Summary of the RSV vaccine findings on prematurity and how it informed impact studies.

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Systematic Review of Association of Maternal RSV Vaccination and Preterm Birth.

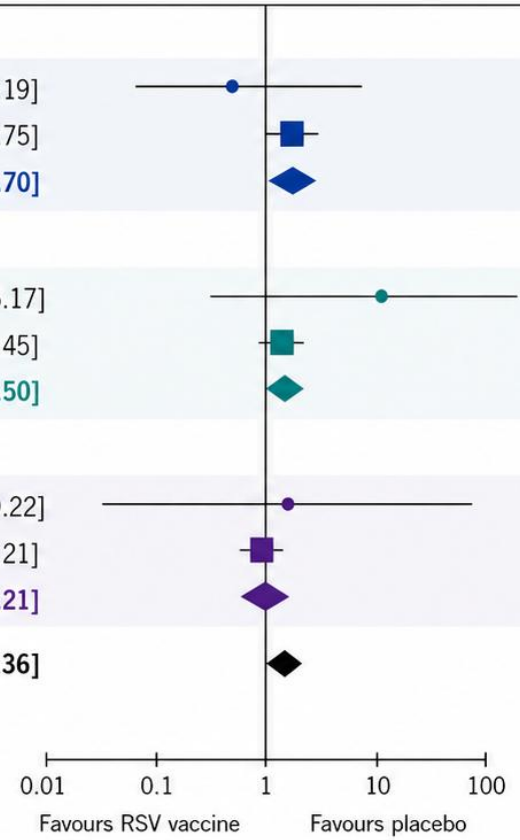
Preterm birth rate on placebo group ~5.1% (4.9% to 6.2%).

Study or Subgroup	RSV vaccine Events (%)	RSV vaccine Total	Placebo Events (%)	Placebo Total	Weight (%)	Risk Ratio M-H, Random, 95% CI
GSK preF vaccine						
Bebia 2023 (Phase II)	5 (3.6%)	140	3 (4.5%)	66	1.3	0.79 [0.19, 3.19]
Dieussaert 2023 (Phase III)	238 (6.8%)	3496	86 (4.9%)	1739	30.0	1.38 [1.08, 1.75]
Subtotal (GSK preF vaccine)		**3636**		**1805**	**31.3**	**1.34 [1.05, 1.70]**
Pfizer bRSV-preF vaccine						
Simões 2022 (Phase II)	14 (4.3%)	325	1 (1.3%)	78	0.6	3.36 [0.45, 25.17]
Kampmann 2023 (Phase III)	201 (5.6%)	3568	169 (4.8%)	3558	38.1	1.19 [0.97, 1.45]
Subtotal (Pfizer bRSV-preF vaccine)		**3893**	**3636**	**3636**	**38.7**	**1.23 [1.01, 1.50]**
RSV nanoparticle vaccine						
Muñoz 2019 (Phase II)	1 (4.5%)	22	1 (3.6%)	28	0.3	1.27 [0.08, 19.22]
Madhi 2020 (Phase III)	175 (5.9%)	2986	96 (6.2%)	1554	29.7	0.95 [0.75, 1.21]
Subtotal (RSV nanoparticle vaccine)		**3008**		**1582**	**30.0**	**0.96 [0.76, 1.21]**
Total (95% CI)		**10537**		**7023**	**100.0**	**1.16 [0.99, 1.36]**
Total events:	634 (6.0%)		356 (5.1%)			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.06$, df = 5 (P = 0.30); $I^2 = 17\%$

Test for overall effect: Z = 1.86 (P = 0.06)

Test for subgroup differences: $Chi^2 = 3.87$, df = 2 (P = 0.14), $I^2 = 48.3\%$



CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; RSV, respiratory syncytial virus.
Study phase and vaccine type are indicated in parentheses.

Adapted: Phijffer EW, Cochrane Database Syst Rev. 2024;5(5)

Risk-averse Inclusion and Exclusion Criteria for MATISSE (and Other Maternal RSV Vaccine Trials).

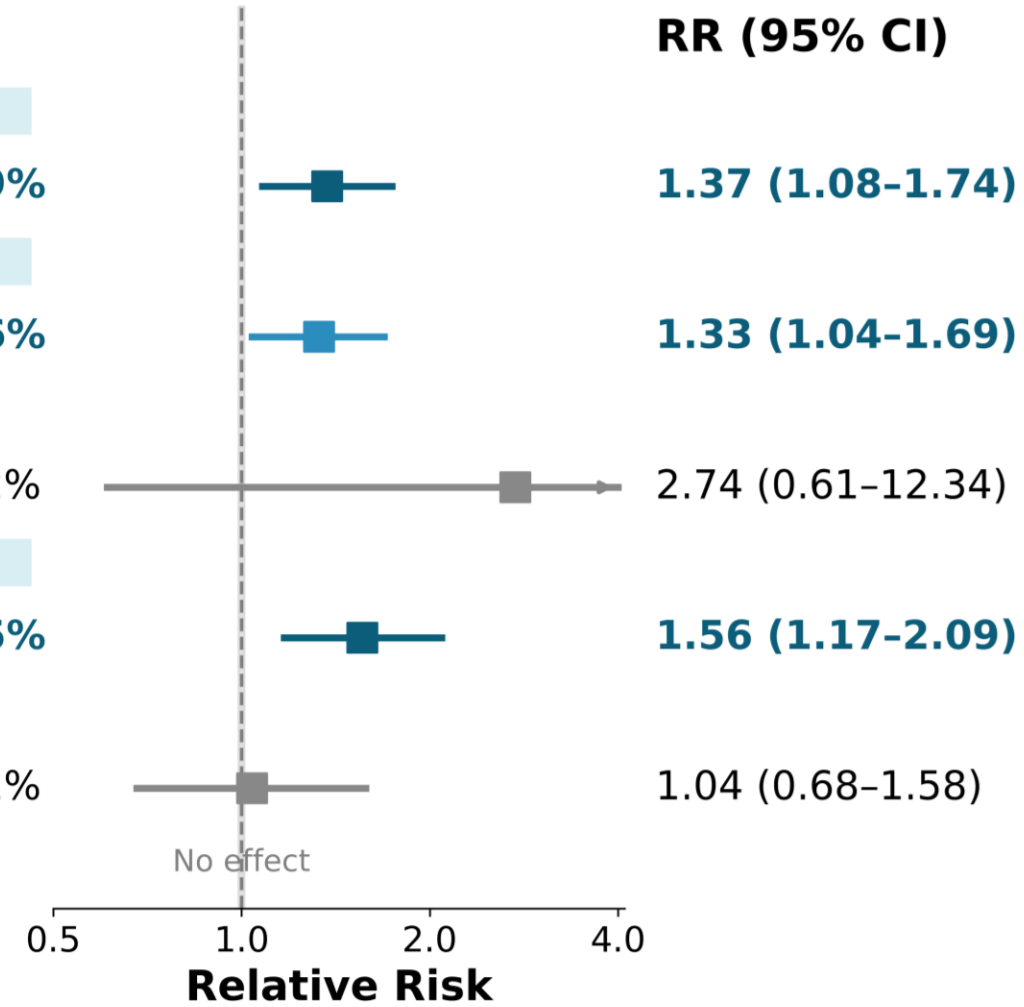
Exclusion criteria related to the current pregnancy included in vitro fertilization; pregnancy complications or abnormalities at the time of consent that would increase the risk associated with participation in and completion of the study (including but not limited to preeclampsia, eclampsia, or uncontrolled gestational hypertension; placental abnormality; polyhydramnios or oligohydramnios; significant bleeding or a blood clotting disorder; endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism or disorders of glucose intolerance antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent; any signs of premature labor with the pregnancy or having ongoing intervention [medical/surgical] to prevent preterm birth).

Exclusion criteria related to prior pregnancies included those that would increase the risk associated with the participation in and completion of the study **(including but not limited to prior preterm delivery at ≤34 weeks' gestation; prior stillbirth or neonatal death; previous infant with a known genetic disorder or significant congenital anomaly).**

Other exclusion criteria for maternal participants were congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, …….

Maternal RSV-preF Vaccine and Preterm Births in Phase III Trial (GRACE, GSK).

