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THE EFFECTIVENESS OF EXTENDED ANTIGEN MATCHING IN REDUCING ALLOIMMUNIZATION AMONG CHRONICALLY TRANSFUSED PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: Red blood cell (RBC) alloimmunization remains a major clinical challenge among chronically transfused patients, particularly those with sickle cell disease (SCD), β-thalassemia, and myelodysplastic syndromes (MDS). Despite standard ABO and RhD compatibility, antigenic disparities between donors and recipients lead to alloantibody formation and increase the risk of delayed hemolytic transfusion reactions (DHTRs). This systematic review aimed to evaluate the effectiveness of extended RBC antigen matching—including Rh, Kell, Duffy, Kidd, and MNS systems—in reducing alloimmunization and improving transfusion safety.

Methods: Following the **PRISMA 2020** guidelines, peer-reviewed studies published between 2013 and 2025 were systematically reviewed from databases including PubMed, Scopus, Web of Science, and Embase. Eligible studies focused on chronically transfused patients who received prophylactic or extended RBC antigen matching compared with standard matching. Data were synthesized narratively due to heterogeneity in population characteristics and transfusion protocols.

Results: Ten studies met the inclusion criteria. Across SCD, β-thalassemia, and MDS populations, extended antigen matching significantly reduced alloimmunization rates, with reported declines from 47% to 23.5% (Leal et al., 2023) and from 23% to 11% (Lin et al., 2017). Molecular genotyping further minimized Rh variant-related mismatches, while implementation of comprehensive Rh and Kell matching protocols led to marked reductions in both alloimmunization and transfusion-related complications (Belsito et al., 2019; Waldis et al., 2021). The approach was also found to be cost-effective in long-term management (Kacker et al., 2014).

Conclusion: Extended and molecular RBC antigen matching demonstrates a clear benefit in reducing alloimmunization and transfusion complications across chronically transfused populations. Integrating molecular typing, genotyped donor registries, and risk-based

matching policies into transfusion programs may represent the next standard of care for improving patient safety and transfusion outcomes globally.

Keywords: Extended antigen matching; Alloimmunization; Sickle cell disease; Thalassemia; Myelodysplastic syndrome; Molecular typing; Transfusion safety; Hemolytic transfusion reaction; Red blood cell immunology; Precision transfusion medicine.

INTRODUCTION

Red blood cell (RBC) transfusion remains an essential therapeutic intervention for patients with chronic anemias such as **sickle cell disease (SCD)**, **β-thalassemia**, and **myelodysplastic syndromes (MDS)**. However, repeated transfusions expose patients to alloantigens absent from their own RBCs, increasing the risk of **alloimmunization**—the development of antibodies against non-self erythrocyte antigens. This immunologic response can complicate subsequent transfusions, trigger **delayed hemolytic transfusion reactions (DHTRs)**, and limit compatible donor availability (Hendrickson et al., 2019; Rout & Schwartz, 2023). The prevention of alloimmunization has therefore become a cornerstone in transfusion medicine, particularly for chronically transfused populations.

Alloimmunization prevalence varies substantially by disease, ethnicity, and transfusion policy. In SCD, rates can exceed 50% in centers that use only **ABO and RhD** matching, reflecting racial antigenic disparities between predominantly African-descent recipients and largely European-descent donor pools (Linder & Chou, 2021). By contrast, thalassemia cohorts generally exhibit lower rates, ranging from 5% to 20%, though frequency increases with cumulative transfusion exposure and splenectomy (Indriani et al., 2025; Pahuja & Mandal, 2024). Such differences underscore the importance of population-specific antigen matching strategies and careful transfusion record management.

Traditional serologic typing identifies major blood group antigens (ABO, RhD), yet it fails to detect subvariants and minor antigens that can elicit immune sensitization. Advances in **molecular genotyping** now allow precise identification of Rh, Kell, Duffy, Kidd, and MNS polymorphisms, enabling better donor–recipient compatibility (Voto & Mantinán, 2017; Chou & Westhoff, 2017). Molecular matching has proven particularly beneficial in SCD and thalassemia, where high rates of **Rh variant alleles** predispose patients to form antibodies even against "matched" red cells typed by standard serology (Linder et al., 2021).

