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Review Article

Effectiveness of NIPT on RhD-Negative Pregnant Women on RhIg-Induced Isoimmunisation and Associated Healthcare Costs: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Determining foetal RhD status guides the targeted use of RhIg prophylaxis to prevent sensitisation. While Non-Invasive Prenatal Testing (NIPT) enables this targeted approach in RhD-negative pregnant women, concerns remain about the risk of alloimmunisation and the cost-effectiveness of NIPT. Despite these uncertainties, screening programs are being adopted worldwide.

Objectives: To evaluate the effectiveness of NIPT-guided RhIg prophylaxis in reducing maternal sensitisation and to assess its cost-effectiveness compared with universal RhIg prophylaxis.

Methods: In compliance with PRISMA guidelines, a systematic review was conducted using Google Scholar, PubMed, Scopus, and Embase. Eligible studies included the incidence of RhD alloimmunisation and healthcare costs associated with RhIg prophylaxis. Data were statistically analysed using RevMan (Review Manager) software.

Results and discussion: From 2,856 records, six studies met the inclusion criteria. RhD alloimmunisation was significantly less frequent in the targeted group (0.2%) compared to the routine group (0.4%) ($p<0.001$; 95% CI: 0.39-0.68). However, targeted prophylaxis showed higher mean costs ($p=0.01$; 95% CI: 0.11-0.80), mainly due to genotyping expenses. Despite increased costs, NIPT demonstrated clinical, ethical, and sustainability benefits, including reduced incidence of RhD alloimmunisation, RhIg wastage, lower disease transmission risk, and improved patient compliance through personalised care.

Conclusion: NIPT offers a safe and effective approach for targeted RhIg prophylaxis. Although it is expensive at present, long-term clinical and economic advantages are encouraging. Further studies are required to verify these results and support broader use in routine antenatal care.

Keywords: NIPT; Alloimmunisation; RhIg prophylaxis; Cost; RhD-negative pregnant women.

INTRODUCTION

Background

Over centuries, Rhesus D antigen (RhD) alloimmunisation has been a common concern in obstetric studies for pregnant women in the quest to eliminate the risk of Haemolytic Disease of the Foetus and Newborn (HDFN) [1]. In routine care, antibody screening, invasive diagnosis of the foetus, and administration of anti-D prophylaxis are carried out with close monitoring of the mother and foetus to minimise HDFN in RhD- negative women. Yet, invasive procedures, including Chorionic Villus Sampling (CVS) and amniocentesis, possess a risk of provoking spontaneous miscarriage with a 0.5-1% degree of risk [2,3]. Antibody screening functions as an indirect method for assessing foetal status. However, their sensitivity is lower compared to invasive techniques, highlighting the need for non-invasive diagnostic methods [4]. Thus, in recent years, there has been a shift towards foetal RhD genotyping using Cell-Free DNA (cfDNA) to guide Rh Immunoglobulin (RhIg) usage in pregnant women and to enhance foetal survival. Conversely, the cost and complexity of these tests have impeded the widespread adoption of routine Non-Invasive Prenatal Testing (NIPT) for foetal RhD prediction and the determination of RhIg eligibility [5].

Use of RhIg and associated risk in pregnancy

The development and introduction of postnatal RhIg treatment in the

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1960s led to a significant reduction in the prevalence of HDFN due to Rh incompatibility, from 16% to 2% [5,6]. These figures were further reduced to 0.1%-0.3% with prenatal prophylaxis at a gestational age of 28-34 weeks in the 1970s [6]. Anti-D immunoglobulin is a specific biological product obtained primarily through plasma apheresis from volunteers with strong anti-D antibody titres [6]. This influences the availability of RhIg doses, which are typically limited [6,7]. Many countries rely on importing RhIg due to its non-local production, unavailability of raw materials, or donor shortages [6-8]. Consequently, guidelines for the use of anti-D prophylaxis have been established and vary between countries, particularly regarding the frequency and dosage of both prenatal and postnatal administration [2].

Additionally, application of RhIg increases the chance of disease transmission. Although blood products are screened to minimise the risk, subsequent studies have revealed the existence of tainted RhIg batches containing viruses or prions, such as the Hepatitis C virus [6-8].

