Review Article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

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Safety and efficacy of maternal RSV vaccination: a systematic review and meta-analysis

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Respiratory syncytial virus (RSV) maternal vaccination has emerged as a preventive strategy to confer passive immunity to newborn during their early vulnerable months of life. In this review, we aim to assess the efficacy and safety of maternal RSV vaccines. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines for systematic reviews and meta-analyses. Our literature search covered MEDLINE via PubMed, Scopus, Web of Science, and Cochrane. We included randomized controlled trial (RCTs) that assessed the safety and efficacy of maternal RSV vaccines. The overall effect estimates for efficacy outcomes, including RSV-associated lower respiratory tract infection (LRTI), severe LRTI, and hospitalizations, demonstrated statistically significant benefits favoring the maternal RSV vaccine group (risk ratio [RR], 0.44, 95% confidence interval [CI], 0.31, 0.62, p=0.0001; RR, 0.30, 95% CI, 0.19, 0.48, p=0.0001; RR, 0.53, 95% CI, 0.37, 0.75, p=0.0004, respectively). Additionally, no statistically significant differences were identified for fetal or neonatal safety outcomes, including congenital abnormalities, intrauterine growth restriction, stillbirth, or infant death. Regarding preterm birth, the overall effect estimate did not show a significant difference between the vaccine and control groups (RR, 1.16, 95% CI, 0.96, 1.41, p=0.12). Maternal RSV vaccination provides protection against RSV-associated lower respiratory tract illness in infants with no major safety concerns. However, current evidence remains limited, and additional data from high-quality RCTs are required to confirm or refute these findings.

Trial Registration: PROSPERO Identifier: CRD42024541771

Keywords: Respiratory syncytial viruses; Respiratory tract infections; Infant; Vaccination

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract illness in infants worldwide [1]. Nearly all children are infected with RSV at least once during the first 2 years of life [2]. Annually, RSV is responsible for around 3.6 million hospitalizations and more than 100,000 deaths in children under 5 years old. Almost half of these mortalities occur within the first 6 months of age [3]. In addition, mortality rates are significantly elevated in low- and middle-income countries (LMICs) [4].

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Severe RSV illness in infancy is associated with comorbidities, such as recurrent wheezing and/or asthma in later childhood [5]. Consequently, the urge for the development of an RSV immunization strategy to combat the virus has emerged, and trials have been ongoing for the past 6 decades.

In the 1960s, active immunization of infants and toddlers with a formalin-inactivated, whole-virus vaccine was tested. However, the results revealed that the vaccine group might face a higher risk of more severe illness during subsequent natural RSV infections [6]. Further trials have been impeded by challenges in achieving a balance between side effects and immunogenicity [7]. Moreover, due to the lack of sufficient time after birth for active immunization of infants to induce their immunity [8-10], passive immunization via maternal vaccination has been proposed as an effective strategy to prevent severe infection during early infancy [3,11].

Passive immunity through the transfer of IgG antibodies from immunized pregnant women has already been endorsed by the World Health Organization to protect infants from other pathogens such as pertussis, tetanus, coronavirus (coronavirus disease 2019 [COVID-19]), and influenza [12-14]. Recently, many types of maternal RSV vaccines have been investigated to identify their safety profile and immunogenicity. Published randomized controlled trials (RCTs) data were not harmonious, which created a knowledge gap that needed to be filled. The aim of this study is to summarize data and synthesize evidence regarding the safety and efficacy of the maternal RSV vaccine within a systematic review and meta-analysis framework.

METHODS

Study registration

We registered the protocol in the PROSPERO database (CRD42024541771). This systematic review and meta-analysis was reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [15]. Each procedural step was rigorously executed according to the methodologies outlined in the Cochrane Handbook for Systematic Reviews of Interventions [16].

Literature search strategy

We searched electronic databases including MEDLINE via PubMed, Scopus, Web of Science, and Cochrane. Articles were identified using the following strategy: ("respiratory syncytial virus" AND vaccine AND maternal). No restrictions by language or publication period were employed.

Eligibility criteria

Studies were included in our review if they satisfied the following criteria: (1) Population: pregnant women and their infants; (2) Intervention: RSV vaccine administration in pregnant women; (3) Comparator: placebo; (4) Outcomes: at least one of the following outcomes must have been reported in the included study (RSV-associated lower respiratory tract illness, severe RSV-associated lower respiratory tract illness, RSV-associated hospitalizations, premature birth, time interval between vaccination/delivery, and local/systemic maternal reactions); (5) Study design: RCTs.

We excluded studies that did not match these criteria. Additionally, we excluded studies that were only available as conference abstracts or protocols and those lacking complete full texts.

Selection of studies

Four authors (Farag A, Elkholy MKA, Genidy AM, Eltobgy A) independently screened the studies according to the previously mentioned eligibility criteria. Eligibility screening was performed in 2 steps: the first step was to screen abstracts for eligibility. In the second step, full-text articles of eligible abstracts were retrieved and screened for inclusion eligibility.

Data extraction

Two authors (Genidy AM, Eltobgy A) extracted the data independently using an online data extraction form. The extracted data includes the following: (1) summary of included studies; (2) risk of bias domains; and (3) study outcomes. Discrepancies were resolved through discussion or by 2 other investigators (Farag A, Elkholy MKA).

Assessment of risk of bias

To evaluate the risk of bias in each included study, we used the Cochrane Risk of Bias 2.0 assessment tool for randomized trials (RoB 2) [17]. We assessed bias from an intention-to-treat perspective across 5 domains: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in the measurement of outcomes, and bias in the selection of reported results. Each domain and the overall study were assigned a risk of bias rating of 'low,' 'some concerns,' or 'high.' An overall 'low' risk of bias was given only if all domains were rated 'low'; an overall 'some concerns' rating was assigned if one or more domains were rated 'some concerns'; and an overall 'high' risk of bias was assigned if one or more domains were rated 'high.'

Data synthesis

Dichotomous data were pooled as risk ratios (RRs) and continuous data as mean differences (MDs), each with 95% confidence intervals (CIs). For the meta-analysis, a random effects model using the Mantel-Haenszel method was employed. We conducted the analysis using the meta package (R software, version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Subgroup analysis

Given the variety of RSV vaccine formulations used in the included studies, we performed a subgroup analysis to stratify the impact of each vaccine type on the primary outcomes.

Assessment of heterogeneity

Heterogeneity was assessed through visual inspection of the forest plots and measured using the I^2 and χ^2 tests. Significant heterogeneity was defined as a p-value <0.1 for the χ^2 test. The I^2 test was used to quantify the magnitude of heterogeneity, following the recommendations of the Cochrane Handbook for Systematic Reviews and Meta-Analysis.

Sensitivity analysis

We performed sensitivity analyses to ensure that none of the included studies affected the results and to examine whether the overall effect size is statistically robust. In each scenario, we excluded one study. Additionally, in cases of significant heterogeneity (χ^2 p<0.1), sensitivity analyses were conducted to address the heterogeneity.

Assessment of reporting biases

Reporting biases occur when the publication of research findings is influenced by the nature and direction of results [18]. While funnel plots can offer valuable insights, they may suggest publication bias. However, their ability to detect such effects may be limited when the number of studies is small [19,20]. Therefore, publication bias was assessed using Egger's regression test.

RESULTS

On the 22nd of March 2024, our literature search across electronic databases, including MEDLINE via PubMed, Scopus, Web of Science, and Cochrane, retrieved a total of 4,095 records. Following a meticulous full-text screening process, 7 studies met the eligibility criteria for inclusion in our study (see Methods section for detailed eligibility criteria for inclusion in our study). A comprehensive depiction of the literature search and selection process is delineated in the PRISMA flow diagram **Fig. 1**. A summary of the included studies design, vaccine formulations, and main results is shown in **Table 1**.

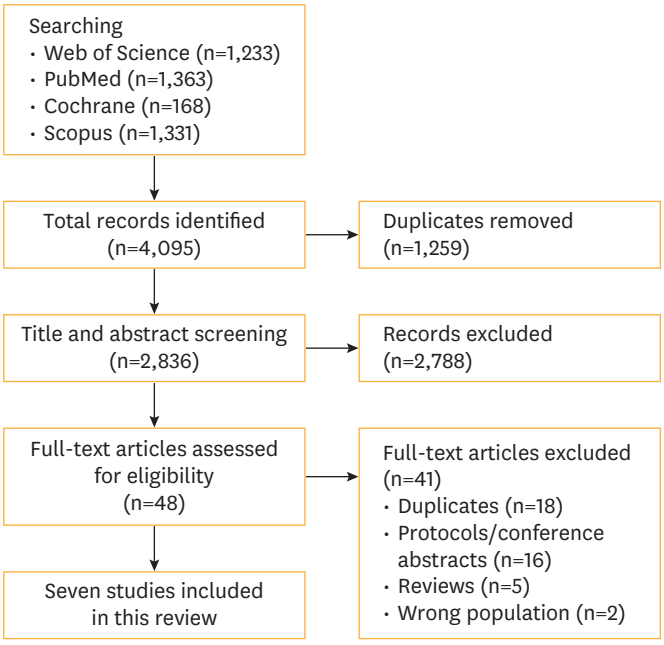

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

We assessed all the included studies [21-27] for risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2). One RCT study [21] was rated as having a high risk of bias, and one RCT study [23] was rated as having some concern regarding the risk of bias. The remaining 5 RCTs [22,24-27] were rated as having a low risk of bias. A summary of the risk of bias (RoB 2) assessment domains of included studies is shown in **Figs. 2** and **3**.

We used Egger's regression test to determine the small-study effects for the primary outcomes. The results of Egger's test for publication bias are illustrated in **Supplementary Table 1**. Also, a summary of the meta-analysis results is shown in **Table 2**.