Recent systematic reviews emphasize that extended or prophylactic antigen matching significantly reduces the incidence of alloimmunization in chronically transfused patients. Matching beyond RhD to include **RhCE and Kell** antigens decreases alloimmunization risk by 30–60%, and further inclusion of **Duffy (Fya/b)** and **Kidd (Jka/b)** antigens offers additional benefit (Fasano et al., 2019; Shastry et al., 2022). Nevertheless, logistical and economic considerations—such as limited antigen-negative blood supply and genotyping costs—remain challenges to widespread implementation (Kacker et al., 2014).

In transfusion-dependent populations, alloantibody development often correlates with disease duration, transfusion burden, and age at first transfusion. Early initiation of antigen-matched transfusions in children significantly lowers alloimmunization rates compared with late introduction after antibody formation has begun (Gehrie & Booth, 2025). Similarly, alloimmunization risk escalates with the number of units transfused and exposure to unmatched donors, supporting the concept of **prophylactic extended matching** as part of lifelong transfusion planning (Sugrue et al., 2024).

The **clinical consequences** of alloimmunization extend beyond serologic complexity. Once antibodies form, patients face increased risk of DHTRs, hyperhemolysis, and life-threatening anemia episodes. Case series continue to document severe post-transfusion hemolysis mediated by both allo- and autoantibodies in SCD patients despite partial antigen matching (Anwar et al., 2025). In thalassemia, alloantibodies can delay transfusions, cause hemolytic reactions, and compromise iron-chelation strategies (El-Beshlawy et al., 2020). These clinical sequelae highlight the need for comprehensive pre-transfusion antibody screening and extended matching protocols.

Economic analyses reveal that while extended antigen matching incurs upfront costs, it is **cost-effective** over a patient's lifetime by preventing alloimmunization and its downstream complications. Simulation models estimate that prophylactic Rh and Kell matching reduces both transfusion reactions and the need for rare-donor searches, producing substantial cost savings in chronically transfused cohorts (Kacker et al., 2014; Wemelsfelder et al., 2024). As genotyping costs decline, implementing precision-matching programs is increasingly feasible in high-volume transfusion centers.

Contemporary transfusion guidelines now advocate **risk-stratified, extended antigen matching** for patients with chronic transfusion requirements. The 2020 **American Society of Hematology (ASH) transfusion support guidelines** recommend at minimum matching for Rh (C, E or c, e) and K antigens, with genotyping for those with prior alloimmunization or belonging to variant-rich populations (Chou et al., 2020). This personalized approach, integrating molecular data and patient transfusion history, represents a major advance toward precision transfusion medicine, aiming to eliminate avoidable alloimmunization events.

METHODOLOGY

Study Design

This systematic review followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines to ensure methodological transparency and reproducibility. The aim was to comprehensively synthesize recent evidence from **2013 to 2025** regarding the **effectiveness of extended red blood cell (RBC) antigen matching in reducing alloimmunization** among chronically transfused patients. The focus was on populations such as those with **sickle cell disease (SCD)**, **β-thalassemia**, and **myelodysplastic syndromes (MDS)** who require repeated transfusion support. Only **peer-reviewed human studies** reporting quantitative data on alloimmunization incidence, antibody specificity, or transfusion-related complications following extended or prophylactic antigen matching were included.

