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A systematic review of red blood cell alloimmunization in pregnant women in Africa: time to do better

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Abstract

Background and objectives The presence of red blood cell (RBC) alloantibodies in pregnant women has been linked to the significant perinatal morbidity and mortality. A limited number of African studies have assessed alloimmunization to RBC antigens in pregnant women, but this literature has not been systematically reviewed. Thus, the aim of this study was to synthetize, by systematic review, the current evidence on RBC alloantibodies among pregnant women in Africa.

Methods We systematically searched MEDLINE, EMBASE and the Africa-Wide Information database to identify relevant studies in any language. Case reports, comments, letters, conference abstracts, editorials and review articles were excluded.

Results Of 269 potentially relevant articles, 12 studies representing 93 871 pregnant women fulfilled our selection criteria. Overall proportions of RBC alloimmunization exhibited a wide variation ranging from 1·1 (95% CI: 1·0, 1·2) to 12·1 (95% CI: 9·8, 14·7) per 100 pregnant women. Among clinically relevant antibodies, anti-D ranked as the most common, followed by anti-K and anti-E.

Conclusion The review of the available literature characterized the clinical challenge of RBC alloimmunization among pregnant women in Africa and revealed the insufficient volume and quality of research conducted in this topic. Improvement of quality of research should be a priority to gather stronger evidence that should drive policy decisions and strengthen practice in favour of RBC alloantibody screening in pregnant women as a standard of care throughout Africa.

Key words: Africa, blood transfusion, haemolytic disease of the newborn, pregnancy, RBC alloantibodies

Background

Red blood cell (RBC) alloantibodies in pregnant women originating either from previous pregnancies or from blood transfusion can pose a significant threat during pregnancy and lead to serious reactions, including haemolytic disease of the fetus and newborn (HDFN), resulting in significant perinatal morbidity and mortality [1, 2]. HDFN is an immunological condition caused by maternal RBC alloantibodies of the IgG class directed against cognate antigens on fetal RBC membranes, which can result in extravascular haemolysis and suppression of RBC progenitors in the bone marrow and cause severe anaemia and hydrops fetalis [3]. Recent evidence suggests that Rhesus and non-Rhesus maternal RBC alloantibodies can also increase the risk of preterm birth and/or stillbirth [4]. Moreover, management of pregnant women with alloantibodies and complications

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such as HDFN imposes enormous medical and economic challenges [5]. Furthermore, as in all alloimmunized patients, the risk of serious haemolytic transfusion reactions (HTRs) is high, and oftentimes, due to lack or delay of compatible RBC units, they may not receive adequate RBC transfusion support. This may have harmful clinical consequences and may contribute to maternal mortality. Maternal alloimmunization with anti-D antibody is recognized as a major contributor to fetal morbidity and mortality [6].

Despite the implementation of antenatal and postnatal anti-D prophylaxis, anti-D still remains the most common cause of HDFN. Other RBC alloantibodies involved in HDFN include anti-c, anti-C, anti-E, anti-K, anti-Jka, anti-Jkb, anti-Fya and anti-Kpa [7]. With more effective management options available and initiation of treatments occurring earlier, it is important to understand the epidemiology of RBC alloimmunization. Thus, routine antenatal RBC antibody screening should be a standard antenatal procedure integrated into any health system to identify patients with the clinically relevant RBC alloantibodies.

Numerous studies reporting the prevalence of RBC alloimmunization in pregnant women have been primarily conducted in more advanced countries where antenatal RBC antibody screening in the first trimester is established as a standard of care [8, 9]. However, only a few studies have reported the prevalence of RBC alloantibodies in the resource-limited settings, specifically in Africa. Thus, it is important that a systematic review of the literature be carried out to summarize the current evidence of the extent of RBC alloimmunization in pregnant women in Africa, which may help inform policy and practice. In addition, this can help determine the need for further studies and contribute to incorporating the lessons learned from previous work into future studies by identifying gaps in research. Thus, the primary aim of this study was to systematically review and summarize the existing literature that addresses the prevalence of RBC alloantibodies in pregnant women in Africa. The secondary aim was to identify the methodological or design limitations of existing studies in order to guide the design of any future studies in this field.