Neonatal clinical outcomes

RSV-associated severe lower respiratory tract illness (primary outcome)

Six studies, representing 17,403 patients, reported data on RSV-associated severe lower respiratory tract illness. The overall effect estimate showed a statistically significant difference favoring the RSV vaccine group (RR, 0.30, 95% CI, 0.19, 0.48, p<0.0001); pooled studies were homogenous (p=0.47; I^2=0%; **Fig. 4**). Similarly, subgroup analysis

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Table 1. Summary of the included studies

References	Study design	Study phase	Study period	Location	Sponsor	Arms	Sample size		Study participants	Intervention			Conclusion	
							Mothers	Infants		Intervention type	Intervention dose	Time of administration	Efficacy	Safety
Munoz et al. (2003) [21]	RCT	N/A	N/A	USA	Wyeth Lederle	Adjuvanted RSV F protein (50 μg)	20	20	Singleton healthy pregnant women (third trimester)	Purified F protein with aluminum hydroxide	Single dose (IM)	30–34 wk of gestation	Efficacious	No evident safety concerns
						Placebo	15	15		Saline	Single dose (IM)			
Muñoz et al. (2019) [24]	RCT	Phase 2	2014–2015	USA	Novavax	Adjuvanted RSV F protein (120 μg)	22	22	Singleton healthy pregnant women (third trimester)	Purified F protein with aluminum phosphate	Single dose (IM)	33–35 wk of gestation	Efficacious	No evident safety concerns
						Placebo	28	28		Saline	Single dose (IM)			
Madhi et al. (2020) [25]	RCT	Phase 3	2015–2018	11 countries	Novavax	Adjuvanted RSV F protein (120 μg)	3,051	3,029	Singleton healthy pregnant women (third trimester)	Purified F protein with aluminum phosphate	Single dose (IM)	28–36 wk of gestation	Suggested potential benefits	No evident safety concerns
						Placebo	1,585	1,574		Formulation buffer (without aluminum)	Single dose (IM)			
Simões et al. (2022) [26]	RCT	Phase 2b	2019–2020	USA, Chile, Argentina, South Africa	Pfizer	Unadjuvanted RSVpreF (120 μg)	79	79	Singleton healthy pregnant women (late second and third trimester)	Bivalent purified prefusion F protein with/ without aluminum hydroxide	Single dose (IM)	24–36 wk of gestation	Efficacious	No evident safety concerns
						Adjuvanted RSVpreF (120 μg)	84	84						
						Unadjuvanted RSVpreF (240 μg)	78	77						
						Adjuvanted RSVpreF (240 μg)	86	85						
						Placebo	79	78			Single dose (IM)			
Bebia et al. (2023) [23]	RCT	Phase 2	2019–2021	9 countries	GSK	Unadjuvanted RSVpreF (60 μg)	70	67	Singleton healthy pregnant women (third trimester)	Purified prefusion F protein	Single dose (IM)	28–33 wk of gestation	Efficacious	No evident safety concerns
						Unadjuvanted RSVpreF (120 μg)	75	73						
						Placebo	68	66		Saline	Single dose (IM)			
Kampmann et al. (2023) [27]	RCT	Phase 3	2020–2022	18 countries	Pfizer	Unadjuvanted RSVpreF (120 μg)	3,695	3,570	Singleton healthy pregnant women (late second and third trimester)	Bivalent purified prefusion F protein	Single dose (IM)	24–36 wk of gestation	Efficacious	No evident safety concerns
						Placebo	3,697	3,558		N/A	Single dose (IM)			
Dieussaert et al. (2024) [22]	RCT	Phase 3	2020–2022	24 countries	GSK	Unadjuvanted RSVpreF (120 μg)	3,557	3,494	Singleton healthy pregnant women (late second and third trimester)	Purified prefusion F protein	Single dose (IM)	24–34 wk of gestation	Efficacious	Major safety concerns related to the risk of preterm birth
						Placebo	1,771	1,739		Sucrose reconstituted in NaCl solution	Single dose (IM)			

RCT, randomized controlled trial; N/A, not available; GSK, GlaxoSmithKline; IM, intramuscular injection.

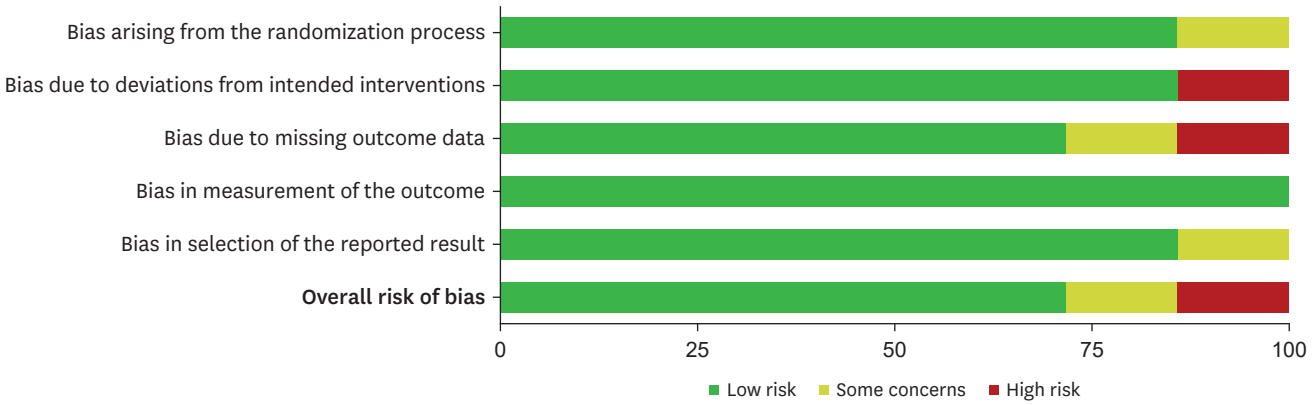

Fig. 2. Risk of bias summary.

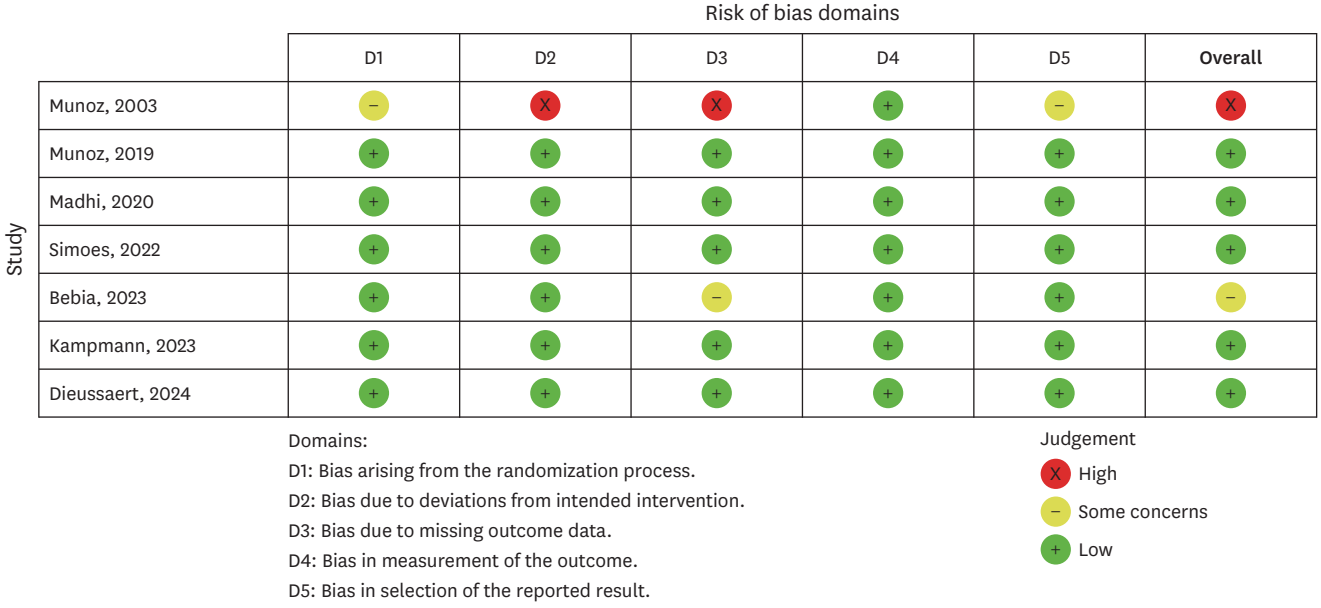

Fig. 3. Risk of bias traffic light.

demonstrated a statistically significant reduction in RSV-associated severe lower respiratory tract illness across all RSV vaccine formulations.

We conducted a sensitivity analysis for RSV-associated severe lower respiratory tract illness by systematically excluding one study at a time (**Supplementary Fig. 1**). The results indicated that the exclusion of any single study did not significantly alter the overall effect size, confirming the statistical robustness of our findings regarding RSV vaccine efficacy.

RSV-associated lower respiratory tract illness (primary outcome)

Five studies, encompassing 17,353 patients, reported data on RSV-associated lower respiratory tract illness. The overall effect estimate indicated a statistically significant difference favoring the RSV vaccine group (RR, 0.44, 95% CI, 0.31, 0.62, p<0.0001); pooled studies were homogenous (p=0.25; I^2=25.8%; **Fig. 5**). Similarly, subgroup analysis demonstrated a statistically significant reduction in RSV-associated lower respiratory tract illness across all RSV vaccine formulations.

We conducted a sensitivity analysis for RSV-associated lower respiratory tract illness by systematically excluding one study at a time (**Supplementary Fig. 2**). The results indicated that the exclusion of any single study did not significantly alter the overall effect size, confirming the statistical robustness of our findings regarding RSV vaccine efficacy.