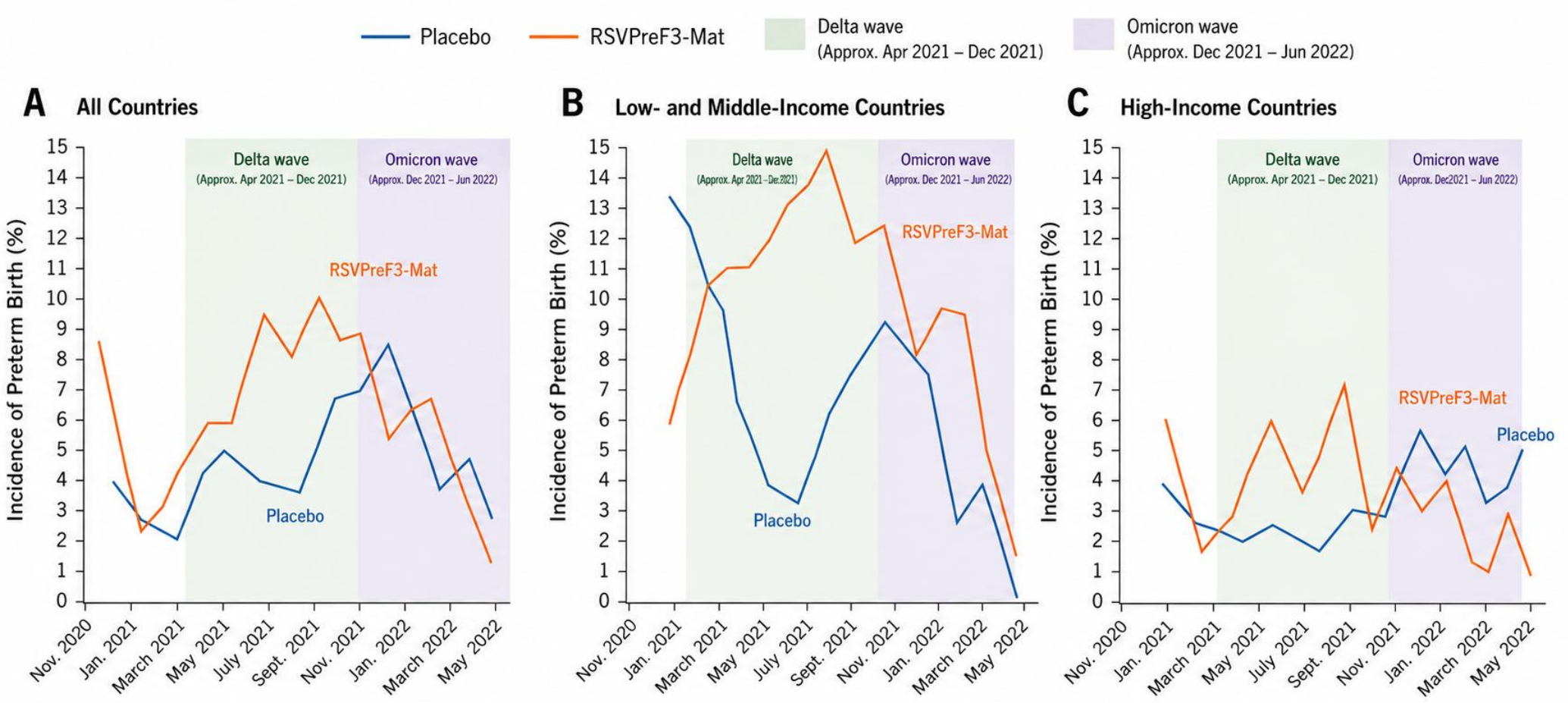
Outcome	RSVPreF3	Placebo	Δ	RR (95% CI)
OVERALL				
Overall preterm birth	6.8%	4.9%	**+1.9%**	**1.37 (1.08–1.74)**
PREMATURITY SEVERITY				
Moderate-late preterm	6.4%	4.8%	**+1.6%**	**1.33 (1.04–1.69)**
Very preterm	0.3%	0.1%	+0.2%	2.74 (0.61–12.34)
COUNTRY INCOME LEVEL				
LMICs	9.8%	6.3%	**+3.5%**	**1.56 (1.17–2.09)**
High-income countries	3.7%	3.6%	+0.1%	1.04 (0.68–1.58)



Dieussaert I et al. NEJM; 2024, 1009-1021

Monthly Incidence of Preterm Birth and Number of Deliveries (GRACE).

Timing of excess in preterm births did not consistently match COVID-19 waves across Countries, and no difference in COVID-19 in mothers by study arm



Shaded areas indicate approximate periods when the Delta and Omicron waves of COVID-19 were predominant globally, based on WHO global data.
Delta wave: ~ April 2021 – December 2021 (B.1.617.2 lineage)
Omicron wave: ~ December 2021 – June 2022 (B.1.1.529 lineage and subvariants BA.1/BA.2 predominant)
Exact timing may vary by country and region.

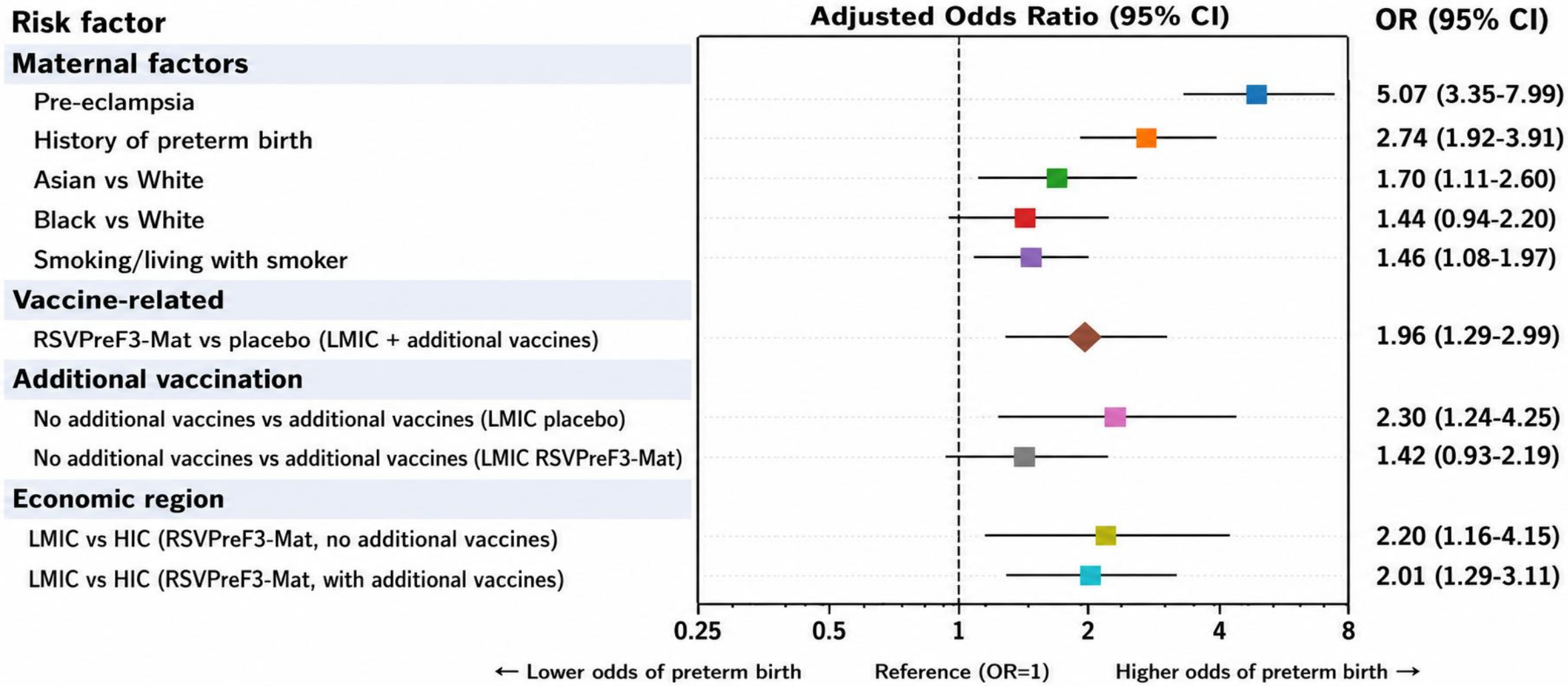
Dieussaert I et al. NEJM; 2024, 1009-1021

No Causal Mechanism Identified for Increased Preterm Birth Rate in the RSVPreF3-Mat arm (GRACE).

Extensive epidemiologic, immunologic, virologic, and manufacturing investigations.