Materials and methods

Methods

Search strategy, study selection and data extraction have been discussed in detail previously [10]. Briefly, we used MEDLINE (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda MD, USA), EMBASE (Copyright © 2016 Elsevier B.V.) and the Africa-Wide Information (© 2016 EBSCO Industries, Inc. All rights reserved) databases to search for studies in any language published up to 1 July 2015. Key search themes are as follows: 'blood transfusion', 'isoantibodies', 'alloantibodies', 'irregular antibodies', 'red cell antibodies', 'rbc antibodies', 'irregular erythrocyte antibodies', 'alloimmunization', 'alloimmunisation' and 'Africa' were described by medical subject heading terms and keywords. These searches were supplemented by citation tracking and hand searches. Studies were included if they reported the frequency of RBC alloantibodies in pregnant women in Africa. Case reports, comments, letters, conference abstracts, editorials or review articles were excluded. Two investigators (A.M.N. and P.M.B.) conducted independent data extraction, and disagreements were resolved by consensus. Extracted data included study design, population under study, study size, the number of alloimmunized patients, the types of alloantibodies detected and the screening method used. We also extracted the quantitative data [proportions and 95% confidence intervals (CIs)] on RBC alloimmunization reported in each study. In studies where 95% CIs were not reported, we calculated these from the data provided in the manuscript.

Quality appraisal of included studies

The methodological quality of included studies was independently appraised by two authors (A.M.N. and P.M.B.), and disagreements were resolved through consensus. Assessment of within-study bias for observational studies was undertaken using an adapted tool based on a validated risk of bias assessment tool for evaluating the prevalence studies as suggested by Hoy *et al.* [11]. The modified tool contained eight domains, three of which focused on external validity including the following: (1) relevance of the target population; (2) appropriateness of the sampling method and (3) likelihood of non-response bias. The five domains of internal validity included the following: (1) directness of data collection from subjects; (2) acceptability of the case definition; (3) reliability and validity of laboratory tests; (4) consistency of data collection methods for all subjects and (5) appropriateness of the numerator and denominator of the parameters. Risk of bias for each domain was assessed as either 'high' or 'low'. Studies were graded as low risk, moderate risk and high risk of bias if on aggregate, there was no high risk of bias domains, only one high risk of bias domain and two or more high risk of bias domains, respectively [12].

Results

Search results, general characteristics and quality of studies

As shown in Fig. 1, we identified a total of 269 citations in the initial electronic search, and an additional 15

