



# Extended RBC Phenotype Matching Reduces the Incidence of Alloimmunization in Patients with Warm Autoimmune Haemolytic Anaemia (wAIHA)

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## ABSTRACT

**Background:** Warm Autoimmune Haemolytic Anaemia (wAIHA) involves autoantibodies destroying red blood cells, often necessitating transfusions. Alloimmunization, the formation of antibodies against non-self-Red Blood Cells (RBC) antigens, complicates future transfusions. This review evaluates whether extended RBC phenotype matching reduces alloimmunization compared to standard ABO and Rh matching.

**Methods:** Databases (PubMed, Scopus, Cochrane Library and Google Scholar) were searched for studies (2014-2024) on wAIHA patients comparing basic, partial and full extended RBC phenotype matching. Eligible data were analysed using a random-effects model to assess alloimmunization risk reduction. Manual searches were performed using relevant references.

**Results:** Ten studies, both retrospective and prospective, were included. Basic matching (ABO and Rh) had the highest alloimmunization rate at 32.8% (95% CI: 13.3%-52.2%;  $I^2=95.79\%$ ,  $p<0.001$ ). Partial matching (Rh and Kell) reduced rates to 22.5% (95% CI: 10.4%-34.6%;  $I^2=49.57\%$ ,  $p=0.046$ ), while full matching lowered it to 11.6% (95% CI: 4.5%-18.7%;  $I^2=73.65\%$ ,  $p=0.001$ ). Despite heterogeneity, results consistently showed extended matching reduced alloimmunization.

**Conclusion:** Extended RBC phenotype matching significantly lowers alloimmunization risk in wAIHA patients, particularly in chronically transfused cases. However, the variability across studies highlights the need for standardised transfusion practices and further research to confirm these results through larger, randomised controlled trials.

**Keywords:** Alloimmunization; RBC phenotype matching; Transfusion; Anaemia; Antibody formation

## INTRODUCTION

### Warm Autoimmune Haemolytic Anaemia (wAIHA)

Autoimmune Haemolytic Anaemia (AIHA) is an acquired disorder characterised by decompensated haemolysis, primarily triggered by the destruction of individual's autologous RBC by autoantibodies. These antibodies may trigger the activation of complement, macrophages, T-lymphocytes and cytokines contributing to the process [1]. AIHA is classified into several subtypes, with the most prevalent being warm AIHA (wAIHA), followed by cold AIHA incomplete cAIHA), mixed AIHA (exhibiting characteristics of both warm and cold forms) and the rare Paroxysmal Cold Haemoglobinuria (PCH) [2]. wAIHA is typically caused by IgG-class autoantibodies, particularly of the IgG1 and IgG3 subclasses, which weakly activate complement and result in extravascular haemolysis. A positive Direct Antiglobulin Test

(DAT) can confirm the presence of immunoglobulins, typically of the IgG class and/or complement components, often C3d, bound to erythrocytes [1,2]. This haemolysis is mediated by Antibody-Dependent Cellular Cytotoxicity (ADCC), primarily occurring in the spleen and lymphoid tissues [3]. These autoantibodies can be clinically significant, leading to AIHA, which is a relatively rare diagnosis (about 2 cases per about 100,000/year), or they can be clinically insignificant and not detrimental to the AIHA patient [4].

### RBC alloimmunization in wAIHA

RBC alloimmunization is a significant complication of transfusion therapy, particularly in patients with AIHA, in which autoantibodies target RBCs at body temperature. Alloimmunization occurs when the immune system recognises donor RBC antigens as foreign, resulting in the production of alloantibodies that complicate future transfusions

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[5]. wAIHA patients frequently require transfusions due to haemolysis and managing these patients becomes more challenging when alloantibodies are present. The incidence of alloimmunization in such patients can result in delays in finding compatible blood, increased haemolytic transfusion reactions and a higher risk of morbidity and mortality [6].

