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Respiratory Syncytial Virus Maternal Vaccination in Infants below 6 Months of Age: Meta-Analysis of Safety, Immunogenicity, and Efficacy

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Keywords
Respiratory syncytial virus · Infant · Respiratory tract infections · Maternal vaccination

Abstract
Introduction: Severe respiratory syncytial virus (RSV) disease is most prevalent during infancy, particularly in those born prematurely, who benefit least from maternal antibody transfers. Maternal immunization is an attractive prevention leading to vaccine clinical trials. This meta-analysis aimed to evaluate recent maternal RSV vaccine trials. ***Methods:*** Following PRISMA-P guidelines for systematic reviews and registered at https://www.crd.york.ac.uk/prospero, this study shortlisted six randomized clinical trials of suitable quality from four databases. Meta-analysis evaluated vaccine safety, immunogenicity, and efficacy in infants and their mothers. ***Results:*** From random-effects and fixed-effects meta-analysis between trial and control arms, the maternal post-vaccination geometric antibody (Ab) titers showed pooled standard mean differences (SMDs [95% CI]) at delivery of (4.14 [2.91–5.37]), (3.95 [2.79–5.11]), and (12.20 [7.76, 16.64]) for RSV neutralizing Ab A, B, and F IgG, respectively. Vaccine administration was more likely than placebo to cause local pain, erythema, swelling, and systemic myalgia. Furthermore, the Ab levels in infants at birth showed pooled SMDs of each RSV A (3.9 [2.81–4.99]), RSV B (1.86 [1.09–2.62]), and RSV F IgG (2.24 [1.24–3.23]). The overall reduction of RSV-related lower respiratory tract infections and hospitalizations in the first 6 months of life was 52% and 48%, respectively. ***Conclusions:*** Not only does antenatal RSV vaccination look safe and immunogenic in vaccinated mothers, but it also reliably provides effective antibody levels in infants and diminishes RSV-related severe disease in infants under 6 months of age.

Introduction

Accountable for severe acute lower respiratory tract infections (LRTI) and hospitalizations in childhood, respiratory syncytial virus (RSV) lies at the root of significant burdens on health services worldwide [1]. Worse outcomes following respiratory infections of this virus in

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young children are strongly associated with underlying risk factors, including prematurity and age below 6 months [2]. RSV-related hospitalizations and mortality peak within the 6 months of life [1, 3], owing to a lack of both pre-exposure to the RSV and the presence of anti-RSV maternal antibody transfers [4]. This period consequently becomes a critical window for RSV infection in newborns reliant on the maternally derived antibodies (MatAbs) present up until 6 months after birth, corresponding to the decay of the MatAbs [5]. Instead, in term infants born during the winter season, lower maternal antibody levels were reportedly lower in newborns with severe RSV infections [6].

Of RSV antigens, glycoprotein F is responsible for viral entry into cells and is considered the primary immunogen of specific neutralizing antibodies (Nabs) against RSV [7, 8]. Accordingly, F protein becomes a desirable target for RSV vaccine developments [8]. Purified recombinant F protein, to emulate RSV F protein, generates anti-F antibodies, thus becoming an intriguing cornerstone [9, 10]. The presence of adequate levels of neutralizing MatAbs during the third trimester, when the transplacental fetal acquisition of antibodies occurs, is essential to reduce the risk of severe RSV disease [11, 12]. RSV vaccinations antenatally administered during the later stages of pregnancy have been purposed to enhance neonatal immunity against RSV exposures. To the best of our knowledge, this is the first meta-analysis of maternal RSV vaccine clinical trials. This study aimed to evaluate the safety, immunogenicity, and efficacy of recent RSV-F-protein-based vaccines both in pregnant women and their infants compared to placebo controls.

Methods

Study Design

A systematic review and meta-analysis were conducted to formulate an appraisal of the clinical safety, immunogenic profile, and efficacy of maternal RSV vaccination. The observed effects were evaluated in the vaccinated pregnant women and babies born to these jabbed women compared to placebo-treated control arms. Vaccine tolerability was conducted by reviewing the reported reactogenicities and adverse effects monitored post-vaccination. The vaccine immunogenic profile was evaluated according to antibody populations promoted following vaccination at certain time points. Furthermore, incidences of RSV-associated LRTI and hospital admissions post-vaccination were assessed to evaluate vaccine efficacy. During the qualitative and quantitative assessment of the eligible studies, this review was designed following the guidelines from The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [13] (online suppl. File 1; for all online suppl. material, see https://doi.org/10.1159/000536031). Ethics reviews and approvals were not necessary for results dissemination. Our systematic review has been registered through the PROSPERO database (https://www.crd.york.ac.uk/prospero) under the protocol number CRD42023405392.

Eligibility Criteria

Any clinical trial studies that reported the safety and/or immunogenicity and/or efficacy of RSV vaccination were deemed eligible. We included all clinical trial studies, up to February 22, 2023, in which participants were mother-infant pairs, regardless of publication language. The exclusion criteria were studies with designs and outcomes out of scope, incomplete information, and poor bias scoring.

Search Strategy

Systematic literature searching was performed via MEDLINE (PubMed), Embase, Web of Science, and the Maternity and Infant Care Database between January 1, 2023, and February 22, 2023. We performed the search strategy using different combinations of the MeSH terms and keywords in MEDLINE and Embase, whereas in the other databases, we combined the most relevant keywords with the previous two databases (online suppl. File 2). All records from 1964 to February 22, 2023, were collected for article eligibility assessment. To remove duplicates from the record list, EndNote software was used. All articles from the record were identified independently by two review authors ($M.P.M._1$ and $M.P.M._2$) using the Rayyan.ai online platform, from the title and abstract screening to full-text eligibility assessment. Disagreements between the two reviewers were discussed with the third and fourth authors. Search strategy process according to the PRISMA flow chart shown in Figure 1.

Data Extraction

Information regarding the author's last name, publication year, study setting and design, sample size, proportion, vaccine type, placebo information, and clinical outcomes were extracted into Microsoft Excel (Microsoft Office Professional Plus 2016).