In the process of RhIg production, Volunteers being immunised against the RhD antigen also subject themselves to a greater risk in future transfusions. This raises ethical concerns about RhIg use, prompting interest in targeted RhIg prophylaxis [5,7,9].

RhIg is relatively expensive due to limited resources and requires optimised management to conserve supply and minimise excessive utilisation. In RhD-negative pregnancies, about 40% of women are at no risk of alloimmunisation [5,10]. Hence, predetermination of foetal RhD status in advance could avoid treatment involving an RhD-negative foetus, including intensive care or RhIg administration [9].

NIPT for foetal RhD detection in prenatal care

Prenatal cfDNA or NIPT is used to efficiently predict foetal RhD status and target RhIg administration in all RhD-negative, non-alloimmunised pregnant women, enabling accurate detection of RhD-positive foetuses and reducing unnecessary RhIg use [6,8,11]. As a result, this approach has been adopted into routine clinical practice in many European countries, enhancing the management of RhD-negative pregnant women [4,11].

Cell-Free DNA (cfDNA) is present at approximately 10% of the total maternal plasma concentration from 10 to 12 weeks of gestation, increases with gestational age, and rapidly disappears from the maternal circulation postpartum [4]. To accurately predict foetal DNA status using cfDNA, it is essential to consider genetic variants, such as point mutations that cause weak D types, which may hinder estimation of the foetal RhD status [10,12]. In Caucasians, the RhD-negative phenotype is often caused by RhD gene deletion, whereas in individuals of African origin, it is typically caused by the RHD Pseudogene (RhDΨ) or the RHD-CE-DS (dCeS) haplotype [5,13,14]. Therefore, the frequencies of RHD variants in different populations should be considered when selecting gene targets. Consequently, multiple combinations including RhD exons 5, 7, and 10 are commonly used as the choice of exon targets [10,12].

By targeting multiple exons in a single assay, high accuracy can be achieved [12]. It is crucial to acquire a high sensitivity during RHD screening assays, as a false negative result may result in omitting anti-D administration, leaving the pregnant woman at risk of sensitisation against anti-D [10].

Scope of the review

In standard care, routine antenatal RhD screening is utilised to identify maternal pregnancies at risk of HDFN, followed by prenatal and postnatal RhIg therapy based on the foetal RhD status in RhD-negative pregnant women [1]. Despite precautions with anti-D prophylaxis administration, residual cases of RhD alloimmunisation still occur in RhD-negative pregnant women [13]. Therefore, using NIPT for foetal RhD identification from maternal plasma enables the withholding of anti-D prophylaxis from RhD-negative pregnant women carrying RhD-negative foetuses, preventing unnecessary administration of RhIg and reducing the risk of alloimmunisation [2,13].

Most investigations in RhD genotyping have employed labour-intensive and extravagant approaches, which are incompatible with large-scale screening. The advent of robotic technologies for isolating foetal DNA and their adaptation to prenatal testing permitted high-throughput analysis, delivering an efficient and cost-effective approach to avoiding the regular administration of RhIg to all RhD-negative pregnant mothers [3].

Consequently, a systematic review and meta-analysis of existing data would be valuable in assessing the impact of NIPT on RhIg-induced isoimmunisation and related healthcare expenses.

The study aims to utilise the PICO framework to compare current data and address the following research question: Does NIPT-guided anti-D prophylaxis (intervention) reduce maternal sensitisation episodes (outcome) in RhD-negative pregnant women (population), relative to universal anti-D prophylaxis (comparison)? A secondary question aims to address: Does employing non-invasive RhD typing (intervention) for RhIg administration mitigate healthcare costs (outcome) when compared to routine RhIg (comparator) in RhD-negative pregnant women (population)?

METHODS

Study design

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in conducting the systematic review to obtain specific studies that investigate the NIPT efficacy in minimising the incidence of Rh-D sensitisation with RhIg administration and associated costs [15].

Search strategy

Database searches were conducted through PubMed, Scopus, Embase, and Google Scholar, with no restrictions on publication dates, to identify relevant literature. "NIPT," "non-invasive prenatal testing," "cell-free DNA," "cfDNA," "Rh-D genotyping," "RhIg prophylaxis," "anti-D prophylaxis," and "Rh-D negative pregnant women" were key search terms included. To ensure complete coverage, both British and American spellings were incorporated where appropriate. No articles were manually added through searches. EndNote was used to save the articles that were found through database searches.

