

Original article

Maternal vaccination with RSVpreF and risk of hypertensive disorders of pregnancy: a systematic review and meta-analysis

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ARTICLE INFO

Keywords:

Respiratory syncytial virus vaccine
RSVpreF
Hypertensive disorders of pregnancy
Maternal vaccination safety
Gestational hypertension

ABSTRACT

Background: A bivalent respiratory syncytial virus (RSV) prefusion F protein-based vaccine (RSVpreF) was approved in the United States in August 2023 for use during pregnancy to prevent infant RSV-associated lower respiratory tract disease. The pivotal phase 3 trial identified a numerical imbalance in hypertensive disorders of pregnancy (HDP) that did not reach statistical significance; postmarketing observational studies have since reported inconsistent findings. We conducted a systematic review and meta-analysis to assess this association.

Methods: We searched MEDLINE, Embase, CENTRAL, Scopus, [ClinicalTrials.gov](https://clinicaltrials.gov), and WHO ICTRP from inception to Jan 26, 2026, for randomized controlled trials (RCTs) and observational studies comparing HDP outcomes in RSVpreF-vaccinated versus unvaccinated or placebo-receiving pregnant individuals. Unadjusted risk ratios (RRs) were pooled using a random-effects model; adjusted estimates from observational studies were pooled separately by inverse variance methods. This study is registered with PROSPERO (CRD420251026835).

Results: Nine studies were included (3 RCTs, 6 retrospective cohort studies; $n = 148,267$). RSVpreF vaccination was associated with a small but statistically significant increase in overall HDP risk (RR 1.08, 95% CI 1.02–1.13; $p = 0.004$; $I^2 = 44\%$), driven by the observational studies group (1.08, 1.02–1.14; $I^2 = 61\%$); RCTs showed a directionally consistent but non-significant RR (1.12, 0.87–1.43; $I^2 = 0\%$). The association was attributable to gestational hypertension, with no significant association for preeclampsia/eclampsia.

Conclusion: Maternal RSVpreF vaccination was associated with a small increase in HDP attributable to gestational hypertension and driven primarily by observational studies, in which residual confounding remains possible. The benefits of infant RSV prevention remain substantial, and these findings support continued postmarketing surveillance and informed shared decision-making.

1. Introduction

Respiratory syncytial virus (RSV) is the leading cause of infant hospitalization for lower respiratory tract disease worldwide, with the highest burden of severe disease concentrated in the first months of life [1]. Developing a vaccine against RSV has proven to be particularly difficult. In the 1960s, a formalin-inactivated RSV vaccine failed to protect infants and primed them for enhanced respiratory disease upon natural infection, leading to hospitalizations and fatal outcomes [2,3]. This led to years of caution on subsequent vaccine development.

Progress eventually came through advances in structural biology: stabilization of the RSV fusion (F) protein in its prefusion conformation enabled the design of subunit vaccines capable of eliciting potent neutralizing antibodies [4,5]. When administered during pregnancy, such vaccines confer passive protection to newborns through transplacental antibody transfer [6]. In August 2023, a bivalent RSVpreF vaccine became the first vaccine approved for use in pregnancy to prevent RSV-associated lower respiratory tract disease in infants [4,7]. Its approval followed closely on the termination of a clinical trial on a structurally similar candidate, which was halted after an interim

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<https://doi.org/10.1016/j.vaccine.2026.129070>

Received 10 April 2026; Received in revised form 15 August 2026; Accepted 17 August 2026

Available online 29 August 2026

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analysis revealed an excess of preterm births in the vaccine group [8]. In the phase 3 trial of the approved RSVpreF vaccine, preterm births were more frequent among vaccine recipients than placebo recipients, though the differences were not statistically significant, and the available data were insufficient to establish or exclude a causal relationship [9]. The trial also identified a numerical imbalance in hypertensive disorders of pregnancy (HDP) between groups, again without achieving statistical significance [10]. The U.S. Food and Drug Administration addressed these uncertainties by narrowing the approved gestational window to 32 through 36 weeks and requiring postmarketing studies to further evaluate both signals; other regulatory agencies adopted different approval windows [11,12].

The HDP signal warrants particular scrutiny. HDP, encompassing gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), complicates approximately 10% of pregnancies globally and accounts for 15% of maternal deaths [13]. Unlike preterm birth, which the narrowed gestational window may mitigate, HDP could theoretically occur at any point in the third trimester. Because delivery remains the definitive treatment, any vaccine-associated increase in HDP risk has implications for the timing of birth and, by extension, for preterm-related neonatal morbidity.

We conducted a systematic review and meta-analysis to evaluate the association between maternal RSVpreF vaccination and hypertensive disorders of pregnancy, synthesizing evidence from RCTs and post-market observational studies.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and registered with PROSPERO (CRD420251026835).

2.1. Eligibility criteria

Randomized controlled trials (including clinical trials conducted prior to its authorization) and observational studies satisfying the following criteria were eligible for inclusion: (i) studies that included pregnant individuals of any age or gestational stage who received at least one dose of an RSVpreF vaccine approved for use during pregnancy; (ii) studies that compared maternal outcomes to pregnant individuals who did not receive the vaccine (placebo or unvaccinated); and (iii) studies that reported on maternal safety outcomes or adverse events related to hypertensive disorders of pregnancy. No restrictions were placed on language of publication or country of study.

