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RSVpreF vaccination in pregnancy: a meta-analysis of maternal-fetal safety and infant efficacy

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In May 2023, the United States Food and Drug Administration approved a Pfizer©-sponsored (Pfizer, New York, NY, USA) bivalent respiratory syncytial virus prefusion F protein-based vaccine (RSVpreF) RSV vaccine (Abrysvo™ [Pfizer]) for use during pregnancy to prevent neonatal/infant RSV infection. In February of 2022, trials sponsored by GSK© (Brentford, England, UK) on a similar RSVpreF vaccine were halted because of the identification of a safety signal related to preterm births. As these vaccines use identical pre-fusion F-protein technology, we sought to synthesize the existing data on their effectiveness and safety. We identified all randomized controlled trials and used RevMan 5.4.1 (The Cochrane Collaboration, England, UK) to perform the analysis with 95% confidence intervals and risk ratios (RRs). We found many maternal side effects were more prevalent in the RSVpreF group, with more local reactions, blood disorders, fatigue, joint pain, cardiac disorders, headache, fever, gastrointestinal disorders and pregnancy complications. The vaccinated group demonstrated significant reductions in RSV-lower respiratory tract cases (RR, 0.44 [0.33, 0.57]; *P*<0.00001), severe respiratory illness (RR, 0.29 [0.19, 0.44]; *P*<0.00001), and hospitalizations (RR, 0.40 [0.24, 0.67]; *P*=0.0005). RSVpreF vaccination was associated with a higher incidence of preterm delivery (RR, 1.24 [1.08, 1.44]; *P*=0.003). No significant difference in neonatal deaths was observed (RR, 1.42 [0.70, 2.89]; *P*=0.34). In conclusion, RSVpreF vaccination results in systemic adverse events and an increase in preterm delivery. Vaccination appears to have acceptable short-term newborn safety, but is not related to a significant decrease in neonatal death.

Keywords: Vaccination; Respiratory syncytial virus vaccines; Neonatology; Meta-analysis

Introduction

Respiratory syncytial virus (RSV) is a mild and highly contagious respiratory pathogen; it does not affect most healthy infants in a severe manner, but can have more severe manifestations in vulnerable populations of infants. Its high prevalence and ability to precipitate severe lower respiratory tract infections in some infants make it one of the leading causes of hospitalization in early childhood [1]. There has been a concerted public health effort to devise strategies that shield these infants from the adverse effects of RSV [2,3]. Globally, RSV is estimated to cause the deaths of approximately 118,200 children each year [4]. Of these deaths, approximately half occur in infants under 6 months old, with the vast majority occurring in developing countries; in developed countries, the infection is easily treated with nebulizer therapy with beta-agonists, corticosteroids, and in severe cases, monoclonal antibodies [4,5]. In the United States, an estimated 300-600 deaths are associated with RSV hospitalization; however, many of these children have significant underlying cardiopulmonary disease and have fallen through the safety net of early ambulatory therapy. In the

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absence of adequate ambulatory nebulization therapy, RSV infection is a leading cause of infant hospitalization in the United States, with an estimated yearly frequency surpassing 2,000 instances of RSV-induced pneumonia per 100,000 infants. Given the heightened vulnerability of infants, the opportunity to reduce the risk of RSV infection using preventive strategies is attractive, particularly in countries with limited access to ambulatory respiratory care [6-8]. Maternal immunization presents a unique opportunity to harness the maternal immune system to protect against RSV transmission [9]. Through the strategic activation of the maternal immune response, there is a theoretical opportunity to confer passive protection to newborns, bolstering their defenses during this critical phase of development [10-12]. However, maternal vaccination in the third trimester has never been attempted, given the risks of vaccine reactions, including a pro-inflammatory response that could trigger preterm labor and result in prematurely born infants with medical problems far exceeding those of easily treated RSV infections in full-term healthy infants. A recently approved RSV vaccine used during pregnancy, administering an RSV prefusion F protein-based vaccine (RSVpreF) in the late second or third trimester, has been deployed to offer protection against severe RSV-related illnesses in infants during their initial months of life; however, there are no assurances of long-term safety or studies of mutational pressure applied on the virus to worsen the public health problem in the years to come [13].

The RSV pre-fusion F protein is a critical component of the RSV virion. This protein facilitates viral entry into host cells, making it a prime target for immunization strategies. Understanding its structure and function is pivotal for the development of effective interventions against RSV [14-16].

Although selective, the placental barrier allows the transference of maternal antibodies to the developing fetus. This process, which occurs primarily in the third trimester, equips the newborn with a reservoir of protective immunoglobulin G antibodies against RSV, providing a critical second line of defense against invasive diseases that break through the mucosal immune defense system. Strategically timed immunization during pregnancy capitalizes on this natural mechanism, ensuring optimal systemic antibody levels in both mother and infant at the time of birth. This temporal alignment maximizes the potential for shielding the newborn from the perils of RSV; however, there is no evidence that this strategy influences critical mucosal cellular and immunoglobulin A defenses against respiratory pathogens [17].

The United States Food and Drug Administration (FDA), has recently considered two RSVpreF vaccines for approval. The first, sponsored by Glasko Smith Kline (GSK©) (Brentford, England, UK) [18], was halted in February of 2022 after GSK© (Brentford) reported detecting a "safety signal" in the study when approximately three times the number of preterm births were seen in the vaccinated group as opposed to placebo [19]. Accordingly, the application was withdrawn based on this safety concern and approval was not granted. The other RSVpreF vaccine, Abrysvo™ (Pfizer, New York, NY, USA), was sponsored by Pfizer© (Pfizer) and ultimately received FDA approval in May of 2023, following phase 2B [20] and phase III [21] FDA randomized controlled trials (RCTs). The data from the GSK© trial (Brentford) [22] and the two Pfizer© trials (Pfizer) [20,21] have been subsequently published and make up the three RCTs included in this meta-analysis.

The anticipated outcomes include a critical understanding of both maternal safety and the consequences of premature delivery for the infant, a better understanding of RSV immunization strategies, and tangible contributions to the arsenal of interventions available to potentially safeguard maternal and infant health. Through this exploration, it is possible to envision a future in which RSV-related morbidity and mortality in infants are significantly mitigated. However, this may occur at a cost in terms of maternal-fetal safety and mutational pressure on RSV strains that will invariably become resistant to the vaccinated human host.