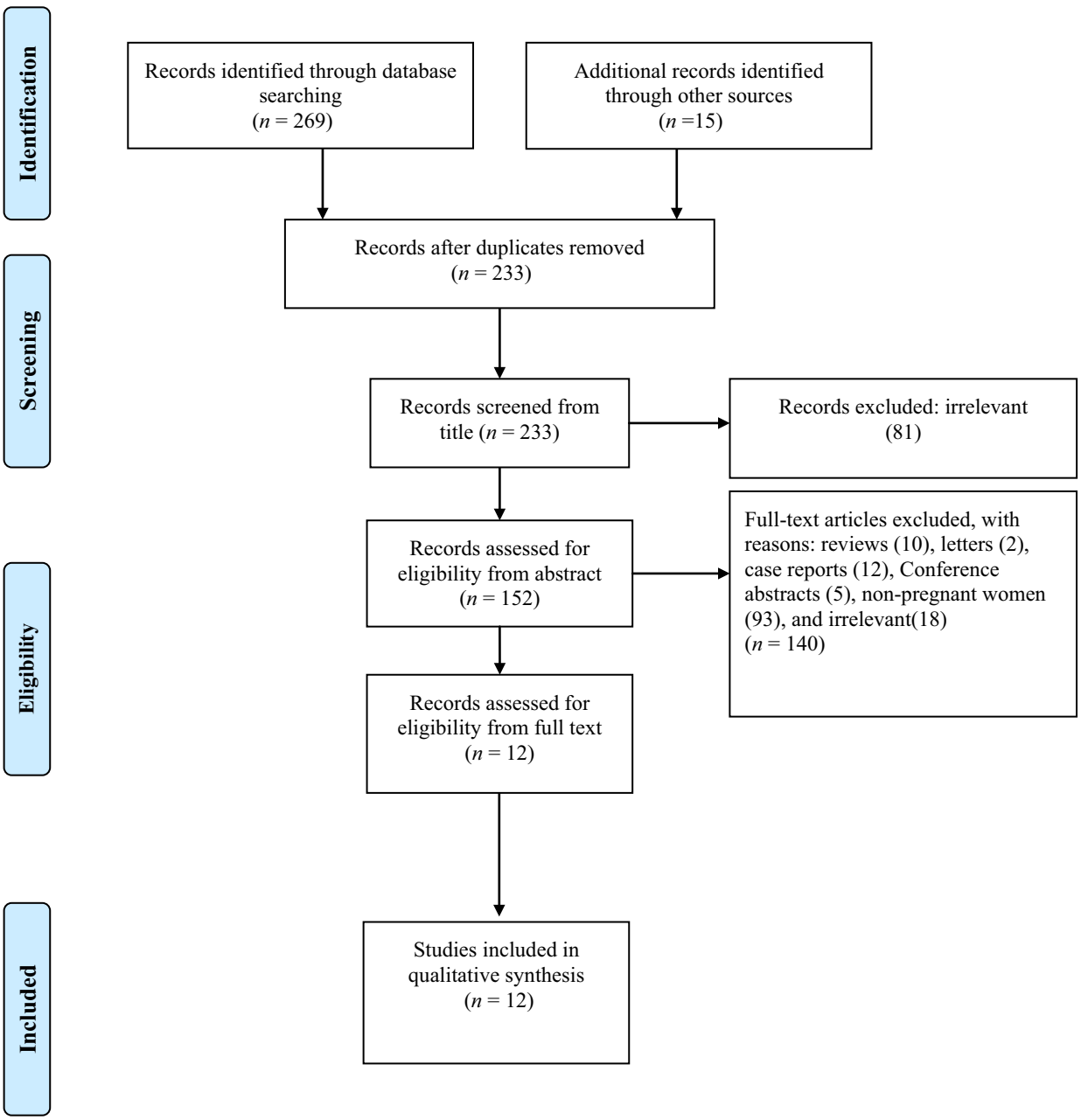

Fig. 1 Summary of data extraction history.

citations were identified through hand searching. After duplicates were removed, 233 citations were screened by title, and 81 were excluded because titles were unrelated to our focus. The remaining 152 citations were assessed by abstract, including predefined eligibility criteria, and 140 were excluded (93 non-pregnant women, 18 irrelevant, 12 case reports, 10 reviews, 5 conference abstracts and 2 letters). A total of 12 articles were assessed in the full-text review. In the end, 12 relevant studies meeting all the inclusion criteria were selected for data extraction and qualitative synthesis. Table 1 summarizes the general characteristics of the 12 included studies. Three were conducted in Uganda [13–15], two in Tunisia [16, 17] and two in Sudan [18, 19], and the five others were conducted in Nigeria [20], Tanzania [21], Benin [22], Zimbabwe [23] and Cameroon [24]. These studies were conducted between 1983 and 2015. The 12 studies reported results for 93 871 participants. Among the 12 original studies, 10 studies (83%) had a high risk of bias, and 2 (17%) had a moderate risk of bias (Table 2). Due to multiple