Risk of Bias Assessment

Critical appraisal of data quality was done based on the Cochrane Risk of Bias Tool for clinical trial studies [14]. The criteria to define the risk of bias assessment were classified using a high, low, and unclear risk of bias per each item. Disagreements between reviewers were discussed with the third and fourth authors. Studies with poor scoring were excluded.

Effect Measures

Data regarding the proportion of women showing post-vaccination safety and tolerability following RSV vaccination, including solicited local and systemic reactions, unsolicited adverse events (AEs), serious AEs (SAEs), and AEs of special interests (AESIs) observed in the pregnant women and infant participants, were further evaluated. The data about vaccine immunogenicity of RSV vaccines were investigated from maternal serum and umbilical cord blood geometric mean titers (GMTs) or concentrations (GMCs) of IgG, Nab, and palivizumab competitive antibody (PCA) measurements. RSV vaccine efficacy was defined as the reported incidence of RSV-related respiratory tract infections in hospitalized infants. Vaccination safety and efficacy data were pooled to estimate the risk ratio (RR) and odds ratio (OR),

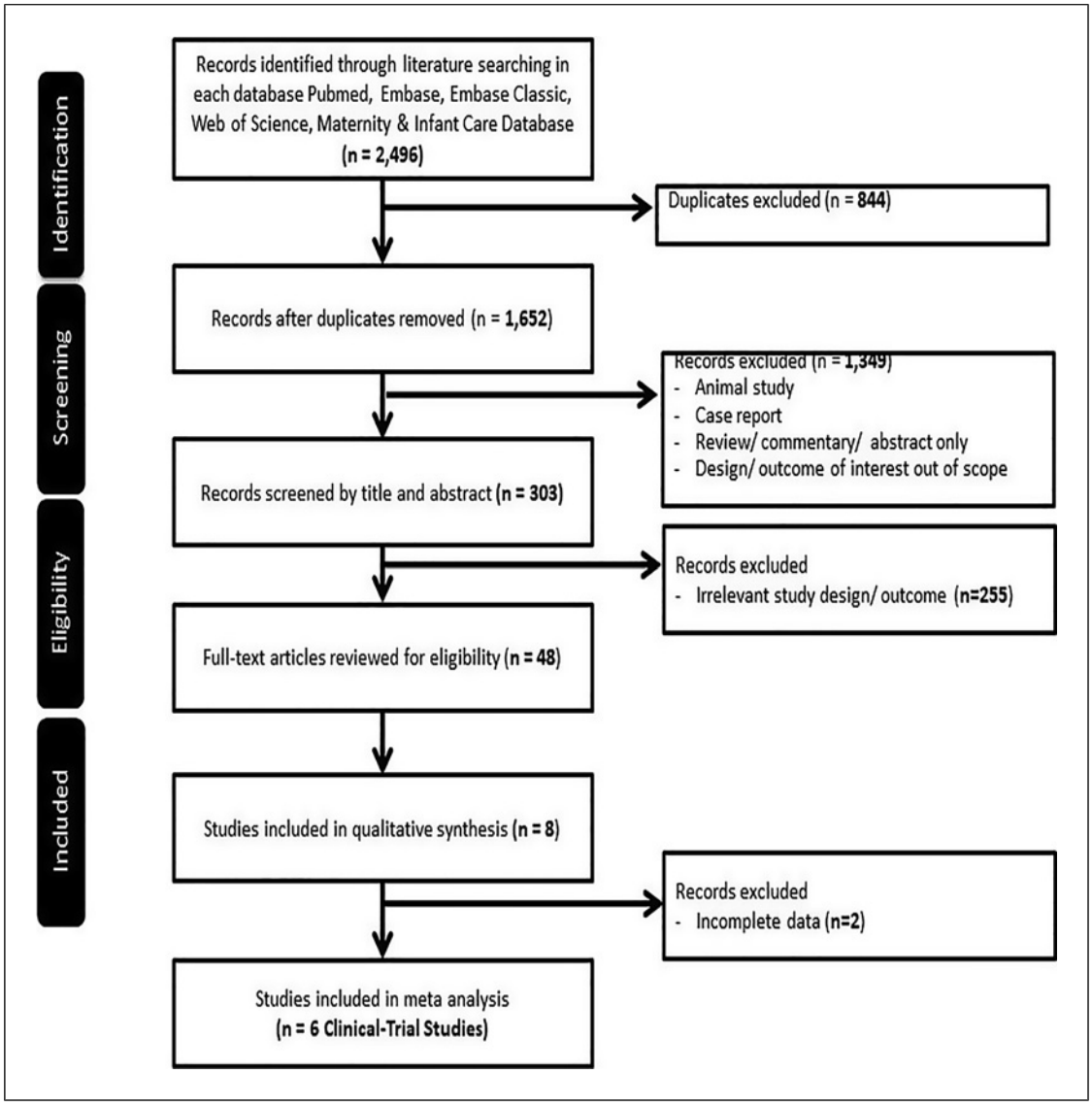

Fig. 1. Flow chart of study selection and inclusion in this study.

respectively, with a 95% confidence interval (95% CI). Meanwhile, data on the vaccine immunogenicity were pooled in standardized mean difference (SMD).

Meta-Analysis Synthesis

The quantitative and statistical analysis of pooled data was conducted with Review Manager (RevMan) software version 5.4. The extracted data comparing the proportion between RSV-vaccinated mothers and placebos were pooled using random effect models with generic inverse variance. Statistical heterogeneity was determined by the I^2 value, which refers to the outlined criteria of I^2 value of 40%–100% representing the study heterogeneity, which as therefore pooled using a random-effect model [15]. A fixed-effect model was used for studies with an I^2 value <40%. Due to the non-applicable subgroup and sensitivity analysis of the limited number of studies, we did not explore the study heterogeneity.