Hypothesis investigated	Analysis performed	Outcome
Baseline risk factors	Characteristics/multivariable modelling	No imbalance in known PTB risk factors
Maternal COVID-19	COVID-19 cases, Delta-wave analyses	Similar excess risk with and without
Asymptomatic SARS-CoV-2 infection	N-antibody seroconversion analyses	No association with PTB
COVID-19 vaccination	Vaccinated vs unvaccinated analyses	Signal regardless of vaccination
Other maternal vaccines	Concomitant vaccine analyses	No specific vaccine implicated
Timing of RSVPre-F vaccination	Interval from vaccination to delivery	No clustering shortly after vaccination
Humoral immune response	RSV-A neutralizing titres and RSVPreF3 IgG	Similar responses in preterm and term
Inflammatory response	48-cytokine panel	No cytokine signature with PTB
Natural RSV infection	Western blot infection profiling	No evidence of association

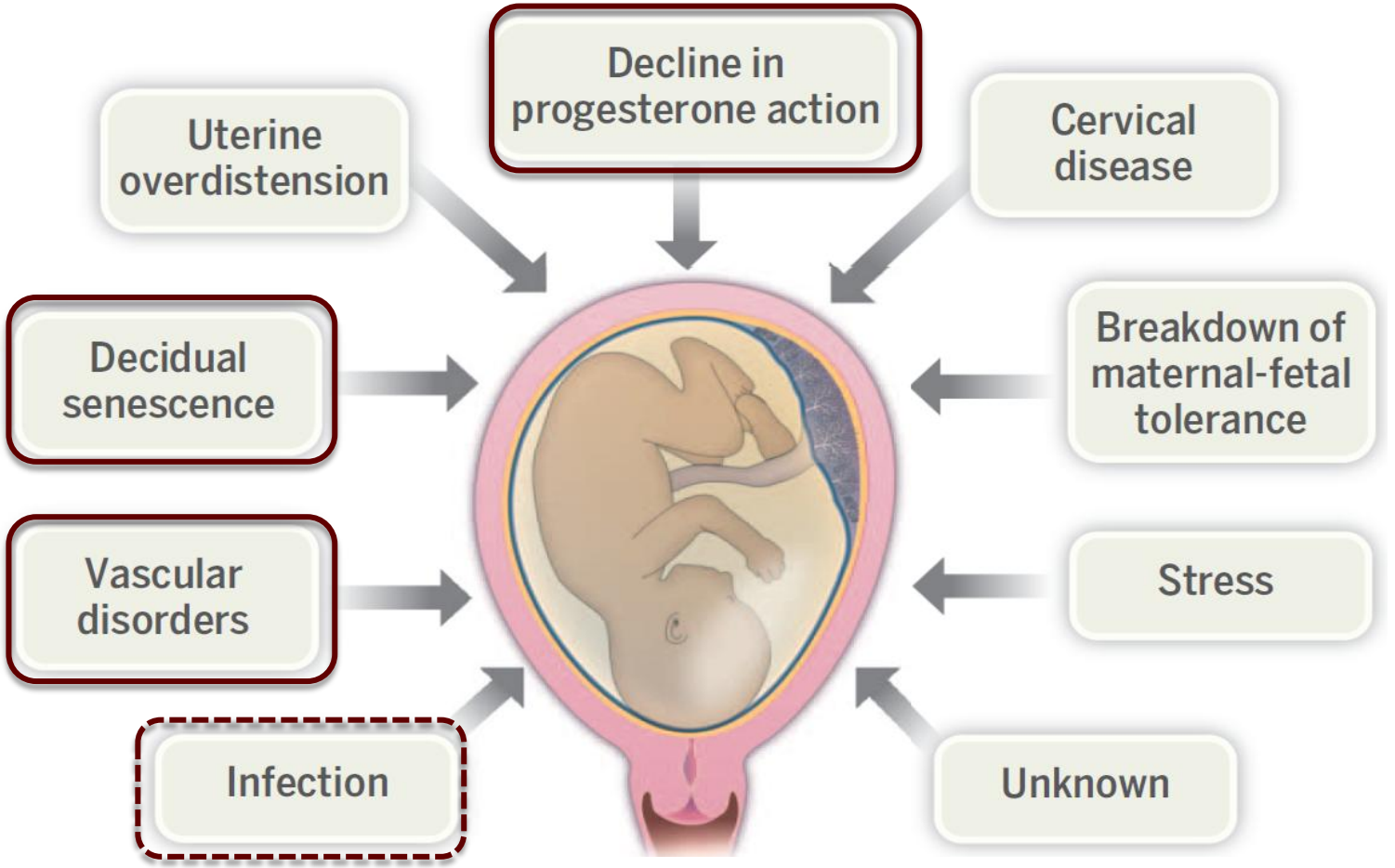
Significant Risk Factors Identified with Preterm Birth in Multivariable Analysis (GRACE).



Dieussaert I et al. NEJM; 2024, 1009-1021

Preterm labor: One Syndrome, Many Causes.

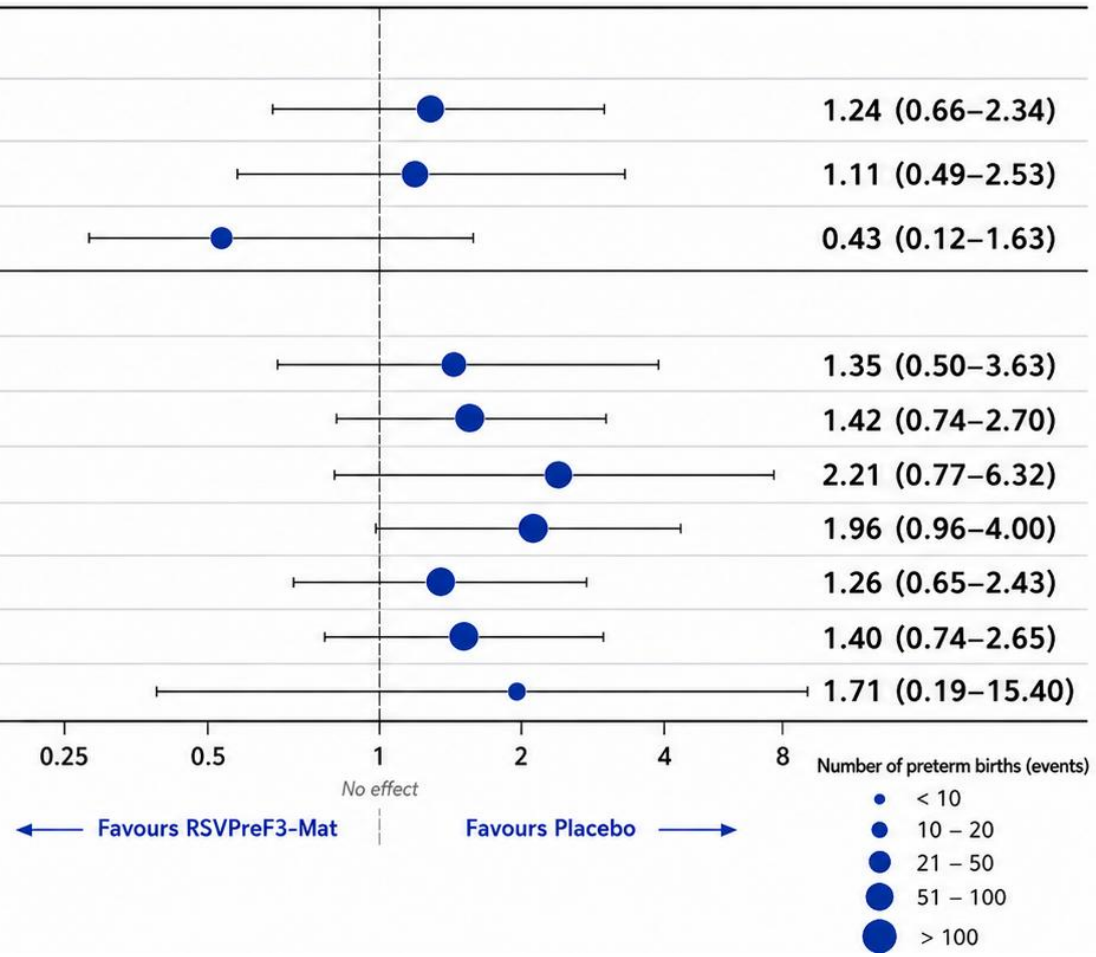
Placenta development and integrity important role in pregnancy outcome.



Romero et al. Science 2014. Aug 15;345(6198):760-5.

Association of Maternal RSV-preF Vaccine and Preterm Birth by Countries with >5 preterm Births (GRACE).

Country	RSVPreF3-Mat Preterm births n/N (%)	Placebo Preterm births n/N (%)	RR (95% CI)
High-income countries			
United States	32/724 (4.4)	13/365 (3.6)	1.24 (0.66–2.34)
Spain	18/507 (3.5)	8/251 (3.2)	1.11 (0.49–2.53)
Taiwan	4/76 (5.3)	4/33 (12.1)	0.43 (0.12–1.63)
Low- and middle-income countries			
Argentina	14/187 (7.5)	5/90 (5.6)	1.35 (0.50–3.63)
Bangladesh	31/211 (14.7)	11/106 (10.4)	1.42 (0.74–2.70)
Colombia	18/167 (10.8)	4/82 (4.9)	2.21 (0.77–6.32)
Panama	36/440 (8.2)	9/216 (4.2)	1.96 (0.96–4.00)
Philippines	29/226 (12.8)	11/108 (10.2)	1.26 (0.65–2.43)
South Africa	35/347 (9.5)	12/177 (6.8)	1.40 (0.74–2.65)
Thailand	3/35 (8.6)	1/20 (5.0)	1.71 (0.19–15.40)



Notes
Percentages indicate preterm birth rate among live births (<37 weeks gestation).