Table 1 General characteristics of eligible studies

Authors (year)	Country	Design	Sample size	Alloimmunized patients	Proportion (95% CI)	Screening method[a]
Afra MH (2012)	Sudan	Cross-sectional	80	8	10·0 (4·4, 18·8)	Column method
Belinga S *et al.* (2009)	Cameroon	Cross-sectional	225	15	6·7 (3·8, 10·8)	Tube technique
Bigot A *et al.* (1988)	Benin	Prospective	800	38	4·8 (3·4, 6·5)	Tube technique
Cakana *et al.* (2000)	Zimbabwe	Retrospective	3000	50	1·7 (1·2, 2·2)	Not described
Eipl K *et al.* (2012)	Uganda	Retrospective	1001	21	2·1 (1·3, 3·9)	Tube technique
Gargouri J *et al.* (2002)	Tunisia	Prospective	2093	71	3·7 (2·9, 4·6)	Tube technique
Jeremiah ZA *et al.* (2010)	Nigeria	Cross-sectional	500	17	3·4 (1·9, 5·4)	Tube technique
Kiango JS *et al.* (1983)	Tanzania	Cross-sectional	77 949	855	1·1 (1·0, 1·2)	Tube technique
Mbalibulha Y *et al.* (2015)[b]	Uganda	Cross-sectional	726	88	12·1 (9·8, 14·7)	Tube technique
Natukunda B *et al.* (2010)	Uganda	Cross-sectional	2001	45	2·2 (1·6, 3·0)	Tube technique
Rehab EA (2013)	Sudan	Cross-sectional	100	10	10·0 (4·9, 17·6)	Tube technique
Rekik T *et al.* (2012)	Tunisia	Cross-sectional	5396	198	5·2 (4·6, 5·8)	Tube technique

[a]Principle of the procedure involves testing unknown serum/plasma against a set of a standard group O reagent red cells.
[b]Anti-D alloimmunization only.

methodological gaps and substantial heterogeneity across included studies, a qualitative synthesis was performed. We narratively synthesized key findings, highlighting critical deficiencies in the current literature and the methodologies used.

Proportion of RBC alloantibodies

Proportion of RBC alloimmunization ranged from 1·1 (95% CI: 1·0, 1·2) to 12·1 (95% CI: 9·8, 14·7) per 100 pregnant women. The median proportion of RBC alloimmunization reported in papers included in this review was 4·3 (interquartile range (IQR) 2·2–8·4) per 100 pregnant women.

RBC alloantibody specificities in pregnant women

The majority of alloantibodies belonged to the Rh, Lewis, MNS and Kell blood group systems. Among clinically relevant antibodies, anti-D ranked as the most common followed by anti-K and anti-E (Table 3).

Studies reporting the association between alloimmunization and blood transfusion, parity and abortion

Of the 12 studies, 7 reported association between RBC alloimmunization and some risk factors, including parity, abortion and blood transfusion, with conflicting results. Of studies that assessed association, two had not found any significant association between obstetric history, gestational age and previous immunizing events with the rate of alloimmunization [13, 24], and one has not found significant association between history of blood transfusion and alloimmunization, but the association was significant with obstetric history [19]. On the other hand, 4 studies found a significant association between obstetric history (parity, history of stillbirth, abortion, miscarriage and post-partum haemorrhage) and anti-D [15–18].

Discussion

Summary of main findings

This systematic review assessed the literature on the rate of RBC alloimmunization in pregnant women in Africa and has revealed that there are relatively limited data addressing the topic. They reported a wide range of rates of RBC alloimmunization. With regard to antibody specificities, anti-D was the most common clinically relevant antibodies detected, followed by anti-K and anti-E. Anti-D injections for Rh prophylaxis have been available for many decades, but usage is still not very widespread in the resource-limited settings, likely because of lack of awareness, the cost of the injection and the logistics of the availability of such treatment in the remote areas [25]. Thus, comprehensive programmes are needed to screen and improve access to prenatal Rh-D immunoglobulin (RhIG) prophylaxis. In addition to screen alloantibodies in the Rh system, it might also be relevant to search for Kell alloantibodies. In the fetus, Kell antibodies have been involved in the suppression of Kell-positive erythroid precursor cells, which may lead to fetal anaemia, hydrops and perinatal death [26]. Furthermore, a recent study has suggested that implementation of routine screening for Kell antibodies in pregnancy was associated with a higher perinatal survival rate after a timely intrauterine treatment [27]. Finally, efforts to prevent alloimmunization should include the use of prophylactic matching for Rh/Kell RBC transfusions in females of