Results

Search Results

Of 2,496 studies eligible in accordance with the search term, 844 were removed due to duplications, and 303 abstracts were considered for further screening. Following detailed analysis, 6 identified full-article randomized clinical trial (RCT) studies [16–21] were

included concerning the maternal RSV vaccine based on purified F protein given to healthy pregnant women with uncomplicated singleton pregnancies (Fig. 1). These identified studies recruited 7,266 and 5,468 pregnant women into the vaccination arm and the control arm, respectively.

Study Characteristics

The RCTs congregated are further meta-analyzed for the selected outcomes, including either safety and immunogenicity in both maternal and infant participants as well as vaccine efficacy. The aspect of vaccine immunogenicity took into account GMTs of Nabs, GMCs of specific IgG (RSV F IgG), and GMCs of PCA performed in four, three, and two RCTs, respectively. Safety in maternal participants was in relation to post-vaccination adverse reactions, including both local and systemic 1-week reactogenicity (solicited AE) upon vaccination, unsolicited AEs, SAEs, and AESIs observed in participants for at least a month post-vaccinated.

Vaccines were administered mostly within the last trimester of pregnancy in all the RCTs, according to mean values of gestational age at injection. Stage-wise, two RCTs collected data from phase III of the clinical trial while four others from phase IIb. Al $(OH)_3$-adjuvanted vaccine was evaluated in four RCTs, whereas two RCTs tested the unadjuvanted vaccine. An administration dose of 120 μg was given to pregnant women in the trial-arm from all six RCTs, yet two of these also additionally administered vaccine doses of either 60 μg or 240 μg. The further details of RCTs included in this study are presented in Table 1. The risk-of-bias assessment of the included studies was deemed low, where incomplete datasets mainly served as the major risk factor (Fig. 2, 3).

Meta-Analysis of Vaccine Reactogenicity and Safety

Vaccine Reactogenicity

Vaccine reactogenicity is described by occurrences of solicited AEs in study groups from the time of vaccine administration to day 7 after vaccination. This consists of both localized and generalized reactions. Across the RCTs, our meta-analysis results showed that the local reactogenicity of maternal RSV vaccines was significantly higher than placebo controls. These local reactions included local pain, redness, and swelling. All six studies provided local administration pain following vaccination in recruited participants, yet a study by Munoz in 2003 did not report local redness and swelling after vaccination. In comparison to placebo-treated pregnant women in the control groups, pregnant women receiving maternal RSV vaccination were at significantly higher risks of local pain (RR: 4.30, 95% CI: 3.94–4.70), local redness (RR: 6.19, 95% CI: 4.67–8.19), and local swelling (RR: 5.82, 95% CI: 4.48–7.57) following vaccine administration (Fig. 4).

Regarding systemic Solicited AEs or reactogenicity within 1-week post-vaccination surveillance, there were reported fatigue and headache incidences experienced by the vaccine recipients from five studies, of which four reported generalized muscle, vomiting, and joint pain events. There were slight but significant upsurges in risks of fatigue (RR: 1.05, 95% CI: 1.01–1.11), headache (RR: 1.08, 95% CI: 1.02–1.15), vomiting (RR: 1.15, 95% CI: 1.01–1.31) (Fig. 5), joint pain (RR: 1.13, 95% CI: 1.01–1.26), and, noteworthy, significantly heightened probability of generalized muscle pain (RR: 1.64, 95% CI: 1.42–1.91) among vaccine receivers was found (Fig. 6). In contrast, other systemic reactions following vaccination among individuals administered with the maternal vaccination, including nausea, diarrhea, and fever, were not statistically different between study groups and control groups.

Vaccine Safety in Maternal Participants and Their Newborn Outcomes

The proportion of immunization receivers who witnessed at least one episode of unsolicited AEs, SAEs, and AESIs showed similarity to the control groups according to our meta-analysis results. With no statistical difference between study and control groups, unsolicited AEs, serious AEs, and AESIs showed pooled RR of 1.03 (95% CI: 0.98–1.08), 1.06 (95% CI: 0.97–1.16), and 1.07 (95% CI: 0.92–1.25), respectively. Regarding the safety profile of the maternal RSV vaccine in newborn infants born to vaccinated mothers, the relative risks of AEs between trial and control groups showed no statistical difference between the study groups and control groups.

Meta-Analysis of Vaccine Immunogenicity

Immunogenicity in Maternal Participants

Meta-analysis for the immunogenic profile of the maternal RSV vaccine in vaccinated women across different trials took account of antibody measurements before primary vaccination and at the time of delivery – post-immunization – as two-time points. Meta-analysis of Nabs against RSV A (Nab-A) and RSV B (Nab-B) GMTs at the time of delivery included four studies. Out of the latter, three additionally reported these GMTs in maternal participants' preimmunization and likewise GMCs of anti-RSV F protein-specific IgG (F-IgG) at the two-time points. Furthermore, two of the aforesaid studies also highlighted PCA GMCs only at

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Table 1. Characteristics of the included studies