2.2. Search Strategy

A systematic literature search was conducted in the following databases: Cochrane Central Register of Controlled Trials (from inception), MEDLINE (1946 to present), EMBASE (1974 to present), [ClinicalTrials.gov](https://www.clinicaltrials.gov) (2000 to present), SCOPUS, and WHO International Clinical Trials Registry Platform, with a cutoff date of January 26, 2026 [14]. Grey literature sources and regulatory agencies websites were also searched (detailed search strategy in Appendix S1).

2.3. Study selection

Records were imported into EndNote and deduplicated [15]. Two investigators (AA & ML) independently performed title and abstract screening using ASReview, an active machine-learning based screening tool [16,17]. We used the random forest classifier with SBERT feature extraction (RF + SBERT), which captures semantic and contextual information rather than frequency counts of keywords, and has demonstrated the high sensitivity and specificity in simulation studies [18]. A data-driven stopping criterion was applied, stopping screening after

classifying 10% consecutive irrelevant abstracts [18]. Records identified as potentially relevant were imported into Covidence for full-text review by the same two investigators.

2.4. Data extraction

Data extraction was conducted independently and cross-checked by the two reviewers using a standardized data extraction form. Key information extracted included study details, participant characteristics, intervention details, outcomes reported, and results.

2.5. HDP outcome definitions

Anticipating that diagnostic criteria and case ascertainment methods would differ across studies, and lacking a universally accepted case definition for HDP following immunization [13], we included all reported HDP events. Where available, we extracted the study-defined composite HDP outcome directly. For studies reporting individual HDP components only, we derived a composite overall HDP by summing the number of all reported diagnoses (gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome), consistent with a hierarchical clinical spectrum in which each participant is typically classified by their most severe diagnosis [13,19].

2.6. Data synthesis

Meta-analyses were conducted using RevMan Web (Cochrane Collaboration) [20] with random-effects models (DerSimonian-Laird) [21]. Risk ratios (RR) with 95% confidence intervals (CI) were the summary measure, with $RR < 1$ indicating lower risk in the vaccinated group. The primary analysis pooled unadjusted RRs for any HDP using raw event counts. Stratified analyses were performed by study design (RCTs vs observational studies). Adjusted estimates from observational studies were pooled separately using the generic inverse variance method on the log RR scale [22], given low outcome prevalence [23]. Secondary analyses examined individual HDP components among studies reporting these outcomes. Statistical heterogeneity was assessed using the I^2 statistic and Cochran Q test, with $I^2 > 50\%$ indicating substantial heterogeneity [22]. Publication bias was evaluated by funnel plot inspection and Egger's test [24]. Sensitivity analyses included leave-one-out influence analysis.