Hospitalization (primary outcome)

Four studies, including 12,216 patients, presented data on RSV-associated hospitalization. The overall effect estimate demonstrated a statistically significant difference in favor

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Table 2. Meta-analysis summary

Category	Outcome	Effect size type	Value	95% CI	p-value	Heterogeneity (I^2)	Effect direction
Neonatal clinical outcomes	RSV-associated severe LRTI	RR	0.30	0.19, 0.48	<0.0001	0.00%	↓ Lower with the vaccine
	RSV-associated LRTI	RR	0.44	0.31, 0.62	<0.0001	25.80%	↓ Lower with the vaccine
	Hospitalization	RR	0.53	0.37, 0.75	0.0004	18.50%	↓ Lower with the vaccine
	Infant death	RR	0.74	0.35, 1.54	0.5978	49.40%	No significant difference
Obstetric outcomes	Preterm birth	RR	1.16	0.96, 1.41	0.1231	16.40%	No significant difference
	Time interval between vaccination and delivery	MD	0.04	–1.03, 1.10	0.9443	0.00%	No significant difference
	Stillbirth	RR	0.89	0.49, 1.61	0.7066	0.00%	No significant difference
	Preeclampsia	RR	1.01	0.81, 1.25	0.9498	0.00%	No significant difference
	Intrauterine growth restriction	RR	1.27	0.73, 2.24	0.3994	0.00%	No significant difference
	Congenital abnormalities	RR	0.96	0.88, 1.04	0.3082	0.00%	No significant difference
Maternal safety outcomes	Local swelling	RR	5.71	4.40, 7.40	<0.0001	0.00%	↑ Higher with the vaccine
	Local pain	RR	4.28	3.86, 4.76	<0.0001	0.00%	↑ Higher with the vaccine
	Local erythema	RR	6.01	4.29, 8.42	<0.0001	0.00%	↑ Higher with the vaccine
	Vomiting	RR	1.16	1.02, 1.32	0.0213	0.00%	↑ Higher with the vaccine
	Headache	RR	1.10	0.97, 1.24	0.1435	45.60%	No significant difference
	General joint pain	RR	1.12	1.00, 1.25	0.0430	0.00%	↑ Higher with the vaccine
	Fever	RR	0.94	0.75, 1.18	0.5837	0.00%	No significant difference
	Fatigue	RR	1.06	1.01, 1.12	0.0253	0.00%	↑ Higher with the vaccine
	Diarrhea	RR	0.91	0.51, 1.65	0.2850	0.00%	No significant difference

CI, confidence interval; RSV, respiratory syncytial virus; LRTI, lower respiratory tract infection; RR, risk ratio; MD, mean difference.

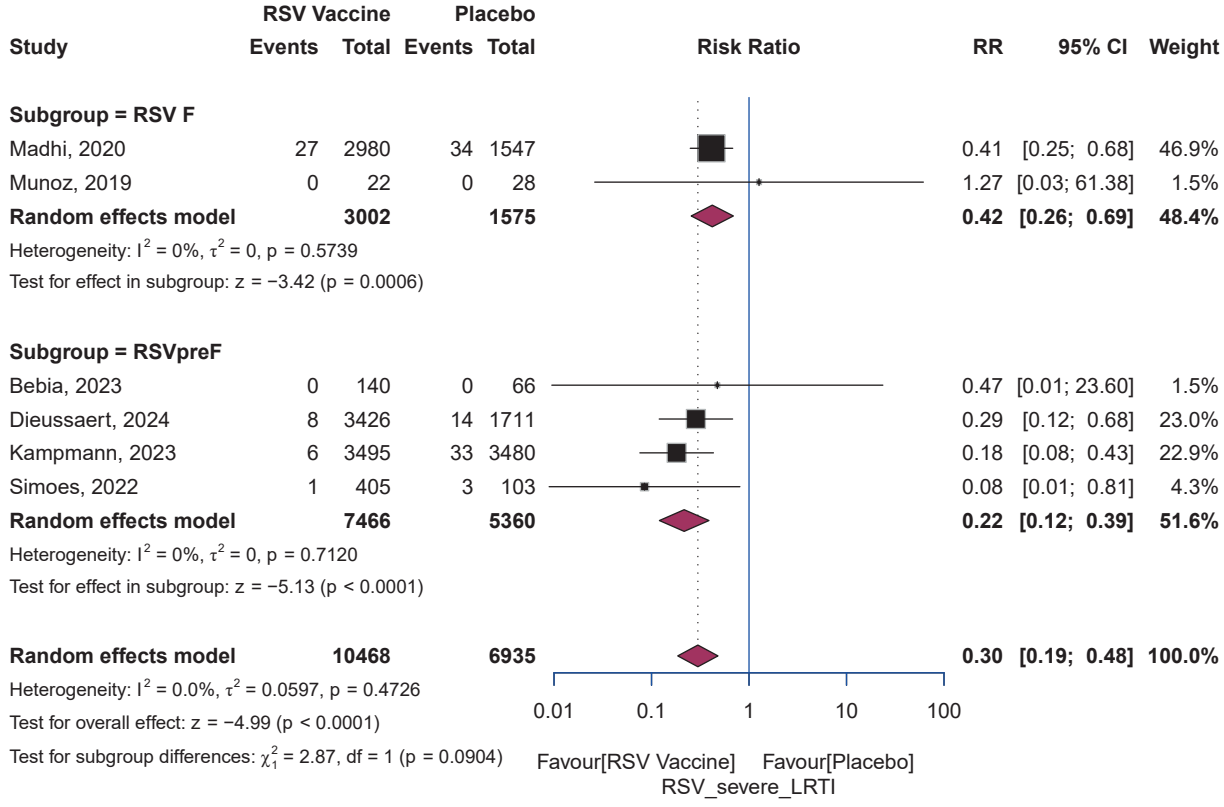

Fig. 4. RSV severe LRTI.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval; LRTI, lower respiratory tract infection.

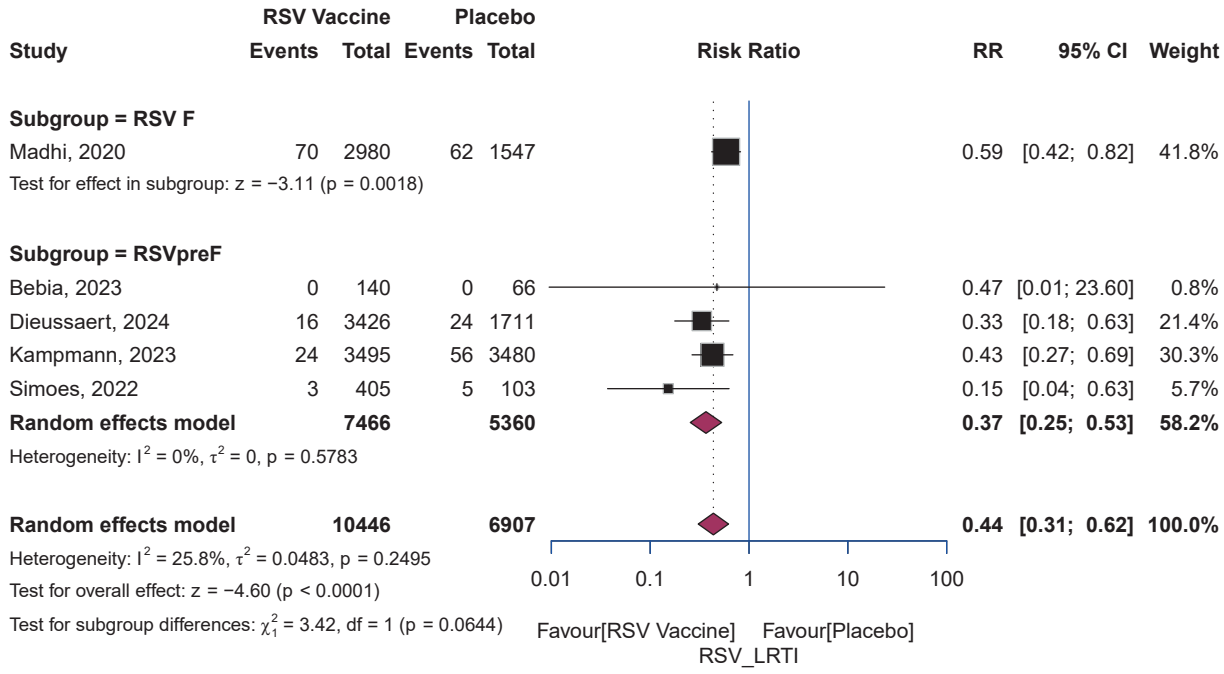

Fig. 5. RSV LRTI.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval; LRTI, lower respiratory tract infection.

of the RSV vaccine group (RR, 0.53, 95% CI, 0.37, 0.75, p=0.0004); pooled studies were homogenous (p=0.298; I^2=18.5%; **Fig. 6**). Similarly, subgroup analysis demonstrated a statistically significant reduction in hospitalization across all RSV vaccine formulations.

We conducted a sensitivity analysis for RSV-associated hospitalization by systematically excluding one study at a time (**Supplementary Fig. 3**). The results indicated that the exclusion of the study by Kampmann et al. (2023) [27], altered the overall effect size, resulting in a statistically insignificant difference.

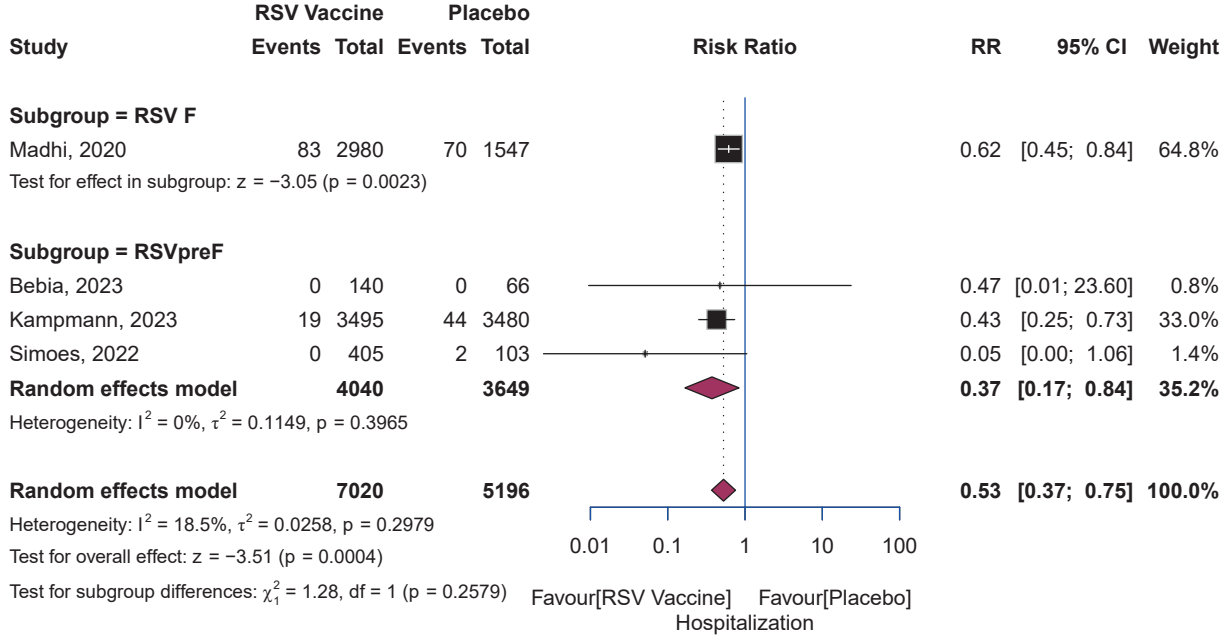

Fig. 6. Hospitalization.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

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Infant death

Three studies, including 16,930 patients, reported on infant death. The overall effect estimate did not favor either group (RR, 0.81, 95% CI, 0.36, 1.79, p=0.598); pooled studies were heterogeneous (p=0.14; I^2=49.4%; **Fig. 7**). Subgroup analysis demonstrated a statistically significant reduction in hospitalization with all RSV vaccine formulations.