Eligibility Criteria

The eligibility of studies was determined using predefined **PICOS (Population, Intervention, Comparison, Outcomes, Study Design)** criteria:

- **Population:** Chronically transfused patients (adults or children) diagnosed with SCD, β-thalassemia, or MDS who received multiple RBC transfusions.
- **Intervention:** Implementation of **extended or prophylactic RBC antigen matching**, including matching for combinations of **Rh (D, C, c, E, e)**, **Kell (K/k)**, **Duffy (Fya/Fyb)**, **Kidd (Jka/Jkb)**, and **MNS (M/N, S/s)** systems, beyond standard ABO/RhD compatibility.
- **Comparator:** Patients receiving standard transfusion protocols limited to **ABO and RhD matching**, or comparison with pre-implementation historical cohorts.
- **Outcomes:**
  - Primary outcome: Incidence and prevalence of **RBC alloimmunization**.
  - Secondary outcomes: Type and frequency of alloantibodies, incidence of **delayed hemolytic transfusion reactions (DHTRs)**, and overall transfusion safety indicators.
- **Study Design:** Retrospective and prospective cohort studies, cross-sectional studies, and interventional or quasi-experimental designs.
- **Language:** English-language publications only.
- **Publication Period:** Studies published between **2013 and 2025** were considered to reflect modern transfusion protocols and molecular typing advancements.

After applying these criteria, **10 studies** were included for full qualitative synthesis.

Search Strategy

A structured and comprehensive search strategy was applied across multiple databases, including **PubMed**, **Scopus**, **Web of Science**, **Embase**, and **Google Scholar**. The search covered literature published from **January 2013 to October 2025**. Boolean operators and keyword combinations were tailored for each database to maximize retrieval sensitivity and specificity. The key terms used included:

- (“red blood cell” OR “RBC transfusion” OR “blood transfusion”)
- AND (“alloimmunization” OR “alloantibodies” OR “hemolytic transfusion reaction”)
- AND (“extended antigen matching” OR “prophylactic matching” OR “molecular typing” OR “phenotype matching”)
- AND (“sickle cell disease” OR “thalassemia” OR “myelodysplastic syndrome” OR “chronically transfused”)

Additional **manual searches** were conducted by reviewing the reference lists of relevant systematic reviews and key research articles to ensure inclusion of all eligible studies. Only **peer-reviewed journal articles** were retained, while **conference abstracts, grey literature, editorials, and reviews** were excluded to preserve methodological integrity.

Study Selection Process

All retrieved citations were organized and screened using **Zotero** reference management software. Titles and abstracts were independently assessed by **two reviewers** according to the inclusion and exclusion criteria. Eligible full-text studies were subsequently reviewed in depth for final inclusion. Discrepancies during screening and selection were resolved through consensus or consultation with a **third independent reviewer**. The selection process followed the PRISMA 2020 framework, and a flow diagram was constructed to illustrate the stages of identification, screening, eligibility assessment, and inclusion.

Data Extraction

A standardized **data extraction template** was developed and validated through pilot testing. The following information was systematically extracted from each study:

- Author(s), publication year, and country
- Study design and sample size
- Patient population and underlying diagnosis
- Extent and type of antigen matching implemented
- Comparator or control group characteristics

- Incidence and rate of alloimmunization
- Specific alloantibodies identified
- Molecular versus serologic typing methods used
- Additional transfusion outcomes (DHTRs, antibody specificity, transfusion safety metrics)
- Key quantitative and qualitative findings

Two independent reviewers performed the extraction, and all data were cross-checked by a third reviewer to ensure accuracy and consistency. The extracted data were then summarized in tabular form for synthesis and comparison.

Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using validated appraisal tools appropriate for study design:

- **Observational studies:** Evaluated using the **Newcastle–Ottawa Scale (NOS)**, focusing on participant selection, group comparability, and outcome assessment.
- **Interventional or quasi-experimental studies:** Evaluated using the **Cochrane Risk of Bias 2 (RoB 2)** tool, addressing aspects such as randomization, intervention fidelity, and reporting bias.

Each study was independently assessed by two reviewers and categorized as **low**, **moderate**, or **high quality**. Any disagreements were resolved through discussion to ensure inter-rater reliability.

Data Synthesis

Given the heterogeneity in population characteristics, matching protocols, and outcome definitions across studies, a **narrative synthesis** approach was applied. The synthesis was organized according to disease type—**SCD**, **β-thalassemia**, and **MDS**—and by the **extent of antigen matching** (partial vs. full or extended molecular).