Abbreviations
CI, confidence interval; RR, relative risk; RSVPreF3, respiratory syncytial virus prefusion F protein–based vaccine.

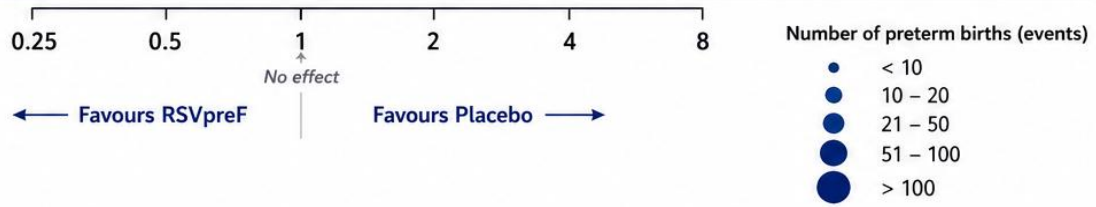
Dieussaert I et al. NEJM; 2024, 1009-1021

Preterm Births by Country in the MATISSE Trial

(countries with > 5 preterm births shown)

Rates are percentage of live births (<37 weeks gestation). Countries with >5 preterm births shown.

Country	RSVpreF Preterm births n/N (%)	Placebo Preterm births n/N (%)	RR (95% CI)
Overall	207/3,659 (5.7)	172/3,646 (4.7)	**1.24 (0.95–1.62)**
High-income countries			
Japan	7/231 (3.0)	13/231 (5.6)	0.54 (0.22–1.33)
Taiwan	6/130 (4.6)	7/130 (5.4)	0.86 (0.30–2.48)
Netherlands	3/97 (3.1)	3/95 (3.2)	0.98 (0.20–4.73)
United States	95/1,654 (5.7)	87/1,645 (5.3)	1.09 (0.82–1.44)
Chile	7/86 (8.1)	6/85 (7.1)	1.15 (0.40–3.29)
Spain	4/118 (3.4)	3/124 (2.4)	1.40 (0.32–6.13)
Upper-middle-income countries			
Argentina	31/467 (6.6)	20/458 (4.4)	1.55 (0.90–2.66)
South Africa	39/469 (8.3)	19/471 (4.0)	**2.06 (1.21–3.51)**



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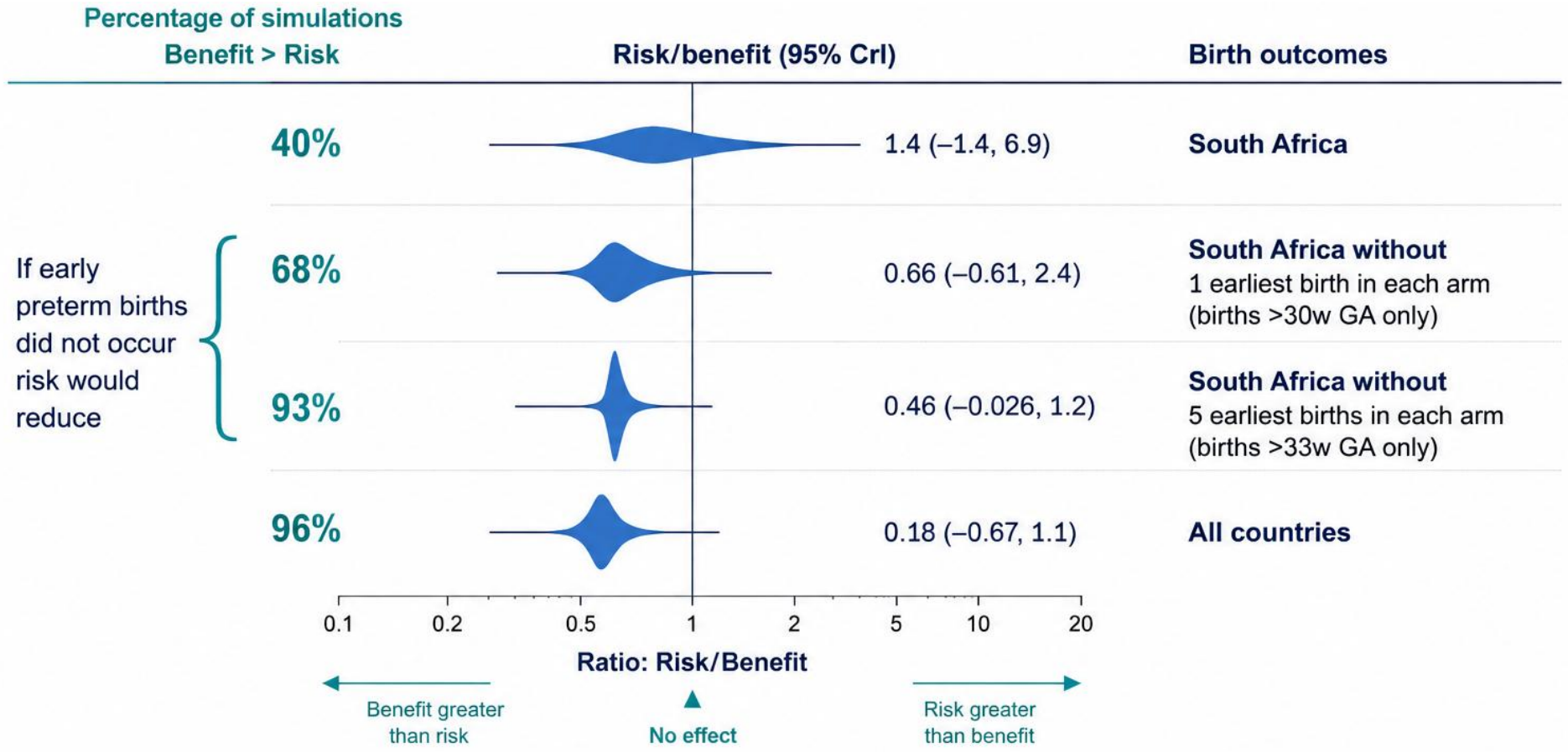
Abbreviations
CI, confidence interval; RR, relative risk; RSVpreF, respiratory syncytial virus prefusion F protein–based vaccine.

Data derived from MATISSE (Maternal Immunization Study for Safety and Efficacy) trial participants in countries with >5 preterm births.

Madhi SA et al. Obstet Gynecol. 2025;145:147–156.

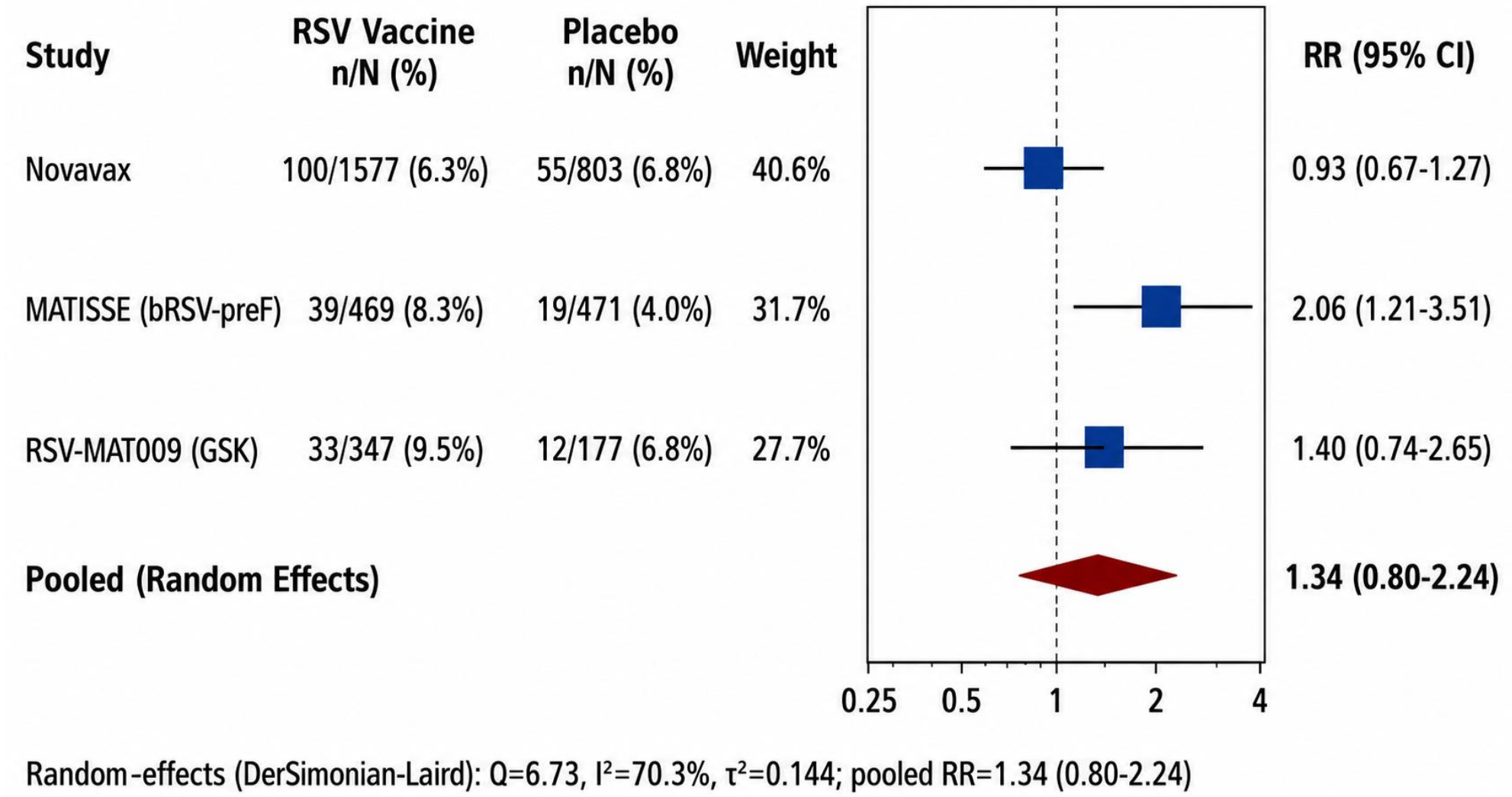
Modelling risk (preterm deaths)-benefit (RSV deaths avoided) of maternal RSV vaccination and preterm births in South Africa.