Obstetric outcomes

Preterm birth (primary outcome)

Six studies, with data from 17,558 patients, reported on the outcome of preterm birth. The overall effect estimate did not favor either of the 2 groups (RR, 1.16, 95% CI, 0.96, 1.41, p=0.21); pooled studies were homogenous (p=0.31; I^2=16.4%; **Fig. 8**). Conversely, subgroup analysis revealed a statistically significant difference in preterm birth associated with the RSVpreF subgroup (RR, 0.22, 95% CI, 0.12, 0.39, p<0.0001).

We conducted a sensitivity analysis for preterm birth by systematically excluding one study at a time. The overall effect estimate was altered by the exclusion of the study by Madhi et al. (2020) [25], resulting in a statistically significant difference against the RSV vaccine group (**Supplementary Fig. 4**). We further investigated by conducting a sensitivity analysis for preterm birth on the RSVpreF subgroup, which revealed that the statistical significance obtained depends solely on the study by Dieussaert et al. (2024) [22] (**Supplementary Fig. 5**).

Time interval between vaccination and delivery

Three studies, representing 10,101 patients, reported on the time interval between vaccination and delivery. The overall effect estimate did not favor either group (MD, 0.04, 95% CI, −1.03, 1.10, p=0.94); pooled studies were homogenous (p=0.41; I^2=0%; **Fig. 9**).

Stillbirth

Four studies, with data from 12,602 patients, reported on stillbirth. The overall effect estimate did not favor either of the 2 groups (RR, 0.89, 95% CI, 0.49, 1.61, p=0.71); pooled studies were homogenous (p=0.47; I^2=0%; **Fig. 10**).

Preeclampsia

Six studies, involving 17,980 patients, reported on preeclampsia. The overall effect estimate did not favor either of the 2 groups (RR, 1.01, 95% CI, 0.81, 1.25, p=0.95); pooled studies were homogenous (p=0.77; I^2=0%; **Fig. 11**).

Intrauterine growth restriction (IUGR)

Four studies, representing 12,545 patients, assessed IUGR. The overall effect estimate did not favor either of the 2 groups (RR, 1.27, 95% CI, 0.73, 2.24, p=0.399); pooled studies were homogenous (p=0.63; I^2=0%; **Fig. 12**).

Congenital abnormalities

Four studies, with a combined 12,304 patients, evaluated congenital abnormalities. The overall effect estimate did not favor either group (RR, 0.96, 95% CI, 0.88, 1.04, p=0.31); pooled studies were homogenous (p=0.45; I^2=0%; **Fig. 13**).

Maternal safety outcomes

Local swelling

Five studies, totaling 12,550 patients, reported on local swelling. The overall effect estimate showed a statistically significant difference against the RSV vaccine group (RR, 5.71, 95% CI, 4.40, 7.40, p<0.0001); pooled studies were homogenous (p=0.94; I^2=0%; **Fig. 14**).

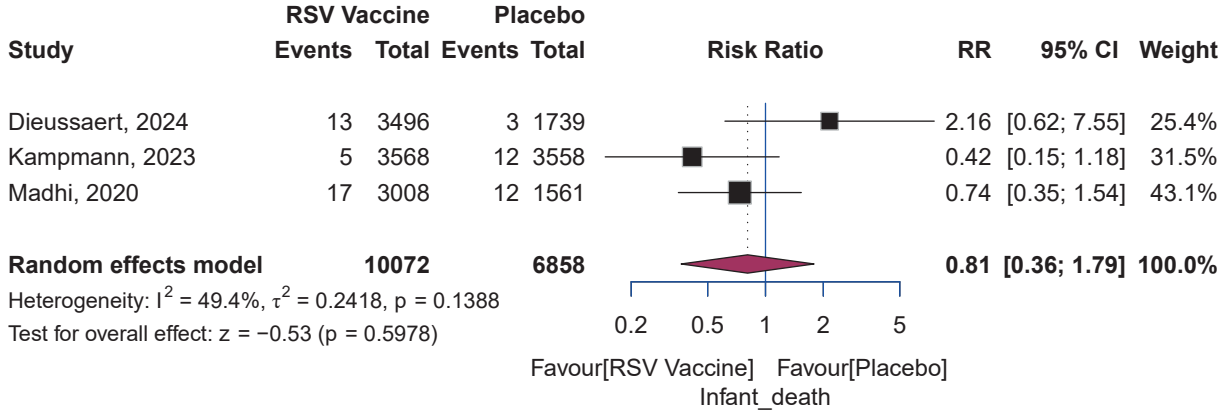

Fig. 7. Infant death.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

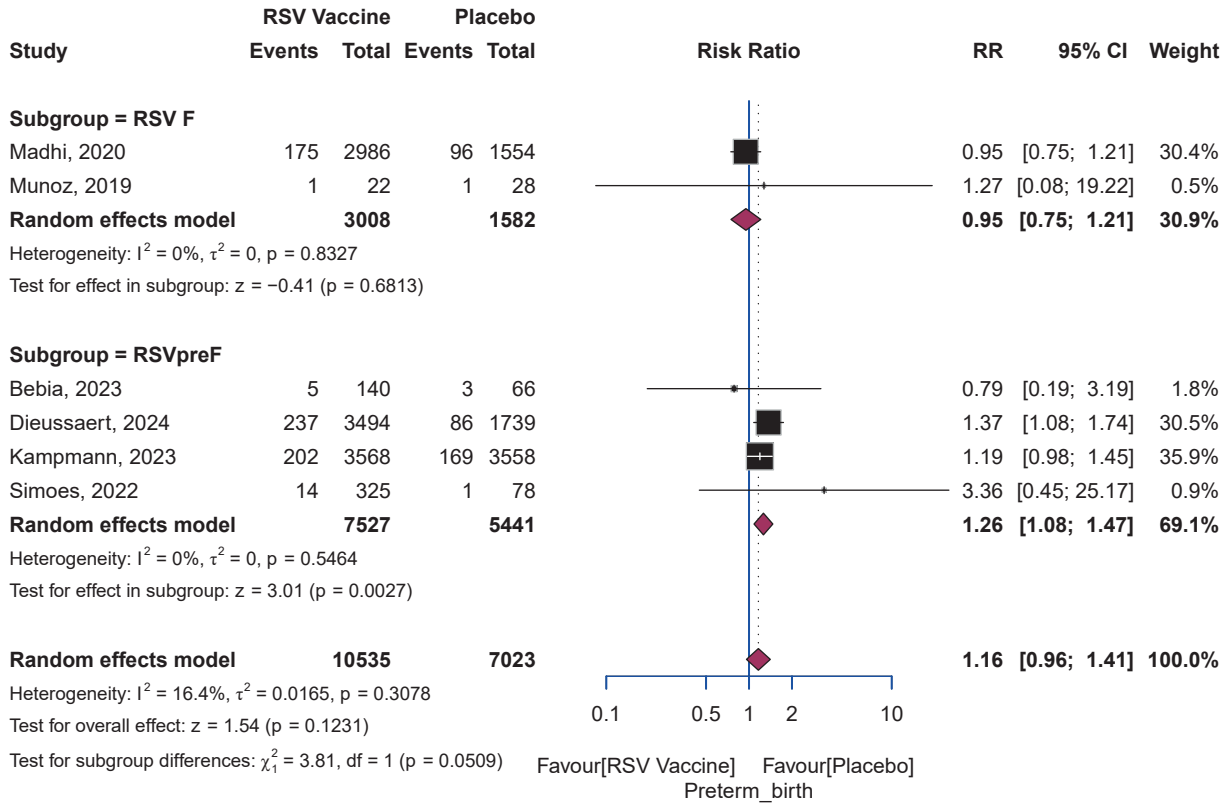

Fig. 8. Preterm birth.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

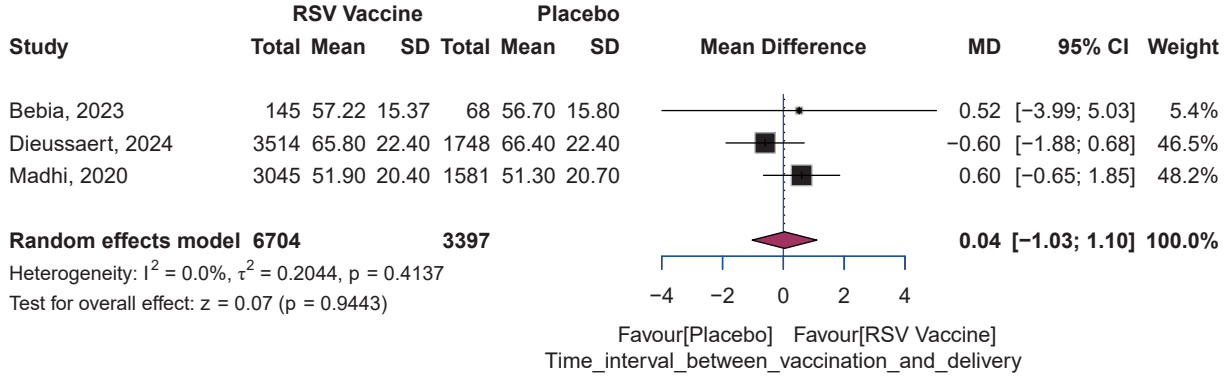

Fig. 9. Time interval between vaccination and delivery MD.
RSV, respiratory syncytial virus; SD, standard deviation; MD, mean difference; CI, confidence interval.

