole blood use in specific situations (Table 2) and none of these recommendations were referenced. These 7 guidelines were appraised using AGREEII. The highest scaled domain score was for scope and purpose (median scaled score 57%), which is concerned with how well the overall aim and target population of the guideline are described. Clarity of presentation (median scaled score 48%), which is related to the clarity of language and layout of the guideline, had the second highest score. The lowest scores were for rigour of development (median scaled score 14%), which deals with the process used to search for and synthesise evidence and the way recommendations were developed and updated, and editorial independence (median scaled score 6%), which assesses how guideline developers ensured that competing interests did not influence guideline recommendations (Figure 3).

Published Evidence Comparing Packed Red Cells or Whole Blood for Clinical Use

33 publications identified from the initial literature search underwent full-text review and only one met the criteria for inclusion (Figure 4). This was a single centre observational study from the USA comparing packed cells with whole blood use in obstetric haemorrhage (20). In this study, case notes of 1,540 women who were transfused for obstetric haemorrhage with haemodynamic instability from March 2002 to June 2006 were reviewed. 659 (43%) women were transfused whole blood only,

593 (39%) were transfused packed red cells only and 288 (19%) were transfused combinations of blood components including thawed plasma, cryoprecipitate and platelets. Although the rate of complications was low, women given only whole blood had a significantly higher incidence of transfusion-associated circulatory overload than those who received packed red cells (7% versus 4%, p<0.001). They also had a significantly lower incidence of acute tubular necrosis than women given packed red cells alone or those given combinations of blood components (0.3% versus 2% and 4%, *P*<0.001). Women given combinations of blood components had a higher incidence of adult respiratory distress syndrome, hypofibrinogenaemia and intensive care unit admission than women given either packed red cells or whole blood alone. However, this result may have been confounded by this group having more comorbidities leading to greater surgical risk, as well as having more obstetric complications such as placenta praevia (20). Potential limitations of the study included reporting data from a single centre and lack of blinding of researchers to the study groups. However, data were prospectively recorded and the hospital transfusion committee regularly audited compliance with pre-specified transfusion criteria.

Discussion

We found no published clinical evidence comparing packed red cells with whole blood for severe paediatric anaemia or pregnancy-related anaemia, and only one retrospective study comparing their use in obstetric haemorrhage. There were no published studies from SSA. There is therefore a total and critical lack of evidence comparing packed red cells with whole blood for common clinical indications for transfusion in SSA and there are no data on which to base recommendations for choosing between packed red cells and whole blood for the commonest causes of life-threatening severe anaemia.

This lack of evidence is reflected in inconsistencies and absence of references to published literature in clinical guidelines from SSA concerning the use of packed red cells or whole blood. 78% of guidelines that mentioned packed red cell or whole blood use did not offer any justification for their recommendations. Of those that did, none backed it up with references to published literature. Although there was broad, but unsubstantiated, consensus across the guidelines in recommending packed red cells for the correction of anaemia, there were discrepancies between guidelines recommending whole blood and packed red cell use in, for example, haemorrhage and decompensated anaemia.

There are several reasons why packed red cells may be preferred over whole blood and are therefore internationally recommended as the component of choice. Splitting whole blood into components increases the utility of each donation since the different constituents can be made

available for multiple recipients. Packed cells are less likely than whole blood to cause transfusion-associated circulatory overload due to the smaller volume of blood needed to increment mean haemoglobin concentration. In many high-income countries packed red cells are leucodepleted (21) and therefore less likely to be associated with febrile and allergic reactions. Centralised blood processing systems required for blood component separation and distribution may make it easier for services to develop standardised procedures for screening and manipulating blood to improve safety.