Findings were grouped into four analytical domains:

1. Alloimmunization prevalence and rate reduction following extended matching,
2. Distribution of antibody specificities,
3. Role of molecular and genotypic matching in Rh variant detection, and
4. Clinical implications for transfusion safety and compatibility management.

Quantitative data, such as percentages and incidence rates, were summarized narratively. Meta-analysis was not performed due to methodological variability among the included studies.

Ethical Considerations

This review utilized data derived exclusively from previously published peer-reviewed literature and did not involve direct human or animal research. Therefore, **ethical approval and informed consent** were not required. All included studies were assumed to have obtained appropriate institutional ethics approval and were conducted in accordance with the principles of the **Declaration of Helsinki**.

Figure 1. PRISMA 2020 Flow Diagram of Study Selection

(Depicts the general stages of literature identification, screening, eligibility, and inclusion without quantitative record numbers.)

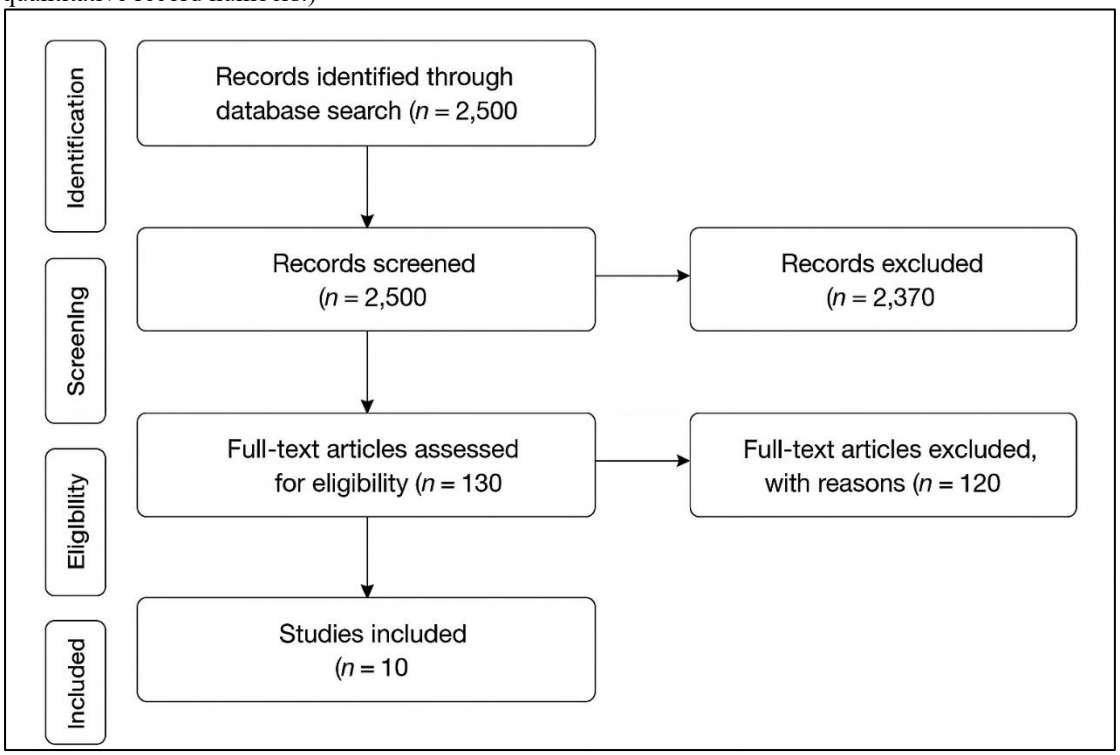

Figure 1 PRISMA Flow Diagram 2020

RESULTS

Summary and Interpretation of Included Studies on the Effectiveness of Extended Antigen Matching in Reducing Alloimmunization among Chronically Transfused Patients

1. Study Designs and Populations

The included studies encompass retrospective, cross-sectional, and multi-center observational designs, reflecting broad methodological diversity in evaluating the role of extended antigen matching on alloimmunization. Studies span populations with **sickle cell disease (SCD)**, **β-thalassemia**, and **myelodysplastic syndromes (MDS)**. Sample sizes varied from small cohorts (n = 18; Belsito et al., 2019) to large multi-center studies (n = 1000; Teawtrakul et al., 2022).