Local pain

Six studies, involving 12,585 patients, addressed local pain. The overall effect estimate showed a statistically significant difference against the RSV vaccine group (RR, 4.28, 95% CI, 3.86, 4.76, p<0.0001); pooled studies were homogenous (p=0.54; I^2=0%; **Fig. 15**).

Local erythema

Five studies, covering 12,550 patients, evaluated local erythema. The overall effect estimate showed a statistically significant difference against the RSV vaccine group (RR, 6.01, 95% CI, 4.29, 8.42, p<0.0001); pooled studies were homogenous (p=0.62; I^2=0%; **Fig. 16**).

Vomiting

Five studies, with a total of 12,594 patients, reported data on vomiting. The overall effect estimate showed a statistically significant difference against the RSV vaccine group (RR,

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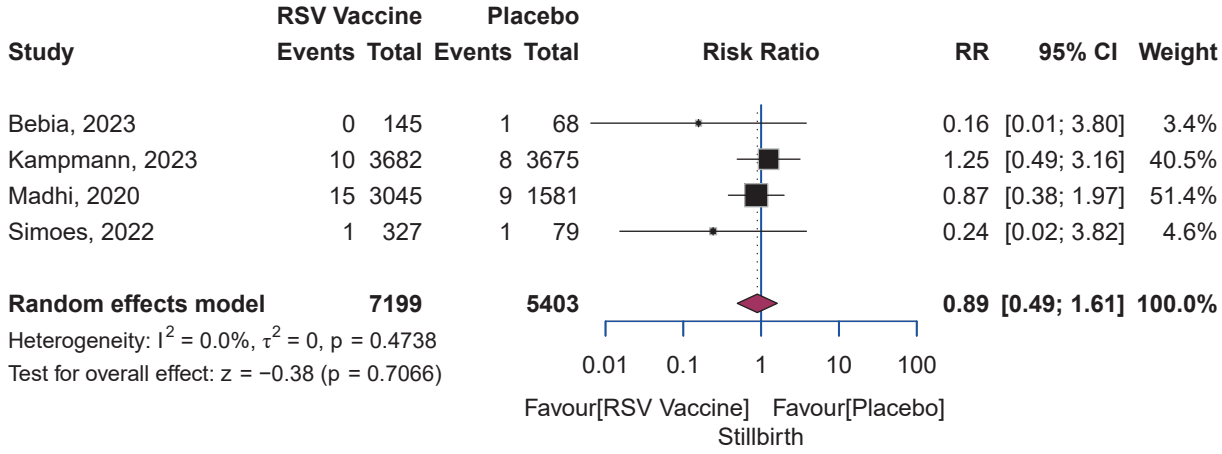

Fig. 10. Stillbirth.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

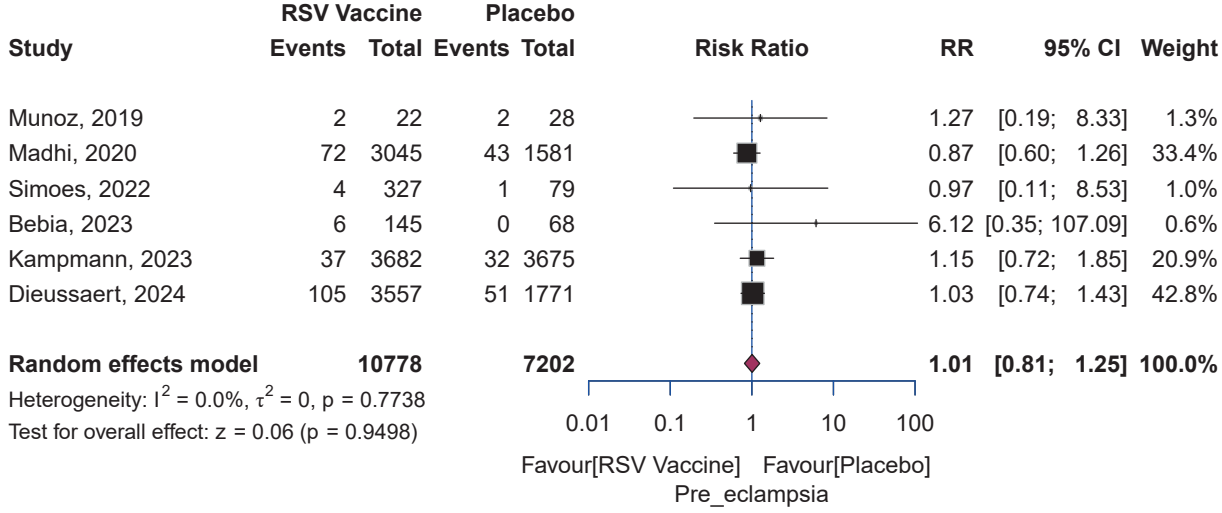

Fig. 11. Pre eclampsia.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

1.16, 95% CI, 1.02, 1.32, p=0.02); pooled studies were homogenous (p=0.49; I^2=0%; **Fig. 17**).

Headache

Five studies, with a total of 12,594 patients, reported data on headache. The overall effect estimate did not favor either of the 2 groups (RR, 1.10, 95% CI, 0.97, 1.24, p=0.14); pooled studies were heterogeneous (p=0.12; I^2=45.6%; **Fig. 18**).

General joint pain

Four studies, totaling 12,381 patients, reported on general joint pain. The overall effect estimate did not favor either group (RR, 1.12, 95% CI, 1.00, 1.25, p=0.04); pooled studies were homogenous (p=0.51; I^2=0%; **Fig. 19**).

Fever

Six studies, including 17,922 patients, examined the outcome of fever. The overall effect estimate did not favor either group (RR, 0.94, 95% CI, 0.75, 1.18, p=0.58); pooled studies were homogenous (p=0.42; I^2=0%; **Fig. 20**).

Fatigue

Five studies, including 12,594 patients, examined the outcome of fatigue. The overall effect estimate showed a statistically significant difference against the RSV vaccine group (RR, 1.06, 95% CI, 1.01, 1.12, p=0.03); pooled studies were homogenous (p=0.63; I^2=0%; **Fig. 21**).

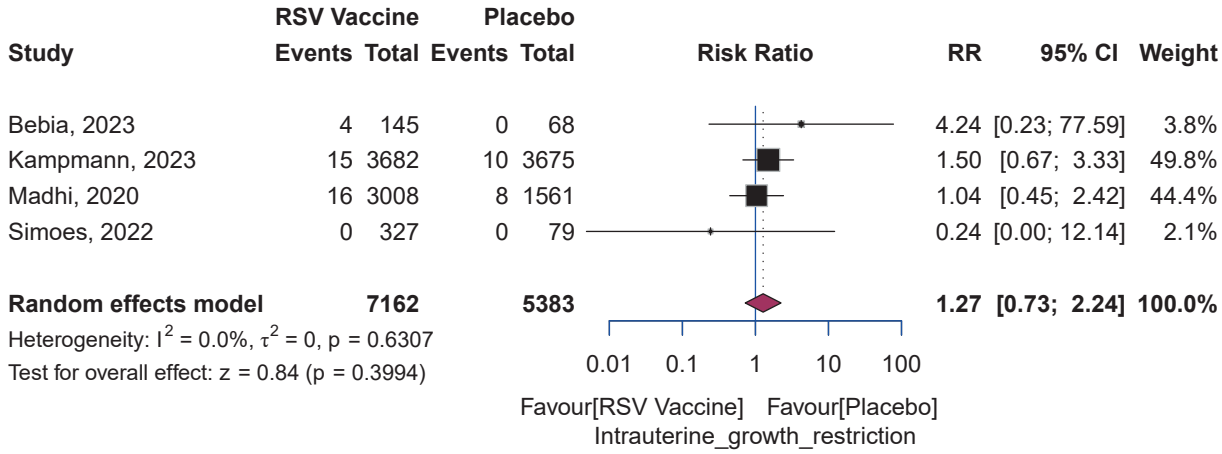

Fig. 12. Intrauterine growth restriction.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

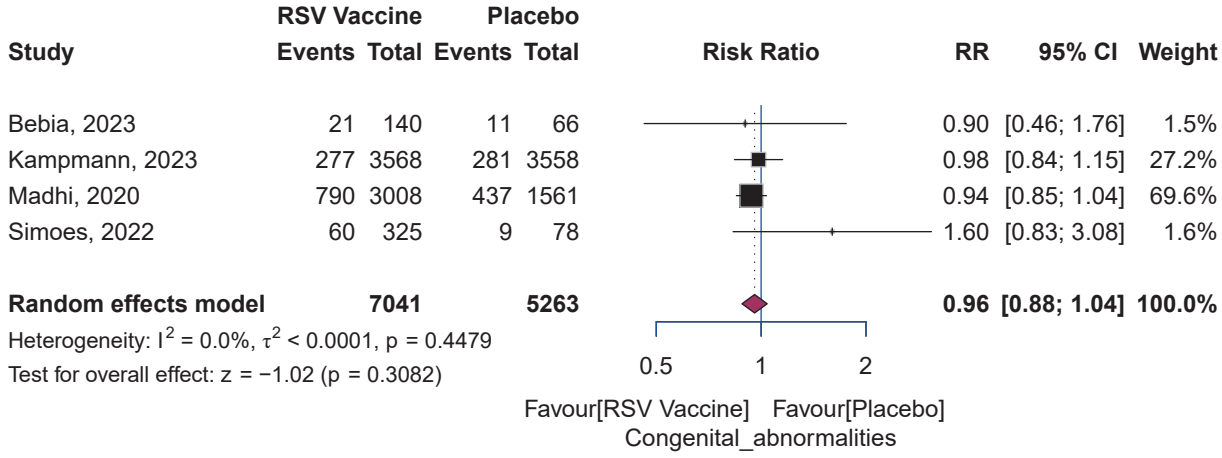

Fig. 13. Congenital abnormalities.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