In resource-constrained settings, such as SSA, reasons underlying the choice between packed red cells and whole blood are likely to be different from those in developed regions. Separation and storage of blood components reduces costs to transfusion services and potentially to recipients. An economic study in Zimbabwe showed that the cost of a unit of packed red cells was higher than the cost of a unit of whole blood (22). Where resources are scarce, the additional cost of component preparation may contribute to making transfusions unaffordable and unsustainable for transfusion services to maintain in the absence of external donor funding. A requirement for centralised blood processing may deter family replacement donors or local community donors from donating (23) and may jeopardise blood from reaching remote areas where distribution infrastructure is weak. Although some countries such as South Africa have implemented selective leucodepletion of red cell concentrates, leucodepletion is very uncommon in much of SSA, and currently likely to be unaffordable. There is a lack of data comparing the incidence and clinical impact of febrile reactions in SSA with non-leucodepleted whole blood and packed red cells. There has been recent interest in high-income countries in the use of whole, fresh (i.e. 1-2 days old) blood to improve haemostasis since in some studies it has been shown to reduce blood loss, possibly through improved platelet function (24). In SSA, where blood shortages are extensive and chronic, the turnover of blood stocks is rapid and much of the transfused blood would be considered 'fresh' (25). Transfusion of whole fresh blood might be a more appropriate blood component in SSA for common clinical indications for transfusion such as obstetric haemorrhage, which is often complicated by dysfunctional haemostasis.

An important secondary reason for preferring packed red cells over whole blood is that the process of packing red cells allows the separation of plasma which can be frozen for clinical use or fractionated to make plasma-derived products. However, fresh frozen plasma is frequently regarded as the most inappropriately administered blood component (26, 27) and evidence for its use in many settings is lacking (28). In SSA, evidence concerning indications for using fresh frozen plasma, and clinical experience of its use, are particularly scarce. Furthermore, almost none of the plasma produced in SSA is processed into products since there is currently only one plasma fractionation

facility, which is located in South Africa, and much of the separated plasma in SSA is not of suitable quality to undergo fractionation (11). There are examples from SSA of plasma wastage when whole blood is routinely split into packed cells and plasma, despite low demand for plasma for clinical use or fractionation (11).

Our study has various strengths and limitations. It combined a comprehensive review of national guidelines with a systematic review of the current evidence available to support recommendations regarding the use of whole blood or packed red cells for clinical use in SSA. In addition to searching for guidelines specifically related to transfusion, we also searched for relevant guidelines by speciality and clinical conditions. However, we were only able to include guidelines that were in English and available on the internet, so we may have missed some that were in clinical use but not available on-line or not in English. Nevertheless, we identified guidelines developed by national bodies and hence likely to have significant influence over clinical practices within their countries. When more than one edition of a guideline was identified, we included only the most recent edition. Despite this, some of the guidelines included were more than ten years old. However, these were considered relevant for inclusion as it is likely that such guidelines continue to be used by clinicians. Since only a small number of guidelines gave a justification for their recommendations and could be appraised using AGREE II, we make no attempt to generalise findings about quality to other guidelines.

The literature search was conducted using best practice 'PRISMA' principles with no date limitations. However we only included English-language studies. Transfusion issues cover virtually all medical specialities; so, to keep the search focused and manageable, it was necessary to restrict our search to patient groups that are the biggest users of transfusion in SSA which are maternal and non-surgical paediatric patients. This means that our results should not be extrapolated to other clinical situations that commonly require transfusion such as trauma or gastrointestinal bleeding. In practice, facilities for packing red cells by centrifugation are not always possible, and transfusion of plasma-reduced red cells may be used, which are made by hanging donated whole blood to allow only the red cells that have sedimented at the bottom of the blood collection bag to be transfused. We recognise that this technique for producing red cells may not be covered by the review search terms."

In addition to potentially resulting in sub-optimal patient care, inconsistencies in guidelines about when to use packed red cells and whole blood in SSA will inevitably lead to difficulties in defining goals for quality improvement, effective audit of appropriate blood use and in allocating scarce resources. We suggest that increased focus on formulating clinical transfusion guidelines that follow accepted international best practices for guideline development, including transparent

management of conflicts of interests, and consideration of available evidence through use of the GRADE approach would allow guideline developers to demonstrate consideration of practical issues to strengthen their recommendations (29). This would help to define locally relevant standards of care. The lack of evidence to support the current promotion of widespread use of packed red cells over whole blood in SSA urgently needs to be rectified with carefully designed clinical trials conducted in different settings in SSA, and economic and implementation research to investigate affordability and scalability. There is an emerging research agenda focusing on developing the evidence base around African obstetric and paediatric transfusion practices (30). We suggest that comparisons of whole blood with packed red cells should be factored into the design of future clinical trials in African transfusion medicine. Dedicated cluster-randomised controlled trials comparing packed red cells with whole blood, and integrating an economic evaluation component, would provide valuable evidence of cost-effectiveness of providing blood for transfusion in settings where transfusion services face sizeable logistic constraints. Simply transferring practices from high income settings to SSA which has very different clinical indications for transfusion, resources and infrastructure, risks producing detrimental unintended consequences such as plasma wastage (11). Routine separation of red cells and plasma by national blood services has resource implications, which need to be balanced against the potential benefits and effectiveness. This is particularly important in the context of SSA where there are legitimate concerns about reliance on external funding and sustainability of transfusion series that are based on wealthy country models (22, 31). Without high quality research about the appropriate use of whole blood and packed red cells in SSA, it will not be possible to develop evidence-informed policies (32). This will potentially have significant negative consequences for the clinical effectiveness of transfusions, and the cost, availability, and equity of access to blood transfusions in SSA (33).