### The role of autoantibodies in transfusion management of wAIHA patients

In patients with wAIHA, the management of RBC transfusion presents unique challenges. Due to the presence of autoantibodies, cross matching can be problematic, often leading to delays in finding compatible blood. In warm AIHA, autoantibodies against Rh and Kell antigens are more prevalent due to the high immunogenicity of the core polypeptide. In emergency situations, particularly when Haemoglobin (Hb) levels fall below 6 g/dL, it may be necessary to administer type-specific blood without cross matching to stabilise the patient [7]. Notably, alloantibodies are more likely to exacerbate haemolysis than autoantibodies [5]. The situation becomes complicated when transfusions are required because these autoantibodies can mask the detection of alloantibodies, making it difficult to find compatible blood for transfusion. Studies have demonstrated that approximately 30% of patients with wAIHA develop alloantibodies following transfusions, further complicating their treatment [8]. This highlights the necessity for strategies that can minimise the risk of alloimmunization, especially in patients who receive multiple transfusions over their lifetime [9].

### Challenges in transfusion for chronically transfused patients

For wAIHA patients, frequent transfusions are often required to manage haemolysis. However, the development of alloantibodies complicates the transfusion process and increases the risk of haemolytic transfusion reactions. Conventional transfusion protocols mainly involve matching ABO and Rh antigens; however, this approach does not account for other minor erythrocyte antigens, such as Kell, Duffy, Kidd and MNS, which can still induce an alloimmune response [9,10]. Masking of alloantibodies by autoantibodies in wAIHA further exacerbates the difficulty of providing safe transfusions [5,9,10]. RBC selection in wAIHA patients is not yet standardised, with some institutions opting for more closely antigen-matched units to mitigate the risk of future alloimmunisation and haemolytic transfusion reactions, reducing the need for repeated adsorption procedures in subsequent serological testing [11].

### Extended RBC phenotyping

Extended RBC phenotype matching involves screening for and matching a broader range of minor antigens, such as Kell, Duffy, Kidd and MNS, to reduce the risk of alloimmunization in chronically transfused patients [11]. Evidence from studies involving chronically transfused patients, such as sickle cell disease and thalassaemia, suggests that extended RBC matching significantly decreases the incidence of alloimmunization, reducing haemolytic complications and improving transfusion outcomes [10,12]. The rationale behind extended matching is to minimise exposure to foreign antigens, thereby lowering the immune response and decreasing the likelihood of alloantibody formation [13]. Although extended RBC phenotyping has shown promise in reducing alloimmunization rates in other chronically transfused populations, the application in patients with wAIHA has been less explored. Taking these factors into consideration, this study

will evaluate the feasibility of comparing standard RBC matching protocols with extended RBC phenotype matching in patients with wAIHA to determine its effectiveness in reducing alloimmunization rates.

### Aim of study

The primary research question for this systematic review and meta-analysis, formulated using the Population, Intervention, Comparison and Outcome (PICO) framework, is: Does extended RBC phenotype matching (including partial and full phenotype matching) in patients with wAIHA (population) reduce alloimmunization rates (outcome) compared to standard RBC matching limited to ABO and Rh antigens (comparator) [14]? The secondary aim of this review is to explore the significant benefits of extended phenotype matching in improving transfusion safety and guiding the development of more efficient transfusion protocols for patients with wAIHA.

### Study hypothesis

The extended RBC phenotype matching, including partial (Rh and Kell) and full (including Kell, Duffy, Kidd, MNS, etc.) phenotype matching beyond the standard ABO and Rh antigens, will reduce alloimmunization rates in patients with wAIHA.

## MATERIALS AND METHODS

### Study design

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a comprehensive and structured approach to identifying and collating peer-reviewed studies [15]. Additionally, the quality of the selected papers was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist to ensure methodological rigor and reliability of the included studies [16].