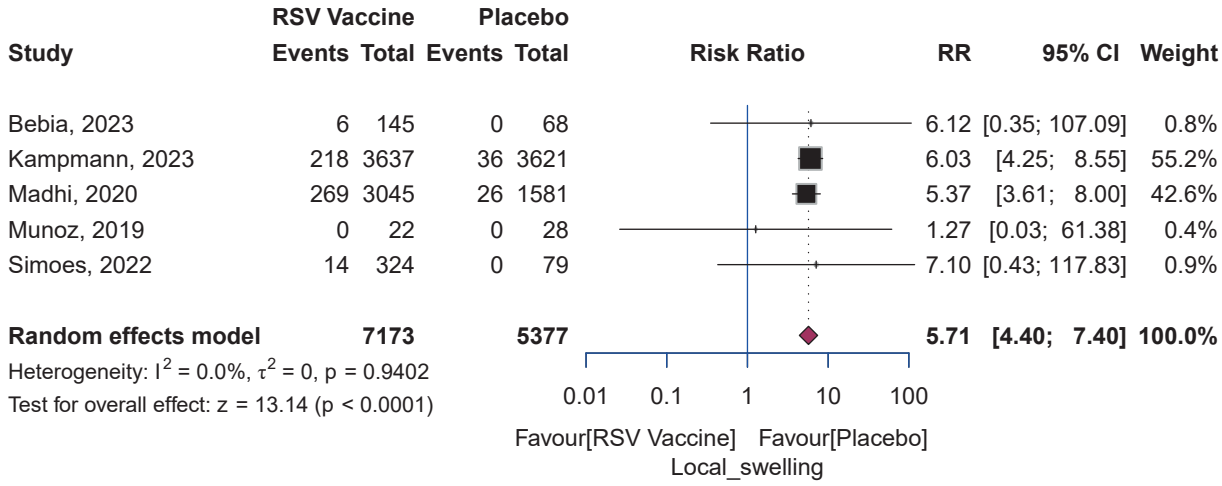

Fig. 14. Local swelling.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

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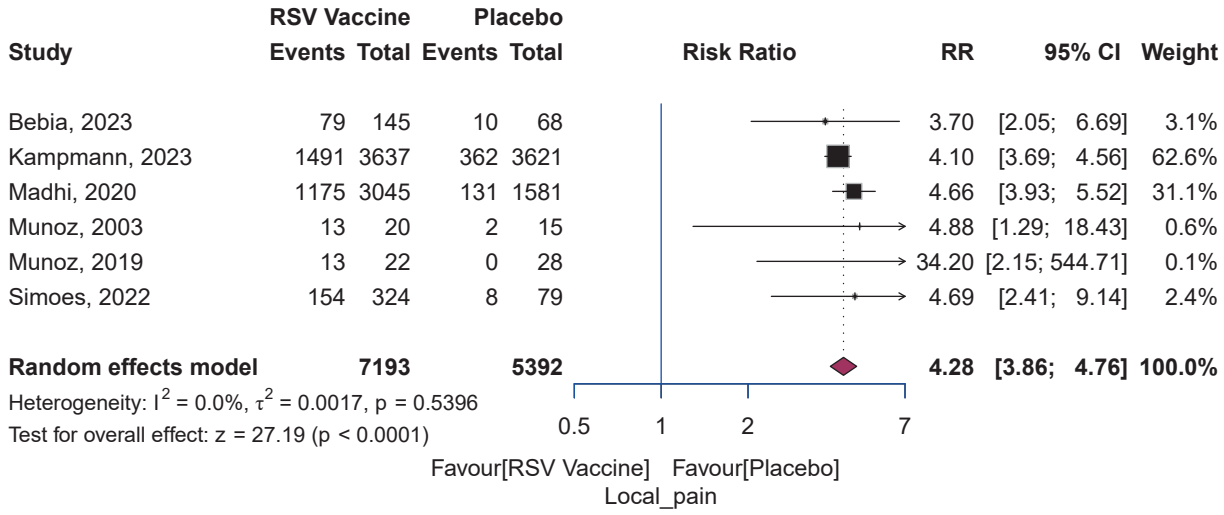

Fig. 15. Local pain.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

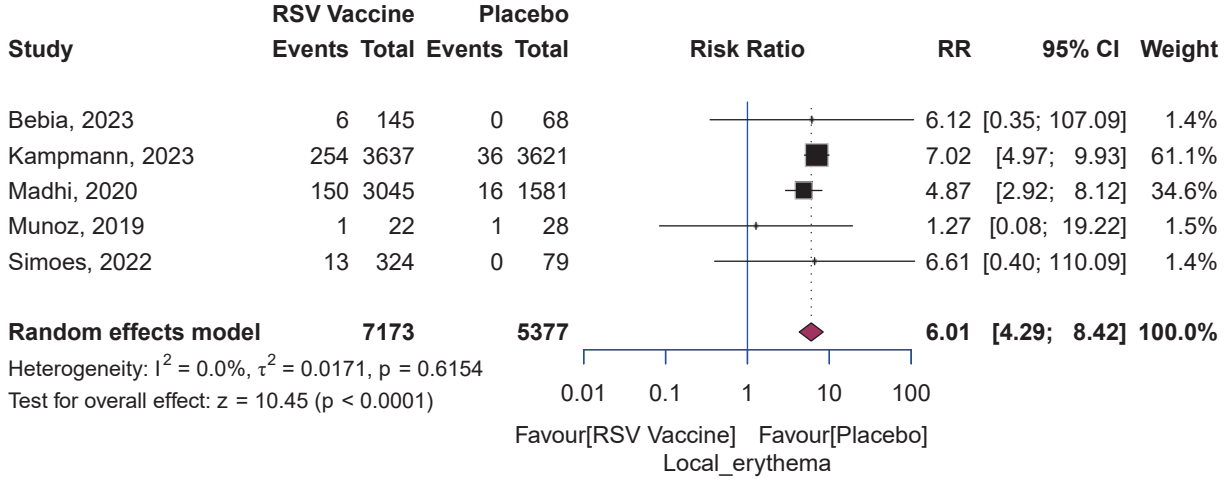

Fig. 16. Local erythema.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

Diarrhea

Five studies, representing 12,594 patients, reported on diarrhea. The overall effect estimate did not favor either of the 2 groups (RR, 0.95, 95% CI, 0.85, 1.05, p=0.29); pooled studies were homogenous (p=0.86; I^2=0%; **Fig. 22**).

DISCUSSION

The concept of maternal vaccination has been studied, and its effect was established for multiple diseases [28-31]. In 2023, 2 maternal vaccines were introduced in the United States against RSV infections, one of which was licensed by the Food and Drug Administration and recommended for administration during pregnancy to protect delivered infants from acute lower respiratory tract infections from birth [32]. However, recent trials have emerged to question further maternal RSV vaccine safety concerns. These safety concerns prompted us to gather the most recent publications and synthesize robust evidence based on a meta-analysis model. Our meta-analysis highlights multiple outcomes, including maternal, fetal, and neonatal outcomes.

Regarding the efficacy of RSV vaccines, previous clinical data have shown that the RSVpreF vaccine is effective, providing protection of up to 57% against RSV-associated lower respiratory tract infections (LRTIs) and up to 82% against medically attended severe RSV LRTIs in infants up to 3 months of age [27]. Consistent with these findings, all