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Table 1 Sub-Saharan African guidelines that mention packed red cell or whole blood transfusion

Country	Guideline	Publication Year
Botswana	Guidelines for the Diagnosis and Treatment of Malaria in Botswana	2007
Ethiopia	National Malaria Guideline	2012
Ethiopia	Standard Treatment Guidelines for General Hospital	2014
Ghana	Standard Treatment Guideline	2010
Ghana	National Guidelines for the Clinical use of Blood and Blood Products	2013
Ghana	Guidelines for the case management of Malaria in Ghana	2014
Kenya	National Guidelines for Quality Obstetric and Perinatal Care	-
Kenya	Guidelines for the Appropriate Use of Blood and Blood Products	2004
Kenya	Clinical Guidelines for the Management and Referral of Common Conditions at Levels 4 – 6	2009
Kenya	National Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya	2010
Kenya	Basic Paediatric Protocols for Ages up to 5 Years	2016
Malawi	Guidelines for the Clinical Use of Blood and Blood Products in Malawi, 1st Edition	-
Malawi	Guidelines for safe blood transfusion	2012
Malawi	Guidelines for the treatment of malaria in Malawi	2013
Malawi	Standard Treatment Guidelines	2015
Namibia	Standard treatment Guideline	2011
Nigeria	Standard Treatment Guidelines	2014
Nigeria	National guidelines for the diagnosis and treatment of malaria	2015
Rwanda	Gynaecology and obstetrics clinical protocols and treatment guidelines	2012
Rwanda	Internal Medicine Clinical Treatment Guideline	2012
Rwanda	Paediatrics Clinical Treatment Guidelines	2012
Rwanda	Neonatology Clinical Treatment Guidelines	2014
South Africa	Standard treatment guideline and essential medicines list for South Africa, Hospital level, Paediatrics	2013
South Africa	Navigation to a safer blood transfusion	2014
South Africa	Clinical Guidelines for the use of Blood Products in South Africa	2014
South Africa	Standard treatment guidelines and essential medicines list for South Africa, Hospital level, Adults	2015
Swaziland	National guideline for the appropriate use of blood and blood products	2011
Swaziland	Standard Treatment Guidelines and Essential Medicines List of Common Medical Conditions in the Kingdom of Swaziland	2012
Tanzania	Standard Treatment Guidelines and Essential Medicines List	2013
Uganda	Uganda Clinical Guidelines: National Guidelines for Management of Common Conditions	2012
Zambia	Standard Treatment Guidelines	2008
Zimbabwe	6th Essential Medicines list and standard treatment guideline for Zimbabwe	2011

Table 2 Reasons for recommending either packed red cell or whole blood transfusions given in Sub-Saharan African guidelines

Rationale given in African guidelines for using either packed red cells or whole blood	Guideline	Country
Separating whole blood into components including packed red cells may reduce the degradation of platelets and labile clotting factors under whole blood storage conditions. This may mean that platelets and plasma products given separately are more effective clinically.	Clinical Guidelines for the use of Blood Products in South Africa (2008)	South Africa
	Standard Treatment guidelines (2011)	Namibia
	Standard Treatment Guidelines (2008)	Nigeria
	Guidelines for the Clinical Use of Blood and Blood Products in Malawi	Malawi
Whole blood contains more plasma, leucocyte, citrate, hydrogen, potassium, ammonia than packed red cells, which may increase the risk of certain side effects	National Guidelines for the Clinical Use of Blood and Blood Products (2013)	Ghana
	Standard Treatment guidelines (2011)	Namibia
	Standard Treatment Guidelines (2008)	Nigeria
A larger volume of whole blood compared with packed red cells is needed to increase haemoglobin concentration by 10g/L, which may increase the risk of transfusion associated circulatory overload – There packed red cells are preferred for selected "at risk" groups	National Guidelines for the Clinical use of Blood and Blood Products (2013)	Ghana
	Guidelines for the Appropriate Use of Blood and Blood Products (2004)	Kenya
	The Clinical Use of Blood	World Health Organisation
	Standard Treatment Guidelines (2012)	Namibia
A larger volume of whole blood compared with packed red cells is needed to increase haemoglobin concentration by 10g/L, which may increase the risk of transfusion associated circulatory overload - lower doses of either packed red cells or of whole blood preferred	Clinical Guidelines for the use of Blood Products in South Africa (2012)	South Africa
	Uganda Clinical Guidelines: National Guidelines for Management of Common Conditions (2012)	Uganda
	A Paediatric Handbook for Malawi (2011)	Malawi