Eligibility criteria

Articles were arranged for eligibility assessment using EndNote [16]. Using Covidence, duplicates were removed, and the process of including and excluding articles was initiated [17]. Before being assessed for eligibility, articles were first excluded based on their abstract and title. Those that examined the risk or incidence of RhIg-induced alloimmunisation, and healthcare costs associated were considered eligible. Case studies, systematic reviews, meta-analyses, abstracts only, and articles that were not relevant to the research issue or that were not written in English were all excluded.

Methodology quality assessment

Using the Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) criteria, the methodological quality of the eligible studies was assessed [18].

Data management and extraction

Primary author, research design, country of publication, study period, sample size, and parameters assessed for analysis were among the data collected from eligible studies. The selected characteristics comprised sensitisation events and the costs related to target and routine anti-D prophylaxis.

Statistical analysis

RevMan (Review Manager) software (Version 5.4.1, The Cochrane Collaboration, and UK) was used to perform the meta-analysis. The frequency of sensitisation events along with costs associated with the targeted anti-D versus routine anti-D prophylactic groups were compared using a two-way proportional analysis.

When Standard Deviations (SDs) for cost data were not reported, we estimated them using an assumed Coefficient of Variation (CV). Following methods commonly employed in health economic evaluations (e.g. Weir, et al. 2018), we adopted a base CV of 0.5. As the costs were presented in different currencies, all values were converted to Australian Dollars (AUD) for analysis (AUD 1$=0.56 euro/ 0.91 CAD/0.66 USD).

Sensitisation events were analysed using the Mantel-Haenszel method, and a random-effects model was employed to compute the Odds Ratio (OR). A random-effects model was used to analyse costs and determine the standardised mean difference using the Inverse Variance approach. Forest plots were used to illustrate the results for each parameter. In addition to the 95% CI and I2 statistic to examine research heterogeneity, RevMan software computed the total P-value to determine statistical significance. Further, associated heterogeneity was taken into account. Statistical significance is defined as a P-value of less than 0.05.

Using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool, the risk of bias for the studies was evaluated [19]. Each study was independently reviewed and assigned a risk level (low, unclear, high) across these domains [20-23].

RESULTS

The inclusion and exclusion criteria displayed served as the basis for the study selection (Figure 1). A total of 2856 possibly pertinent studies were found in the database search [24,25].After identifying and eliminating duplicates, 2104 studies remained. 1,836 of these studies were excluded after initial filtering based on their titles and abstracts [26-28].The eligibility of the remaining 268 studies was then evaluated. The primary exclusion criterion, which led to the elimination of 184 papers, was insignificant to the investigated question. Similarly exempt were case studies, abstract-only papers, review articles, and publications not in English. The meta-analysis comprised six papers in total that fulfilled the qualifying requirements [29,30].