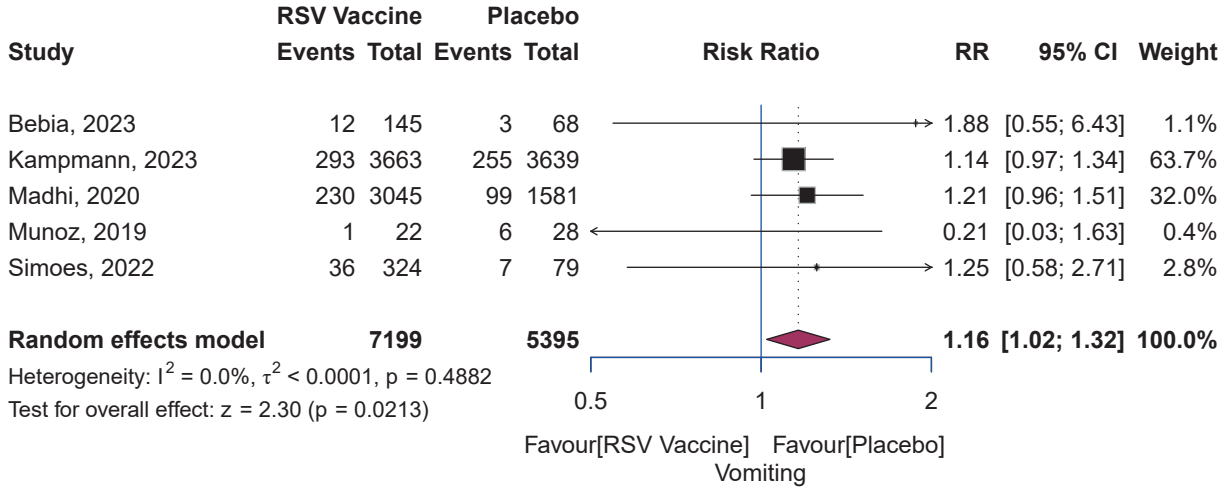

Fig. 17. Vomiting.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

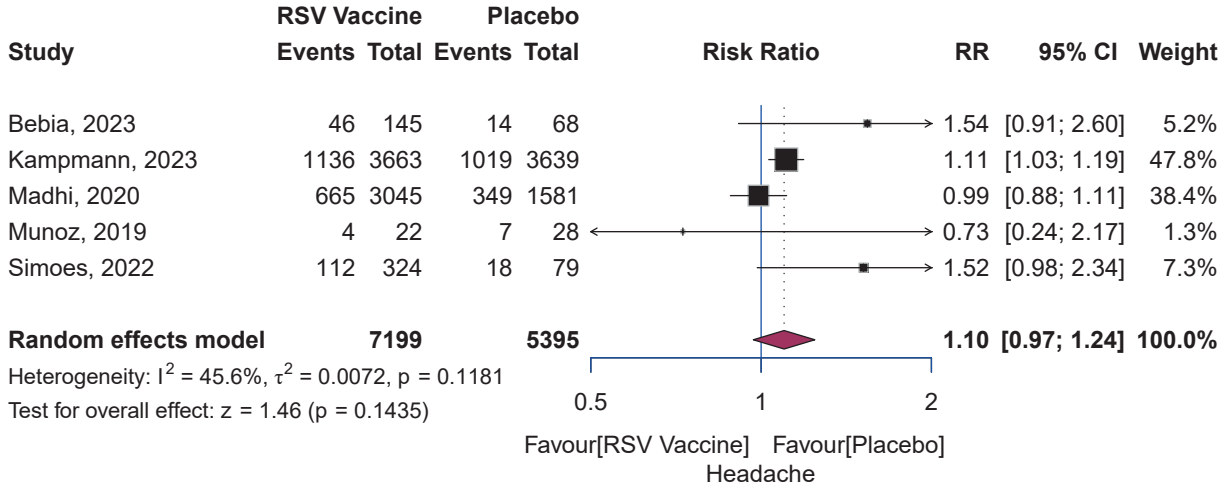

Fig. 18. Headache.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

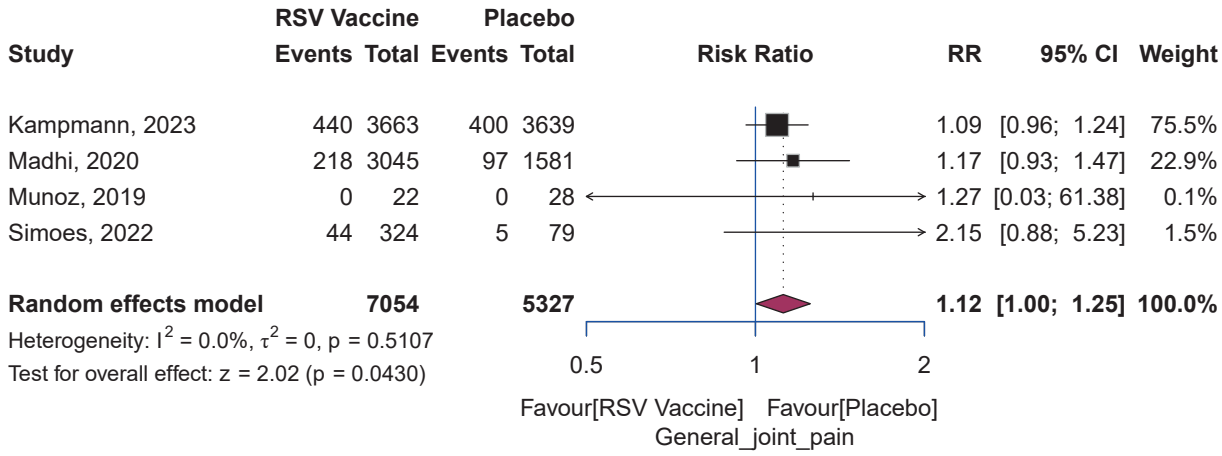

Fig. 19. General joint pain.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

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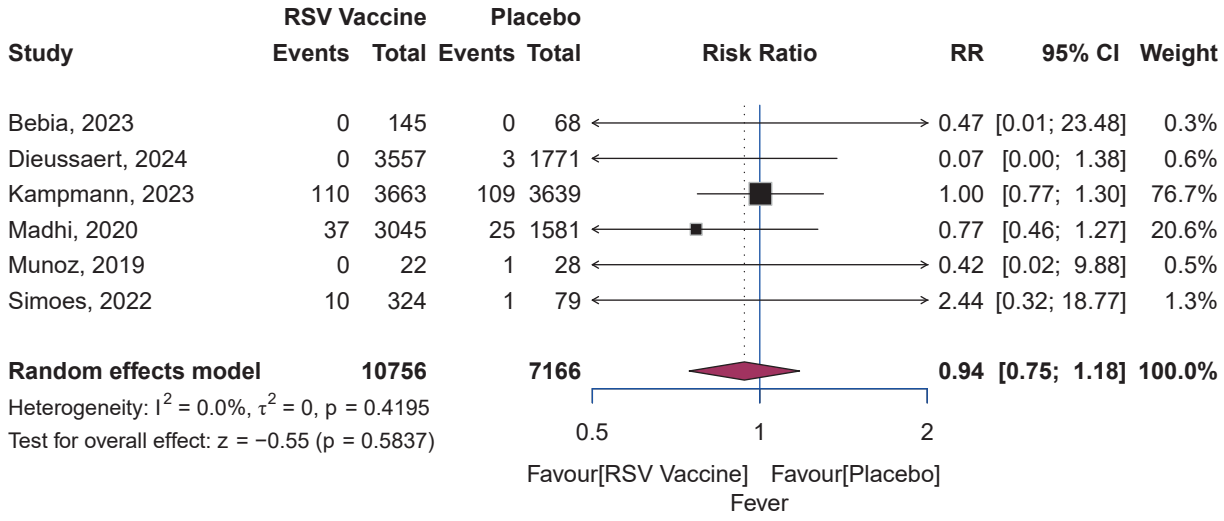

Fig. 20. Fever.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

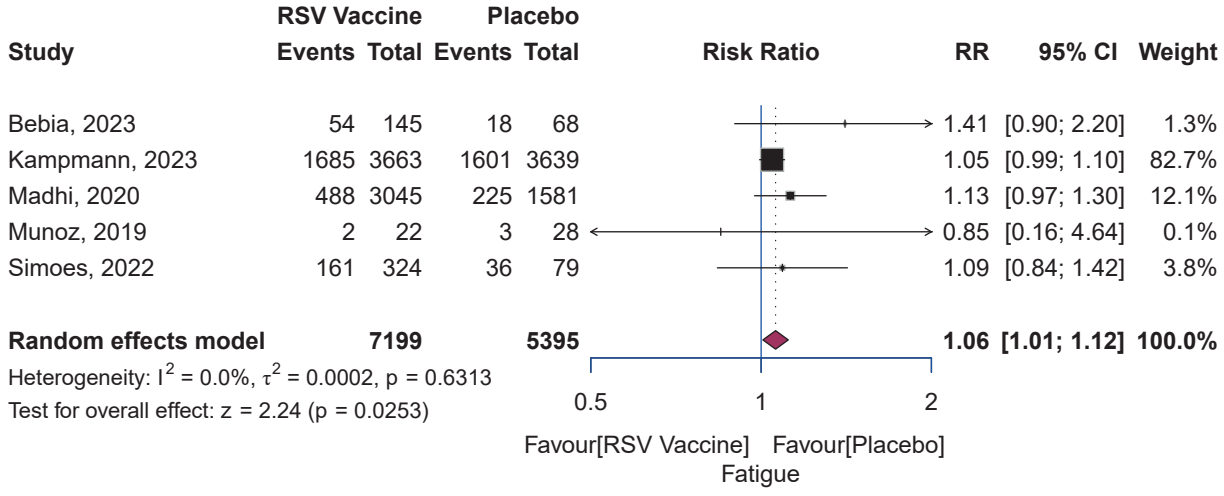

Fig. 21. Fatigue.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

trials included in our analysis reported favorable efficacy outcomes. Our meta-analysis demonstrated that RSV vaccination significantly reduced rates of RSV-associated LRTIs, severe LRTIs, and RSV-related hospitalizations, underscoring the protective benefits of the vaccine in infants.

Considerable heterogeneity was observed across the efficacy outcomes, which may be attributable to variations in study populations. This variation is illustrated in the trial conducted by Madhi et al. [25], which reported higher vaccine efficacy against RSV LRTIs and RSV-related hospitalizations in LMICs compared to high-income countries. The lower observed efficacy in high-income settings could be explained by factors such as a higher likelihood of hospitalization for milder cases, lower breastfeeding prevalence, and reduced rates of severe RSV LRTIs due to lower household crowding and limited social contact.

While the efficacy of the RSV vaccine in protecting infants has been clearly demonstrated, no significant maternal safety concerns. Regarding preterm birth, our findings showed no statistically significant increase in risk among vaccinated women. This observation aligns with a recent cohort study conducted at 2 New York City hospitals, which reported comparable rates of preterm birth among vaccinated and unvaccinated pregnant women (5.9% vs. 6.7%, respectively) following RSVpreF vaccination [33]. Similarly, another cohort study reported a lower prevalence of preterm birth among vaccinated women (8.5%) compared to unvaccinated women (18.5%) [34]. Additionally, all previously

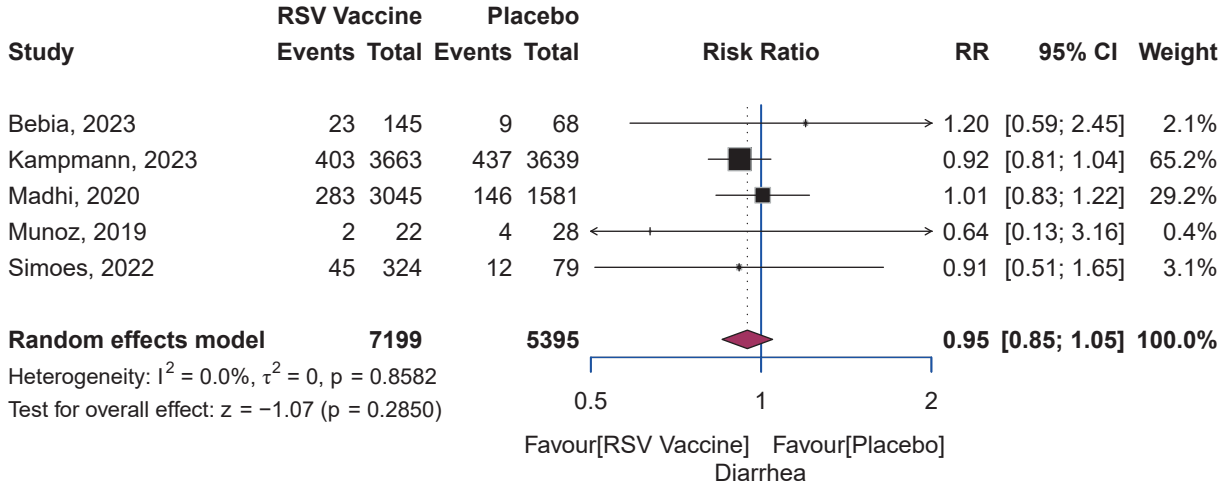

Fig. 22. Diarrhea.
RSV, respiratory syncytial virus; RR, risk ratio; CI, confidence interval.

conducted clinical trials have demonstrated no increased risk of preterm birth following RSV vaccination [21,23-27]. However, a recent trial conducted by Dieussaert et al. [22], following the phase 3 RSVpreF and RSVpreF-Mat trials, raised safety concerns regarding a potential increased risk of preterm birth in the vaccinated group compared to placebo, which led to the early discontinuation of enrollment.