### Search strategy

To identify appropriate studies for this review, comprehensive searches were conducted in PubMed, Scopus, Cochrane Library and Google Scholar, covering the period from January, 2014 to August, 2024. Search terms included "RBC phenotype" and "alloimmunization," with alternate combinations, including the American English spelling "alloimmunization," also employed. Additionally, manual searches were performed to capture studies that might have been missed during the database searches, with further papers identified using PubMed and Google Scholar. The number of articles retrieved and those included in the final analysis are documented in the PRISMA flowchart.

### Selection criteria

Papers identified through the specified search terms were initially screened based on their titles and abstracts. Eligible studies included those involving patients with wAIHA that examined the impact of extended RBC phenotype matching on the reduction of alloimmunization. Articles were excluded if they met any of the following criteria: Non-English language, full text not available, results not related to RBC phenotype, alloimmunization and wAIHA, single case studies, reviews or meta-analyses. All articles meeting the inclusion criteria were subsequently evaluated using the STROBE checklist to ensure methodological quality [16].

## Data extraction

Data from the studies included in this analysis, which organises the primary author's name, year of publication, country of origin, study period, sample size and other relevant information pertinent to the review. Raw data used for statistical analysis, categorised by study, alloimmunization rates, number of transfusion units received and the formation of alloantibodies in wAIHA patients.

## Statistical analysis

Open Meta-Analyst software was used to combine data from the included studies for the meta-analysis. The extracted data from tables underwent binomial random-effects proportion-based analysis using the Arcsine-transformed proportion metric with the Maximum Likelihood (ML) random-effects method applied (Tables 1 and 2), [17]. This approach generated forest plots to assess the relative risk reduction of alloimmunization following RBC phenotype matching using Open Meta-Analyst. The software calculated the overall p-value, 95% confidence intervals (95% CI) and the  $I^2$  statistic to assess heterogeneity, along with its corresponding p-value [18]. In this review, a p-value of  $<0.05$  was considered statistically significant.