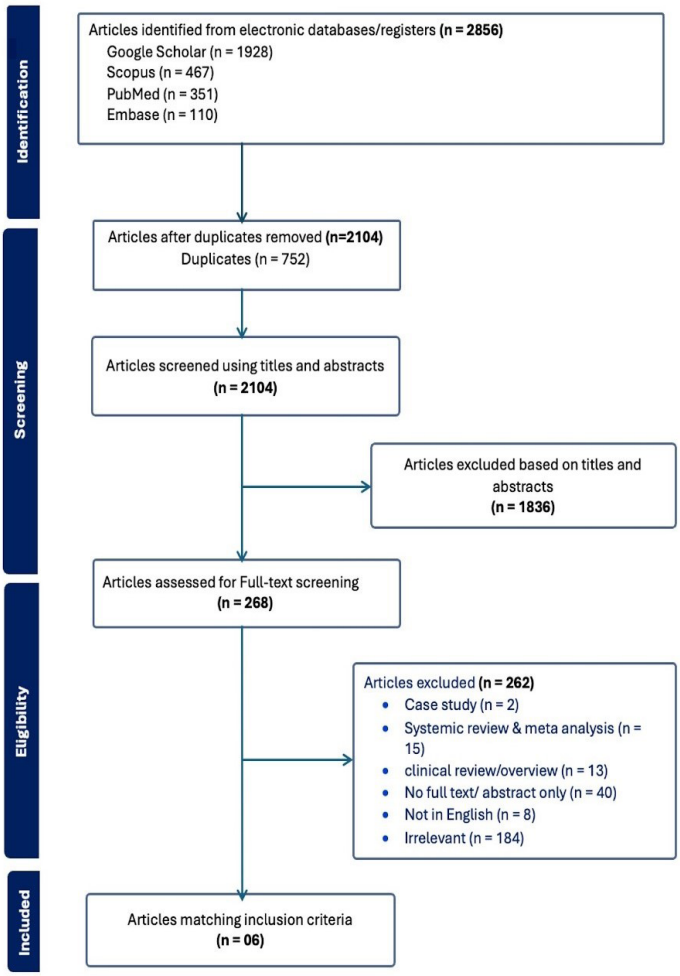

Figure 1: PRISMA flowchart. For the purpose of retrieving the studies that were included in the meta-analysis, the selection method comprised scanning four databases, eliminating duplicates, screening using titles and abstracts, and determining eligibility.

Study characteristics

The characteristics of the six studies that assessed the effects of NIPT on reducing RhIg-associated sensitisation events, and healthcare costs are shown in (Table 1). Among the studies incorporated, four emphasised the incidence of isoimmunisation, and four focused on the healthcare costs involved per pregnancy following RhIg administration. The studies conducted spanned mostly over European countries, which were either retrospective, prospective, or model-based analyses. The total number of pregnant women who are Rh-D-negative comprises the sample size.

The study data entailed in the meta-analysis (Table 2). The proportion of total sensitisation events that occurred and the healthcare costs associated were calculated per pregnancy. When measuring the sensitisation events that occurred, the data were used over the total number of RhD-negative mothers given routine or targeted RhIg prophylaxis to determine if it impacted the incidence of alloimmunisation. The costs were measured as the average number per pregnancy, giving routine or targeted anti-D to assess cost-effectiveness.

Assessment of methodological quality

The STROBE checklist was used to assess the methodological quality of the studies included in the systematic review (Table 3). All studies received favourable scores for providing adequate detail in the title/abstract, introduction, findings, and discussion sections. In the methodology sections, the majority also demonstrated comparatively high quality. However, four studies merely mentioned the inclusion criteria, and only two studies described the steps used to fulfil the eligibility requirements during participant selection. The majority of the studies were of excellent methodological quality overall, as displayed which mitigates the possibility of obtaining insufficient studies for the analysis.

Table 1: Eligible study characteristics for the NIPT effectiveness in reducing RhIg-associated sensitisation events and healthcare costs.

Study	Study design	Country	Study period	Sample size	Parameters measured
Darlington, et al. 2018 [28]	Prospective	France	2009-2013	850	Foetal RhD status, RhIg administration, direct health costs per pregnancy
Neovius, et al. 2015 [29]	Model based analysis	Sweden	2008-2011	13,822	Cost per pregnancy, incidence of RhD immunisation
Teitelbaum, et al. 2015 [31]	Model based analysis	Canada	2010	69,286	Cost per pregnancy, RhIg doses administered, incidence of RhD immunisations
Tiblad, et al. 2013 [32]	Prospective	Sweden	2009-2011	9,380	Foetal RhD status, incidence of RhD immunisation
Demirel, et al. 2018 [27]	Retrospective	Turkey	2011-2015	1135	Cost per pregnancy
Thorup, et al. 2025 [20]	Retrospective	Denmark	2004-2020	506	Incidence of RhD immunisation

Table 2: Eligible study data reporting sensitisation events and costs associated with routine RhIg and targeted RhIg prophylaxis.