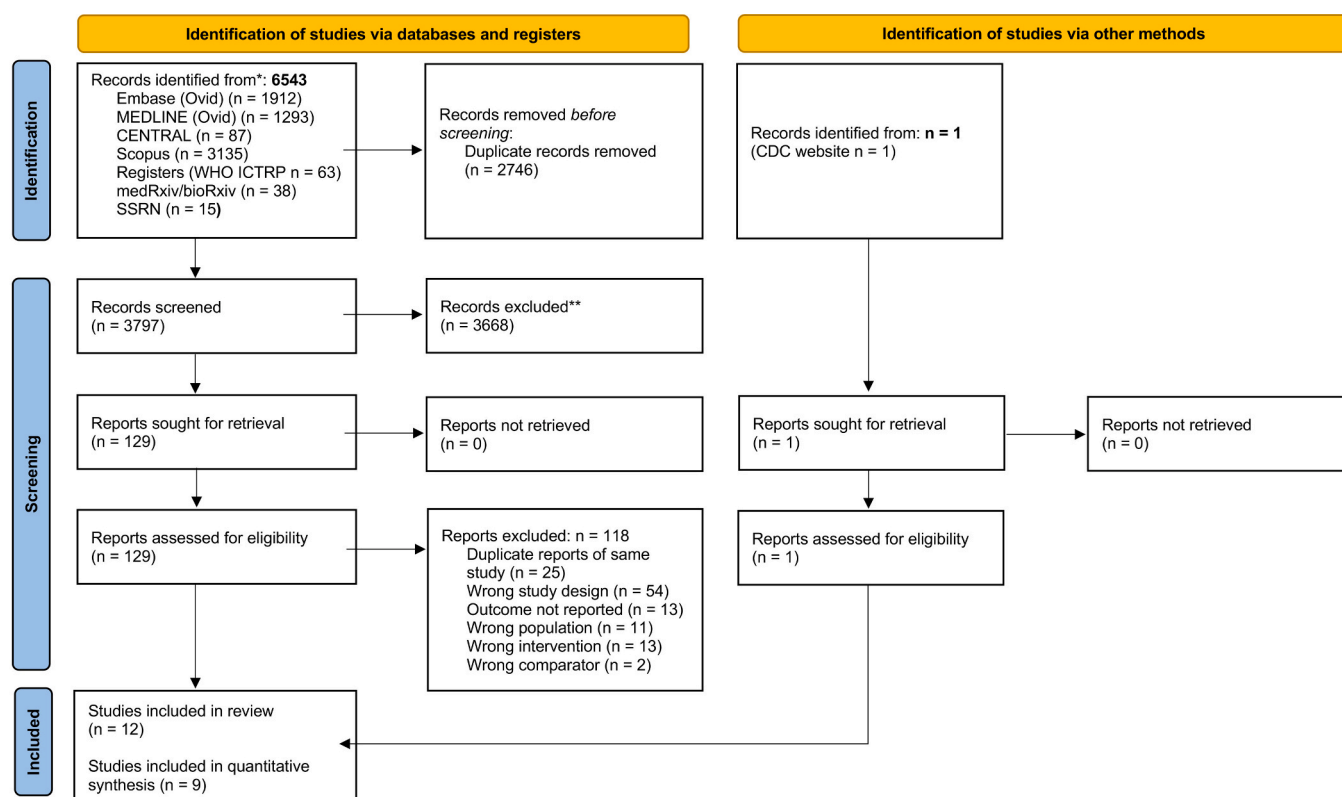
2.7. Risk of bias assessment

Studies were assessed for potential risks of bias independently by the two reviewers. RCTs were assessed using the Cochrane Risk of Bias 2.0 tool (RoB 2) [25]. Observational studies were assessed with the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [26]. Risk-of-bias assessments were visualized using the Risk-of-bias Visualization (robvis) tool [27].

3. Results

3.1. Study selection

Electronic database searches identified 6543 records, with 1 additional record identified from a presentation to the Advisory Committee on Immunization Practices. After deduplication and title/abstract screening, 130 full-text reports were assessed for eligibility, of which 118 were excluded (Fig. 1). Twelve studies initially met the inclusion criteria. Three were subsequently excluded: two for reporting on the same clinical trial [28,29], and one owing to an overlapping population with a larger included study [30]; we retained the study with the larger analytic cohort [31], and the one reporting numeric event counts [10]. The final sample comprised 9 studies: 3 RCTs [10,32,33] and 6 observational studies (Table 1) [31,34–38].



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Fig. 1. PRISMA 2020 flow diagram illustrating the study selection process, from database searches through inclusion of eligible studies in the final synthesis.

3.2. Study characteristics

Included studies spanned North America, Europe, Africa, and the Asia-Pacific region, with 2 multinational trials enrolling as many as 18 countries (Table 1). All studies were conducted between August 2019 and July 2025; most observational studies (5 in the USA and 1 in France) were conducted during the first post-authorization RSV season (September 2023 through February 2024). Three RCTs evaluated the approved RSVpreF vaccine. The phase 2b trial enrolled 406 pregnant individuals and provided preliminary immunogenicity and safety data [32]. The phase 3 MATISSE trial enrolled 7420 participants at 24 to 36 weeks' gestation, and served as the pivotal trial assessing efficacy and safety supporting regulatory approval [10]. The phase 3 MORISOT trial enrolled pregnant individuals living with HIV across 14 South African sites [33].

Six retrospective cohort studies utilized large-scale administrative databases or electronic health records to evaluate post-market safety. DeSilva et al. reported on a target trial emulation within the Vaccine Safety Datalink, a collaborative surveillance system involving the Centers for Disease Control and Prevention and integrated healthcare organizations representing approximately 3% of the US population [38]. Kitano et al. analyzed data from TriNetX, a federated electronic health record network comprising 75 healthcare institutions [31]. Michnick et al. utilized Sentinel-affiliated claims and electronic health record data from five US health plans [35]. Solsman et al. linked statewide birth and fetal death certificates to the Utah Immunization Information System [36]. Son et al. examined health records from two New York City hospitals within a single healthcare system [37]. Gabet et al. analyzed nationwide data from the French National Health Data System, capturing nearly the entire French population [34].

RCTs enrolled between 343 and 7420 participants; observational cohorts ranged from approximately 3000 to nearly 50,000, for a combined total of 148,267 pregnant individuals. Maternal age was broadly similar across studies (means 29–33 years; medians 27–35 years), and gestational age at vaccination spanned 24–36 weeks in the randomized trials and the approved 32- to 36-week window in the post-market studies. Follow-up extended through delivery in most studies (Table 1). Confounding in observational studies was addressed through propensity score matching or multivariable regression, adjusting for gestational age at vaccination, maternal age, obstetric history, and comorbidities.

3.3. Risk of bias of included studies

The three RCTs were considered to have a low risk of bias across all five domains (Appendix Fig. S1). Among the six observational studies, two (Gabet and DeSilva) were rated as low risk, two (Michnick and Son) as moderate risk due to concerns regarding residual confounding and participant selection, and two (Kitano and Solsman) as serious risk driven primarily by limited confounding control. Beyond domain-level ratings, several observational studies had specific methodological considerations that are detailed in the appendix (Fig. S1).

3.4. RSVpreF vaccination and HDP

Table 2 summarises HDP event counts and reported effect estimates. Phase 2b [32] and MORISOT trials [33] had too few events for meaningful comparison. In the MATISSE trial [10], HDP occurred in 3.0% of vaccinated versus 2.6% of placebo recipients. A secondary analysis restricted to participants who delivered preterm reported HDP rates of

Table 1
Characteristics of studies included in the synthesis.