Table 2 Assessment of risk bias for prevalence studies

	External validity			Internal validity					
Author (year)	**Relevance of target population (Was the study's target population a close representation of the national population in relation to relevant variables?)**	**Appropriateness of sampling method (Was some form of random selection used to select the sample OR was a census undertaken?)**	**Likelihood of non-response bias (Was the likelihood of non-response bias minimal?)**	**Directness of data collection from subjects (Were data collected directly from the subjects as opposed to a proxy?)**	**Acceptability of case definition (Was an acceptable case definition used in the study?)**	**Reliability & validity of lab tests (Was the study instrument that measured the parameter of interest shown to have validity and reliability?)**	**Consistency of data collection methods for all subjects (Was the same mode of data collection used for all subjects?)**	**Appropriateness of numerator & denominator of parameters (Were the numerator(s) and denominator(s) for the parameter of interest appropriate?)**	**Overall risk of bias**
Afra MH (2012)	High	Low	Low	Low	Low	Low	Low	Low	Moderate
Belinga S *et al.* (2009)	High	High	Low	Low	Low	Low	Low	Low	High
Bigot A *et al.* (1988)	High	High	Low	Low	Low	Low	Low	Low	High
Cakana *et al.* (2000)	High	High	High	Low	Low	Low	Low	Low	High
Eipl K *et al.* (2012)	High	High	Low	Low	Low	Low	Low	Low	High
Gargouri J *et al.* (2002)	High	High	Low	Low	Low	Low	Low	Low	High
Jeremiah ZA *et al.* (2010)	High	Low	Low	Low	Low	Low	Low	Low	Moderate
Kiango JS *et al.* (1983)	High	High	Low	Low	Low	Low	Low	Low	High
Mbalibulha Y *et al.* (2015)	High	High	Low	Low	Low	Low	Low	Low	High
Natukunda B *et al.* (2010)	High	High	Low	Low	Low	Low	Low	Low	High
Rehab EA (2013)	High	High	Low	Low	Low	Low	Low	Low	High
Rekik T *et al.* (2012)	High	High	Low	Low	Low	Low	Low	Low	High

Table 3 Red blood cell alloantibody specificities in pregnant women and antigen frequency in black population

Blood group system	RBC allo antibodies	Number of antibodies	Antigen frequency (%)*
RH	D	284	92
	C	11	27
	c	1	96
	E	16	22
	e	1	98
	C^w	1	0·01
	Subtotal	314	
MNS	M	28	74
	N	35	75
	S	28	31
	Subtotal	91	
Kidd	JK^a	5	92
	JK^b	1	49
	Subtotal	6	
Kell	K	22	2
	Kp^a	1	<1
	JS^b	4	99
	Subtotal	27	
Duffy	Fy^a	2	10
	Fy^b	1	23
	Subtotal	3	
Lewis	Le^a	214	23
	Le^b	56	55
	Subtotal	270	
Lutheran	Lu^a	2	5
	Subtotal	2	
	Total	209	

*Source: Adapted from Reid ME, Lomas-Francis C, Olsson ML. The Blood Group Antigen FactsBook. Third Edition, 2012, Academic Press. We would caution that allele frequencies in the 'black' population in Marion Reid's book are, in fact, US individuals who have self-identified that ethnicity for the most part and genetically may represent a more genetically diverse background than individuals in various subregions of Africa.
[a]represents allele "a"
[b]represents allele "b"
[w]represents allele "w"

childbearing age, whenever possible. Regarding association between alloimmunization and risk factors, it has been shown that RBC transfusion, parity, major surgery and haematological diseases were the most important independent risk factor for non-RhD immunization in pregnancy [28]. However, studies included in this review have not brought about any consistent evidence of a link between rate of alloimmunization and immunizing events. This is likely due to the following reasons: first, sample sizes varied. Some studies with smaller sample sizes were not powered to detect any association. Second, it is also possible that poor recall played a role in that not all the women in these studies could recall immunizing events such as transfusion in early childhood or miscarriage, which may partly explain the absence of previous transfusion, miscarriage or stillbirth as risk factors for maternal alloimmunization in some studies. Finally, the possibility of underreporting bias could not be ruled out especially for sensitive exposure such as abortion.