Study	n (total population)	RhIg dose	Week of administration	Sensitisation		Cost per pregnancy (AUD$)	
				Routine	Targeted	Routine	Targeted
Darlington, et al. 2018 [28]	850	300 μg (1500 IU)	28 ± 1	-	-	804.1	804.1
Neovius, et al. 2016 [29]	13,882	250-300 μg (1250-1500 IU)	29	33/7099	11/6723	2060.39	2060.39
Teitelbaum, et al. 2015 [31]	69,286	300 μg (1500 IU)	28	13/10,393	13/10,393	78.51	78.51
Tiblad, et al. 2013 [32]	9,380	250-300 μg (1250-1500 IU)	28-30	86/18546	24/9380	-	-
Demirel, et al. 2018 [27]	1,135	-	-	-	-	393.13	393.13
Thorup, et al. 2025 [20]	75,156	250-300 μg (1250-1500 IU)	29	282/60,952	167/75,156	-	-

Table 3: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist-based methodological quality evaluation of included studies.

	Title and abstract	Introduction		Methods			Results		Discussion
	Clear title and abstract with study design indicated	Explains scientific background, rationale and objectives for study	Detailed study methods given	Eligibility criteria for participant selection shown	Give sources of data and details of methods of assessment (measurement)	Describes statistical methods	Give characteristic of study participants	Report number of outcome events or summary measures over time	Summarise key results and discusses limitations
Darlington, et al. 2018 [28]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Neovius, et al. 2016 [29]	Y	Y	Y	P[a]	Y	Y	Y	Y	Y
Teitelbaum, et al. 2015 [31]	Y	Y	Y	P[a]	Y	P[b]	Y	Y	Y
Tiblad, et al. 2013 [32]	Y	Y	Y	P[a]	Y	Y	Y	Y	Y
Demirel, et al. 2018 [27]	Y	Y	Y	Y	Y	Y	Y	Y	Y
Thorup, et al. 2025 [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y

Note: Y: Criteria fulfilled; P: Criteria partially fulfilled; [a]: Study exclusion criteria not described; [b]: Incorporated statistical methods were not explicitly mentioned.

Meta-analysis on the proportion of RhIg-induced isoimmunisation and cost associated

The construction of a meta-analysis and a forest plot for overall sensitisation events associated with RhIg administration in RhD-negative pregnant women (Figure 2).

With an overall P-value of <0.001, the two-arm proportional analysis of RhIg-induced alloimmunisation was statistically significant, as shown in part A. With an I2 value of 33%, the findings of the four included studies demonstrated heterogeneity. The I2 value shows substantial heterogeneity. As a result, the data exhibits moderate fluctuation. The findings suggest that, in comparison to routine RhIg prophylaxis, NIPT reduces RhIg-induced alloimmunisation in maternal care (95% CI, 0.39, 0.68).