Methods

This meta-analysis aimed to systematically synthesize and evaluate the existing literature on the effectiveness and safety of RSVpreF vaccine administered during pregnancy. By aggregating and analyzing relevant studies, we sought to provide a comprehensive assessment of the impact of this intervention on maternal and infant health outcomes, with a primary focus on safety events and the secondary aim of preventing severe RSV-associated lower respiratory tract illnesses in infants.

1. Literature search

This systematic review and meta-analysis were performed us-

ing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA). From the inception of each database until March 15, 2024, we scanned the following electronic databases: Cochrane Library, PubMed, Scopus, Web of Science, FDA, and clinicaltrials.gov. We restricted our search to studies published in English. We performed our search using the following search terms: ("Respiratory syncytia virus", "Protein–Based Respiratory Syncytial Virus", and "Pregnancy").

2. Eligibility criteria

In this analysis, we included all studies that included women who received the RSVpreF vaccine during pregnancy for RSV prevention in neonates versus a placebo. Only randomized clinical trials were included. We excluded studies with different designs, single-arm studies, non-English language studies, and studies that did not include any of our preselected outcomes.

3. Review and selection of studies

Two authors independently reviewed the titles and abstracts of all potentially relevant articles. Subsequently, the full text was thoroughly assessed to determine its suitability for inclusion in our systematic review. Disagreements were planned to be resolved through discussion with a third author; however, no disagreements ultimately arose.

4. Data extraction

Two authors independently recorded the relevant data using a computer spreadsheet. These included 1) baseline characteristics and demographic information of the study population; 2) data relevant to the outcome measures; and 3) details about the assessment of the risk of bias.

5. Data synthesis

We used Review Manager Software (RevMan 5.4.1; The Cochrane Collaboration, England, UK) to perform the data analysis. We utilized 95% confidence intervals (CIs) and risk ratios (RRs) as assessment metrics. To assess the heterogeneity among the included studies, we employed Cochran's Q-test and the I^2 test. In cases where significant heterogeneity was observed ($P<0.05$; $I^2>50\%$), we applied a random-effects model to synthesize effect sizes. Conversely, a fixed effects model was utilized when outcomes exhibited homogeneity (with $P\geq0.05$ and $I^2\leq50\%$).

Results

1. Results of our literature search

Our literature review is illustrated in Fig. 1 using a PRISMA diagram. Ultimately, three studies [20-22] from various databases met our inclusion criteria. Study designs were extremely similar in that participants in all three studies were randomly assigned to receive either RSVpreF 120 μg or a placebo. The average age of the individuals included in the study at the time of vaccination was 29.1±5.6 years in the RSVpreF group and 28.0±5.4 years in the placebo group. The gestational age at the time of vaccination was 30.8±3.6 weeks in the RSVpreF group and 30.8±3.5 weeks in the placebo group. Approximately 94% of the infants in the vaccination group were born full-term, whereas in the placebo group, this figure was 96%, as shown in Tables 1, 2.

2. Results of risk of bias assessment

According to Cochrane's tool, the collective risk of bias was deemed low for all three trials. All included trials were judged to be adequately randomized. Additionally, they provided sufficient information regarding the blinding of both the participants and outcome assessors. A full summary of the risk of bias in the included studies is shown in Fig. 2.

Outcomes

1. Efficacy outcomes

1) Efficacy measurement within 180 days (medically assessed RSV-associated lower respiratory tract disease)

Vaccine efficacy was evaluated by measuring the incidence of medically assessed RSV-associated lower respiratory tract disease (LRTD), medically attended severe RSV-associated lower respiratory tract illness, and the rate of hospitalization related to RSV within 180 days of vaccination. Among the 7,326 vaccinated individuals, only 76 reported RSV-LRTD cases, compared to 146 cases among the 5,294 individuals in the placebo group (RR, 0.44 [0.33, 0.57]; $P<0.00001$). The data were homogeneous ($P=0.20$), with an I^2 value of 39%. Furthermore, the incidence of RSV-associated severe lower respiratory tract illness was significantly lower in the vaccinated group than in the placebo group (RR, 0.29 [0.19,

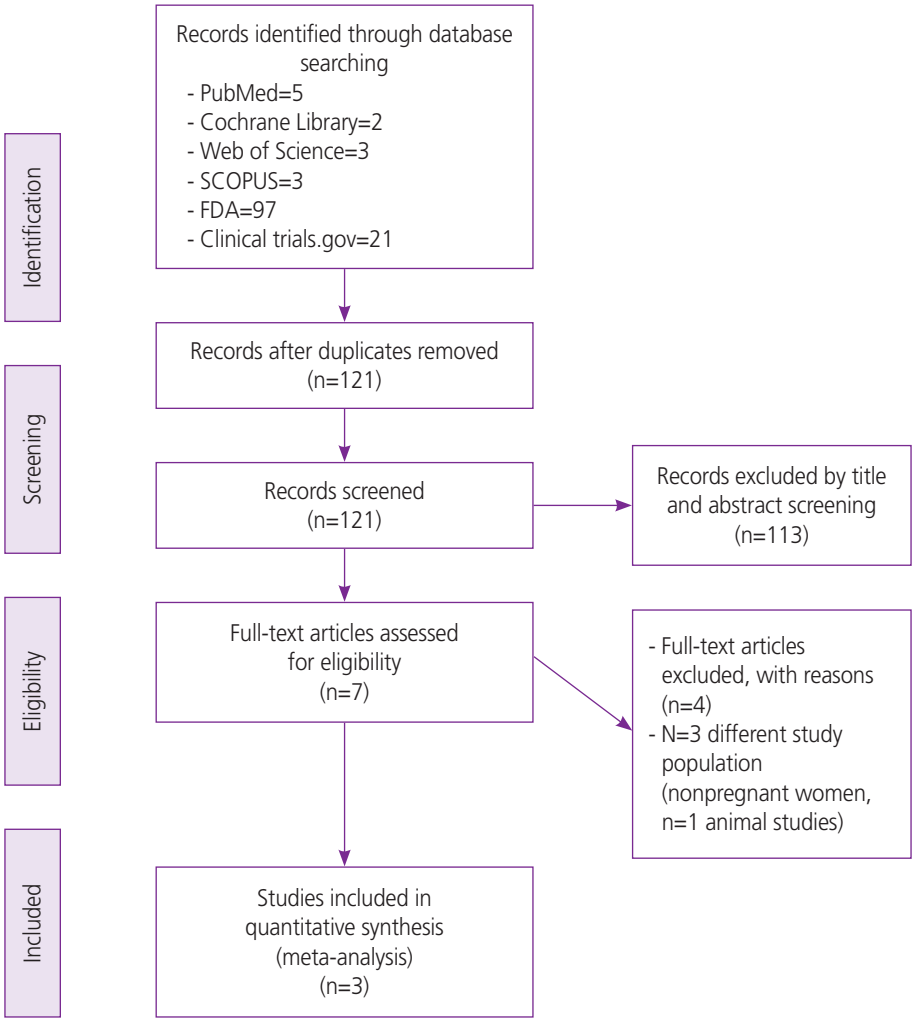

Fig. 1. PRISMA flow diagram of our literature search. FDA, Food and Drug Administration; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

