Preterm Birth Risk: GSK's Phase 3 RSV Prefusion F Maternal Vaccine Trial

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References

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GRACE trial: https://clinicaltrials.gov/study/NCT04605159

Preterm birth safety signal in GSK's Ph 3 RSV maternal immunization trial

- GRACE trial (RSV MAT-009): FSFV November 2020
- 18 February 2022: GSK voluntarily paused enrollment and vaccination following IDMC recommendation which was based on an observed imbalance in preterm births
  - Voluntary pause also implemented for 2 other trials investigating the unadjuvanted RSVPreF3 vaccine candidate in pregnant women
- 25 February 2022: GSK took decision to stop enrollment and vaccination in all RSV maternal immunization trials involving pregnant women, due to imbalances in proportion of **preterm births and neonatal deaths** in treatment vs. placebo group in RSV MAT-009
  - Unblinded treatment assignments to give guidance to investigators and participants
  - Approx. 33% of the 5328 maternal participants (approx. half of target enrollment) in GRACE trial had not yet delivered
  - All participants followed to end of trial (6 months post-birth) for safety

RSV MAT-009 trial design

- Phase 3, randomized (2:1 ratio), double-blind, placebo-controlled trial
- Participants from 24 countries
  - High-income countries (HIC): AUS, BEL, CAN, ESP, FIN, FRA, GBR, ITA, KOR, NZL, TWN, USA
  - Low- or Middle-income countries (LMIC): ARG, BGD, BRA, COL, DOM, HND, IND, MEX, PAN, PHL, THA, ZAF
- Maternal participants were $24^{0/7}$ to $34^{0/7}$ weeks gestation at time of trial vaccination
  - Confirmed by LMP date and ultrasonography
- Healthy pregnancy with singleton fetus
- Concomitant vaccination with recommended vaccines (as per national immunization guidelines) allowed two weeks before or after trial vaccination

ARG, Argentina; AUS, Australia; BEL, Belgium; BGD, Bangladesh; BRA, Brazil; CAN, Canada; COL, Colombia; DOM, Dominican Republic; ESP, Spain; FIN, Finland; FRA, France; GBR, Great Britain; HND, Honduras; IND, India; ITA, Italy; KOR, Republic of Korea; MEX, Mexico; NZL, New Zealand; PAN, Panama; PHL, Philippines; THA, Thailand; TWN, Taiwan; USA, United States of America; ZAF, South Africa.

Baseline characteristics of participants generally balanced across groups

Maternal participants:

- Mean age at vaccination = 29 yrs; ~20% in each group 35^{+} yrs
- 50% from LMIC
- 58% vaccinated in third trimester; 41% in second trimester
- 59% were multiparous and 6% had history of at least 1 prior preterm birth

Infant participants:

- Mean gest. age at birth = 39 weeks
  - Preterm (< 37 wks): 6.8% vs. 4.9% RSV MAT vs. pcbo
- Length, weight, head circumference, 5 min-Apgar score balanced

Imbalance in preterm births greater in LMIC than HIC

	RSV MAT N=3496*		Placebo N=1739†			
	n/N	% (95% CI)	n/N	% (95% CI)	Relative risk (95% CI)	P value
Overall	238/3496	6.81 (6.0, 7.7)	86/1739	4.95 (4.0, 6.1)	1.38 (1.08, 1.75)	0.0090
LMIC	173/1755	9.8 (8.5, 11.3)	55/875	6.31 (4.8, 8.1)	1.57 (1.17, 2.10)	0.0026
HIC	65/1741	3.7 (2.9, 4.7)	31/864	3.6 (2.5, 5.1)	1.04 (0.68, 1.58)	0.8528

*Infants born to mothers who received RSVPreF3 120 µg dose; †Infants born to mothers who received placebo.
CI, confidence interval.