Benefit: infant deaths due to RSV averted though vaccination per **1000** live births born to vaccinated mothers

Risk: excess neonatal deaths potentially associated with the vaccines per **1000** live births born to vaccinated mothers

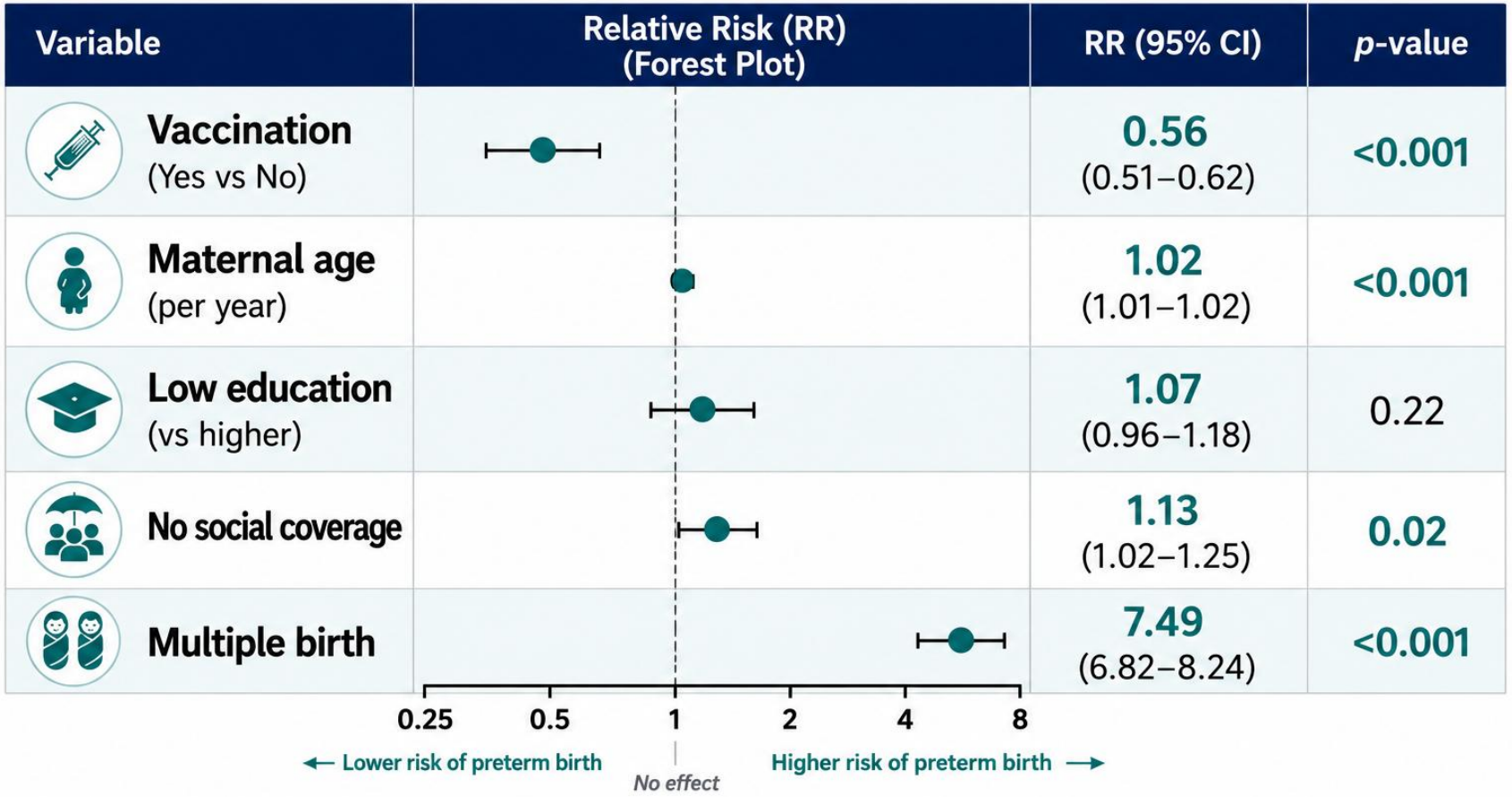
Meta-analysis of Maternal RSV Vaccines and Preterm Births in South Africa Across Three Phase-III Randomised Controlled Trials.



Post-licensure Studies on bRSV-preF and Preterm Births.

Quasi-experimental Observational Study on Safety of the bRSV-preF Vaccine in Pregnant Women at 32-36 weeks GA; Argentina.

Total of 21,303 births ≥32 weeks → 12,210 vaccinated mothers → 9,093 unvaccinated mothers → outcomes analyzed: preterm birth and/or low birth



CI, confidence interval; RR, relative risk.

Scruzzi GF et al. MEDICINA (Buenos Aires) 2025; 85: 999-1007

USA: No increased risk of preterm birth, SGA, or stillbirth among pregnant individuals receiving RSVpreF at 32-36 weeks GA and their infants

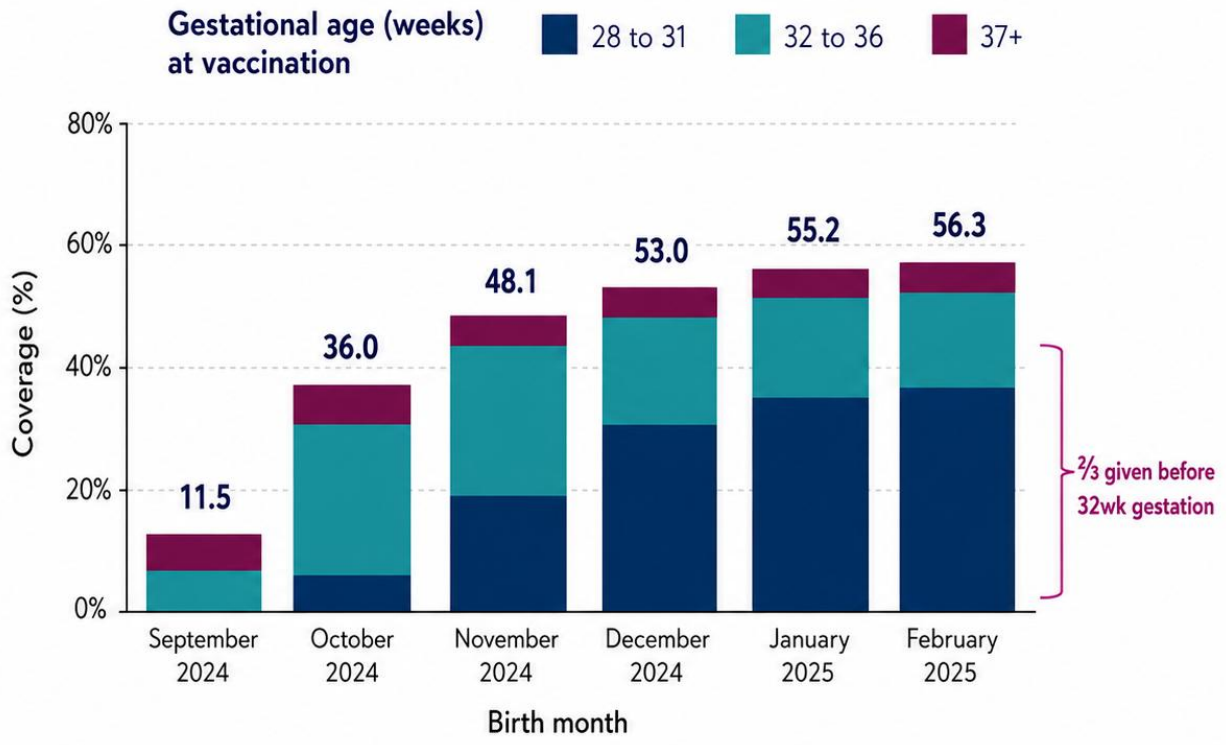
Outcome	Matched pairs, N	RSV vaccinated		Unvaccinated match		Adjusted risk ratio (95% CI)†
		Events,* N	%	Events,* N	%	
Preterm births‡	13,966	563	4.0	627	4.5	0.90 (0.80, 1.00)
SGA at birth§	11,822¶	799	6.8	774	6.5	0.99 (0.90, 1.09)
Stillbirth	13,966	11	Stillbirths per 1000 0.79	10	Stillbirths per 1000 0.72	1.09 (0.46, 2.58)