0.44]; *P*<0.00001) I^2 value of 0%. In all cases exhibited RSV-associated only 19 cases required hospitalization in the vaccinated group, while 46 cases required hospitalization in the placebo group, with a significant difference between the groups (RR, 0.40 [0.24, 0.67]; *P*=0.0005) and an I^2 value of 46%. A pooled analysis revealed that the RSVpreF vaccine during pregnancy was associated with a significant decrease in the overall incidence of RSV-associated lower respiratory tract disease (RR, 0.39 [0.31, 0.48]; *P*<0.00001) I^2 value of 20% (Fig. 3).

2. Safety outcomes

1) Local reactions

Two studies have reported on this outcome [20,21]. Local reactions were defined as redness, swelling, and pain at the injection site. A subgroup analysis was conducted for each symptom. The incidence of redness at the injection site was notably lower in the placebo group. Additionally, the rates of injection-site pain and swelling were significantly lower in the placebo group (RR, 4.04 [3.65, 4.48]; *P*<0.00001), (RR, 5.98 [4.24, 8.42]; *P*<0.00001). The data remained homogeneous (*P*=0.38), (*P*=0.91) with an I^2 value of 0%. A combined analysis of these subgroups demonstrated a significantly lower incidence of local reactions in the placebo group (RR, 5.01 [3.68, 6.83]; *P*<0.00001). Data from the pooled analysis were heterogeneous (*P*=0.02; I^2=64%) as seen in Fig. 4.

2) Systemic maternal adverse events

Three studies reported on this outcome [20-22] which

Table 1. Demographic and clinical characteristics of the maternal and neonatal participants

Study	Sample size		Age at vaccination (yr)		Sex				Gestational age at vaccination (weeks)		Gestation at vaccination								Full-term		Apgar score at 5 minutes		Apgar score of 7-10 at 5 minutes	
					RSVpreF 120 μg		Placebo				RSVpreF 120 μg				Placebo									
	RSVpreF 120 μg	Placebo	RSVpreF 120 μg	Placebo	Male	Female	Male	Female	RSVpreF 120 μg	Placebo									RSVpreF 120 μg	Placebo	RSVpreF 120 μg	Placebo	RSVpreF 120 μg	Placebo
Maternal participants																								
Kampmann et al. [21] (2023)	3,682	3,675	29.1 (5.6)	29 (5.7)					30.8 (3.5)	30.8 (3.6)	<24 weeks	24 weeks, 0 days-28 weeks, and 6 days	29 weeks, 0 days-34 weeks, and 0 days	>34 weeks and 0 days	<24 weeks	24 weeks, 0 days-28 weeks, and 6 days	29 weeks, 0 days-34 weeks, and 0 days	>34 weeks and 0 days						
Simões et al. [20] (2022)	79	79	26.9 (4.7)	26.4 (5.0)					31.1 (3.3)	31.1 (2.9)	NR	NR	NR	NR	NR	NR	NR	NR						
Dieussaert et al. [22] (2024)	3,557	1,771	29.0 (6.0)	29.0 (6.0)							1 (<0.1)	1,469 (41.3)	2,079 (58.4)	8 (0.2)	2 (0.1)	727 (41.1)	1,036 (58.5)	6 (0.3)						
Neonatal participants																								
Kampmann et al. [21] (2023)	3,568	3,558			1,816 (50.9)	1,752 (49.1)	179 (50.4)	1,765 (49.6)											3,348 (93.5)	3,372 (94.5)	9 (1-10)	9 (2-10)	3,491/3,528 (99.0)	3,485/3,517 (99.1)
Simões et al. [20] (2022)	3,557	1,771			34 (43.0)	45 (57.0)	41 (52.6)	37 (47.4)											75 (94.9)	77 (97.5)	NR	NR	NR	NR
Dieussaert et al. [22] (2024)	3,494	1,739			1,753 (50.2)	1,741 (49.8)	873 (50.2)	866 (49.8)											NR	NR	NR	NR	3,381 (96.8)	1,685 (96.9)

Values are presented as mean±standard deviation, median (range), or number (%).
RSVpreF, RSV prefusion F protein-based vaccine; NR, not reported; RSV, respiratory syncytial virus.

included nine selected maternal adverse events. The vaccinated group showed a slightly higher incidence of blood disorders. However, the difference was not statistically significant (RR, 1.07 [0.69, 1.66]; *P*=0.78; I^2=0%), cardiac disorders (RR, 1.19 [0.80, 1.77]; *P*=0.38; I^2=0%), headache (RR, 0.80 [0.30, 2.10]; *P*=0.65; I^2=0%), joint pain (RR, 1.39 [0.68, 2.86]; *P*=0.37; I^2=59%), fever (RR, 0.90 [0.20, 4.16]; *P*=0.89; I^2=57%), gastrointestinal disorders (RR, 1.04 [0.70, 1.56]; *P*=0.83; I^2=0%), fatigue (RR, 1.05 [1.00, 1.10]; *P*=0.07; I^2=0%), and conditions complicating pregnancy, which was defined as any systemic disease affecting pregnancy, the puerperium or the perinatal period (RR, 1.01 [0.65, 1.56]; *P*=0.97; I^2=17%). However, a significant difference between the two groups was observed in the following outcomes, with a higher incidence in the vaccine group: muscle pain (RR, 1.60 [1.46, 1.74]; *P*<0.00001; I^2=0%). After pooling the data, the overall analysis indicated comparable rates of systemic adverse events in infant participants across both

Table 2. Demographic and clinical characteristics of the maternal and neonatal participants