## RESULTS

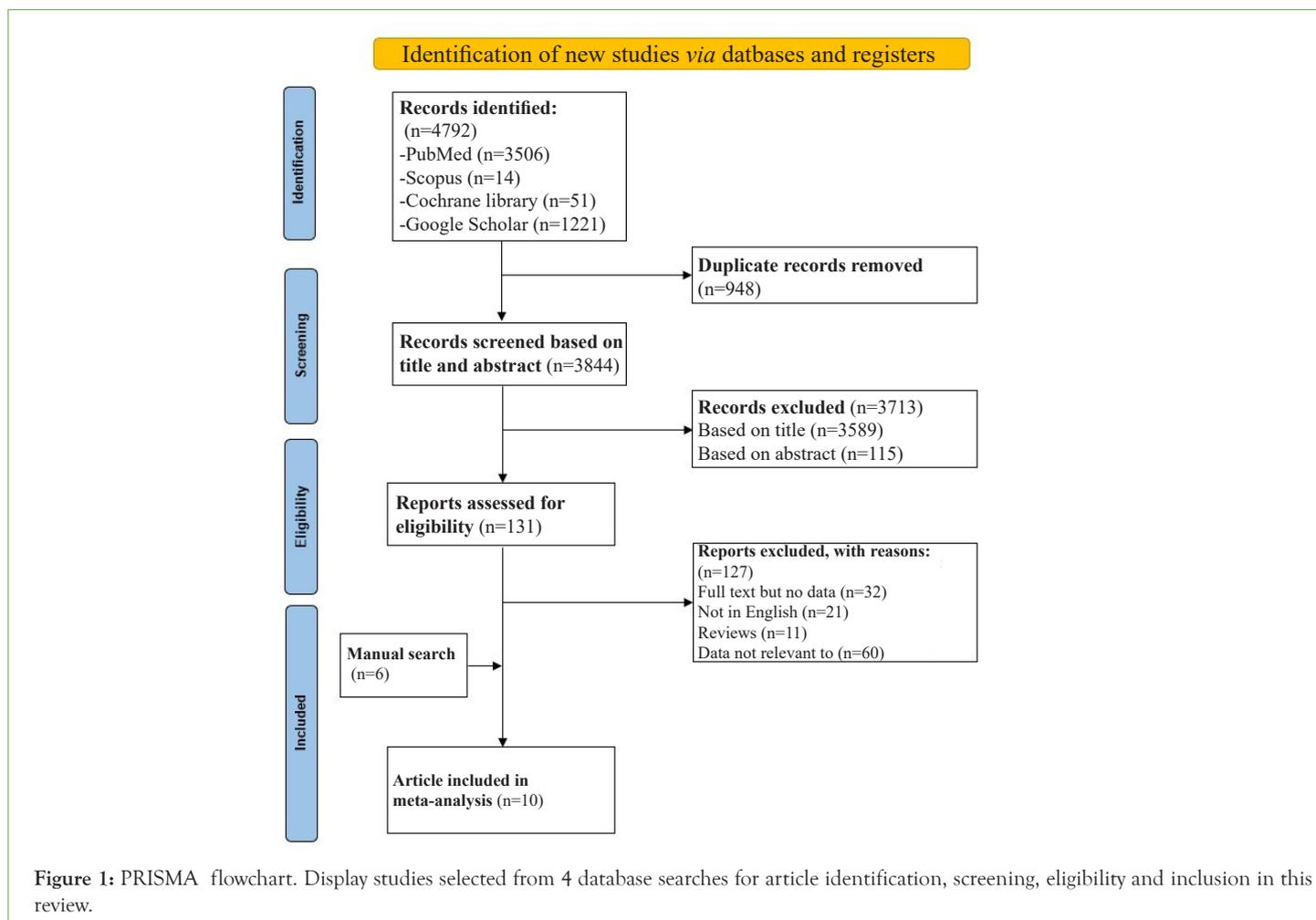
### Study selection

The search yielded 4792 significantly relevant articles from PubMed (n=3506), Scopus (n=14), Cochrane Library (n=51) and Google

Scholar (n=1221). After removing 948 duplicates, 3844 articles were screened by title and abstract. Most were excluded due to irrelevance (n=3713), with 3589 eliminated based on titles and 115 based on abstracts. This left 131 articles for full-text review. Of these, 127 were excluded for reasons including insufficient relevant data (n=60), non-English language (n=21), incomplete data in the full text (n=32) and review articles (n=11). A manual search in Google Scholar identified 6 additional studies outside the original date range. After full-text assessment, 10 cohort studies met the inclusion criteria, comparing whether extended erythrocyte phenotypic matching reduces RBC alloimmunization rates (Figure 1).

### Study characteristics

A total of 10 cohort studies were included in this meta-analysis after a thorough screening process. These studies focused on patients with wAIHA and assessed the effects of extended RBC phenotypic matching on reducing alloimmunization rates. As shown in Table 1, the studies comprised a mix of retrospective and prospective cohort designs and were conducted across various regions, including the United States, Brazil, South Korea, India and Germany [11,19-24]. The studies were categorised into three groups: Basic phenotype matching, partial extended phenotype matching and full extended phenotype matching. These approaches included standard ABO and Rh matching, along with additional antigens such as Kell, Duffy, Kidd and MNS. The major outcomes measured across the studies were alloimmunization rates and the development of alloantibodies [11,25-27].



**Table 1:** Characteristics of 10 studies included in the investigation of RBC alloimmunisation and phenotype matching in WAIHA patients.

Study	Year	Study design	Study period	Country	Sample size	Measurement of RBC alloimmunization
Park et al. [25]	2015	Retrospective	2006-2011	South Korea	161	Basic phenotype matching
Branch et al. [20]	1999	Retrospective	1982-1999	-	647	Basic phenotype matching
Barros et al. [19]	2008	Prospective	2008	Brazil	36	Basic phenotype matching
Cruz et al. [21]	2023	Retrospective	-	Brazil	24	*Partial extended phenotype matching
Das et al. [23]	2014	Prospective	2014	India	14	*Partial extended phenotype matching
Das et al. [22]	2009	Retrospective	2004-2006	India	71	*Partial extended phenotype matching
Shirey et al. [26]	2002	Retrospective	1999-2000	USA	20	*Partial extended phenotype matching
Leger et al. [24]	1999	Retrospective	1998	USA	694	**Full extended phenotype matching
Yurek et al. [27]	2015	Retrospective	2000	Germany	36	**Full extended phenotype matching
Delaney et al. [11]	2020	Retrospective	2007-2016	USA	1002	**Full extended phenotype matching