*Events only included through date of censoring when unvaccinated pair crosses over to vaccinated. †Adjusted for nulliparity. ‡Preterm birth = birth <37 weeks gestational age. §SGA at birth = birth weight <10th percentile for gestational age compared with a US reference population. ||18,22 matched pairs with complete infant weight data (85%).
CI, confidence interval; SGA, small for gestational age.

DeSilva M. Prenatal RSVpreF vaccine safety 2023–2024 respiratory season. The Vaccine Safety Datalink (VSD). ACIP Meeting, June 25, 2025.
https://www.cdc.gov/acip/downloads/slides-2025-06-25-26/04a-DeSilva-Mat-Peds-RSV-508.pdf

RSV Vaccine Coverage by Month of Birth and Gestational Week of Vaccination, UK.

Coverage (%) of infants born to vaccinated mothers



Over 500,000 doses now given in the UK

No signal for preterm birth in preliminary analysis of >30,000 preterm baby-mother pairs and their controls

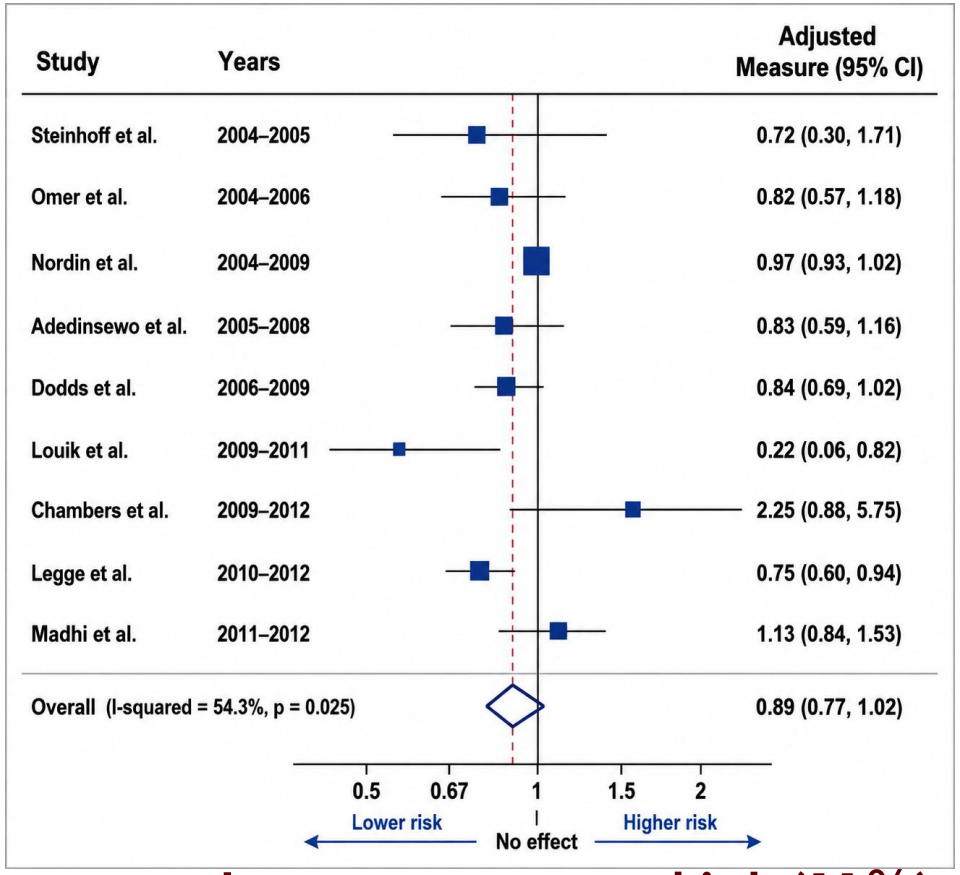
JCVI have discussed starting vaccination from 24 weeks gestation

Source: Surveillance of respiratory syncytial virus (RSV) in the UK: winter 2024 to 2025
https://www.gov.uk/government/publications/surveillance-of-respiratory-syncytial-virus-winter-2024-to-2025/

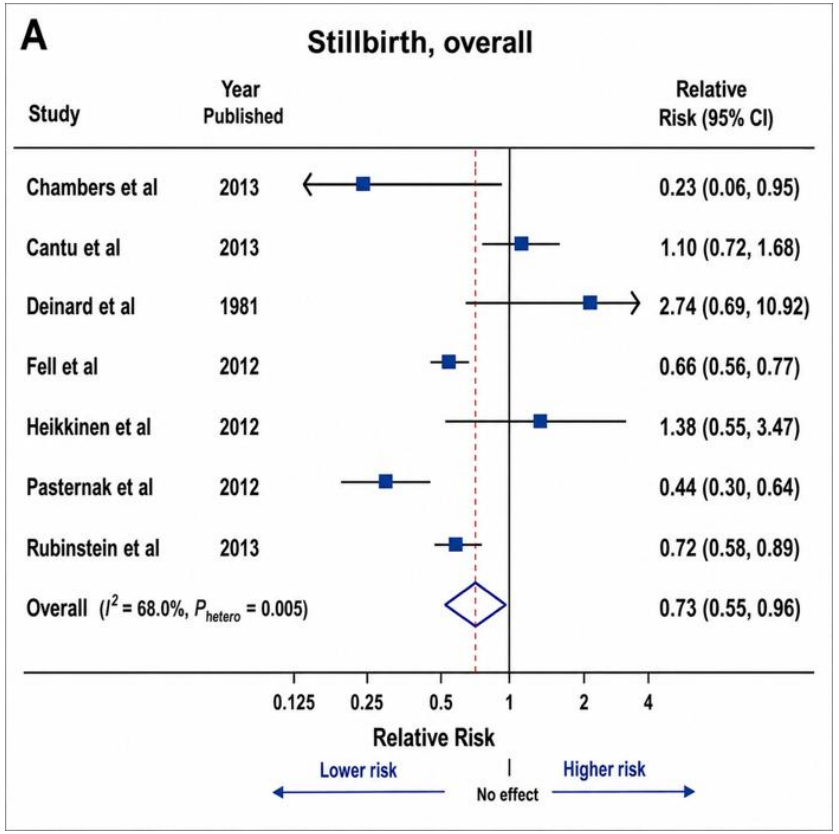
Whitaker H et al. RSVVW, Rome, 20 Feb 2026

Effect of Maternal Seasonal Influenza Vaccination on Pre-term births and Stillbirths, Mainly in Observational Studies.