Author, year	Study design and settings	Study participants	Vaccine (sponsor)	Placebo	Dose	Gestational weeks at injection (mean±SD of vaccine injection)	No. of study participants		Effect measures
							mother	infants	
Munoz et al. [16] (2003)	Placebo-controlled RCT (double-blinded); USA	Uncomplicated singleton pregnant women (third trimester)	$Al(OH)^3$-adjuvanted purified F protein (Wyeth Lederle)	Sterile isotonic saline	Single dose (50 μg)	30–34 weeks of gestation (mean±SD is unavailable)	35 (20 vaccinated vs. 15 controls)	35 (20 trials vs. 15 controls)	Safety
Munoz et al. [17] (2019)	Placebo-controlled RCT (observer-blinded); USA	Uncomplicated singleton pregnant women (third trimester)	Purified F protein nanoparticle (NovaVax)	Sterile isotonic saline	Single dose (120 μg)	33–35 weeks of gestation (mean±SD is unavailable)	50 (28 vaccinated vs. 22 controls)	50 (28 trials vs. 22 controls)	Safety, immunogenicity, and efficacy
Madhi et al. [18] (2020)	Placebo-controlled RCT (observer-blinded); multicountry	Uncomplicated singleton pregnant women (third trimester)	$Al(OH)^3$-adjuvanted purified F protein nanoparticle (NovaVax)	Buffer without aluminum	Single dose (120 μg)	28–36 weeks of gestation (32±2.6)	3,045 vaccinated versus 1,581 controls	3,008 trials versus 1,561 controls	Safety, immunogenicity, and efficacy
Simoes et al. [19] (2022)	Placebo-controlled RCT (observer-blinded); USA, Chile, Argentina, South Africa	Uncomplicated singleton pregnant women (third trimester)	$Al(OH)^3$-adjuvanted OR unadjuvanted bivalent purified pre-F protein (Pfizer)	Not mentioned	Single dose (120 μg or 240 μg)	24–36 weeks of gestation (31.1±3.1)	327 vaccinated versus 79 controls	325 trials versus 78 controls	Safety, immunogenicity, and efficacy
Bebia et al. [20] (2023)	Placebo-controlled RCT (observer-blinded); multicountry	Uncomplicated singleton pregnant women (third trimester)	Unadjuvanted purified pre-F protein (GlaxoSmithKleine)	Saline solution	Single dose (60 μg or 120 μg)	28–33 weeks of gestation (mean±SD is unavailable)	145 vaccinated versus 68 controls	140 trials versus 66 controls	Safety, immunogenicity, and efficacy
Kampmann et al. [21] (2023)	Placebo-controlled RCT (observer-blinded); multicountry	Uncomplicated singleton pregnant women (third trimester)	Unadjuvanted bivalent purified pre-F protein (Pfizer)	Not mentioned	Single dose (120 μg)	24–36 weeks of gestation (30.8±3.5)	3,695 vaccinated versus 3,697 controls	3,570 trials versus 3,558 controls	Safety and efficacy

RCT, randomized control trials.

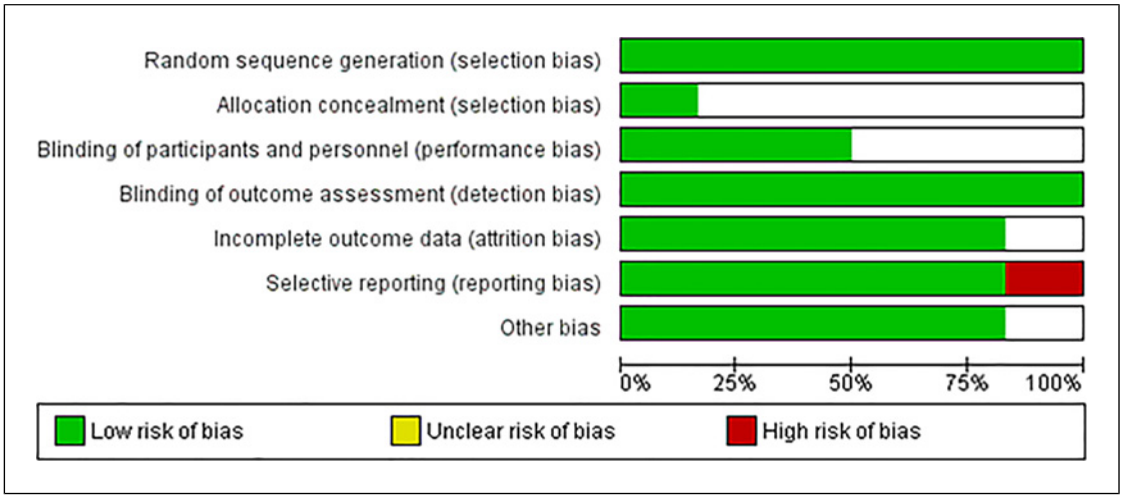

Fig. 2. Risk-of-bias graph of the included studies.

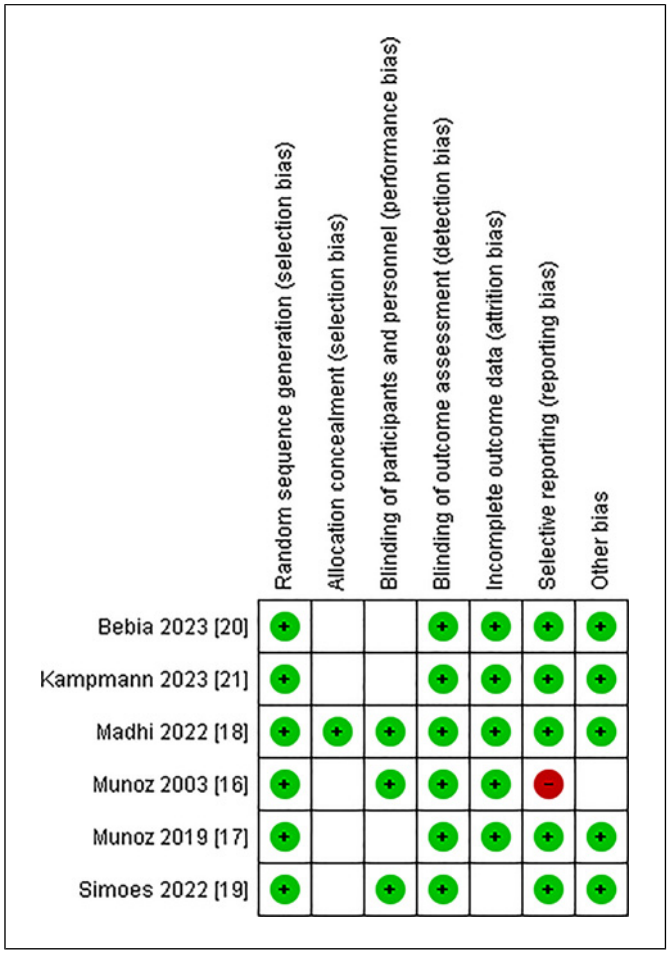

Fig. 3. Risk-of-bias summary of the included studies. Green = low-risk bias; blank = unclear-risk bias, red = high-risk bias.