Race-no and ethnicity	Kampmann et al. [21] (2023)		Simões et al. [20] (2022)		Dieussaert et al. [22] (2024)	
	RSVpreF 120 μg	Placebo	RSVpreF 120 μg	Placebo	RSVpreF 120 μg	Placebo
White	2,383 (64.7)	2,365 (64.4)	62 (78.5)	71 (89.9)	1,669 (46.9)	838 (47.3)
Black	720 (19.6)	723 (19.7)	14 (17.7)	5 (6.3)	517 (14.5)	251 (14.2)
Asian	454 (12.3)	464 (12.6)	1 (1.3)	0 (0.0)	663 (18.6)	326 (18.4)
Multiracial	30 (0.8)	21 (0.6)	0 (0.0)	2 (2.5)	707 (19.9)	356 (20.1)
Race not reported	41 (1.1)	45 (1.2)	2 (2.5)	0 (0.0)	NR	NR
Hispanic or Latinx	1,049 (28.5)	1,075 (29.3)	21 (26.6)	25 (31.6)	1,196 (33.6)	582 (32.9)
Non-Hispanic/non-Latin	2,603 (70.7)	2,567 (69.8)	58 (73.4)	54 (68.4)	2,360 (66.3)	1,189 (67.1)
American Indian or Alaska Native	38 (1.0)	37 (1.0)	0 (0.0)	1 (1.3)	14	7
Native Hawaiian or Pacific Islander	9 (0.2)	12 (0.3)	NR	NR	8	4
Ethnic group not reported or mixed	30 (0.8)	33 (0.9)	NR	NR	685	345

Values are presented as number (%).
RSVpreF, RSV prefusion F protein-based vaccine; NR, not reported; RSV, respiratory syncytial virus.

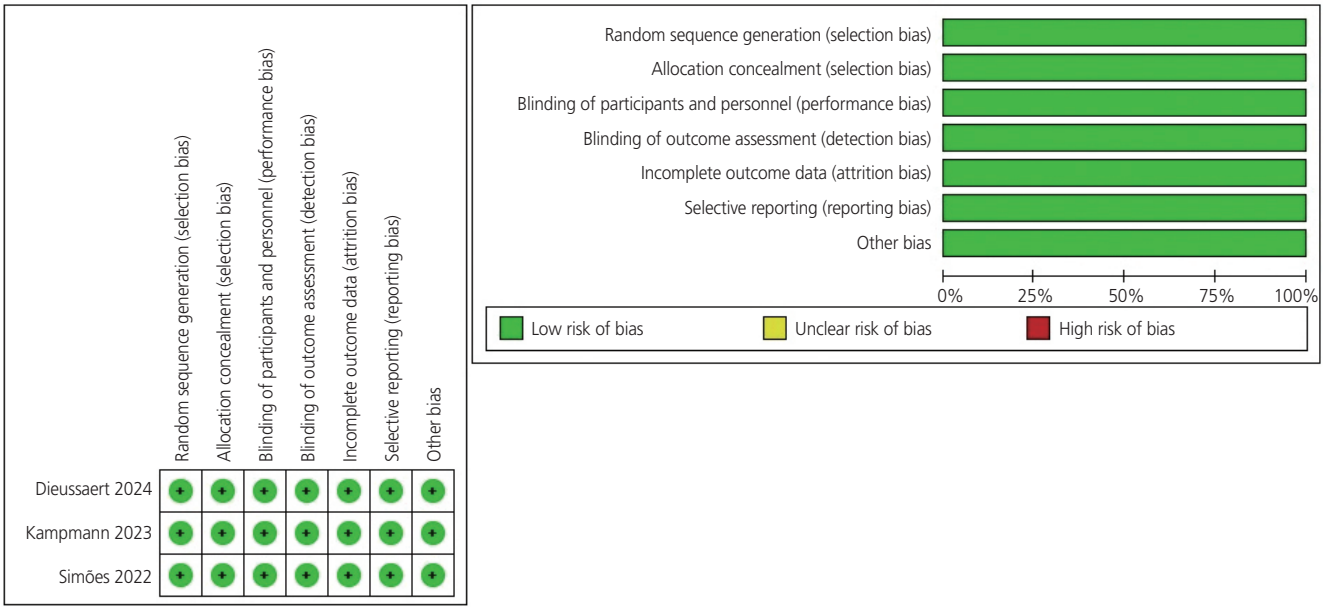

Fig. 2. Risk of bias assessment for the included RCTs. RCTs, randomized controlled trials.

Study or subgroup	RSVpreF 120 µg Events	RSVpreF 120 µg Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, fixed, 95% CI
1.1.1 Medically assessed RSV-associated lower respiratory tract illness						
Dieussaert 2024	16	3,426	24	1,711	11.0%	0.33 [0.18, 0.63]
Kampmann 2023	57	3,495	117	3,480	40.3%	0.49 [0.35, 0.66]
Simões 2022	3	405	5	103	2.7%	0.15 [0.04, 0.63]
Subtotal (95% CI)		**7,326**		**5,294**	**54.1%**	**0.44 [0.33, 0.57]**
Total events	76		146			
Heterogeneity: Chi²=3.27; df=2 (*P*=0.20); I²=39%						
Test for overall effect: z=5.93 (*P*<0.00001)						
1.1.2 Medically attended severe RSV-associated lower respiratory tract illness						
Dieussaert 2024	8	3,426	14	1,711	6.4%	0.29 [0.12, 0.68]
Kampmann 2023	19	3,495	62	3,480	21.4%	0.31 [0.18, 0.51]
Simões 2022	1	405	3	103	1.6%	0.08 [0.01, 0.81]
Subtotal (95% CI)		**7,326**		**5,294**	**29.4%**	**0.29 [0.19, 0.44]**
Total events	28		79			
Heterogeneity: Chi²=1.18; df=2 (*P*=0.55); I²=0%						
Test for overall effect: z=5.65 (*P*<0.00001)						
1.1.3 Hospitalizations due to RSV occurring within 180 days						
Kampmann 2023	19	3,495	44	3,480	15.2%	0.43 [0.25, 0.73]
Simões 2022	0	405	2	103	1.4%	0.05 [0.00, 1.06]
Subtotal (95% CI)		**3,900**		**3,583**	**16.5%**	**0.40 [0.24, 0.67]**
Total events	19		46			
Heterogeneity: Chi²=1.84; df=1 (*P*=0.18); I²=46%						
Test for overall effect: z=3.48 (*P*=0.0005)						
Total (95% CI)		**18,552**		**14,171**	**100.0%**	**0.39 [0.31, 0.48]**
Total events	123		271			
Heterogeneity: Chi²=8.79; df=7 (*P*=0.27); I²=20%						
Test for overall effect: z=8.84 (*P*<0.00001)						
Test for subgroup differences: Chi²=2.55; df=2 (*P*=0.28); I²=21.7%						