Author (Year)	Study Period	Country	Study Design	Data Source/Trial Registration	Sample Size	N Controls	N Vaccine	Maternal Age	GAV (weeks)	Outcome(s) reported
DeSilva (2025)	Sep 2023 - Feb 2024	USA	Retrospective cohort study	Target trial emulation, Vaccine Safety Datalink (network-based surveillance system)	26,948	13,474	13,474	NR*	32 – <37	HDP composite, gHTN, PE, eclampsia, HELLP
Gabet (2026)	Sep 2024 - Dec 2024	France	Retrospective cohort study	French National Health Data System: Système National des Données de Santé (SNDS)	49,782	24,891	24,891	Mean (SD): 30.9 (5.0)	Median (IQR): 34.7 (33.4–35.7)	HDP composite (included PE, eclampsia, HELLP)
Kampmann (2023)	Jun 2020 - Oct 2023	Multinational (18 countries)	Randomized controlled trial	Phase 3, multicenter, double-blinded, placebo-controlled MATISSE trial (NCT04424316)	7358	3675	3682	Mean (SD): V: 29 (5.6); C: 29 (5.8)	24–36	gHTN, PE, eclampsia, HELLP
Kitano (2026)	Sep 2023 - Jul 2025	USA	Retrospective cohort study	Multi-institutional (TriNetX global database – EHR with the US as a major contributor)	22,530	11,265	11,265	Mean (SD): V:30.3 (5.5); C: 30.2 (5.6)	32–36	HDP composite, gHTN, PE
Michnick (2026)	Sep 2023 - Jun 2024	USA	Retrospective cohort study	U.S. Food & Drug Administration Sentinel-affiliated administrative healthcare records derived from 5 U.S. health plans	13,714	6857	6857	Mean (SD): V: 33.3 (4.4); C: 33.2 (4.4)	32–36	HDP composite, gHTN, PE/eclampsia, HELLP
Myer (2025)	Mar 2024 - Jun 2025	South Africa	Randomized controlled trial	Multicenter Phase 3 trial (MORISOT trial: NCT06325657)	343	171	172	Mean (SD): V:31.3 (5.8); C: 31.0 (6.0)	24–36	gHTN, PE
Simões (2022)	Aug 2019 - Jan 2020	United States, Chile, Argentina, South Africa	Randomized controlled trial	Phase 2b randomized, placebo-controlled trial (NCT04032093)	406	79	327	Median (IQR): 27 (18–42)	24–36.9	gHTN, PE
Solsman (2026)	Sep 2023 - Feb 2024	USA	Retrospective cohort study	Utah Statewide Immunization Information System (USIIS)	24,213	21,480	2733	NR*	32–36	HDP composite
Son (2024)	Sep 2023 - Jan 2024	USA	Retrospective cohort study	Electronic health records (EHR): 2 New York City hospitals within 1 health care system	2973	1962	1011	Median (IQR): V: 35.3 (33.1–38.1); C: 34.6 (31.9–37.3)	32–36	HDP composite, gHTN, PE, HELLP

Abbreviations: C, control/placebo group; EHR, electronic health record; GAV, gestational age at vaccination; gHTN, gestational hypertension; HDP, hypertensive disorders of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelet count; NR, not reported; PE, preeclampsia; RCT, randomized controlled trial. * Only maternal age categories were reported.

Table 2
HDP outcomes and reported effect estimates.

Study ID	Vaccinated		Control		Reported Effect Measure	
	Events	N	Events	N	%	Estimate (95% CI)
Simões, 2022	6	327	2	79	2.5	-
Kampmann, 2023†	112	3682	94	3675	2.6	NA*
Myer, 2025	13	172	16	170	9.4	NA*
DeSilva, 2025	2344	13,474	2056	13,474	15.3	aRR
Gabet, 2026‡	267	24,891	255	24,891	1.0	wIRR
Kitano, 2026	3130	11,265	3099	11,265	27.5	OR
Michnick, 2026	939	6857	858	6857	12.5	aHR
Solsman, 2026	267	2733	1959	21,480	9.1	aOR
Son, 2024	203	1011	355	1962	18.1	HR
						aOR
						HR§
						1.43 (1.16–1.77)

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio; HR, hazard ratio; NA, not applicable; OR, odds ratio; wIRR, weighted incidence rate ratio.
† Composite HDP events derived by summing gestational hypertension and preeclampsia from the serious adverse events table and eclampsia and HELLP events from the primary report; severe or life-threatening preeclampsia events within one month of vaccination are nested within these counts.

‡ Reported a composite HDP outcome defined as preeclampsia, eclampsia, and HELLP syndrome.

§ Time-dependent Cox regression to address immortal time bias.

* RCTs reported event counts for individual HDP components only; no effect measures were reported. The overall HDP composite was derived by summing events across reported categories.