Preterm births



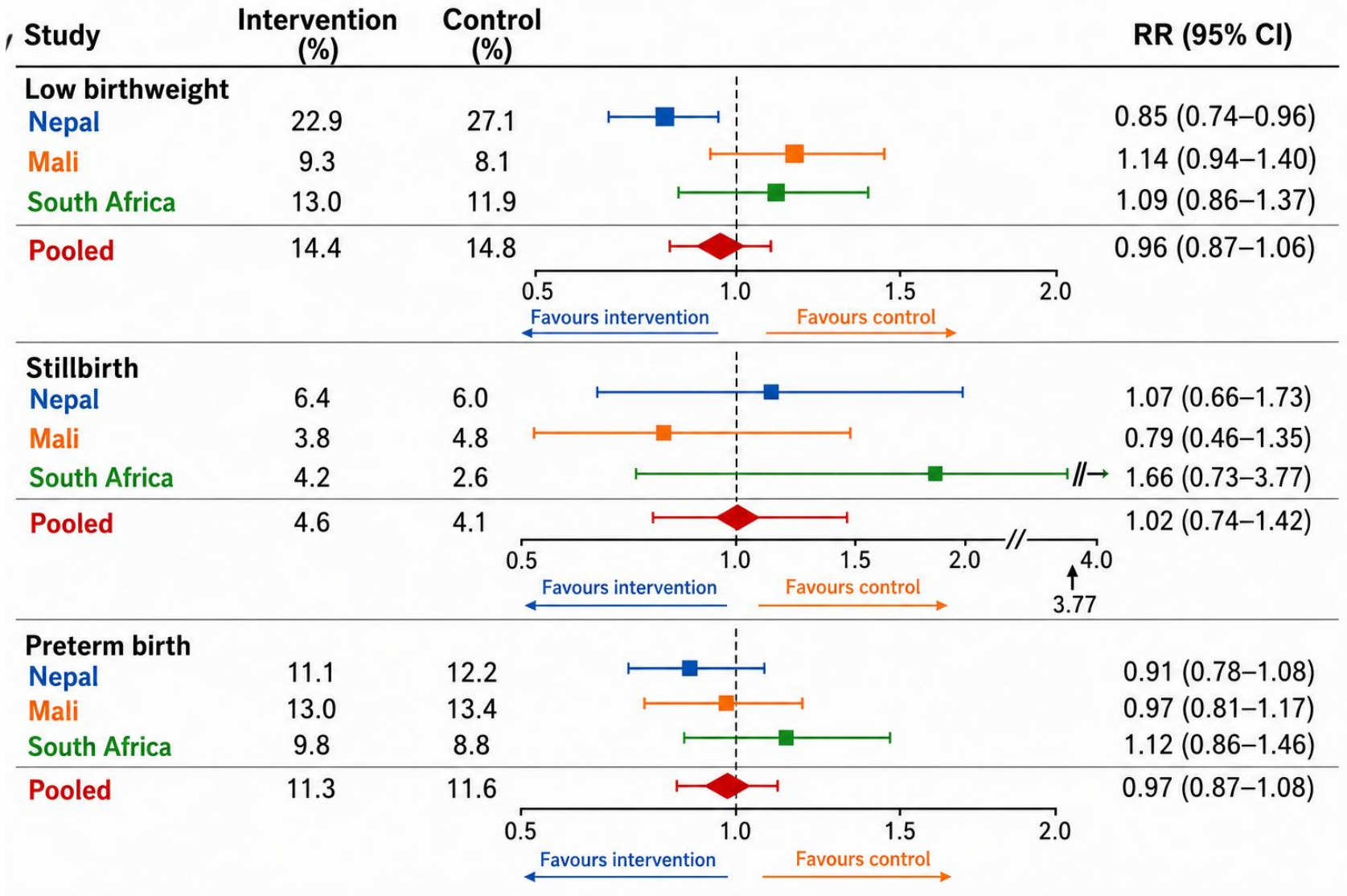
Stillbirths



Lower rate pre-term birth (11%) and stillbirth (27%) among women who received seasonal influenza vaccine. Moderate heterogeneity across studies.

Nunes MC, et al. Am J Perinatol 2016,33:1104-1114; Bratton KN, et al. Clin Infect Dis 2015,60:e11-19.

Maternal Inactivated Influenza Vaccine Not Associated with Favourable or Unfavourable Birth Outcomes in RCTs in LMICs.



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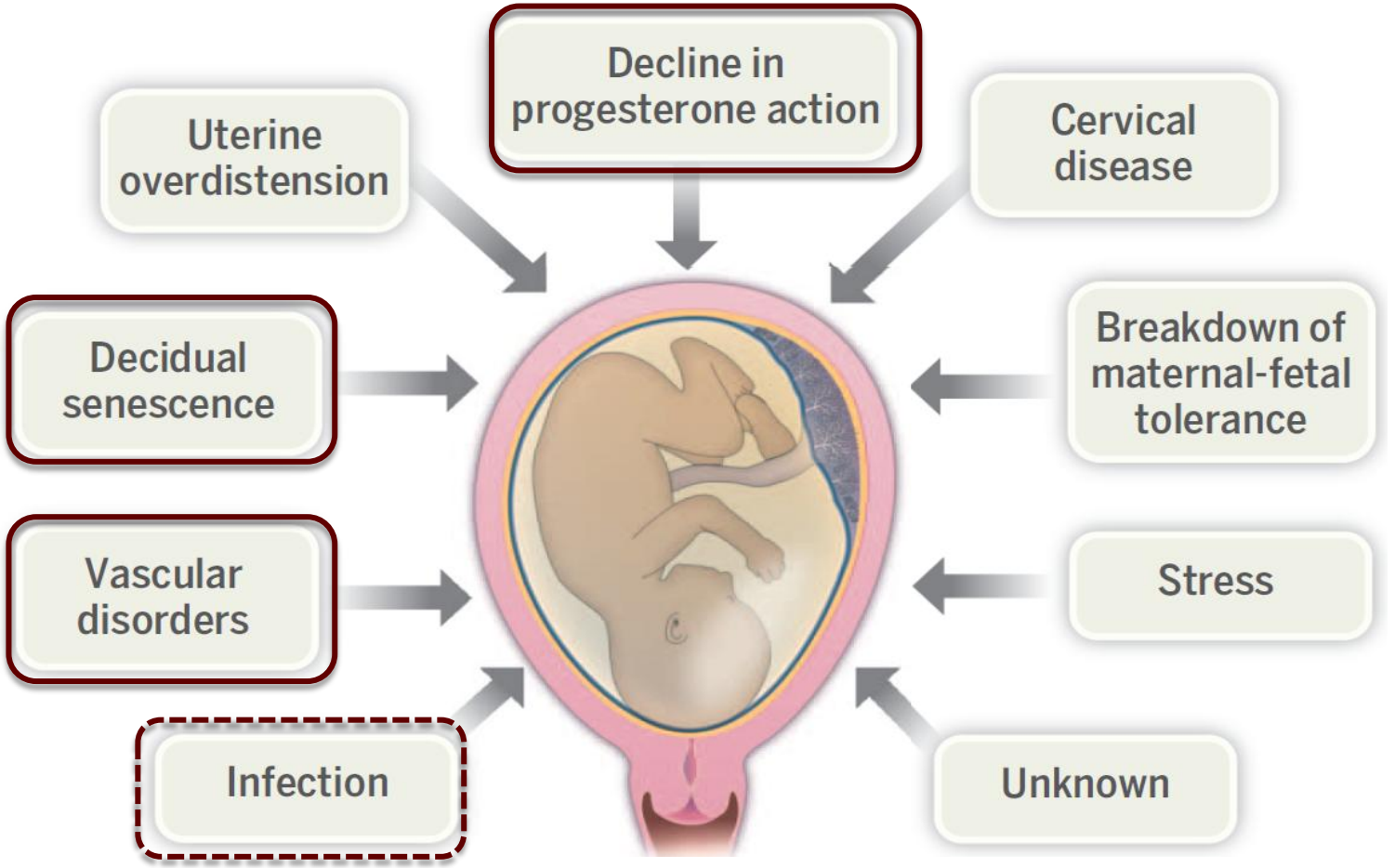


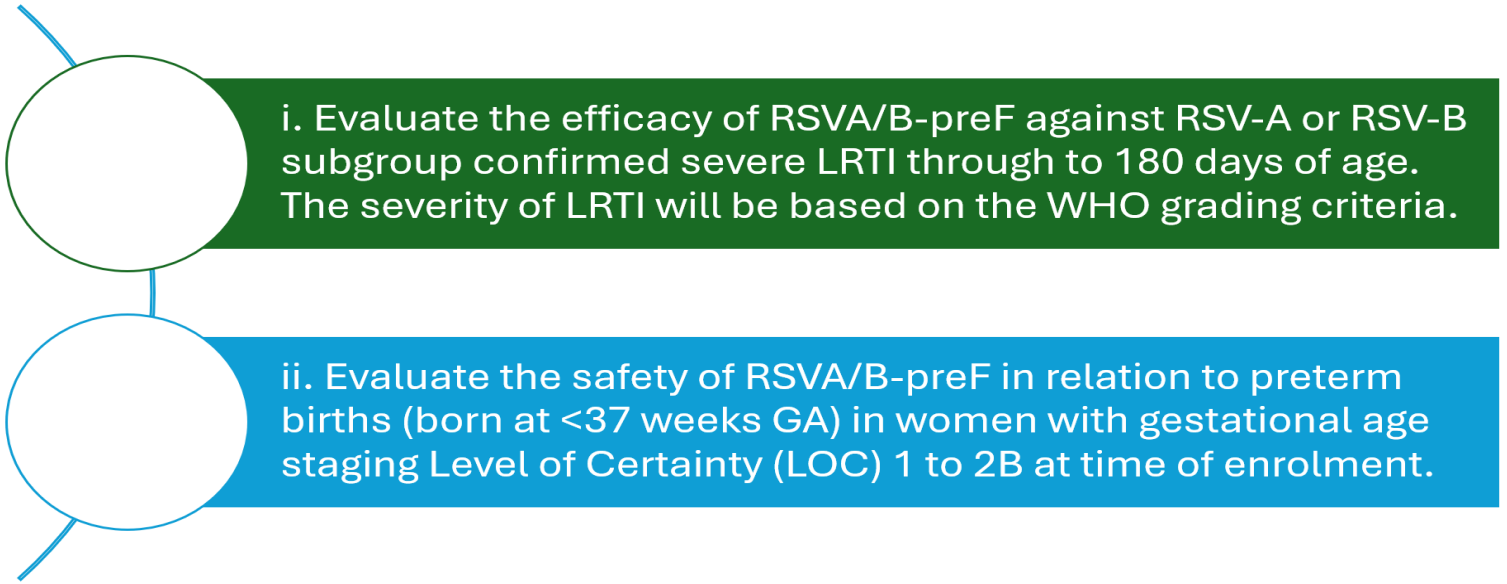
Romero et al. Science 2014. Aug 15;345(6198):760-5.