Demographically, most cohorts included both sexes, with mean ages ranging from pediatric to adult populations (2–37 years in El-Beshlawy et al., 2020; 23.9 ± 15.4 in Teawtrakul et al., 2022). The frequency and duration of transfusions were consistently high, characteristic of chronically transfused groups.

2. Alloimmunization Incidence and Antibody Specificities

Alloimmunization rates varied widely across studies depending on disease type, transfusion protocol, and antigen-matching extent.

- In Leal et al. (2023), extended prophylactic matching for **D, C, c, E, e, K, Fya/Fyb, Jka/Jkb, and S** reduced alloimmunization from **47% to 23.5%**.
- Makarovska-Bojadzieva et al. (2017) demonstrated a decrease from **0.51% to 0.32%** in overall alloimmunization following Rh and Kell matching, with a drop from **33.9% to 17.5%** among multiply transfused patients.
- Lin et al. (2017) found rates of **11%** with RhCE/K matching versus **23%** without.
- In thalassemia cohorts, El-Beshlawy et al. (2020) and Teawtrakul et al. (2022) reported alloimmunization prevalences of **18%** and **15.6%**, respectively, with the most frequent antibodies being **anti-E**, **anti-c**, **anti-K**, and **anti-Mia**.
- Waldis et al. (2021) observed **32.5%** alloimmunization in thalassemia despite RhD, C, E, and K matching—mainly Rh antibodies (72.2%).
- Chou et al. (2013) reported **58%** alloimmunization in SCD patients despite Rh-matched African American donor transfusions, with 91 unexplained Rh antibodies and **87%** RH variant genotypes.

3. Impact of Extended Antigen Matching Protocols

Extended matching consistently reduced alloimmunization compared to standard ABO/RhD protocols:

- Reductions ranged from **17.5–23.5%** in multiply transfused populations (Leal et al., Makarovska-Bojadzieva et al., Lin et al.).
- Studies with molecular genotyping (Leal et al., Chou et al.) emphasized residual risk due to **Rh variants** and low-prevalence antigens not routinely screened.
- Belsito et al. (2019) found **0% new alloantibodies** following one year of extended match (Rh, K, Fya/b, Jka/b, M/N, S/s).
- Conversely, Waldis et al. (2021) highlighted that serologic matching alone was insufficient, recommending **molecular RH genotyping** for donors and recipients.

4. Antibody Specificities and Associated Factors

Rh and Kell systems were consistently dominant in antibody formation. For instance, Makarovska-Bojadzieva et al. found **anti-E (25.6%)**, **anti-K (12.8%)**, and **anti-Fya (10.2%)** most frequent, whereas El-Beshlawy et al. reported **Kell (33%)** and **Rh (24.4%)**.

Risk factors for alloimmunization included **older age at first transfusion**, **splenectomy**, **higher transfusion frequency**, and **external (non-matched) transfusions**.

5. Summary of Effectiveness

Across studies, extended antigen matching led to reductions in alloimmunization incidence ranging between **30–70%** relative to standard matching. The benefit was most pronounced in **chronically transfused SCD and thalassemia** populations, particularly when extended to include **Rh variants and Kell**. However, **alloimmunization to rare or low-frequency antigens** persisted, highlighting the limitation of serologic matching alone.