20.4% versus 14.5% (RR, 1.40; 95% CI, 0.89–2.20) [39]. Across the 6 observational studies, point estimates for overall HDP were above 1.0 in all six (Table 2). Two reported associations that excluded the null: DeSilva et al. reported an adjusted risk ratio of 1.09 (95% CI, 1.03–1.15) [38], and Son et al. found an increased risk when addressing immortal time bias through time-dependent Cox regression (HR, 1.43; 95% CI, 1.16–1.77) [37], with stratified analyses suggesting the association varied by insurance type and hospital site. In sensitivity analyses, several studies observed elevated HDP risk: Kitano et al. [31] reported increased risk when the vaccination window was expanded to 28–36 weeks' gestation (OR, 1.09; 95% CI, 1.03–1.15), and when vaccination ascertainment was restricted to procedure codes (OR, 1.16; 95% CI, 1.11–1.20). The 28–36 week window falls outside the licensed indication in the United States but within those approved in the European Union (from 24 weeks) and the United Kingdom (from 28 weeks). Gabet et al. [34], in an analysis restricted to pertussis-vaccinated women, found increased preeclampsia risk among those vaccinated at or before 32 weeks' gestation (wIRR, 1.73; 95% CI, 1.06–2.83).

3.5. Meta-analysis results

Pooling unadjusted RR across included studies, RSVpreF vaccination was associated with a statistically significant increased risk of HDP (RR 1.08; 95% CI, 1.02–1.13; $P = 0.004$; $I^2 = 44\%$) (Fig. 2). The leave-one-out analysis demonstrated robustness of the primary findings, with pooled estimates ranging from 1.04 to 1.12 across iterations (Table S1). No single study disproportionately influenced the overall result, and the direction of effect persisted across all iterations. Stratified by study design, both RCTs (RR 1.12; 95% CI, 0.87–1.43; $I^2 = 0\%$) and observational studies (RR 1.08; 95% CI, 1.02–1.14; $I^2 = 61\%$) showed same direction of effect, with statistical significance reached only in the observational stratum (Fig. S2).

3.6. Adjusted analysis

Six observational studies reported adjusted effect estimates accounting for potential confounders through propensity score methods or multivariable regression (Table S2). The pooled estimate was directionally concordant with the primary analysis (RR 1.07; 95% CI, 1.00–1.15; $I^2 = 57\%$) (Fig. 3).

3.7. Gestational hypertension

Among the seven studies reporting on gestational hypertension ($n = 71,516$), RSVpreF vaccination was associated with a 9% increased risk (RR 1.09; 95% CI, 1.04–1.13; $P < 0.0001$) (Fig. 4).

3.8. Preeclampsia/eclampsia

Among seven studies reporting on preeclampsia/eclampsia ($n = 74,270$), no significant association with RSVpreF vaccination was observed (RR 1.04; 95% CI, 0.89–1.21; $P = 0.62$), though heterogeneity was substantial ($I^2 = 80\%$; $P < 0.0001$) (Fig. 5).

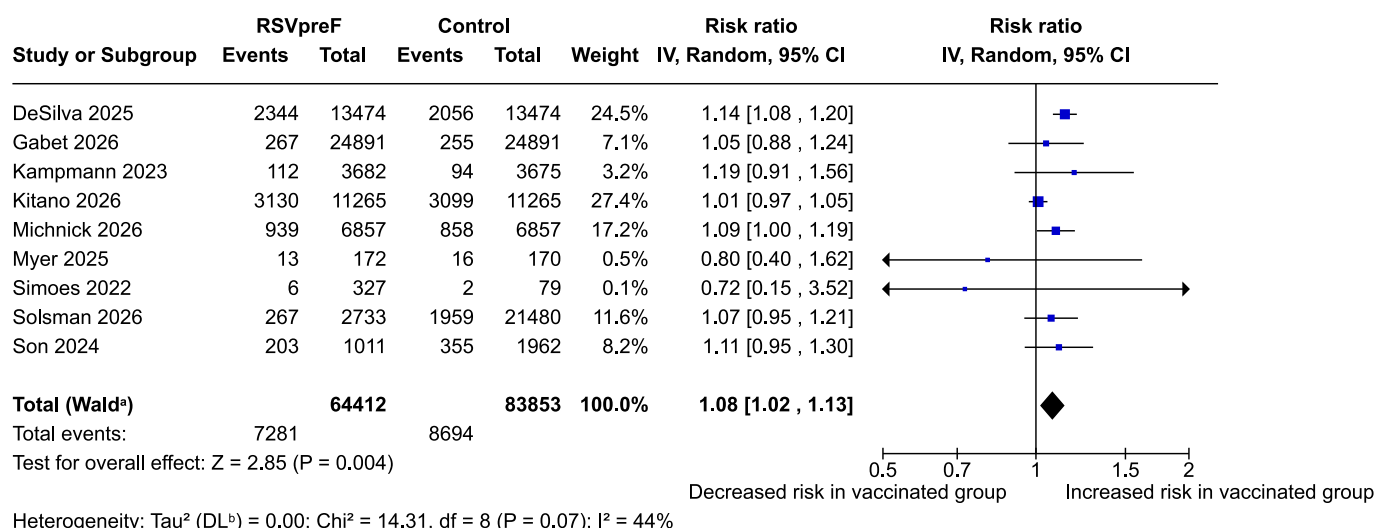
3.9. Publication Bias

Funnel plot inspection revealed no marked asymmetry, and Egger's test indicated no evidence of publication bias ($P = 0.45$) (Fig. S3).