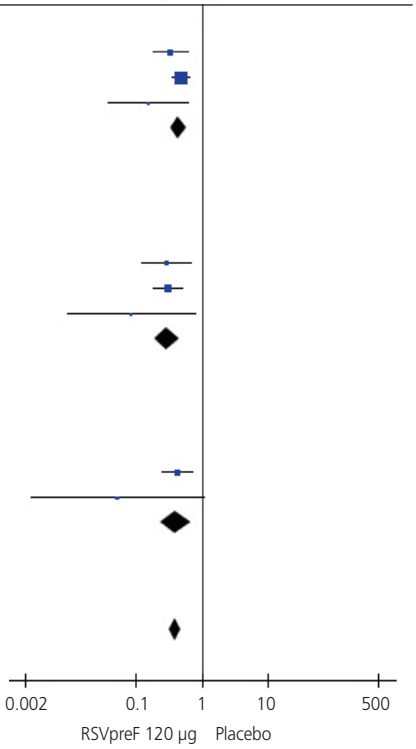

Fig. 3. Meta analysis of the incidence of RSV-associated lower respiratory tract illness. RSVpreF, RSV prefusion F protein-based vaccine; M-H, mantel-haenszel test; CI, confidence interval; RSV, respiratory syncytial virus.

Study or subgroup	RSVpreF 120 µg Events	RSVpreF 120 µg Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, random, 95% CI
1.4.1 Injection site pain						
Kampmann 2023	1,509	36,821	370	3,675	35.3%	4.07 [3.67, 4.52]
Simões 2022	23	78	8	79	11.9%	2.91 [1.39, 6.11]
Subtotal (95% CI)		**3,760**		**3,754**	**47.2%**	**4.04 [3.65, 4.48]**
Total events	1,532		378			
Heterogeneity: Tau²=0.00; Chi²=0.77; df=1 (*P*=0.38); I²=0%						
Test for overall effect: z=26.56 (*P*<0.00001)						
1.4.2 Redness						
Kampmann 2023	258	3,682	37	3,675	25.4%	6.96 [4.95, 9.79]
Simões 2022	4	78	0	79	1.1%	9.11 [0.50, 166.49]
Subtotal (95% CI)		**3,760**		**3,754**	**26.5%**	**6.99 [4.98, 9.81]**
Total events	262		37			
Heterogeneity: Tau²=0.00; Chi²=0.03; df=1 (*P*=0.86); I²=0%						
Test for overall effect: z=11.23 (*P*<0.00001)						
1.4.3 Swelling						
Kampmann 2023	221	3,682	37	3,675	25.3%	5.96 [4.22, 8.42]
Simões 2022	3	78	0	79	1.1%	7.09 [0.37, 135.01]
Subtotal (95% CI)		**3,760**		**3,754**	**26.3%**	**5.98 [4.24, 8.42]**
Total events	224		37			
Heterogeneity: Tau²=0.00; Chi²=0.01; df=1 (*P*=0.91); I²=0%						
Test for overall effect: z=10.22 (*P*<0.00001)						
Total (95% CI)		**11,280**		**11,262**	**100.0%**	**5.01 [3.68, 6.83]**
Total events	2,018		452			
Heterogeneity: Tau²=0.07; Chi²=13.75; df=5 (*P*=0.02); I²=64%						
Test for overall effect: z=10.19 (*P*<0.00001)						
Test for subgroup differences: Chi²=12.71; df=2 (*P*=0.002); I²=84.3%						

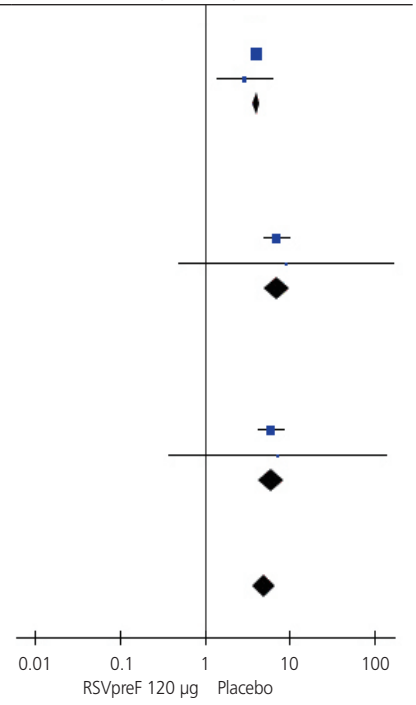

Fig. 4. Meta-analysis of the incidence of local reactions. RSVpreF, RSV prefusion F protein-based vaccine; M-H, mantel-haenszel test; CI, confidence interval; RSV, respiratory syncytial virus.