delivery time. Prior to vaccination, the pooled SMDs of GMTs for Nab-A and Nab-B were −0.30 (95% CI: −0.78 to 0.19) and 0.00 (95% CI: −0.38 to 0.38), respectively. Following vaccine administration, the pooled SMDs of Nab-A and Nab-B GMT were 3.40 (95% CI: 1.35–5.45) and 1.67 (95% CI: 0.26–3.08), respectively, at the time of delivery. Also, the meta-analysis results showed that the SMD of F-IgG GMCs preimmunization and at delivery were −0.32 (95% CI: −0.91 to 0.22) and 7.48 (95% CI: 3.13–11.83), respectively. In addition, the pooled SMD of PCA GMCs at delivery was 1.79 (95% CI: 1.72–1.08). A random-effects model was employed in the analysis, except for PCA GMCs, due to significant heterogeneity among studies. The results presented suggested significantly higher antibodies of all types in vaccinated mothers than those of control groups, with significant differences between preimmunization and at delivery (Table 2).

Immunogenicity in Infant Participants at Birth

The immunogenicity profile of the RSV vaccine in newborn infants is depicted by the levels of induced cord blood antibodies. Four of six trials were congregated in the meta-analysis for cord blood Nab-A and Nab-B GMTs, of which three of these studies also reported cord blood F-IgG GMCs. Based on our meta-analysis, the cord blood Nab-A and Nab-B GMTs showed random-effects pooled SMD of 2.67 (95% CI: 1.12–4.22) and 1.22 (95% CI: 0.26–2.18), respectively. Moreover, the fixed-effects pooled SMD of F-IgG was 1.49 (95% CI: 1.42–1.56). There were only two studies that showed PCA GMCs results in cord blood, resulting in a fixed-effects

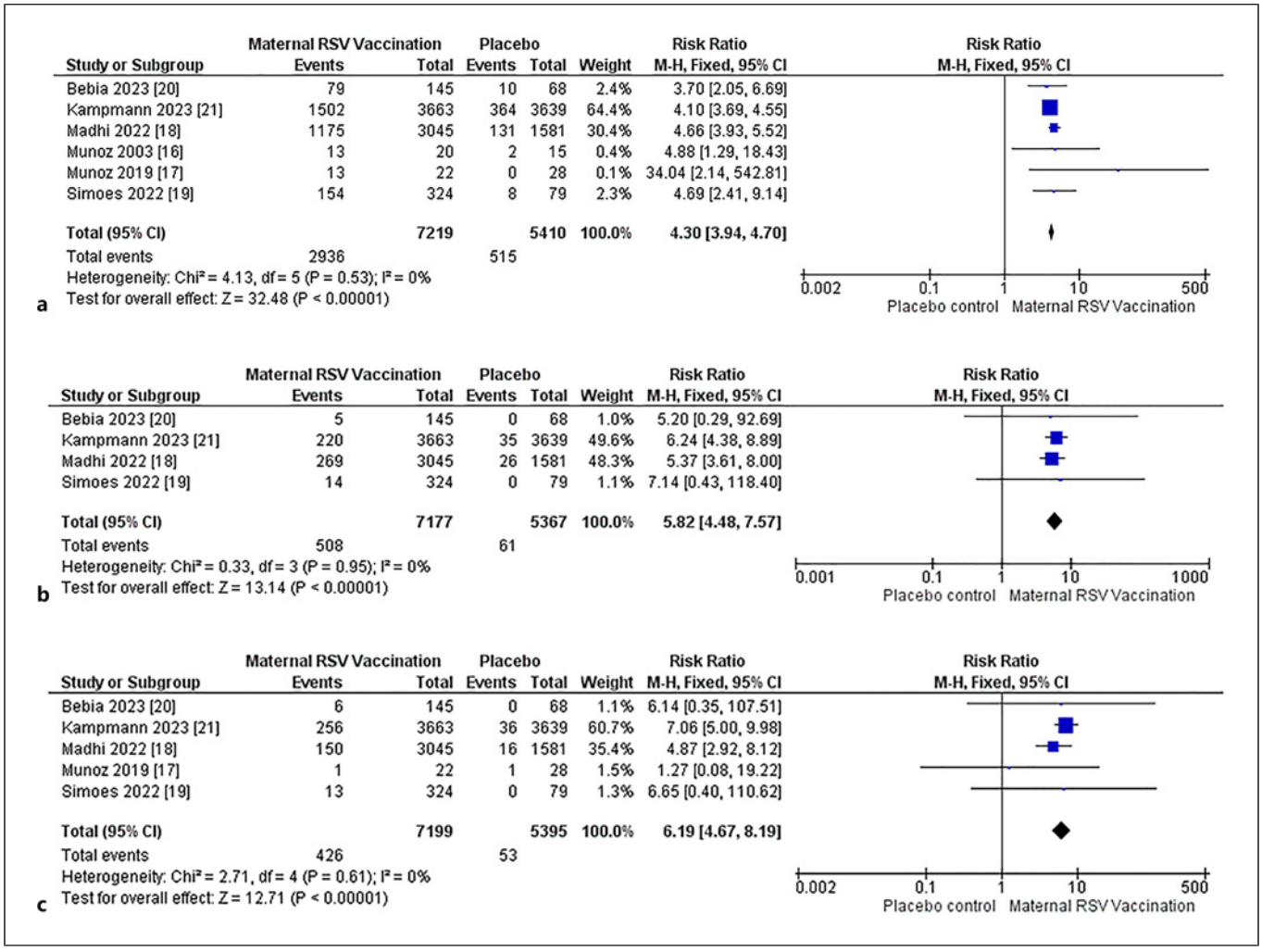

Fig. 4. Forest plots of local site reaction following vaccine administration within 1-week monitoring: local pain (**a**); local swelling (**b**); local erythema (**c**).

pooled SMD of 1.65 (95% CI: 1.57–1.73). As is shown in (Table 2), there were significantly higher antibody levels of all types in infants born to vaccinated mothers compared to control groups.