**Note:** (-): The data does not provide; \*Phenotype-matching (Rh and Kell); \*\*Phenotype-matching (Rh, Kell, Duffy, Kidd, MNS, etc.).

### Characteristics of included studies

The characteristics of the 10 included studies assessed in this review are summarised in (Table 2). Most studies were prospectively designed. These studies analysed alloimmunization rates based on different matching protocols, categorising them into Basic, Partial extended and Full extended phenotype matching [11,20-27]. The number of patients in these studies varies significantly, with some studies including as few as 14 patients and others as many as 647. Transfusion units received and specific alloantibodies formed, such as Anti-D, Anti-C and Anti-K, were recorded across the studies in Table 2. All studies were conducted to eliminate interference from antibodies before detecting alloantibodies. There is only one other study for Full extended phenotype matching that uses Basic phenotype matching as a control group to compare differences [11].

### Quality assessment of included studies

The methodological quality of each study in this review was evaluated using the STROBE checklist, Table 3 presents the included studies along with the specific STROBE criteria applied for quality assessment (Table 3). The majority of the studies demonstrated high

methodological standards, successfully meeting most of the relevant STROBE requirements. Nevertheless, it should be noted that one article failed to summarise major results and discuss limitations [22].

### Meta-analysis of prevalence of alloimmunization

A forest plot was created representing the prevalence of RBC alloimmunization (Figure 2). Examining the prevalence of alloimmunization across three different phenotypic matching strategies: In Figure 2, a) Basic phenotype matching, b) Partial extended phenotype matching and c) Full extended phenotype matching. First of all, Basic phenotype matching (ABO and Rh) shows an overall alloimmunization prevalence of 32.8% (95% CI: 13.3-52.2%) across 844 participants, with high heterogeneity ( $I^2=95.79\%$ ,  $p<0.001$ ), suggesting significant variability among the studies. Additionally, Partial extended phenotype matching (ABO, Rh and Kell) reveals a lower prevalence of 22.5% (95% CI: 10.4-34.6%) in a smaller sample of 81 participants, with moderate heterogeneity ( $I^2=49.57\%$ ,  $p=0.046$ ). Furthermore, Full extended phenotype matching (ABO, Rh, Kell, Duffy, Kidd, MNS, etc.) results in a further reduced alloimmunization prevalence of 11.6% (95% C.I: 4.5-18.7%) in 738 participants, but with high heterogeneity ( $I^2=73.65\%$ ,  $p=0.001$ ).

**Table 2:** Summary of alloimmunisation rates, units receiving transfusions, and alloantibody formation among WAIHA patients in eligible studies.