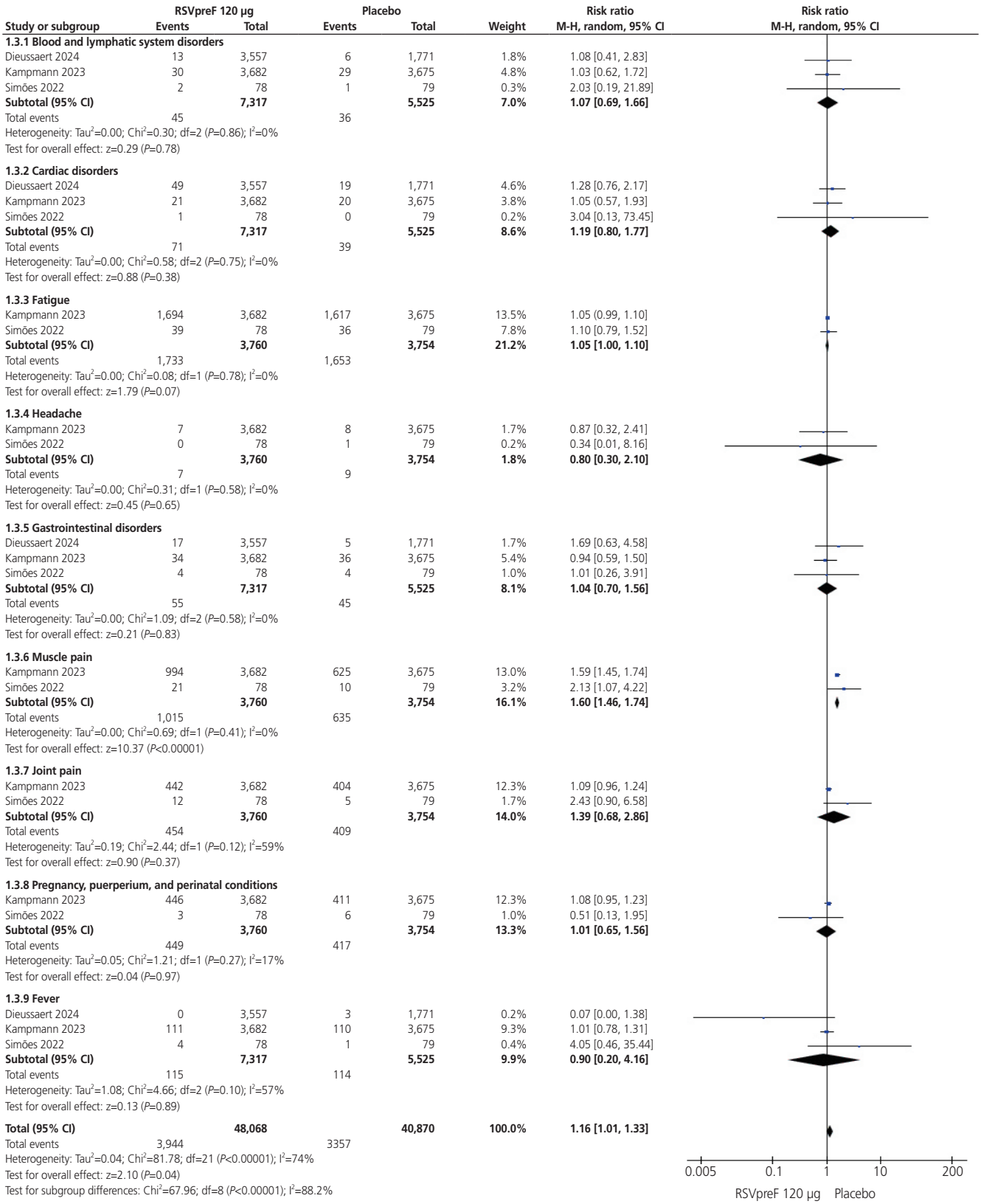

Fig. 5. Meta-analysis of the incidence of systemic maternal adverse events. RSVpreF, RSV prefusion F protein-based vaccine; M-H, mantel-haenszel test; CI, confidence interval; RSV, respiratory syncytial virus.

groups (RR, 1.16 [1.01, 1.33]; *P*=0.04) with a high level of heterogeneity (I^2=74%) (Fig. 5).

3) Systemic infant adverse events

Three studies reported on this outcome [20-22]. In terms of systemic adverse events among infant participants, we observed similar rates of congenital, familial, and genetic disorders in both groups (RR, 0.99 [0.86, 1.13]; *P*=0.88) with a high degree of homogeneity (I^2=0%). Similarly, the occurrence of cardiac disorders (RR, 0.99 [0.58, 1.68]; *P*=0.97) showed no significant difference between the groups, and the data displayed no heterogeneity (I^2=0%). Similarly, there were comparable rates of eye disorders (RR, 1.08 [0.33, 3.60]; *P*=0.90), with a minimal degree of heterogeneity (I^2=22%), whereas injury, poisoning, and procedural complications (RR, 1.23 [0.28, 5.35]; *P*=0.78) displayed a moderate degree of heterogeneity (I^2=54%). A significant difference was reported between both groups in the incidence of congenital gastrointestinal disorders (RR, 1.25 [0.98, 1.59]; *P*=0.07), with no observed heterogeneity (I^2=0%). After pooling the data, the overall analysis indicated comparable rates of systemic adverse events in infant participants across both groups (RR,