It is also worth noting that the Dieussaert trial was conducted during the circulation of the SARS-CoV-2 delta variant—a period linked to a higher risk of adverse pregnancy outcomes, including preterm birth, as reported by multiple studies [35-37]. Furthermore, more than 70% of pregnant women in the trial had received at least one additional vaccine—including pertussis-containing, COVID-19 mRNA, influenza, tetanus, or tetanus–diphtheria vaccines—either at least 2 weeks before or 2 weeks after the administration of RSVpreF3-Mat or placebo. The risk of preterm birth associated with RSVpreF3-Mat, as compared with placebo, appeared to be higher among infants born to mothers who received at least one additional vaccine, with the highest relative risk observed in LMIC settings [22].

In our study, we further explored the potential association between maternal RSV vaccination and the timing of delivery by analyzing the interval between vaccination and delivery, which showed no statistically significant difference between the 2 groups. No fetal or neonatal safety concerns—including congenital abnormalities, IUGR, stillbirth, or infant death—were identified in our meta-analysis. All included studies reported data on local reactions at the site of RSV vaccine administration, such as pain, swelling, and erythema. Our meta-analysis demonstrated a statistically significant increase in these local reactions among vaccinated individuals compared to placebo, which was anticipated given the local deposition of biological products following vaccination. These reactions are typically mild and transient, reflecting localized inflammatory responses.

Systemic reactions, such as fatigue and vomiting, were also found to be statistically significant following vaccination. However, these reactions are nonspecific and could be attributed to normal physiological changes during pregnancy or to inflammatory responses associated with antibody production. Conversely, other systemic reactions, including fever, headache, joint pain, and gastrointestinal symptoms such as diarrhea, were not statistically significant in vaccinated women compared to placebo.

CONCLUSION

Our findings suggest that maternal RSV vaccination is associated with a significant reduction in the risk of RSV-associated LRTIs and RSV-related hospitalizations in infants during the early months of life. No major safety concerns were identified in either vaccinated mothers or their infants. Nevertheless, the current evidence remains limited, and additional data from high-quality RCTs involving larger and more diverse populations are warranted to confirm or refute these findings.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Assessment of small-study effects using Egger's regression test

Supplementary Fig. 1
Respiratory syncytial virus severe lower respiratory tract infection sensitivity analysis.

Supplementary Fig. 2
Respiratory syncytial virus lower respiratory tract infection sensitivity analysis.

Supplementary Fig. 3
Hospitalization sensitivity analysis.

Supplementary Fig. 4
Preterm birth sensitivity analysis.

Supplementary Fig. 5
Preterm birth sensitivity analysis.

REFERENCES

1. Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS; WHO RSV Vaccine Consultation Expert Group. WHO consultation on respiratory syncytial virus vaccine development report from a World Health Organization meeting held on 23-24 March 2015. Vaccine 2016;34:190-7. PUBMED | CROSSREF
2. Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. J Pediatr 1981;98:708-15. PUBMED | CROSSREF
3. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet 2022;399:2047-64. PUBMED | CROSSREF
4. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375:1545-55. PUBMED | CROSSREF
5. Wu P, Hartert TV. Evidence for a causal relationship between respiratory syncytial virus infection and asthma. Expert Rev Anti Infect Ther 2011;9:731-45. PUBMED | CROSSREF
6. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969;89:422-34. PUBMED | CROSSREF
7. Wright PF, Karron RA, Belshe RB, et al. Evaluation of a live, cold-passaged, temperature-sensitive, respiratory syncytial virus vaccine candidate in infancy. J Infect Dis 2000;182:1331-42. PUBMED | CROSSREF
8. Johnson PR, Spriggs MK, Olmsted RA, Collins PL. The G glycoprotein of human respiratory syncytial viruses of subgroups A and B: extensive sequence divergence between antigenically related proteins. Proc Natl Acad Sci U S A 1987;84:5625-9. PUBMED | CROSSREF
9. Olmsted RA, Elango N, Prince GA, et al. Expression of the F glycoprotein of respiratory syncytial virus by a recombinant vaccinia virus: comparison of the individual contributions of the F and G glycoproteins to host immunity. Proc Natl Acad Sci U S A 1986;83:7462-6. PUBMED | CROSSREF
10. Stott EJ, Taylor G, Ball LA, et al. Immune and histopathological responses in animals vaccinated with recombinant vaccinia viruses that express individual genes of human respiratory syncytial virus. J Virol 1987;61:3855-61. PUBMED | CROSSREF
11. Sheffield JS, Munoz FM, Beigi RH, et al. Research on vaccines during pregnancy: reference values for vital signs and laboratory assessments. Vaccine 2013;31:4264-73. PUBMED | CROSSREF
12. Halasa NB, Olson SM, Staat MA, et al. Maternal vaccination and risk of hospitalization for COVID-19 among infants. N Engl J Med 2022;387:109-19. PUBMED | CROSSREF
13. Aranda SS, Polack FP. Prevention of pediatric respiratory syncytial virus lower respiratory tract illness: perspectives for the next decade. Front Immunol 2019;10:1006. PUBMED | CROSSREF
14. Abu-Raya B, Maertens K, Edwards KM, et al. Global perspectives on immunization during pregnancy and priorities for future research and development: an international consensus statement. Front Immunol 2020;11:1282. PUBMED | CROSSREF
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. PUBMED | CROSSREF
16. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142. PUBMED | CROSSREF
17. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. PUBMED | CROSSREF
18. Sterne JA, Egger M, Moher D. Addressing reporting biases. In: Higgins JP, Green S, editors. Cochrane handbook for

systematic reviews of interventions. Chichester: John Wiley & Sons, Ltd; 2008. p.297-333.

19. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. Stat Med 2003;22:2113-26. PUBMED | CROSSREF
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34. PUBMED | CROSSREF
21. Munoz FM, Piedra PA, Glezen WP. Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women. Vaccine 2003;21:3465-7. PUBMED | CROSSREF
22. Dieussaert I, Hyung Kim J, Luik S, et al. RSV prefusion F protein-based maternal vaccine - preterm birth and other outcomes. N Engl J Med 2024;390:1009-21. PUBMED | CROSSREF
23. Bebia Z, Reyes O, Jeanfreau R, et al. Safety and immunogenicity of an investigational respiratory syncytial virus vaccine (RSVPreF3) in mothers and their infants: a phase 2 randomized trial. J Infect Dis 2023;228:299-310. PUBMED | CROSSREF
24. Muňoz FM, Swamy GK, Hickman SP, et al. Safety and immunogenicity of a respiratory syncytial virus fusion (F) protein nanoparticle vaccine in healthy third-trimester pregnant women and their infants. J Infect Dis 2019;220:1802-15. PUBMED | CROSSREF
25. Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. N Engl J Med 2020;383:426-39. PUBMED | CROSSREF
26. Simões EAF, Center KJ, Tita ATN, et al. Prefusion F protein-based respiratory syncytial virus immunization in pregnancy. N Engl J Med 2022;386:1615-26. PUBMED | CROSSREF
27. Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med 2023;388:1451-64. PUBMED | CROSSREF
28. Blencowe H, Lawn J, Vandelaer J, Roper M, Cousens S. Tetanus toxoid immunization to reduce mortality from neonatal tetanus. Int J Epidemiol 2010;39 Suppl 1:i102-9. PUBMED | CROSSREF
29. Merdrignac L, Acosta L, Habington A, et al. Effectiveness of pertussis vaccination in pregnancy to prevent hospitalisation in infants aged <2 months and effectiveness of both primary vaccination and mother's vaccination in pregnancy in infants aged 2-11 months. Vaccine 2022;40:6374-82. PUBMED | CROSSREF
30. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis 2010;51:1355-61. PUBMED | CROSSREF
31. Vojtek I, Dieussaert I, Doherty TM, et al. Maternal immunization: where are we now and how to move forward? Ann Med 2018;50:193-208. PUBMED | CROSSREF
32. Fleming-Dutra KE, Jones JM, Roper LE, et al. Use of the Pfizer respiratory syncytial virus vaccine during pregnancy for the prevention of respiratory syncytial virus-associated lower respiratory tract disease in infants: recommendations of the advisory committee on immunization practices - United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:1115-22. PUBMED | CROSSREF
33. Son M, Riley LE, Staniczenko AP, et al. Nonadjuvanted bivalent respiratory syncytial virus vaccination and perinatal outcomes. JAMA Netw Open 2024;7:e2419268. PUBMED | CROSSREF
34. Blauvelt CA, Zeme M, Natarajan A, et al. Respiratory syncytial virus vaccine and nirsevimab uptake among pregnant people and their neonates. JAMA Netw Open 2025;8:e2460735. PUBMED | CROSSREF
35. Seasely AR, Blanchard CT, Arora N, et al. Maternal and perinatal outcomes associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) delta (B.1.617.2) variant. Obstet Gynecol 2021;138:842-4. PUBMED | CROSSREF
36. Favre G, Maisonneuve E, Pomar L, et al. Maternal and perinatal outcomes following pre-delta, delta, and omicron SARS-CoV-2 variants infection among unvaccinated pregnant women in France and Switzerland: a prospective cohort study using the COVI-PREG registry. Lancet Reg Health Eur 2023;26:100569. PUBMED | CROSSREF
37. Mupanomunda M, Fakih MG, Miller C, et al. Comparison of severe maternal morbidities associated with delivery during periods of circulation of specific SARS-CoV-2 variants. JAMA Netw Open 2022;5:e2226436. PUBMED | CROSSREF