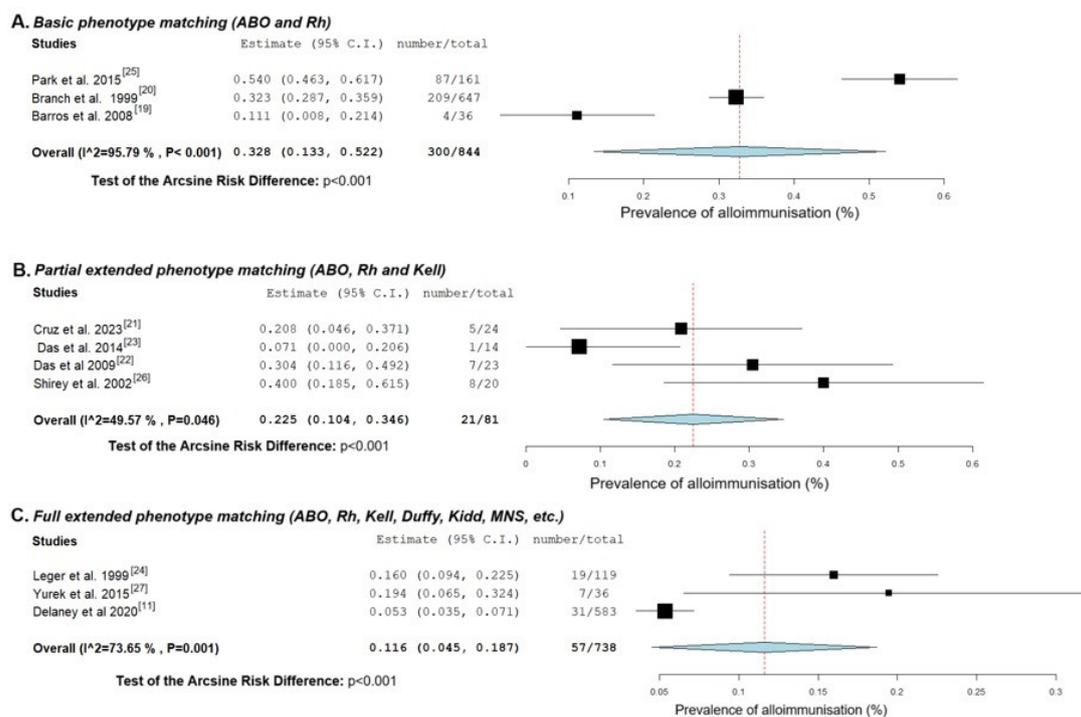
Study	Year	Total participants	Number of patient presented alloantibody	Prevalence of alloimmunisation rate (%)	Exclude the interference of autoantibodies	Transfusion received (unit)	Alloantibody formed
Park et al. [25]	2015	161	57	54	Yes	-	Anti-C, E, c, e, M
Branch et al. [20]	1999	647	209	32.3	Yes	-	Anti-D, C, E, c, e, Jk <sup>a</sup> , Jk <sup>b</sup> , Fy <sup>a</sup> , s
Barros et al. [19]	2008	36	4	11.1	Yes	-	Anti-C, E, K
Cruz et al. [21]	2023	24	5	20.8	Yes	29	Anti-D, C, E, C <sup>w</sup> , K, Kp <sup>a</sup> , S, s, M, Fy <sup>a</sup> , Fy <sup>b</sup> , Jk <sup>a</sup> , Jk <sup>b</sup> , Di <sup>a</sup>
Das et al. [23]	2014	14	1	7.1	Yes	167	Anti-C
Das et al. [22]	2009	23	7	30.4	Yes	-	Anti-D, C, E
Shirey et al. [26]	2002	20	8	40	Yes	144	Anti-C, E, K, Fy <sup>a</sup> , S
Leger et al. [24]	1999	119	19	16	Yes	-	Anti-D, E, K, Jk <sup>b</sup>
Yurek et al. [27]	2015	36	7	19.4	Yes	-	Anti-c, E, Jka
Delaney et al. [11]	2020	583	31	5.3	Yes	192	Anti-D, C, E, C <sup>w</sup> , K, Kp <sup>a</sup> , S, s, M, Fy <sup>a</sup> , Fy <sup>b</sup> , Jk <sup>a</sup> , Jk <sup>b</sup> , Lu <sup>a</sup> , Di <sup>a</sup> , Wt <sup>a</sup>

Note: \*The data just provide medium (range) of Unit of transfused RBCs.