Figure 1. Selection process for Sub-Saharan African guidelines mentioning whole blood or packed red cell transfusion

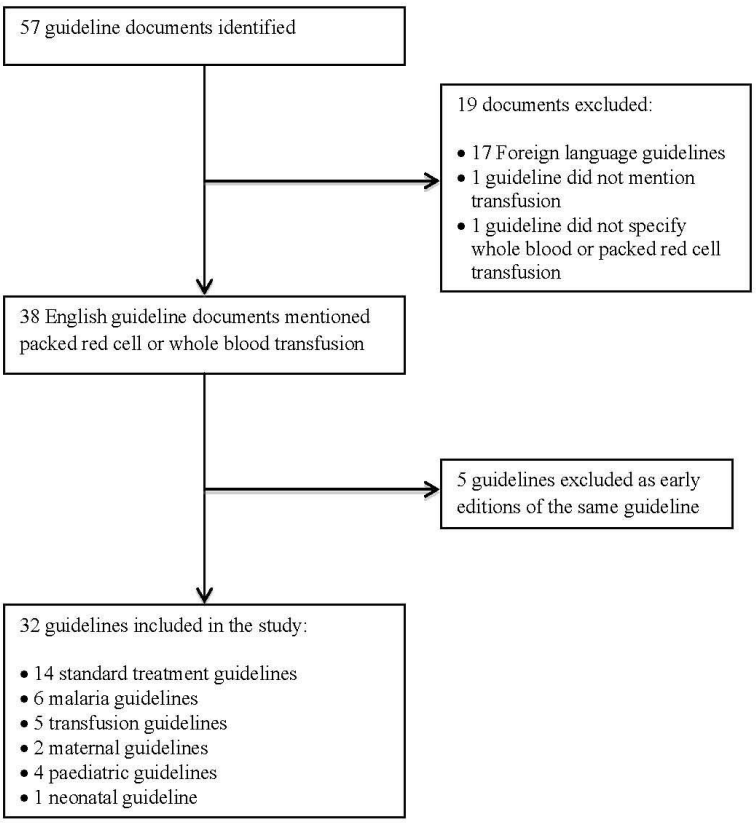
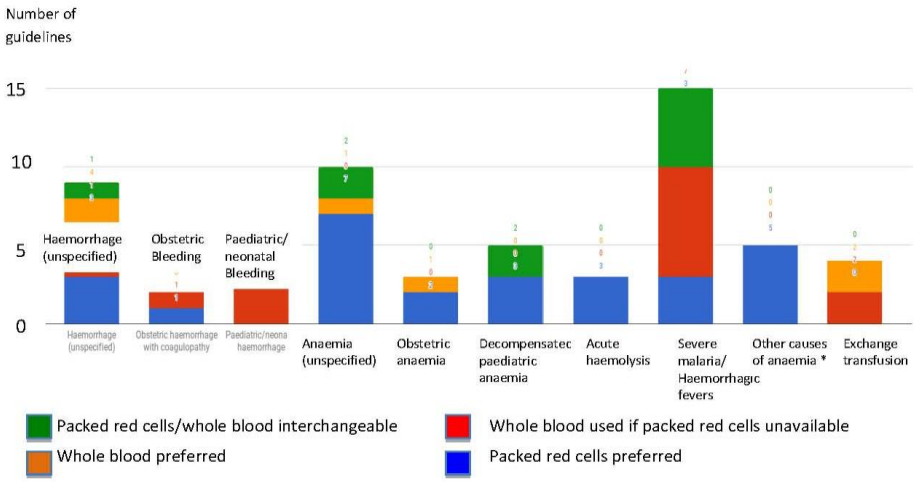
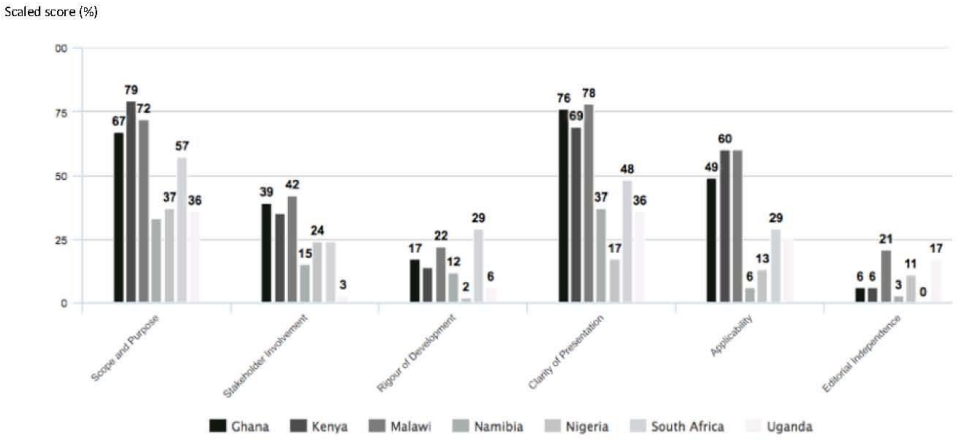