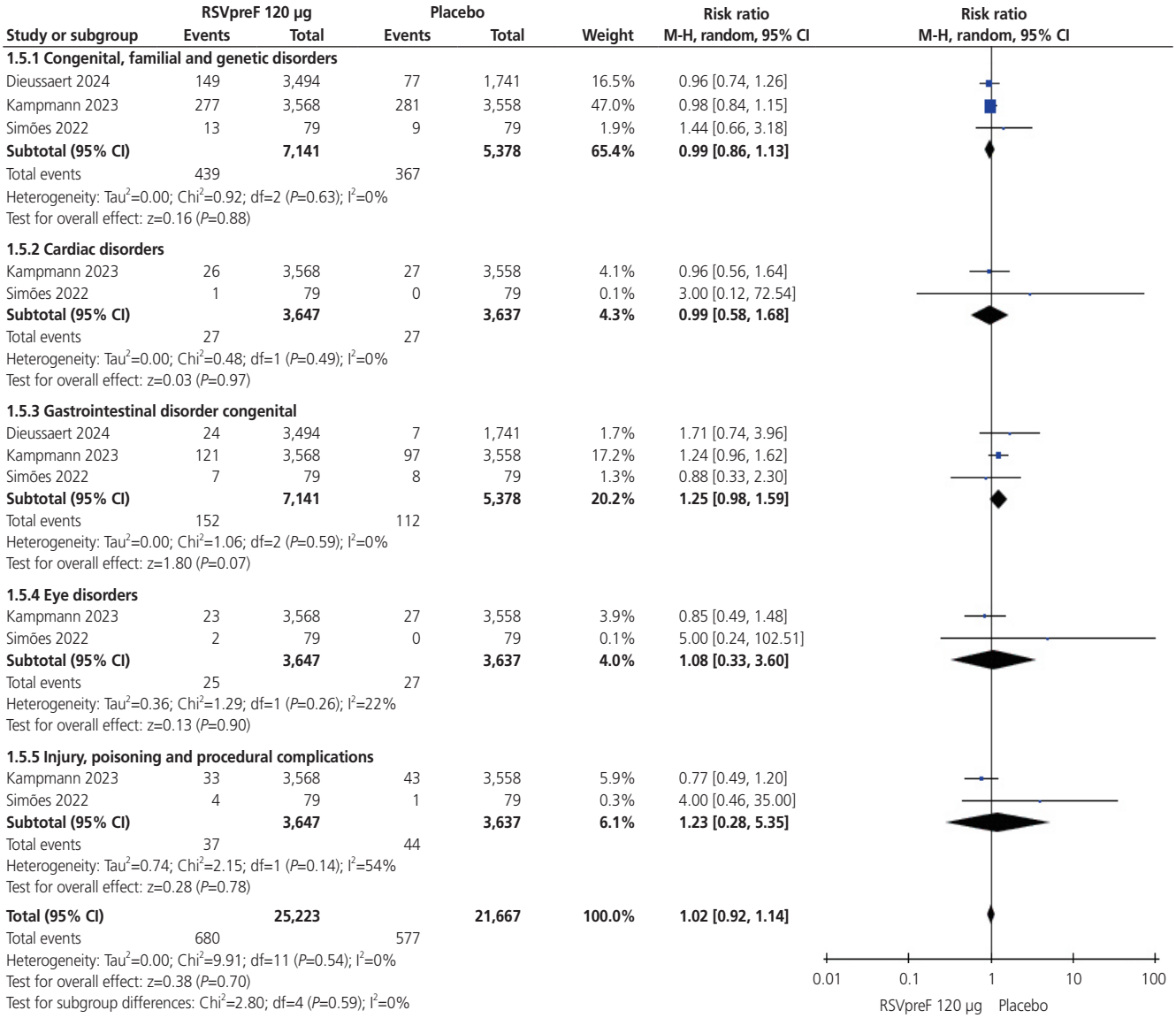

Fig. 6. Meta-analysis of the incidence of systemic neonatal adverse events. RSVpreF, RSV prefusion F protein-based vaccine; M-H, mantel-haenszel test; CI, confidence interval; RSV, respiratory syncytial virus.

1.02 [0.92, 1.14]; *P*=0.70) with a high level of homogeneity (I^2=0%), as seen in Fig. 6.

3. Preterm delivery

All three RCTs included this outcome [20-22]. RSVpreF vaccination was associated with a significantly higher incidence of preterm delivery, occurring in 470 of 7,152 mothers (6.6%) who received the vaccination but only in 285 of the 5,387 mothers (5.3%) who received a placebo (RR, 1.24 [1.08, 1.44]; *P*=0.003). The data were homogeneous (*P*=0.30; I^2=17%), as seen in Fig. 7.

4. Neonatal death

Three studies [20-22] reported neonatal death outcomes. Twenty-three and twelve deaths were reported in the vaccination and placebo group, respectively. However, the difference between both groups was not significant (RR, 1.42 [0.70, 2.89]; *P*=0.34). The data were homogeneous (*P*=0.52; I^2=0%] (Fig. 8).

Conclusion

We found that RSVpreF vaccination was associated with a 24% increased risk of preterm delivery. In addition, although vaccination resulted in a decrease in severe illness and hospitalization, there was no significant difference in neonatal mortality, with 23 and 12 deaths reported in the vaccination and placebo group, respectively. The consequences of this serious adverse event, including the need for neonatal intensive care, fetal complications, and maternal complications, were not described in the original manuscript and are concerning for application in practice on a broad scale. These data curb enthusiasm for RSV maternal mass vaccination and stress the importance of informed consent for mothers, including serious warnings about the risks of premature labor. However, it is important to note that the exact pathogenesis of preterm labor, infectious or non-infectious, has not yet been identified.

In terms of efficacy, our meta-analysis aimed to systematically synthesize and evaluate the existing literature on the effectiveness and safety of the RSVpreF vaccine administered during pregnancy. In this study, the RSV preF vaccine showed promising results. Over the 360-day observation period, the

	RSVpreF 120 μg		Placebo			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI	M-H, fixed, 95% CI
Boytchev 2023	238	3,496	86	1,739	36.6%	1.38 [1.08, 1.75]	
Kampmann 2023	229	3,577	198	3,570	63.1%	1.15 [0.96, 1.39]	
Simões 2022	4	79	1	78	0.3%	3.95 [0.45, 34.55]	
Total (95% CI)		**7,152**		**5,387**	**100.0%**	**1.24 [1.08, 1.44]**	
Total events	471		285				
Heterogeneity: Chi^2=2.41; df=2 (*P*=0.30); I^2=17%							
Test for overall effect: z=2.94 (*P*=0.003)							

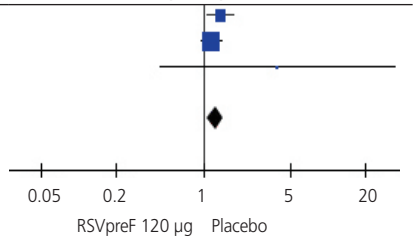

Fig. 7. Meta-analysis of the incidence of preterm delivery. RSVpreF, RSV prefusion F protein-based vaccine; M-H, mantel-haenszel test; CI, confidence interval; RSV, respiratory syncytial virus.

	RSVpreF 120 μg		Placebo			Risk ratio	Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI	M-H, fixed, 95% CI
Simões 2022	0	79	1	79	11.1%	0.33 [0.01, 8.06]	
Kampmann 2023	10	3,682	8	3,675	59.3%	1.25 [0.49, 3.16]	
Dieussaert 2024	13	3,494	3	1,741	29.6%	2.16 [0.62, 7.57]	
Total (95% CI)		**7,255**		**5,495**	**100.0%**	**1.42 [0.70, 2.89]**	
Total events	23		12				
Heterogeneity: Chi^2=1.30; df=2 (*P*=0.52); I^2=0%							
Test for overall effect: z=0.96 (*P*=0.34)							

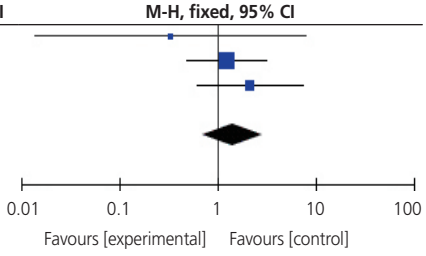

Fig. 8. Meta-analysis of the incidence of neonatal death. RSVpreF, RSV prefusion F protein-based vaccine; M-H, mantel-haenszel test; CI, confidence interval; RSV, respiratory syncytial virus.

vaccine notably reduced, but did not eliminate, instances of RSV-associated lower respiratory tract illnesses in the neonates. However, there were no significant reductions in RSV hospitalizations or deaths among infants.

However, reductions in mild cases of RSV appear to have come with a significant tradeoff, as there was an observed increase in preterm deliveries among the participants who received the vaccine. Likely, this significant difference was not observed in the Kampmann et al. [21] trial that led to the FDA approval of Abrysvo™ (Pfizer) in pregnancy secondary to insufficient power for that outcome. We believe that many strategies can be employed to mitigate the risk of preterm labor if a mother opts for RSV vaccination. Some of these strategies include restricting the use of the vaccine to mothers close to delivery or limiting its usage to pregnancies where there is a significant concern for neonatal susceptibility to viral infection, such as babies with birth defects or those suspected to be delivered prematurely. It is notable that as preterm infants are known to be more susceptible to RSV infection, one likely area of use for this vaccine is in pregnancies that are expected to deliver prematurely, making the practical application of maternal vaccination problematic.