**Table 3:** Quality assessment of studies included in the meta-analysis using the STROBE checklist.

Study	Year	Title and abstract		Introduction		Methods		Results	Discussion
		Clear title and abstract, indicating study design	Explains scientific background and rationale	Detailed study methods provided	Shows the eligibility criteria for selected participants	Statistical methods described	Describes any efforts to address potential bias	Gives characteristics of study participants	Summarise key results and discusses limitations
Park et al. [25]	2015	Y	Y	Y	Y	Y	Y	Y	Y
Branch et al. [20]	1999	Y	Y	Y	Y	Y	Y	Y	Y
Barros et al. [19]	2008	Y	Y	Y	Y	Y	Y	Y	Y
Cruz et al. [21]	2023	Y	Y	Y <sup>a</sup>	Y	Y	Y	Y	Y
Das et al. [23]	2014	Y	Y	Y	Y	Y	Y	Y	Y
Das et al. [22]	2009	Y	Y	Y	Y	Y	Y	Y	N <sup>b</sup>
Shirey et al. [26]	2002	Y	Y	Y	Y	Y	Y	Y	Y
Leger et al. [24]	1999	Y	Y	Y	Y	Y	Y	Y	Y
Yurek et al. [27]	2015	Y	Y	Y <sup>a</sup>	Y	Y	Y	Y	Y
Delaney et al. [11]	2020	Y	Y	Y <sup>a</sup>	Y	Y	Y	Y	Y

Note: Y: Criteria fulfilled; N: Criteria not fulfilled; Y<sup>a</sup>: Study design discussed; N<sup>b</sup>: No limitation discussed.



**Figure 2:** Forest plot. **Note:** Alloimmunization prevalence results between A) Basic phenotype matching; B) Partial extended phenotype matching; C) Fully extended phenotype matching in patients with wAIHA. Data on alloimmunization prevalence rate were expressed as relative risk with 95% confidence intervals (95% CI). Statistical significances of studies were expressed as p-value. Heterogeneity across studies was expressed as I<sup>2</sup> value with respective p-value.

Overall, as the extent of phenotype matching increases, the prevalence of alloimmunization decreases, indicating a protective effect of broader antigen matching in reducing alloimmune responses in transfusion settings. However, heterogeneity remains high in many comparisons, reflecting variations across the included studies.

## DISCUSSION

This meta-analysis aimed to evaluate the impact of extended RBC phenotype matching on the incidence of alloimmunization in patients with wAIHA. Our findings indicate that extended phenotype matching significantly reduces the occurrence of alloantibodies in transfused patients compared to those who received basic or partial matching.

### Alloimmunization in basic phenotype matching

In the basic phenotype matching group (ABO and Rh only), the overall prevalence of alloimmunization was 32.8%, which was the highest among the groups. The significant heterogeneity observed in this group suggests that various factors may influence the risk of alloimmunization in patients receiving transfusions based only on ABO and Rh matching. Factors such as the genetic variability in antigen expression and the transfusion history of the patients may have contributed to this variability. Previous study indicates that in patients with autoantibodies, standard pretransfusion testing may be insufficient due to autoantibodies masking underlying alloantibodies [25]. Extended matching may be especially beneficial in reducing haemolytic risk; as standard ABO/Rh grouping alone can lead to complications in wAIHA patients with high alloimmunization. Nevertheless, the high prevalence of alloimmunization in this group underscores the limitations of basic matching and highlights the need for more comprehensive antigen matching strategies.

### Reduction of alloimmunization with partial extended matching

When matching was extended to include Kell antigens (in addition to ABO and Rh), the prevalence of alloimmunization decreased to 22.5%. This reduction in prevalence is consistent with the hypothesis that extending phenotype matching to include additional clinically significant antigens reduces the risk of alloimmunization. The heterogeneity in this group was moderate, suggesting that while the inclusion of the Kell antigen provided some uniform benefit across the studies, other factors still influenced the outcome. The Kell antigen is highly immunogenic and its inclusion in matching strategies appears to offer partial protection against alloimmunization. This finding aligns with previous reports that emphasise the role of Kell antibodies in alloimmunization events due to their high immunogenicity [23].