Figure 2 Number of SSA guidelines that recommended packed red cells or whole blood for specific clinical indications for transfusion



*Other causes of anaemia include chronic blood loss (1 guideline), haematological malignancy or peri-chemotherapy (two guidelines), and Sickle cell disease (two guidelines)

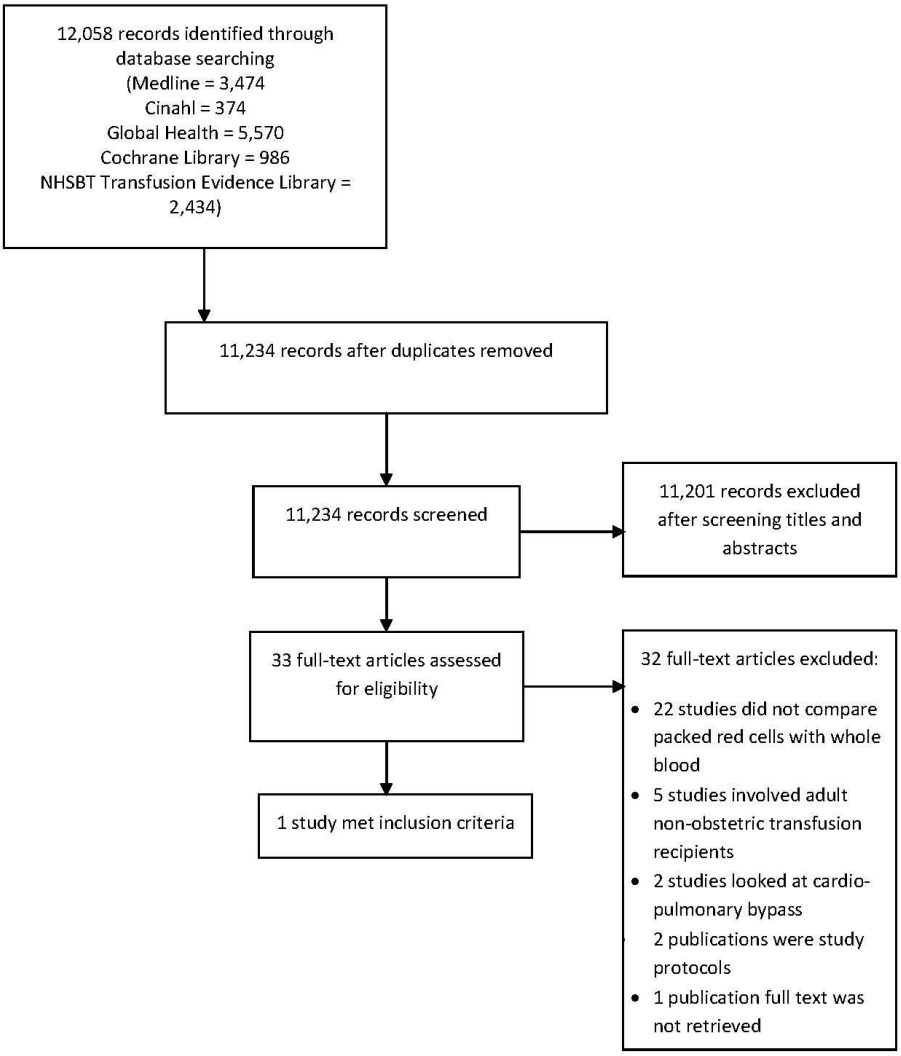
Figure 3. Scaled scores for each domain of AGREEII for 7 SSA guidelines that stated a rationale for using either whole blood or packed red cells