Meta-Analysis of Vaccine Efficacy

Of all included studies, only three reported the effectivity of the maternal RSV vaccine in declining both the incidences of medically attended RSV LRTIs (MA-RSV) and RSV-related hospitalizations. In comparison to the control groups, there were reduced risks of MA-RSV by 53% (OR: 0.47, 95% CI: 0.23–0.98) and RSV-related hospitalizations by 49% (OR: 0.51, 95% CI: 0.38–0.67) in infants born to vaccinated mothers within 6 months after birth (Fig. 7).

Discussion

Emerging literature documented the lower levels of anti-RSV MatAbs, both RSV IgG and Nabs, in RSV-infected infants compared to controls [6, 22, 23], suggesting that higher MatAb levels are rewarding for immunoprotection against RSV in the first few periods of life, especially during the first 6 months of life. In this context, antenatal vaccination in pregnant women, to transfer passive antibody protections to infants during the infancy period of susceptibility, may come in handy [11]. This review demonstrated the advantages of maternal RSV vaccination directed against the F glycoprotein to accentuate the anti-F antibody levels of the vaccinated pregnant women and their newborns. Not only did our

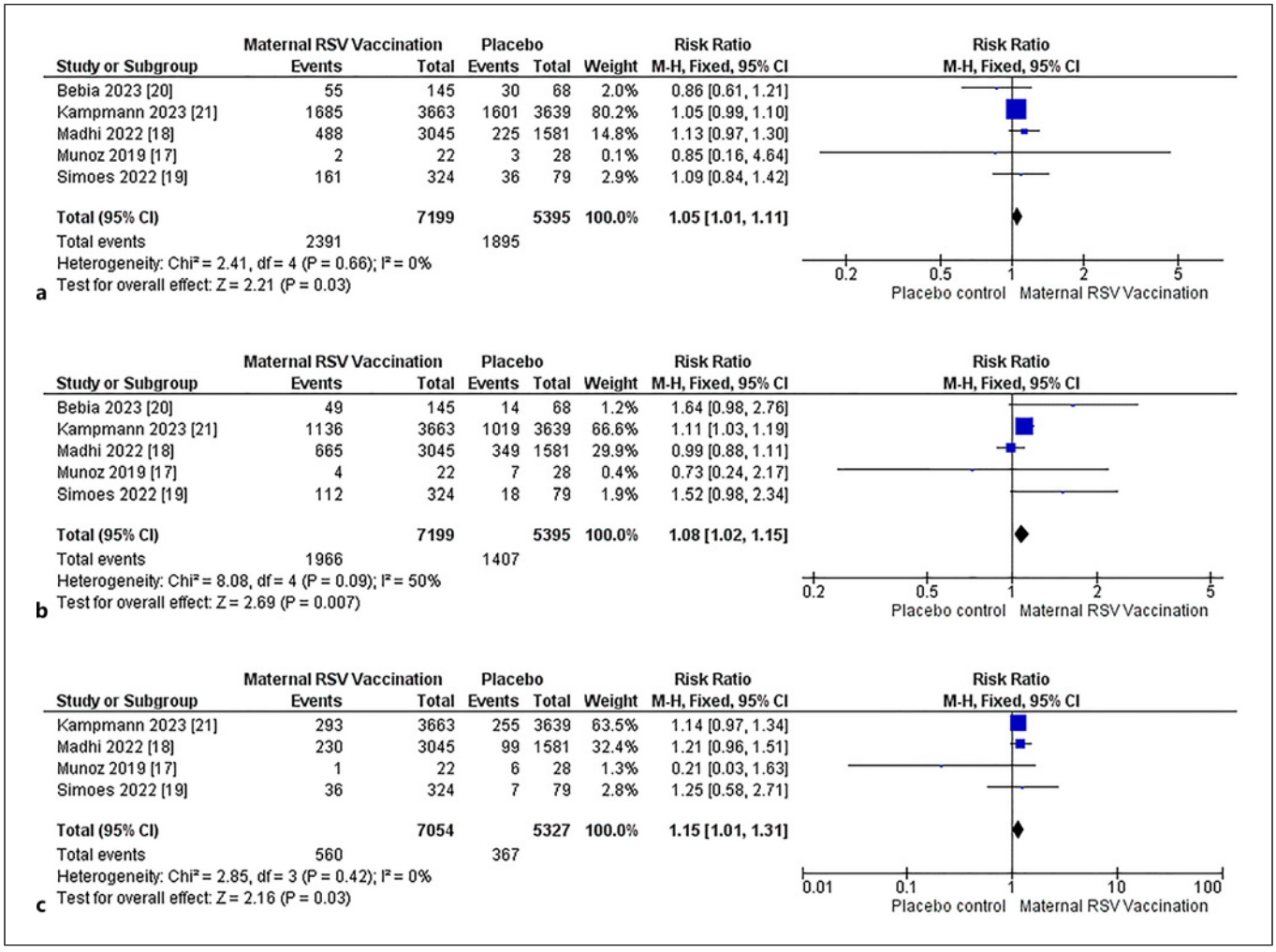

Fig. 5. Forest plots of systemic reactions following vaccine administration within 1-week monitoring: fatigue (**a**); headache (**b**); vomiting (**c**).

meta-analysis indicate considerable rises in post-vaccination antibody levels among recipients at the time of delivery, but it also showed that babies born to these vaccinated recipients obtained higher levels of at-birth antibodies. Similarly, the F-based RSV vaccine was shown to be immunogenic to ameliorate antibody levels in recipients, including non-pregnant healthy women [24] and specific populations, e.g., the elderly and children [25]. A growing body of research in vivo also demonstrated how passive immunization of the offspring by administering F-based RSV jab to the dams is helpful to promote MatAbs, in both the dams and their offspring [26–28].