4. Discussion

4.1. Principal findings

Our synthesis of nine clinical and observational studies encompassing nearly 150,000 pregnant individuals found that maternal RSVpreF vaccination may be associated with a small increase in hypertensive

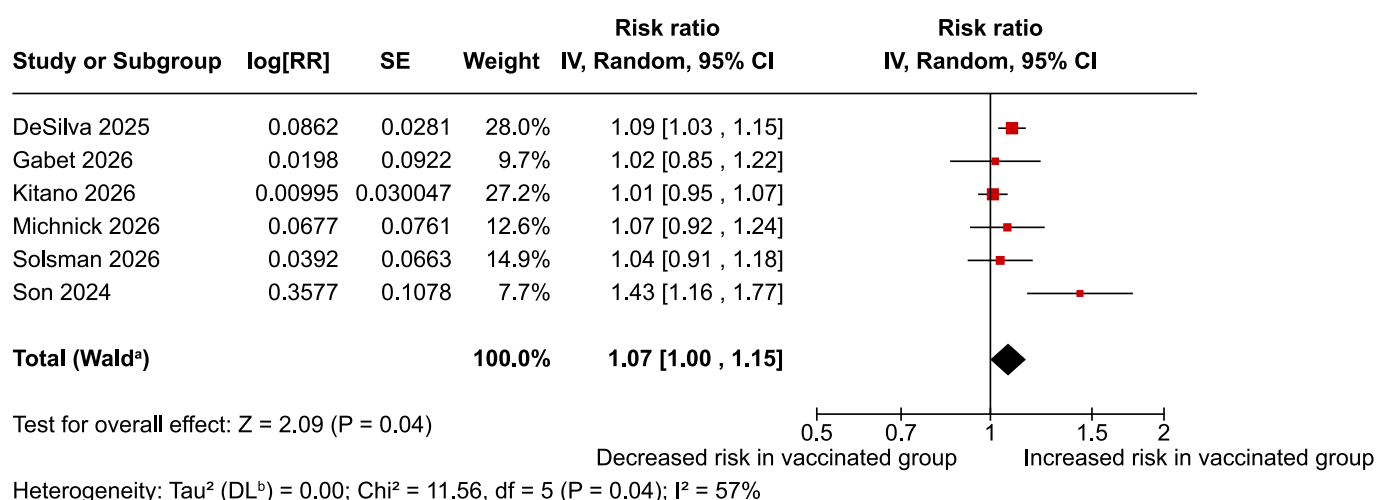


Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

Fig. 2. Forest plot of the association between maternal RSVpreF vaccination and hypertensive disorders of pregnancy. Pooled unadjusted risk ratios from 9 studies using a random-effects model (DerSimonian-Laird). The diamond represents the pooled estimate; horizontal lines represent 95% confidence intervals.



Footnotes

^aCI calculated by Wald-type method.

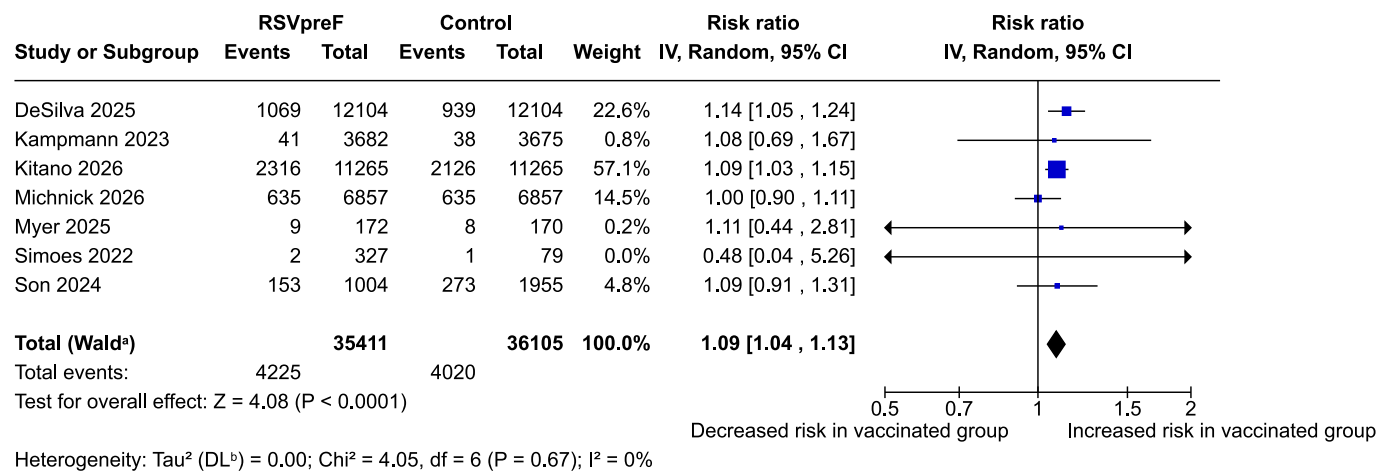
^bTau² calculated by DerSimonian and Laird method.