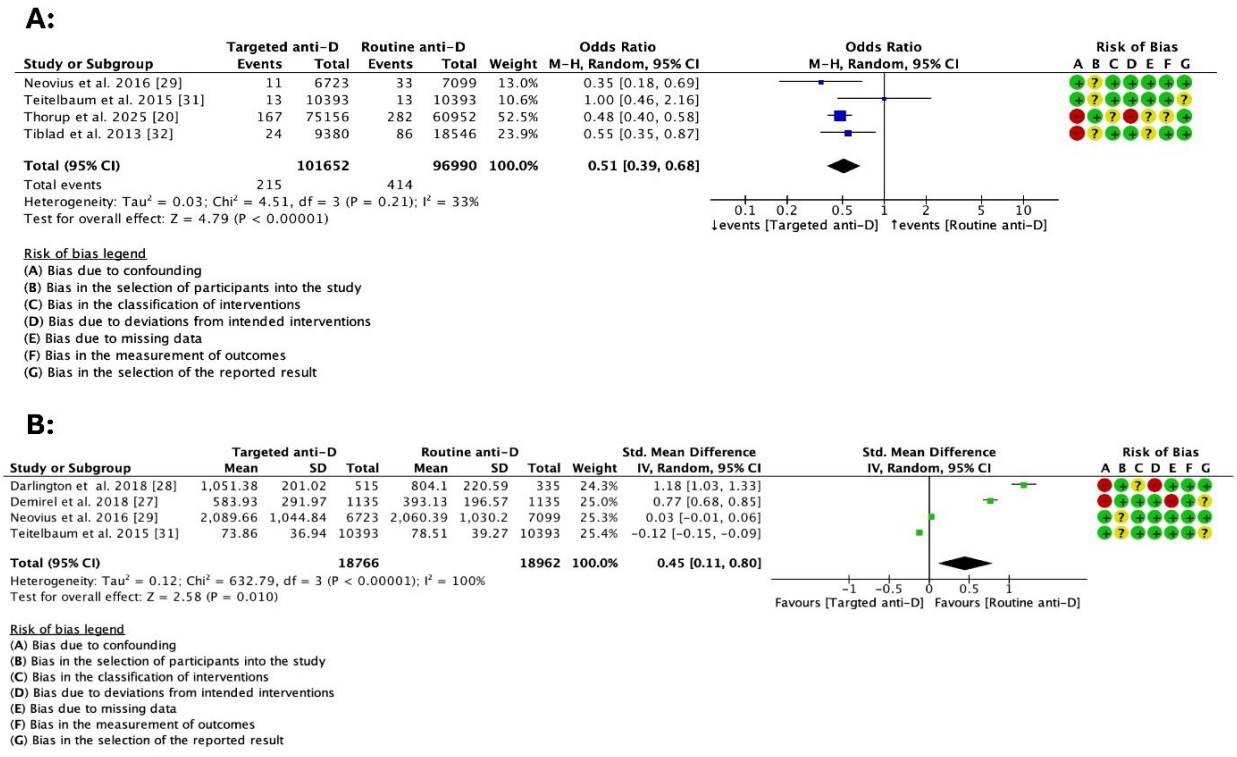

Figure 2: Meta-analysis of forest plots on the effectiveness of NIPT on maternal care management in Rh-D negative pregnant women. **Note:** (A) The incidence of RhIg-associated alloimmunisation as a portion of the total number of pregnancies was determined using two-armed proportion analysis data; (B) Standard mean analysis was used to express the RhIg-associated cost in maternal care. Applying the random-effects model, the 95% CI was used to determine each parameter's maximum probability. The I value and its corresponding P-value were used to assess heterogeneity, while the total P-value was used to estimate statistical significance.

A meta-analysis and forest plot were conducted to determine the overall cost associated with targeted and routine maternal care in RhD-negative pregnant women, and are displayed in part B.

With an overall P-value of 0.01, the two-arm standard mean analysis on total cost was shown to be statistically significant. Based upon the findings of the four included studies, the I2 was 100% and the heterogeneity P-value was less than 0.001. This suggests high heterogeneity, which implies significant data variability. The results suggest that the mean cost associated with targeted anti-D prophylaxis is higher than that of routine RhIg administration (95% CI: 0.11, 0.80).

DISCUSSION

Effective management of RhIg-induced alloimmunisation with NIPT

Following this meta-analysis and systematic review, the incidence of Rh alloimmunisation in pregnant women has decreased due to the integration of NIPT into patient care for RhIg administration. This is supported by statistically significant results showing that a total of 215 (0.2%) events of alloimmunisation occurred with targeted anti-D administration compared to routine, where a total of 414 (0.4%) events occurred (95% CI, 0.39, 0.68). A heterogeneity of I2=33% was observed, indicating variability in the data across studies rather than chance. These results on the incidence of RhIg alloimmunisation represent an enhancement in clinical outcomes and support the incorporation of NIPT into routine antenatal care protocols for RhD-negative mothers.

The Rh incompatibility in RhD-negative mothers carrying an Rh-positive foetus causes sensitisation during the antenatal or postnatal stage. The use of anti-D prophylaxis in clinical practice helps reduce the incidence of HDFN by preventing alloimmunisation. The use of targeted prenatal anti-D prophylaxis is becoming increasingly widespread as the foetal RhD status can be reliably and sensitively determined from maternal blood. This development has resulted in incorporating NIPT RhD genotyping into clinical setting for the targeted prevention and management of RhD-sensitised women [8,20]. A previous study by Manzanares, et al. demonstrated a 98.65% sensitivity in foetal genotyping at a median gestational age of 12 weeks, suggesting that NIPT can be used for early diagnosis and to prevent unnecessary RhIg administration [21].