There are several potential complicated adverse reactions to antenatal vaccination, as reviewed in [29]. Concerning the safety of antenatal RSV pre-F vaccine administration, the meta-analysis in this study had findings of a relatively safe vaccine profile, indicating the well-tolerability of these vaccine candidates in the recipients. This aligned with previous animal studies on rodents indicating the well-tolerability of such vaccine candidates in rodent models, both in the dams and their offspring [30]. This meta-analysis showed post-vaccination localized inflammatory reactions in vaccinated women (Fig. 2) that count as prevalent adverse events following immunization, to varying extents, commonly reported in other vaccines [31]. These local site events are associated with the local deposition of biological products, or antigens, following vaccination that potentially initiates local inflammatory reactions accumulating around the injection site [32]. Our meta-analysis reported onsets of general muscle pain and joint

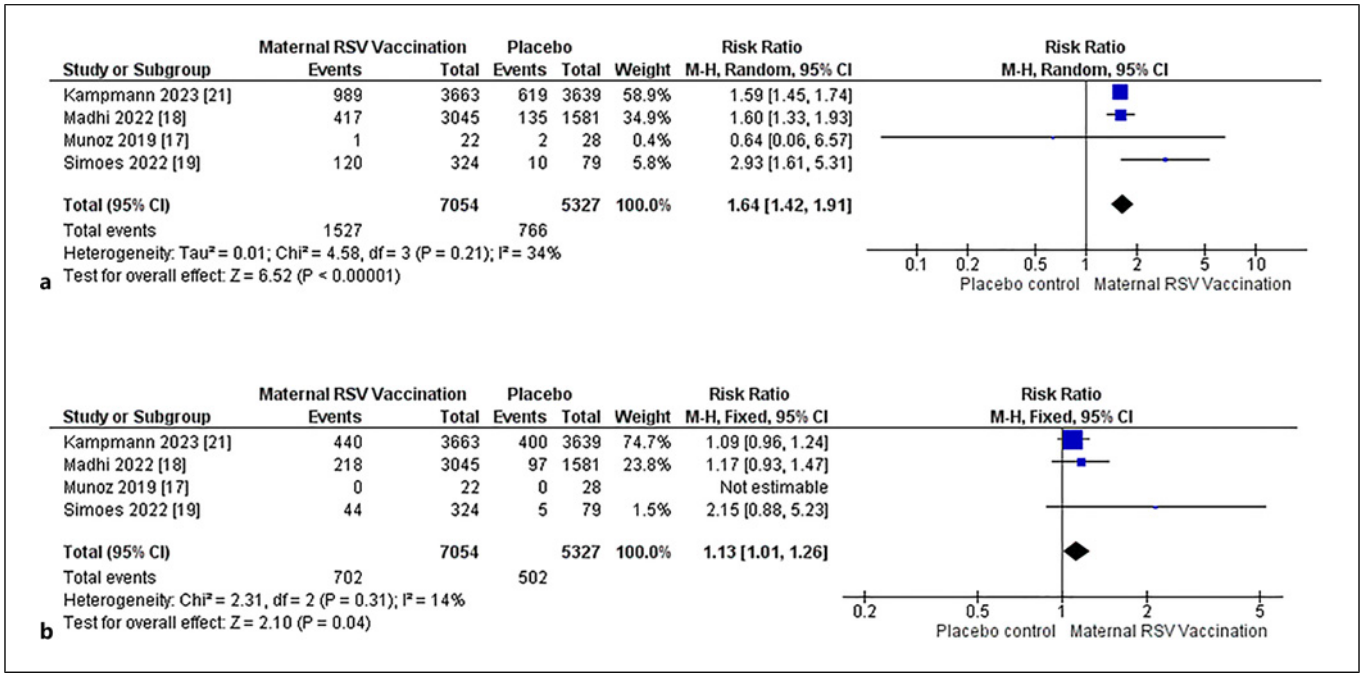

Fig. 6. Forest plots of systemic reactions following vaccine administration within 1-week monitoring: general muscle pain (**a**); general joint pain (**b**).

Table 2. Antibody levels were obtained from maternal sera (before and after vaccination) and infant cord blood sera at birth

	Study number	Pooled SMD (95% CI)	Effect model	I^2 (%)	*p* value
Maternal immunogenicity					
Before vaccination					
Nab-A	3	−0.30 (−0.78 to 0.19)	Random	81	0.23
Nab-B	3	0.00 (−0.38 to 0.38)	Random	71	0.99
F-IgG	3	−0.32 (−0.91 to 0.22)	Random	90	0.21
At delivery (after vaccination)					
Nab-A	4	3.40 (1.35–5.45)	Random	99	0.001
Nab-B	4	1.67 (0.26–3.08)	Random	99	0.02
F-IgG	3	7.48 (3.13–11.83)	Random	99	0.0008
PCA	2	1.79 (1.72–1.08)	Fixed	0	<0.00001
Infant immunogenicity					
Nab-A	4	2.67 (1.12–4.22)	Random	99	0.0007
Nab-B	4	1.22 (0.26–2.18)	Random	98	0.01
F-IgG	3	1.49 (1.42–1.56)	Fixed	0	<0.00001
PCA	2	1.65 (1.57–1.73)	Fixed	0	<0.00001

pain concerning systemic reactions. Such systemic adverse reactions are, however, still worth investigating in the monitoring of maternal RSV vaccination. Both of these were reportedly raised in other vaccination attempts [33, 34].