Fig. 3. Forest plot of adjusted risk ratios for hypertensive disorders of pregnancy following maternal RSVpreF vaccination. Pooled estimates from 6 observational studies using generic inverse variance method. The diamond represents the pooled estimate; horizontal lines represent 95% confidence intervals.

disorders of pregnancy. The pooled estimate indicates an 8% increase in risk (RR 1.08; 95% CI, 1.02–1.13). Statistical significance was reached only in the observational stratum; the pooled estimate from the three randomized trials was consistent in direction but did not reach significance (RR 1.12; 95% CI, 0.87–1.43). These trials had few events to detect a difference of this size, and were restricted to women with uncomplicated pregnancies at no known increased risk of complications. The association appears to be specific to gestational hypertension: we found no statistically significant increase in preeclampsia or eclampsia. Notably, among MATISSE trial participants who delivered preterm, HDP rates were 20.4% in vaccine recipients versus 14.5% in placebo recipients (RR 1.40; 95% CI, 0.89–2.20) [10,39], a difference that was not statistically significant and derives from a small post hoc subgroup.

Given that HDP is a leading indication for medically indicated preterm delivery, the relationship between the two outcomes warrants examination in future studies.

Two included studies reported sensitivity analyses suggesting that gestational timing may modify this risk. One study reported a significant increase when the vaccination window was expanded to 28–36 weeks, earlier than the licensed 32–36 week indication [31], and another restricted to pertussis-vaccinated women, identified elevated preeclampsia risk only among those vaccinated at or before 32 weeks [34]. Both observations remain hypothesis-generating and do not constitute evidence of a timing-dependent effect. Whether HDP risk varies by gestational week within the licensed 32–36 week interval cannot be determined from the available data; addressing this would require



Footnotes

^aCI calculated by Wald-type method.
^bTau² calculated by DerSimonian and Laird method.

Fig. 4. Forest plot of the association between maternal RSVpreF vaccination and gestational hypertension. Pooled unadjusted risk ratios from 7 studies using a random-effects model.

studies with prespecified stratification by gestational age at vaccination.

4.2. Comparison with GSK maternal vaccine and existing literature

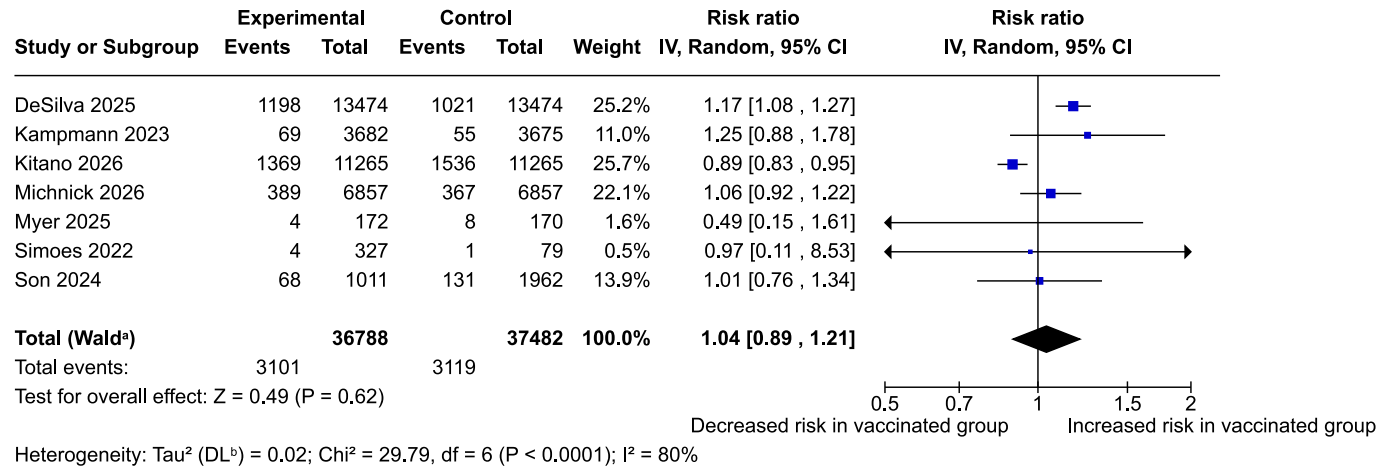
Different RSV vaccines have yielded divergent safety profiles. The GSK RSVPreF3-Mat program was terminated following the phase 3 trial's demonstration of increased preterm birth [8], a safety signal that did not emerge with Pfizer's formulation, despite structural similarities between the two prefusion F proteins [40,41]. Notably, GSK trials did not demonstrate statistically significant increases in hypertensive disorders of pregnancy, though numerical imbalances were observed [42,43]. Prior meta-analyses that pooled phase 3 trials across heterogeneous platforms, including Pfizer's RSVpreF, GSK's RSVPreF3, and Novavax's nanoparticle vaccine, reported a pooled risk ratio for gestational hypertension of 1.10 (95% CI, 0.89–1.36) that did not reach statistical significance [44].

Passive surveillance offers a further, though limited, source of

evidence. Although the Vaccine Adverse Event Reporting System identified few reports of hypertensive disorders of pregnancy, a disproportionality signal for preterm birth was detected, with reports occurring more frequently than statistically expected, predominantly between 32 and 37 weeks of gestation [45]. Given that HDP are among the leading causes of iatrogenic preterm delivery, this finding may represent a downstream manifestation of the HDP signal identified in our meta-analysis and is consistent with the elevated HDP rates observed among participants who delivered preterm in the MATISSE trial. These findings must nonetheless be interpreted cautiously given the inherent limitations of passive surveillance.