Strengths and limitations of this review

Our study has several strengths. To our knowledge, this is the first systematic review to provide a summary of RBC alloimmunization in pregnant women in Africa. We conducted a comprehensive literature search over a diversity of databases. We did not restrict our review by language. Two researchers independently screened all articles, extracted data from research studies included in the systematic review and applied an adapted tool to assess within-study bias. Another major strength of this systematic review was that it included studies from all African regions, including Northern Africa (Tunisia), Eastern Africa (Uganda, Sudan and Tanzania), Western Africa (Nigeria and Benin), Southern Africa (Zimbabwe) and Central Africa (Cameroon). The primary objective of this review was to identify and synthesize the best available evidence of rates of RBC alloimmunization in pregnant women in Africa. However, there are some caveats in the individual studies, as well as with the systematic review, which should be considered when interpreting these findings. First, given the substantial heterogeneity across included studies primarily due to multiple methodological gaps and geographical diversity, we were not able to perform meta-analysis to obtain a summary measure. Second, the quality of evidence summarized in this review was very low, and the vast majority of studies were cross-sectional with variation in sample size and timing of when alloantibodies were screened, which may underestimate the true frequency of alloantibodies, owing to time needed before antibodies can be detected, and, once formed, the chance of titters falling to undetectable levels [29, 30]. Third, the lack of consistency in reporting data on important covariates such as history of transfusions, abortions and parity in most studies might have led to inconclusive evidence regarding the association between alloimmunization and immunizing events. Fourth, most studies used convenience sampling and did not provide information on the representativeness of their samples or study power. Fifth, given that the majority of studies were conducted in urban areas, there may be important differences in exposure to immunizing events or prophylaxis practice with pregnant women in rural areas, where health care provision is even less opti-

mal. Finally, as in any systematic review and despite extensive literature search, we cannot rule out the impact of publication bias. In fact, we may have missed some studies, especially if they were published in languages other than French or English or published in non-indexed journals. However, given the paucity of medical literature about RBC alloimmunization in Africa, this is unlikely to represent a significant impact.

Recommendations for Future Research

There is a clear need for additional well-designed research with greater methodological rigour while conducting these epidemiological studies. In fact, it has been recently suggested that health research systems in Africa should be strengthened to produce and disseminate high-quality research evidence, which can be used for policy and public health action [31]. Future research should have a larger sample size and include a more complete report of information regarding potential immunizing events or risk factors such as history of transfusion, parity or obstetric history. Analysis of these factors could help identify key risk factors involved mostly in non-RhD immunization. This may be particularly relevant to investigate, especially in resource-limited settings because it might increase the efficiency and decrease the burden of the RBC antibody screening program by the so-called subgroup screening, that is restricting this screening to only women at risk of having relevant RBC antibodies [28]. In the long run, it would be more insightful to create national population-based research databases from routine maternal screening records to provide the valuable research resource for investigators to study alloimmunization in pregnant women [32].

Implications for practice

Understanding the extent and the impact of RBC alloimmunization in Africa is central to informing evidence-based prevention interventions. Our review highlights that RBC alloantibodies are relatively common (4·3%), at least in 50% of studies conducted among pregnant women in Africa. Furthermore, anti-D ranked as the most common antibody followed by anti-K and anti-E. Thus, given the high immunogenicity of these antigens, it is critical to re-evaluate and strengthen or implement programs for the prevention of maternal Rh-D and non-RhD alloimmunization.

Conclusions

In conclusion, the review of available literature quantifies and qualifies the clinical challenge of RBC alloimmunization among pregnant women in Africa. Current published data highlight the lack of high-quality evidence on RBC alloimmunization in pregnant women in Africa. Irrespective of the limitations of the available data, there is a clear need for primary (RhD-matched blood products to females of childbearing age) and secondary (screening) preventing measures. We believe that findings from this review are valuable to provide an overview of RBC alloimmunization in pregnant women in Africa. Improvement of quality of research should be a priority to gather the evidence needed to guide policy and practice that should guide decisions in favour of RBC alloantibody screening in pregnant women as a standard of care throughout Africa.

Conflict of interest

The authors declare no conflict of interest.

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