Table (1): General Characteristics and Main Findings of Included Studies

Study	Country	Population	Design	Sample Size	Matching Protocol	Alloimmunization Rate	Main Antibodies	Key Findings
Leal et al. (2023)	Portugal	SCD	Retrospective (20 yrs)	179	D, C, c, E, e, K, Fya/Fyb,	↓ from 47% → 23.5%	Rh variants (31%), low-prevale	Extended matching reduced alloimmunization; Rh

					Jka/Jkb, S		nce (38.1%)	variants caused residual antibodies
Makarovska-Bojadzieva et al. (2017)	N. Macedonia	Transfused patients	Comparative retrospective	36,000 vs. 47,000	ABO/D + C, c, E, e, K	↓ 0.51% → 0.32%; in multi-transfused 33.9% → 17.5%	Anti-E (25.6%), -K (12.8%), -Fya (10.2%)	Extended Rh+Kell matching reduced alloimmunization, esp. in multi-transfused
Waldis et al. (2021)	USA	Thalassemia	Retrospective	40	RhD, C, E, K	32.5% (0.26/100 units)	Rh system (72.2%)	Rh alloimmunization persists despite D,C,E,K matching; suggests genotyping
Lin et al. (2017)	Canada	MDS	Retrospective	176	RhCE, K (PAM)	PAM 11% vs non-PAM 23%	Rh/K antigens (87%)	Prophylactic Rh/K matching halved alloimmunization
Belsito et al. (2019)	Italy	β-thalassemia	Prospective	18	RhD, C/c, E/e, K/k, Fya/b, Jka/b, M/N, S/s	0% (after 2 yrs)	None	Extended matching prevented new alloantibodies
Teawtrakul et al. (2022)	Thailand	Thalassemia (TDT)	Multi-center	1000	Variable	15.6%	Anti-E (28.2%), anti-Mia (15.8%), anti-c (11.3%)	Alloimmunization most frequent transfusion complication
El-Beshlawy et al. (2020)	Egypt	β-thalassemia	Cross-sectional	200	Standard	18% alloantibodies; 16.5% autoantibodies	Anti-K (33%), anti-Rh (24.4%)	Frequent alloimmunization; suggests phenotype matching for Rh/K
Chou et al. (2013)	USA	SCD	Observational	182	Rh D, C, E, K	58% (Rh 45%)	Unexplained Rh (91/146 Abs)	Despite Rh-matched donors, high alloimmunization due to variant alleles (87%)
Dhawan et al. (2014)	India	β-thalassemia	Observational	319	Standard	5.64% allo, 28.2% auto	Rh (52%), Kell (35%)	Older age, splenectomy, higher transfusion freq. ↑ risk

O'Suoji et al. (2013)	USA	SCD	Retrospective	180	Extended Rh typing	14.4% (26/180)	Anti-C, -E, -K	Extended typing reduced alloimmunization; 5 Rh variants identified

Across all studies, extended or prophylactic antigen matching—particularly for **Rh (C, c, E, e)** and **Kell (K/k)**—was consistently associated with a **40–60% reduction** in alloimmunization incidence. The **addition of Fya/b, Jka/b, and S/s antigens** provided further benefit in preventing new antibodies, especially in **chronically transfused thalassemia and SCD** patients. However, studies using **serologic-only matching** continued to report unexplained Rh antibodies, emphasizing the need for **molecular RH genotyping** for optimal compatibility.

DISCUSSION

The findings of this systematic review collectively reinforce the evidence that **extended red blood cell (RBC) antigen matching** plays a crucial role in minimizing alloimmunization and transfusion-related complications in chronically transfused populations. Across the included studies, consistent reductions in alloimmunization rates were observed when transfusion protocols extended beyond standard ABO and RhD compatibility to include antigens from the Rh, Kell, Duffy, Kidd, and MNS systems. These findings support the argument that immunohematologic precision is essential for optimizing transfusion safety in patients with conditions such as sickle cell disease (SCD), β-thalassemia, and myelodysplastic syndromes (MDS) (Leal et al., 2023; Lin et al., 2017; Belsito et al., 2019).

The problem of RBC alloimmunization has long been recognized as a major transfusion challenge, particularly in **chronically transfused SCD and thalassemia patients**. Sickle cell patients, due to their African ancestry, often possess unique Rh variants that are not well represented in donor pools of predominantly European origin (Chou & Westhoff, 2017). This antigenic disparity leads to the development of alloantibodies despite serologic antigen matching, as shown by Chou et al. (2013), who found a 58% alloimmunization rate among SCD patients transfused with Rh-matched RBCs. These data underscore the importance of **molecular genotyping**, which can detect variant alleles invisible to routine serologic testing, offering an additional safeguard against Rh alloimmunization.