With regard to other safety events, the placebo group had fewer local injection site reactions than the vaccine group. Additionally, mothers in the vaccinated group experienced a higher incidence of systemic symptoms within the first month of vaccination. Interestingly, both groups showed comparable rates of systemic adverse events in the infant participants. These findings provide valuable insights into the efficacy and safety of the RSVpreF vaccine administered during pregnancy, which can inform further discussions on the potential benefits and considerations associated with this immunization strategy.

RSV causes significant morbidity and mortality in young infants worldwide, particularly in low- and middle-income nations [23,24]. A phase 3 trial demonstrated that administering nirsevimab, a monoclonal antibody, provided a substantial level of protection against medically attended RSV-related lower respiratory tract infections for up to 150 days after injection, with an efficacy of 74.5% (95% CI, 49.6% to 87.1%) [25]. However, infant death after the use of nirsevimab was not consistent with monoclonal antibody use, and there is no assurance regarding the long-term safety of this novel approach. Although nirsevimab has gained authorization in Europe for use in infants from birth during the RSV season, its affordability in low- and middle-income countries remains uncertain. In many regions, the accessibility of monoclonal antibodies is restricted to high-risk populations. Beyond supportive care, no other therapeutic options are currently available [25]. Recent publications suggest that the wide-scale use of nirsevimab may apply non-sterilizing ecological pressure on RSV, resulting in resistant strains that may break through monoclonal protection or cause *de novo* infections beyond the window of immunity proven by either maternal RSV vaccination or nirsevimab administration at birth.

Vaccination presents the potential for an immune response against various neutralizing epitopes, consequently lowering the risk of immune evasion, as observed with some monoclonal antibody treatments [26]. The passive transmission of maternal antibodies serves as a safeguard for newborns, particularly those who are most fragile, in the critical period immediately after birth, before the development of robust immune responses through active vaccination. Notably, our study revealed that the youngest infant afflicted with severe RSV-related lower respiratory tract illness was a mere 8 days old, underscoring the need for early treatment with hospital or ambulatory nebulization therapy irrespective of RSV vaccination.

Following the approval of Pfizer's© (Pfizer), Abrysvo™ (Pfizer) for lower respiratory tract disease caused by RSV, Melgar et al. [27] evaluated the efficacy of both the GSK© (Brentford) vaccine and the Pfizer© (Pfizer) vaccine. They reported that both vaccine variants showed notable effectiveness in preventing symptomatic RSV-associated LRTD in adults aged 60 years and older with just one dose, however, the crude rates of serious adult RSV infection was <1% in both treatment and placebo groups. On June 21, 2023, the Advisory Committee on Immunization Practices suggested that individuals in this age group consider a single RSV vaccine dose in consultation with their healthcare providers. Vaccination against RSV has the potential to reduce significantly rare RSV illnesses in vulnerable older adults. Ongoing monitoring of its safety and efficacy through post-market surveillance will inform future recommendations.

The prefusion F protein is a key antigen on the RSV surface. It plays a critical role in viral entry into the host cells and is the primary target of neutralizing antibodies. The prefusion form of the F protein is the specific conformation that the protein adopts before undergoing a structural change to

initiate viral fusion with the host cell membrane. Researchers have shown that antibodies targeting the prefusion F protein exhibit higher neutralizing activity than those targeting the post-fusion form, making it an attractive target for vaccine development. Several studies have demonstrated promising results for pre-fusion F-protein-derived vaccines. These vaccines have shown efficacy in preclinical models, eliciting robust immune responses and providing protection against RSV infection. Additionally, early stage clinical trials have shown encouraging results in terms of safety and immunogenicity in human subjects [28-30]. Caveats concerning RSV vaccination include mutational resistance because of limited antigenic immunity with either pre- or post-fusion protein epitopes.

The safety and adverse event profiles observed in mothers receiving the RSVpreF vaccine were concerning and consistent with findings from prior phase 1-2 clinical trials performed on non-pregnant adults [31-33]. Typically, participants experienced mild to moderate levels of reactogenicity. The profiles of adverse events and serious adverse events tended to be consistently greater with vaccination, and the 24% excess risk of preterm labor and delivery remains a major concern. If RSV vaccination is more broadly applied to complicated and high-risk pregnancies (e.g., preeclampsia and eclampsia), the rates of preterm labor and its complications could be much greater with RSV vaccination. Both groups displayed similar frequencies of systemic adverse events among infant participants.

1. Strengths

Our study is the first meta-analysis to assess the safety of RSVpreF vaccination during pregnancy. Because only RCTs were included, our data can be considered to be of high quality. In addition, heterogeneity was low, likely secondary to the nearly identical study designs across the three trials.

2. Limitations

Our study had the limitations of all systematic reviews and meta-analyses. First, all included studies excluded high-risk pregnancies, such as those at a current risk of preterm birth, those with multiple pregnancies, or those who had a previous infant with a clinically significant congenital anomaly. We did not observe the clinical consequences of preterm delivery, which occurred more often in the RSV vaccinated group than in the unvaccinated group. Additionally, our analysis lacked extensive data from low-income countries, where the vaccine could potentially have the greatest impact. Moreover, the analysis did not have sufficient statistical power to evaluate the discrepancies in vaccine efficacy based on specific RSV antigen subgroups.

RSV vaccination in the third trimester of pregnancy is associated with a 24% increased risk of preterm labor and delivery. This may cause avoidable maternal-fetal complications with unknown long-term consequences. Although the vaccine demonstrated notable efficacy in reducing mild RSV illnesses over 360 days after delivery, there was no significant decrease in neonatal mortality. Despite vaccination, a substantial number of breakthrough cases in newborns of vaccinated mothers highlight the need for education and treatment of acute RSV. Moving forward, it is crucial to weigh the theoretical benefits against potential risks, particularly fetal loss and preterm delivery. Additional research and continued surveillance are essential to determine the balance between the risks and benefits of RSVpreF vaccination as a novel strategy in the third trimester of pregnancy.

Conflict of interest

Authors declare no competing interests.

Ethical approval

This Manuscript was reviewed by the Institutional Review Board at the Marchand Institute and was found to be exempt from IRB review (613-09-04-2024 in September 2023).

Patient consent

Not applicable to systematic review.

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