In our study, the effect of targeted RhIg was clearly demonstrated by the decline in new RhD immunisation cases in the first pregnancy when comparing the two cohorts. However, prolonged transplacental haemorrhage, a higher maternal Body Mass Index (BMI), or a failure to deliver RhD immunoglobulin following potentially sensitising events or at an adequate dose might still result in anti-D sensitisation despite these immunoprophylaxis practices [22,23]. According to our study, the recommended dosage of anti-D prophylaxis varies by country, typically 250-300 µg (1250-1500 IU), and this may not always provide adequate protection, leaving the risk of alloimmunisation despite preventive measures. A study by Soothill, et al. reported that a proportion of RhD-negative women declined RhIg administration [24]. This decision could potentially result in RhD alloimmunisation if the foetus is RhD-positive. As a result, implementing NIPT to determine foetal RhD status early could raise maternal awareness and increase uptake of RhIg prophylaxis among RhD-negative women carrying an RhD-positive foetus, thereby reducing the possibility of alloimmunisation. Moreover, using the NIPT guide management not only enhances prophylaxis administration but also builds trust and encourages engagement between patients and healthcare providers. By providing a clear, personalised understanding of the foetal RhD status, pregnant women are more likely to adhere to prophylactic recommendations and actively participate in shared decision-making. This, in turn, enhances patient autonomy and reinforces informed consent practices in antenatal care.

Furthermore, there are notable differences in RhIg dosage regimens and timing across countries, influenced by variations in clinical guidelines, healthcare infrastructure, and product availability. For instance, Norwegian guidelines recommend administering 300 µg (1500 IU), a single dose at 28 weeks of gestation, while in Australia, they employ two-dose regimens (625 IU) at 28 and 34 weeks [11,25,26]. Such inconsistencies can contribute to variability in compliance rates and overall prophylactic effectiveness [20]. Hence, NIPT-guided management improves RhIg compliance by clearly identifying women who require prophylaxis, thereby increasing motivation to complete the recommended dosage schedule and reducing unnecessary administration.

Addressing NIPT and RhIg-associated costs in healthcare

RhD sensitisation remains a major issue, particularly among low socio-economic populations and in developing regions where access to immunoprophylaxis is limited [27]. Therefore, effective cost management is essential in optimising patient care. The findings of our study indicated that, although the incidence of RhD alloimmunisation was low when employing a targeted prophylaxis approach, this strategy was associated with a higher mean cost of patient care compared to routine prophylaxis, with a statistically significant difference (95% CI: 0.11-0.80). High heterogeneity was observed in this study, with I2=100% indicating variability in cost-associated results primarily due to differences in healthcare regulations, prophylaxis guidelines, and RhIg dosing schedules, which are expected given variations in national and regional recommendations. The increased cost observed in the targeted approach can primarily be attributed to the additional expense of foetal RHD genotyping required to determine the foetal RhD status. Unlike routine prophylaxis, which administers RhIg universally to all pregnant women who are RhD-negative, the targeted strategy involves a molecular diagnostic procedure that requires specialised laboratory testing, trained personnel, and advanced equipment. In addition, while the targeted strategy reduces unnecessary RhIg use, the savings from fewer injections often do not outweigh the high upfront cost of genetic testing, especially in settings with limited laboratory infrastructure or low testing volumes [27-30]. Therefore, from a cost perspective, the routine prophylaxis approach remains more economical in many healthcare systems.

Although this approach may initially appear less cost-effective, it offers long-term economic and clinical benefits that support its implementation. NIPT assists in reducing the likelihood of RhD alloimmunisation by precisely identifying RhD-negative foetuses, ensuring that RhD-negative women who carry positive RhD foetuses receive timely and appropriate prophylactic treatment. This precision-based strategy also preserves limited supplies of RhIg, a plasma-derived biological product, for individuals who genuinely require it, thereby promoting more efficient use of healthcare resources [31]. Moreover, by avoiding unnecessary administration of RhIg to women carrying RhD-negative foetuses, the approach minimises exposure to blood products and associated risks, enhances maternal safety and satisfaction, and supports informed decision-making through personalised care [6,28,31].