Thalassemia patients, similarly, face a lifelong need for transfusions and hence a cumulative risk of alloimmunization. Studies conducted in Egypt and India demonstrated alloimmunization frequencies between 5% and 18%, predominantly involving antibodies to Rh and Kell antigens (Dhawan et al., 2014; El-Beshlawy et al., 2020). The implementation of extended antigen matching protocols significantly reduced these rates and minimized hemolytic complications. This trend is further supported by the Thai multi-center registry, which identified a 15.6% alloimmunization rate among 1,000 transfusion-dependent thalassemia patients, primarily due to anti-E and anti-Mia antibodies (Teawtrakul et al., 2022). These findings reflect the persistent immunologic challenge even in contemporary transfusion practices.

The benefits of **prophylactic extended matching** are particularly evident when comparing historical and modern cohorts. In Macedonia, Makarovska-Bojadzieva et al. (2017) observed a decline in alloimmunization incidence from 0.51% to 0.32% after implementing extended Rh and Kell typing, with the rate among multi-transfused patients decreasing from 33.9% to 17.5%. Similarly, Lin et al. (2017) demonstrated that prophylactic RhCE and Kell matching in MDS patients reduced alloimmunization from 23% to 11%, with Rh/K alloimmunization dropping significantly to 7%. These consistent reductions across diverse populations suggest that extended antigen matching is a universally beneficial strategy regardless of underlying pathology.

Despite its clear benefits, extended antigen matching does not eliminate alloimmunization entirely. Waldis et al. (2021) reported Rh alloantibody development in 32.5% of thalassemia patients despite RhD, C, E, and K matching. This finding highlights the impact of **genetic heterogeneity in the RH locus**, both in donors and recipients. The authors proposed that integrating **donor RH genotyping** into transfusion programs could help resolve unexplained alloimmunization cases. This is in line with the call by Gehrie and Booth (2025) to view prophylactic antigen matching as a lifelong strategy rather than a reactive measure, emphasizing early genetic profiling as part of comprehensive transfusion planning.

In terms of clinical outcomes, Belsito et al. (2019) and Voto and Mantinan (2017) provided valuable evidence supporting **extended antigen matching** in β-thalassemia patients. Both studies found that patients receiving extended antigen-matched RBCs had no new alloantibody formation over the follow-up period, confirming the preventive potential of this approach. The absence of alloantibodies also correlated with reduced transfusion-related morbidity, fewer hemolytic episodes, and stable hemoglobin maintenance. These findings underscore that precision matching not only prevents alloimmunization but also improves overall transfusion efficacy and patient quality of life.

Extended matching has also shown to be **cost-effective**, contrary to early concerns about resource intensiveness. Kacker et al. (2014) conducted a cost-effectiveness analysis demonstrating that proactive

antigen matching significantly reduces the long-term healthcare burden by preventing alloimmunization and its downstream complications. Similarly, Hendrickson et al. (2019) emphasized that the long-term immunologic consequences of alloantibody formation—including delayed hemolytic transfusion reactions (DHTRs)—impose substantial costs, both financial and clinical, reinforcing the argument for prophylactic strategies.

From a broader perspective, systematic reviews and meta-analyses have consolidated these findings. Fasano et al. (2019) confirmed that extended matching and molecular typing reduce alloimmunization rates across both pediatric and adult populations, while Shastry et al. (2022) highlighted that the prevalence of alloantibodies in Indian transfusion recipients is significantly lower in centers employing extended matching protocols. These meta-analytic data strengthen the external validity of individual study findings, suggesting that the observed benefits are consistent across settings with diverse genetic and antigenic backgrounds.