The meta-analysis in this study suggested the reduction of both MA-RSV and hospitalizations. Since RSV-associated medical care and hospitalization rates determine the financial burdens on hospitals [35, 36], it then could be stipulated that maternal RSV vaccination may

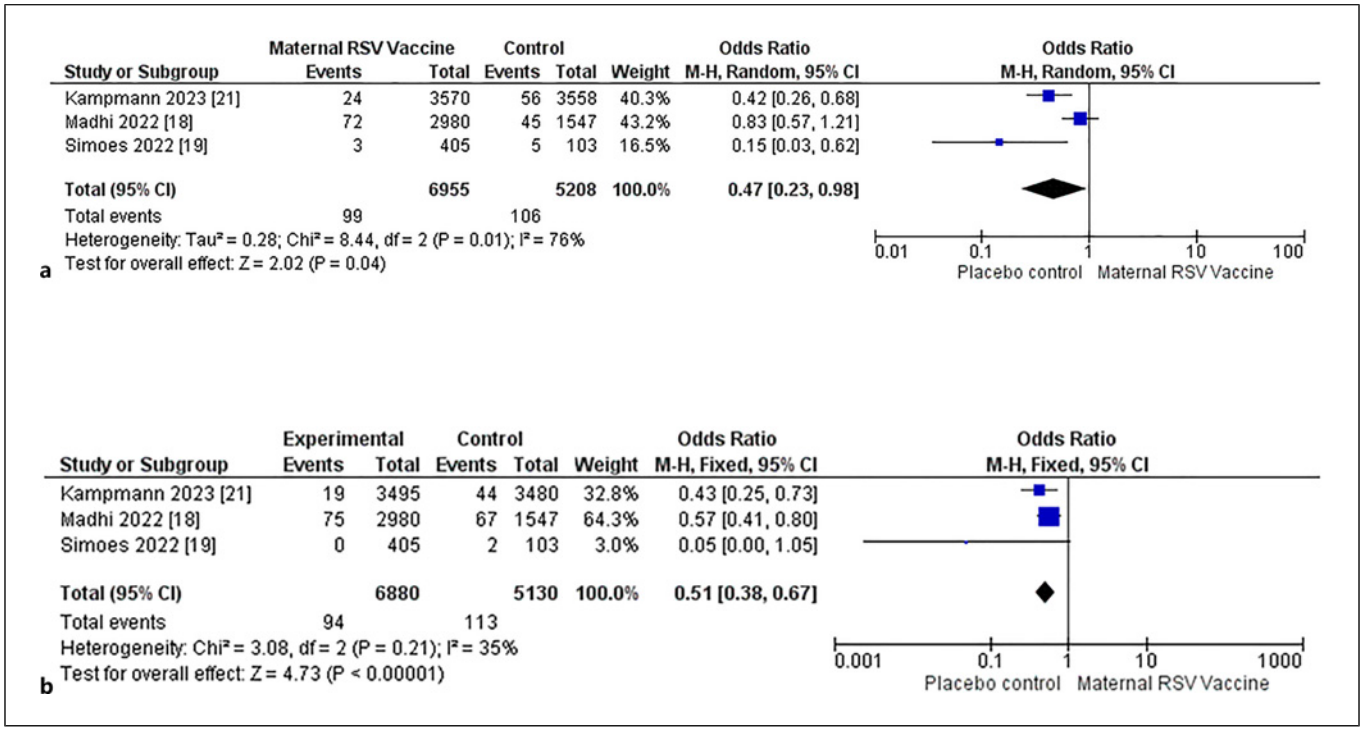

Fig. 7. Forest plots of vaccine efficacy: MA-RSV (**a**); RSV-associated hospitalizations (**b**).

become a paramount alternative to minimize hospital expenditures due to RSV-associated respiratory incidences. Previously reviewed in [37], humanized monoclonal Ab, including palivizumab and nirsevimab, remains a beneficial strategy and is strongly associated with the reduction of RSV-associated diseases in the participants. A cost modeling study previously showed the future cost-efficiency of RSV maternal vaccinations as an RSV-associated LRTI prophylaxis for infants [38]. This indicates the cost-affordability potential of antenatal vaccination to tackle issues of palivizumab use in rural areas.

To summarize, based on our findings, maternal RSV vaccination appears to be a promising strategy, not only well-tolerable and sufficiently immunogenic in both vaccinated mothers and their babies but also effective in minimizing risks of RSV-associated LRTIs and hospital admissions thereafter to curb hospital economic burdens. However, preterm birth remains an issue, whether vaccinating pregnant women is sufficient or not. In this case, discoveries of innate immune enhancers can potentially become an intriguing alternative to opt for.

Regarding limitation, the efficient passage of post-vaccination MatAb was reported within approximately a 30-day interval between vaccination and the time of delivery and potentially only occurs during the third trimester [5, 12]. Recently, the maternal RSV vaccine reportedly predisposed the recipient to premature delivery likelihood, rendering the vaccine impacts on premature delivery important to study more in depth [39]. This study is finite in a number of meta-analyzed studies, making it unlikely to conduct a separate sub-group analysis, including this based on weeks' gestation. Three studies [17, 18, 20] reported post-vaccine immunogenicity of 3rd-trimester pregnant women while 1 study [19] used late 2nd and 3rd trimesters as a range of vaccination which administered the vaccine to the pregnant women within mean value of 31.1 ± 3.1 weeks' gestation and thus assumed to likewise vaccinate those within the 3rd trimester. Furthermore, owing to the demonstrated meta-analysis of reactogenicities, it seems beneficial for future similar clinical trials to observe whether these post-vaccination reactions potentially complicate further to certain clinical conditions. Future reviews with more updates from the upcoming clinical trials assessing clinical safety, immunogenicity, and efficacy of this vaccine candidate in the future remain of great benefit.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization and methodology: M.P.M.$_1$; formal analysis and data curation: M.P.M.$_1$ and M.P.M.$_2$; writing – original draft preparation: M.P.M.$_1$, M.P.M.$_2$, and J.M.; writing – review and editing: M.P.M.$_1$, M.P.M.$_2$, J.M., H.C., P.M., and M.G.S.; supervision: J.M. and H.C.; project administration: M.P.M.$_1$, J.M., H.C., P.M., and M.G.S.; and funding acquisition, P.M. and M.G.S. All authors have read and agreed to the completed manuscript to be published.

Data Availability Statement

The data that support the findings of this study are openly available in [figshare] at https://doi.org/10.6084/m9.figshare.23915904. Any other data are available from the corresponding author upon reasonable request. Further inquiries can be directed to the corresponding author.

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