4.3. Contextualizing HDP risk across maternal vaccines

Prior studies have examined hypertensive disorders of pregnancy following maternal vaccination with other routinely recommended vaccines. Influenza vaccination during pregnancy has not been



Footnotes

^aCI calculated by Wald-type method.
^bTau² calculated by DerSimonian and Laird method.

Fig. 5. Forest plot of the association between maternal RSVpreF vaccination and preeclampsia or eclampsia. Pooled unadjusted risk ratios from 7 studies using a random-effects model.

associated with gestational hypertension or preeclampsia in multiple large cohorts [46–49]. Tdap vaccination during pregnancy has not been consistently associated with hypertensive disorders after confounder adjustment [50,51]. mRNA COVID-19 vaccination before 20 weeks of gestation showed consistently elevated but not statistically significant risk for gestational hypertension and preeclampsia-eclampsia-HELLP syndrome, with a borderline association for preeclampsia among first-trimester recipients [52]. Consistent with this last observation, another study reported that COVID-19 vaccination around the time of conception or in the first trimester was associated with a small increased risk of hypertensive disorders, driven largely by gestational hypertension [53]. This effect size parallels what we observed with RSVpreF.

4.4. Biological plausibility

The biological mechanisms linking maternal vaccination to placental vascular dysfunction remain speculative. Preeclampsia is understood to originate from inadequate spiral artery remodeling in early pregnancy, leading to placental ischemia and a downstream systemic inflammatory and endothelial response [54]. Vaccines induce transient cytokine release and immune activation responses are generally self-limited and mild compared with natural infection [55]. Whether RSVpreF elicits a distinct inflammatory profile, whether immune complex formation could impair placental perfusion, or whether vaccination unmasks pre-existing endothelial vulnerability in susceptible individuals is unknown.

4.5. Clinical implications

These uncertainties have implications for clinical decision-making. Although the relative increase in risk observed in our meta-analysis is small and confined to gestational hypertension, the benefits of infant RSV prevention remain substantial. Clinicians may nonetheless wish to take these findings into account when counselling women whose baseline risk of hypertensive disease is already elevated. Women with history of chronic hypertension, prior preeclampsia, or multifetal gestation may warrant enhanced monitoring following vaccination; current evidence is insufficient to recommend withholding immunization within these or any other group. The availability of long-acting monoclonal antibody administered directly to infants offers an alternative route to infant protection [56,57]. Prevention strategy in practice will depend on accessibility, cost-effectiveness, individual maternal risk profiles, and clinical and patient choice [58].

4.6. Strengths and limitations

This synthesis represents a comprehensive assessment of all relevant studies of HDP risk following maternal RSVpreF vaccination reported to date. We incorporated evidence from randomized trials and real-world data following market authorization across diverse geographic and clinical settings. The inclusion of studies with varied analytic approaches, including randomized trials, target trial emulations, and propensity score-matched cohorts, produced consistent estimates across methodologically distinct designs. The large cumulative sample size and representation of multiple national databases enhance generalizability beyond pivotal trial populations, which applied restrictive obstetric eligibility criteria.

Several limitations are acknowledged. Observational studies remain susceptible to residual confounding, despite adjustment for measured covariates. The direction of any remaining bias is uncertain: healthy vaccinee effects may lead more health-engaged women to seek vaccination, potentially underestimating the true association, while preferential recommendation of vaccination to higher-risk pregnancies could inflate it. A specific concern in the included observational studies is

immortal time bias: women must remain pregnant and outcome-free until approximately 32 weeks to be eligible to receive the vaccine, which could bias the unvaccinated group toward including more early-onset cases. Gestational age at vaccination also differed between study designs: while observational studies captured vaccination within the approved 32–36 weeks window, all three RCTs enrolled participants from 24 weeks' gestation onward, limiting direct comparability and potentially contributing to the heterogeneity observed in pooled analyses. The low HDP rates observed in both arms of the MATISSE trial, well below population-level estimates, further reflect enrolment of a selected lower-risk population during the COVID-19 pandemic, when antenatal care utilization was atypical; this likely attenuated statistical power to detect a vaccine-associated signal within the trial. Also, heterogeneity in HDP outcome definitions introduces variability that could bias effect estimates. Observed HDP prevalence varied across studies, reflecting potential differences in surveillance or diagnostic coding practices. For the included RCTs, we derived composite HDP estimates by summing reported subtypes, although mutually exclusive classification was rarely stated explicitly, overlap was likely minimal given the small number of eclampsia and HELLP events.

5. Conclusion

In summary, this analysis revealed that maternal RSVpreF vaccination is associated with a small increase in the risk of HDP. The association was driven primarily by observational studies, in which residual confounding remains possible. These findings support continued vigilance through postmarketing surveillance and careful consideration of gestational timing within the currently approved window.

CRediT authorship contribution statement

Abdallah Alami: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Meghan Lewis:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Darine El-Chaar:** Writing – review & editing. **Mark Walker:** Writing – review & editing. **Shi Wu Wen:** Writing – review & editing. **Daniel Krewski:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Funding

The study was conducted independently, and no funding is relevant to this study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2026.129070>.

Data availability

This study is a systematic review and meta-analysis based on aggregate data extracted from published studies; no individual participant data were collected or held by the authors.

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