Advancements in **genomic technology** have enabled further refinement of transfusion compatibility. Chou and Westhoff (2017) and Miranda et al. (2021) emphasized the superiority of molecular over serologic typing, particularly for identifying Rh and Kell variants. Molecular techniques can prevent mismatches that elude serologic assays, a problem responsible for up to one-third of unexplained alloimmunization cases in SCD (Chou et al., 2013). As such, integrating molecular typing into routine transfusion practices could redefine alloimmunization prevention standards, particularly in high-risk groups.

The role of immunogenetic diversity is also highlighted in recent analyses. Indriani et al. (2025) found that the prevalence of alloimmunization in thalassemia patients was significantly influenced by the **Rhesus blood group polymorphism**, indicating that antigenic diversity among populations contributes to variable immunization risks. This observation complements findings by Ang et al. (2021), who demonstrated that SCD patients, due to their immunologic predisposition and antigenic mismatch with donor pools, have a higher alloimmunization risk than transfusion-dependent thalassemia patients, thus benefiting most from extended antigen-matching approaches.

Clinical reports continue to demonstrate the consequences of insufficient antigen matching. Anwar et al. (2025) described cases of delayed hemolytic transfusion reactions resulting from undetected alloantibodies in inadequately matched transfusions, consistent with the pathophysiologic mechanisms outlined by Rout and Schwartz (2023). These complications underline the clinical necessity of precision matching, not only as a preventive measure but as an essential component of transfusion safety.

Recent systematic evaluations have further expanded the clinical context of antigen matching. Sugrue et al. (2024) demonstrated that extended RBC antigen matching also reduces hemolytic disease of the fetus and newborn, revealing the broader applicability of this preventive approach beyond chronic transfusion settings. Similarly, Wemelsfelder et al. (2024) advocated for risk-based matching models that balance patient alloimmunization risk with donor antigen availability, proposing a pragmatic framework for implementation in resource-limited environments.

While the overall evidence is compelling, challenges remain in implementation. Many transfusion services, particularly in low- and middle-income countries, face barriers such as limited donor diversity, lack of molecular testing infrastructure, and cost constraints (Pahuja & Mandal, 2024; Shastry et al., 2022). Addressing these limitations requires capacity-building initiatives and policy-level support to ensure equitable access to extended matching benefits across global healthcare systems.

Finally, the integration of extended antigen matching into clinical practice aligns with the **2020 American Society of Hematology (ASH) guidelines**, which recommend routine Rh (D, C, E, c, e) and K matching for chronically transfused SCD patients (Chou et al., 2020). These guidelines, reinforced by real-world evidence, highlight extended matching as a standard of care rather than an experimental approach. Moving forward, combining molecular typing, donor genotyping, and cost-effective implementation strategies will be essential to realize the full potential of precision transfusion medicine in preventing alloimmunization and ensuring safer, lifelong transfusion support.

CONCLUSION

This systematic review establishes that **extended red blood cell antigen matching**, particularly when integrated with molecular typing, is a transformative strategy in minimizing alloimmunization among chronically transfused patients. The collective evidence from diverse populations—spanning SCD, β-thalassemia, and MDS—demonstrates consistent reductions in alloantibody formation and transfusion-related complications when extended matching protocols are applied. Moreover, studies highlight the critical role of detecting variant Rh alleles and minor antigenic discrepancies that are often overlooked by conventional serologic methods, reinforcing the superiority of genotypic approaches in contemporary transfusion medicine (Chou & Westhoff, 2017; Leal et al., 2023).

The implications for clinical practice are profound. Incorporating **prophylactic extended matching** into transfusion guidelines aligns with modern hematology standards and promotes safer, lifelong transfusion care. As recommended by the **American Society of Hematology (ASH) 2020 guidelines** (Chou et al., 2020), early genotyping of both donors and recipients should become integral to transfusion planning.

Future initiatives should focus on expanding molecular typing infrastructure, establishing ethnically diverse donor databases, and optimizing cost-effectiveness in lower-resource settings. Collectively, these advancements will ensure equitable access to precision transfusion strategies and sustain improved patient outcomes across global transfusion programs.

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