Further, the gradual reduction in testing costs, improvements in

assay efficiency, and economies of scale are expected to make NIPT increasingly affordable in the near future. Studies by shown that as implementation expands, per-test costs decline significantly, ultimately offsetting initial expenditure. When combined with digital health record integration and automated reporting, the workflow efficiency of NIPT-based programs can improve, enhancing cost-effectiveness across diverse healthcare systems [28].

Future economic evaluations should also incorporate indirect cost benefits, such as reduced hospital admissions for HDFN management, decreased neonatal intensive care requirements, and improved maternal quality of life. These broader healthcare savings may further justify the adoption of NIPT-based targeted prophylaxis as a sustainable long-term strategy [28]. Over time, as the cost of genetic testing continues to decline and laboratory efficiency improves, the cost-effectiveness and sustainability of NIPT-based targeted prophylaxis are expected to increase, making it a valuable advancement in modern obstetric practice [30].

Sustainability of employing NIPT in maternal care

The use of NIPT for foetal RHD determination can significantly improve the sustainability of immunoprophylaxis programmes. By accurately identifying RhD-negative foetuses early in pregnancy, NIPT assists targeted administration of anti-D prophylaxis solely to mothers in need. This method helps conserve limited donor-derived RhIg supplies, as the global shortage and donor dependency remain ongoing challenges [2]. It also reduces wastage of biological resources and ensures the long-term availability of RhIg, especially for individuals at genuine risk of alloimmunisation [28,31].

In addition, by reducing the number of individuals exposed to donor-derived products, NIPT decreases the potential risk of transfusion-transmissible infections and addresses ethical concerns related to the use of human-derived materials [28]. This approach also promotes responsible healthcare resource utilisation and aids in precision medicine and patient-centred care. Notably, our study showed a lower incidence of RhD alloimmunisation (0.2%) following the implementation of NIPT-guided prophylaxis. This finding demonstrates the positive effect of the NIPT approach on improving clinical outcomes for RhD-negative pregnant women while also supporting the sustainability of the wider immunoprophylaxis programme. Overall, integrating NIPT into standard antenatal care advances personalised medicine and patient-centred approaches, where interventions are tailored to individual risk profiles, thereby enhancing both effectiveness and ethical standards in foetal-maternal health [8,28].

LIMITATIONS

When analysing the meta-analysis's results, several limitations need to be considered. The primary limitations were the scarcity of available studies, resulting in less data variation, and the insufficient number of prospective studies. The majority of studies involved were retrospective or model-based and employed a non-randomised approach, which may introduce confounding factors or bias, thereby compromising the internal validity of the results. Several studies used a historical control group, which may introduce bias, as changes in clinical practice, patient care management, and the availability of patient records could influence study results. Therefore, it was presumed that the documentation had been completed correctly previously. Additionally, the sample sizes between intervention and control groups varied considerably across studies, as some used a nationwide population, potentially affecting the reliability and comparability of pooled results. Finally, the economic analyses were mainly model-based, relying on assumptions about pricing and resource utilisation, and may not fully reflect real-world cost fluctuations or differences in healthcare systems.

CONCLUSION

The results of this systematic review and meta-analysis evidently demonstrate the effectiveness of NIPT in determining foetal RhD status in RhD-negative pregnant women. NIPT-guided management effectively decreases unnecessary RhIg administration and reduces RhD alloimmunisation by accurately identifying women with RhD-positive foetuses. Early determination of foetal RhD status supports personalised maternal care, identifies individuals at risk of sensitisation, and prevents unnecessary RhIg administration. From an economic perspective, the universal RhIg prophylaxis approach remains more cost-effective under current healthcare practices. However, as genotyping technologies become more widely available and cost-efficient, the sustainability and clinical value of NIPT are expected to improve substantially. The evidence presented in this review supports the safe and effective application of NIPT in clinical practice, thereby minimising the incidence of RhD alloimmunisation and optimising the use of RhIg prophylaxis. Further studies are needed to evaluate the long-term clinical effects, cost-efficiency, and feasibility of implementing NIPT across different healthcare settings. Strengthening evidence in these domains will be crucial for developing guidelines, optimising resource allocation, and promoting the wider use of personalised RhD prophylaxis in routine antenatal care.

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DISCLOSURE/CONFLICT OF INTEREST

The Authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data are available upon request.

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