### Full extended phenotype matching yields lowest alloimmunization

The most significant reduction in alloimmunization was observed in the group receiving full extended phenotype matching, which included matching for additional antigens such as Duffy, Kidd and MNS, along with ABO, Rh and Kell. The prevalence of alloimmunization in this group was 11.6%, representing the lowest risk among all the groups analysed. Despite the high heterogeneity observed in this group, which likely reflects differences in study design and patient populations, the protective effect of comprehensive antigen matching is clear. The significant reduction in alloimmunization highlights the importance of implementing full extended matching protocols in transfusion settings where patients are at high risk for alloimmunization, such as those with wAIHA. Studies by Delaney et al., and Leger et al., also showed that full extended phenotype matching could reduce alloimmunization

rates, highlighting the significant for improved patient outcomes and fewer transfusion-related complications [11,24]. Our results align with previous research on the benefits of extended phenotype matching, particularly in patient populations with conditions like sickle cell disease and thalassemia, where alloimmunization poses a major challenge. Kulkarni et al., has indicated a decrease in alloimmunization rates from 33% to 2.8% by providing phenotype-matched blood for Rh and Kell antigens in thalassaemia [28]. This analysis reinforces these findings, but specifically within the context of wAIHA, a less extensively studied population in this regard.

### Clinical implications

These findings have important clinical implications. The data support a more proactive approach to transfusion matching, particularly for patients with chronic transfusion needs or those at high risk for alloimmunization, such as those with wAIHA. Basic phenotype matching (ABO and Rh) is insufficient for preventing alloimmunization in this population, as evidenced by the high prevalence observed in the studies. Partial extended matching that includes the Kell antigen provides some benefit, but the greatest protection is achieved with full extended phenotype matching. This approach minimises the risk of alloimmunization, significantly improving patient outcomes by reducing the likelihood of delayed haemolytic transfusion reactions and the development of complex antibody profiles that complicate future transfusions. Delaney et al., highlighted that while Prophylactic Antigen-Matched (PAM) transfusion practices can be beneficial, the level of protection against new alloimmunization may vary based on the extent of antigen matching. Their study found no significant difference between patients receiving PAM transfusions and those who did not, suggesting that partial antigen matching may not be sufficient to prevent alloimmunization [11]. However, other studies have shown that more extensive matching, including Rh, Kell, Kidd, Duffy and MNS antigens, can lead to improved outcomes by reducing the formation of alloantibodies, as supported by findings in our meta-analysis [11,24,27,29].

### CONCLUSION

In conclusion, this meta-analysis provides evidence that extended RBC phenotype matching reduces the incidence of alloimmunization in patients with wAIHA. By minimising the immune response to transfused RBCs, extended matching offers a promising strategy for improving patient outcomes. However, the limitations of the current literature highlight the need for further research to confirm these findings and refine transfusion practices. Future studies should aim to overcome the current challenges of sample size limitations, lack of control groups and inconsistent bias reporting to enhance the credibility and significance of results. Ultimately, adopting extended phenotype matching could be a major step toward reducing alloimmunization and improving transfusion safety for wAIHA patients.

### LIMITATIONS AND FUTURE SCOPE

While this meta-analysis offers valuable insights, several limitations should be acknowledged. The high degree of heterogeneity in some of the analysed groups, particularly in the basic and fully extended phenotype matching categories, suggests that factors such as study design, patient population characteristics and transfusion history may have influenced the results. Moreover, the lack of control groups in some studies made it difficult to directly compare the outcomes of patients receiving basic *versus* extended matching. Bias reporting was also inconsistent, with some studies failing to detail patient selection

criteria or transfusion practices, which may have influenced the results. These limitations suggest a need for caution in generalising the findings to all wAIHA patients and call for more standardised approaches in future research.

Further research is needed to confirm these results and explore the broader implications of extended phenotype matching. Large-scale, Randomised Controlled Trials (RCTs) should be conducted to directly compare the effectiveness of basic and extended matching protocols. Additionally, more comprehensive reporting on significant biases, patient demographics and the long-term effects of extended matching would improve the reliability of future findings. Expanding the research to include diverse patient populations could also provide insights into the universal applicability of this approach.

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