Domains of AGREEII appraisal tool by which seven SSA guidelines that compared packed red cells with whole blood for maternal anaemia and haemorrhage or paediatric anaemia were assessed

Figure 3 shows the scaled domain scores for each of the six guidelines that were appraised using AGREEII. As a whole, the guidelines tended to score more highly in the "clarity of presentation" and "scope and purpose" domains, and received the lowest scores in the "stakeholder involvement" and "editorial independence" domains.

Figure 4 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18) flow diagram showing studies identified through database searching



Appendix 1 Medline search strategy for titles and abstracts of studies comparing whole blood with packed red cells for pregnancy-related and paediatric anaemia and obstetric bleeding.

1. (MH "Blood Transfusion+") OR (MH "Blood Component Transfusion+") OR (MH "Erythrocyte Transfusion") OR (MH "Transfusion Medicine") NOT ((MH "Blood Transfusion, Autologous") OR (MH "Blood Transfusion, Intrauterine") OR (MH "Exchange Transfusion, Whole Blood") OR (MH "Plasma Exchange") OR (MH "Blood Donors"))
2. (blood component OR packed red cell* OR packed red blood cell* OR red cell concentrate* OR red blood cell* OR erythrocyte* OR RCC OR PRC OR PRBC OR whole blood OR fresh blood OR blood) W3 (transfus* OR haemotransfus* OR hemotransfus* OR haemotherap* OR hemotherap* OR infus* OR administ* OR retransfus*) NOT ("exchange transfusion" OR "autologous transfusion" OR "plasma exchange")
3. S1 OR S2
4. (MH "Postpartum Hemorrhage") OR (MH "Uterine Hemorrhage+") OR (MH "Obstetric Labor, Premature+") OR (MH "Obstetric Surgical Procedures+") OR (MH "Obstetric Labor Complications+")
5. (obstetric OR ante-partum OR intra-partum OR post-partum) W3 (h#emorrhage OR bleeding OR blood loss)
6. (MH "Hemorrhage+/BL/CO/SU/MO") AND (pre-eclampsia OR eclampsia OR HELLP OR placenta Pr#evia OR placenta accreta OR placenta percreta OR pelvic abscess OR ectopic pregnancy OR ectopic gestation OR abortion OR miscarriage OR c#esarean OR C-section OR hysterectomy)
7. S4 OR S5 OR S6
8. MH "Anemia+") OR (MH "Anemia, Hemolytic+") OR (MH "Anemia, Neonatal+") OR (MH "Anemia, Aplastic+") OR (MH "Anemia, Hemolytic, Autoimmune") OR (MH "Anemia, Sickle Cell+")
9. (MH "Malaria+") OR (MH "Malaria, Cerebral") OR (MH "Malaria, Falciparum+") OR (MH "Blackwater Fever")
10. (p#ediatric OR neonatal OR child* OR infant*) N2 an#emia) OR malaria OR malnutrition OR (Sickle cell) OR thalass#emia OR (G6PD deficiency) OR (glucose-6-phosphate-dehydrogenase deficiency) OR h#emoglobinopathy OR (Haematinic deficiency) OR (folate deficiency) OR (folic acid deficiency) OR (p#ediatric HIV) OR (p#ediatric AIDS) OR an#emia OR (an#emia N3 (pregnancy OR obstetric*))
11. S8 OR S9 OR S10
12. S7 OR S11
13. (PT (comparative study OR clinical trial OR randomised controlled trial)) OR (TI (compari* OR versus OR outcome* OR complication* OR manage* OR resuscitation OR practice or trial))
14. S3 AND S12 AND S13

a. Limiters – English language, Human subjects.