RSV
IMPACT
RESEARCH | COLLABORATION | HEALTH IMPACT
Ghana | Kenya | South Africa | The Gambia

RSV-IMPACT Population and Design

- **Phase IIIB**, multicenter, randomized, double-blinded, placebo-controlled trial
- The phase IIIB trial will be undertaken in **The Gambia, Kenya, Ghana**, as well as in **South Africa**.
- Cohort of **13,000 pregnant women** will be enrolled and their live-births will be included. The trial will enroll between **2,000 to 4,000** pregnant women in each of the four countries.
- Enrolment will be targeted at women at the gestational age of **ABRYSVO™** licensure within the country (may differ between countries) based on **GAIA LOC criteria 1 to 2B**.
- The trial will enroll pregnant women over a period of approximately **18 months**.
- Infant follow up for at least **180 days** of age; and up to **730 days** for infants born to mothers enrolled early in the trial.
- Expected completion by **December 2027.**

RSV-IMPACT Co-primary Objectives

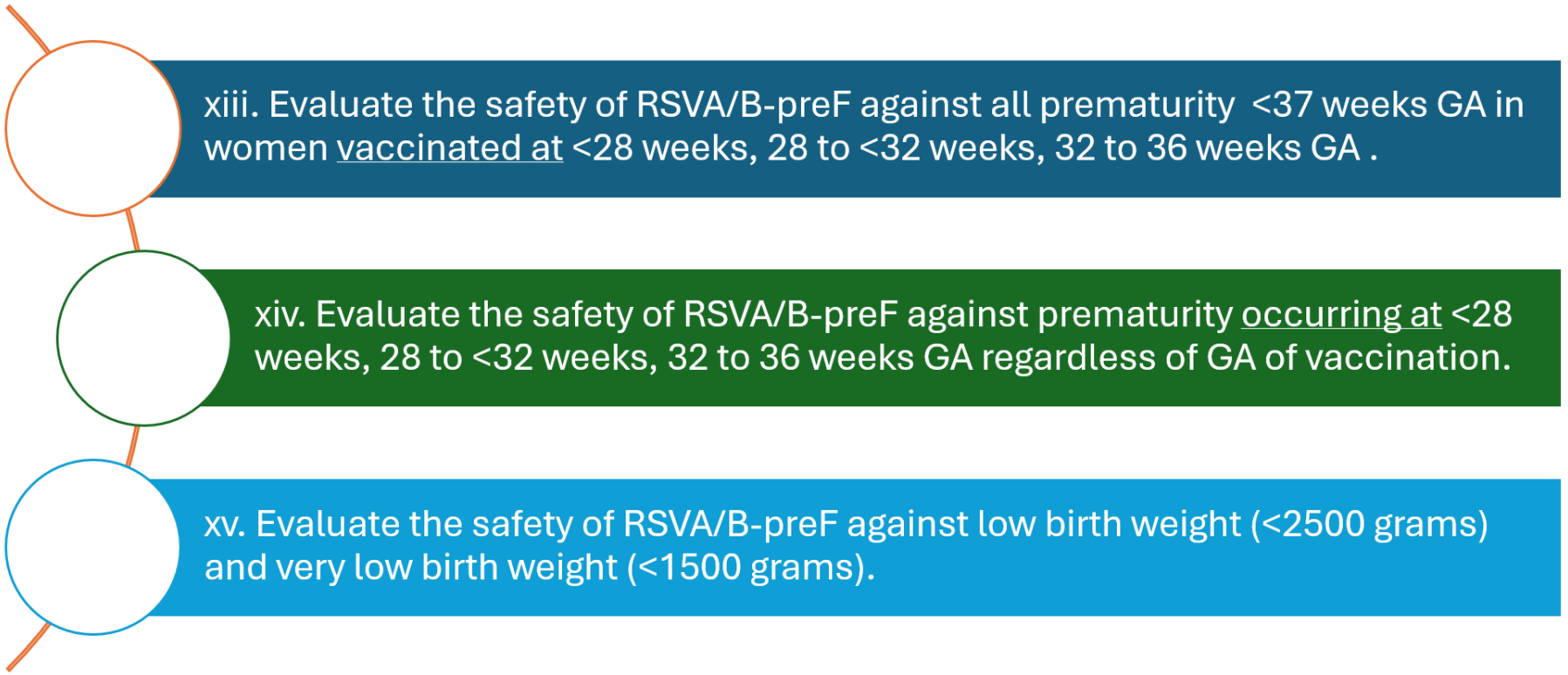


- Sample size (N=13,000): Powered to exclude a 20% increase risk (i.e. upper bound of uncertainty interval < 1.2) in preterm birth from a conservative background rate of 8% among placebo recipients (1-sided test).

- Aim to enrol at least 75% before 28 weeks of GA (enrolment varies by site: 24 to 28 wks. GA lower bound).

- Enrolment limited to women with GA Staging 1-IIB using GAIA criteria, to ensure reasonable accuracy of GA staging.

RSV-IMPACT Secondary Objectives Safety Endpoints



Study includes collection of placenta from preterm and term births, to evaluate whether placental abnormalities.

RSV-IMPACT Trial: Exclusion Criteria Notes.

Inclusion & exclusion criteria less stringent than pivotal Phase III trials, aimed at being more generalisable, including women with risk factors for preterm births.

- At least THREE prior pregnancy complications or abnormalities at the time of consent that could increase the risk associated with the participation in and completion of the trial, including but not limited to the following:
  - a) Prior preterm delivery between 18 to ≤34 weeks gestation, or birth weight <2200 grams ;
  - b) Prior stillbirth or neonatal death within 7 days of birth.
  - c) Previous infant with a known genetic disorder or major congenital anomaly.
- Body mass index (BMI) of >40 kg/m2 at the time of the first obstetric visit during the current pregnancy.
- Mother living with HIV/AIDS considered to have WHO Clinical Stage 3 or 4 AIDS, or considered to be clinically unstable.
- Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the trial, including but not limited to the following:
  - a) More than two fetuses (i.e. twins will be allowed)
  - b) Preeclampsia, eclampsia, or uncontrolled gestational hypertension
  - c) Known Placental abnormality.
  - d) Known Polyhydramnios or oligohydramnios
  - e) Known Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism, or uncontrolled diabetes mellitus.
  - f) Any signs of premature labour with the current pregnancy or having ongoing intervention (medical/ surgical) to prevent preterm birth.

Conclusions

- Signal of preterm-birth associated with maternal RSV pre-F vaccines, particularly in middle income settings.
  - Studies undertaken during COVID-19 pandemic.
  - Imbalance temporally associated with Delta and Omicron waves, but no strong evidence that increase in vaccine group due to COVD-19.
  - No clear temporal association with vaccination, and mechanism unexplained.
  - Differ between GRACE and MATISSE study re: early (<34 wks) or late (34-37 wks) preterm.
- Modelling in Soth Africa indicate favourable risk (RSV deaths)-benefit (lives saved) ratio, if vaccination from 28 weeks GA, even if increases risk of preterm birth.
  - Informed WHO SAGE recommendation for vaccination from 28 wks GA.
- Real life maternal RSV vaccine observational studies: no increase in preterm with vaccination from 28 or 32 wks. onward.
  - Moderate heterogeneity in association of TIV and lower risk of preterm (and stillbirths) with TIV in upper-middle and high income countries.
  - Randomised controlled trials of TIV: No difference in stillbirths or preterm births in LMIC.
- Randomised controlled trial required which is adequately powered to address whether maternal RSV is associated with increased risk of preterm birth.
  - Expected data from RSV-IMPACT, with more inclusive inclusion criteria compared with pivotal phase III trials, and done exclusively in low and middle income settings.

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