Neonatal deaths

Death within first 28 days of life

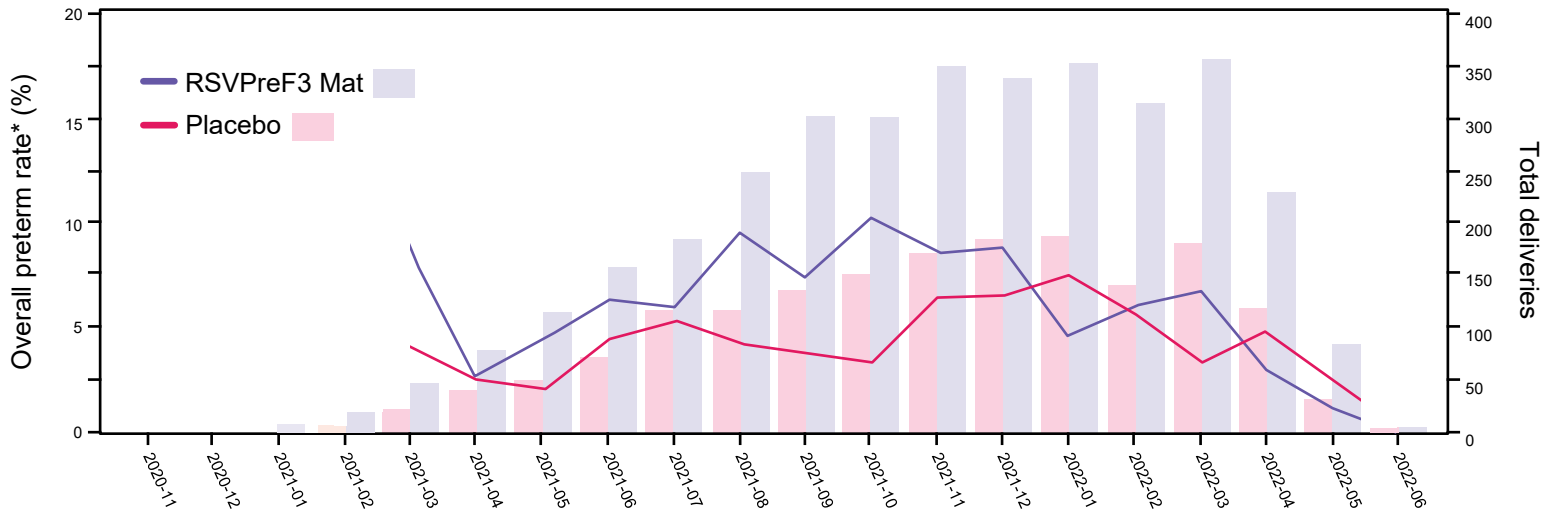
Event	RSV MAT N=3496 n	RSV MAT N=3496 % (95% CI)	Placebo N=1739 n	Placebo N=1739 % (95% CI)	Relative risk (95% CI)
Neonatal death	13	0.37 (0.2, 0.6)	3	0.17 (0.0, 0.5)	2.16 (0.62, 7.55)
Extremely preterm (gestational age at birth: ≤22 weeks to <28 weeks)	2	0.06 (0.0, 0.6)	0	0.00 (0.0, 0.2)	Not estimable
Preterm (gestational age at birth: ≥28 weeks to <37 weeks)	5*	0.14 (0.0, 0.3)	0	0.00 (0.0, 0.2)	Not estimable
Term (≥37 weeks of gestational age at birth)	6	0.17 (0.1, 0.4)	3	0.17 (0.0, 0.5)	0.99 (0.25, 3.97)

* One “very preterm” (28 - <32 weeks) and four “moderate or late preterm” (32 - <37 weeks)

CI, confidence interval.

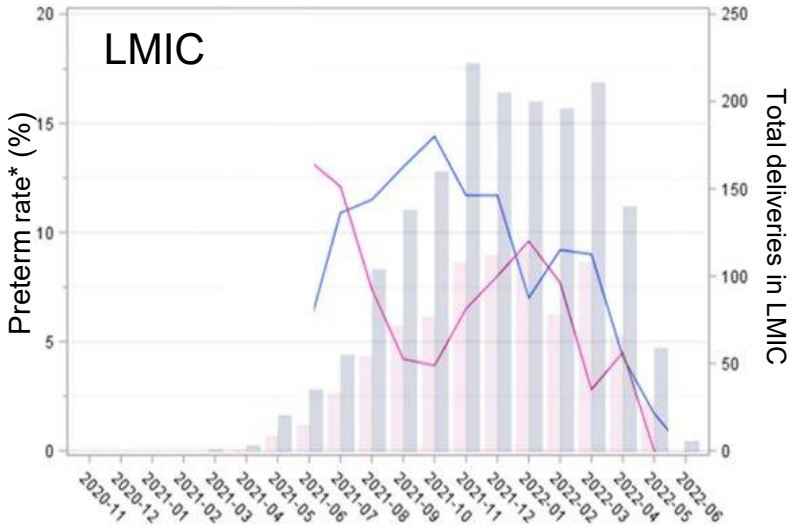
Temporal distribution

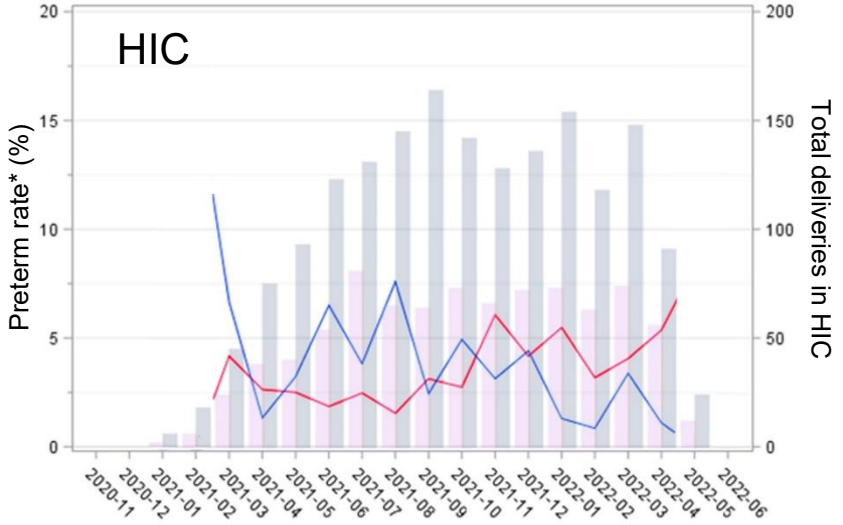
Monthly preterm birth rate and total births, overall and by economic region



The imbalance in preterm birth rates was consistently present between April and December 2021, and afterwards, the difference was not evident

The magnitude and temporal clustering of the imbalance in preterm birth between groups was greater in LMIC than in HIC during the same time period





*Preterm birth rate is shown only for months with ≥50 total deliveries. Data for the day 43 post-delivery safety analysis, with data lock point 4 October 2022.

End of trial safety findings

- Following confirmation of safety signal, trial was unblinded
- Participants continued to be followed for safety until 12 months post-birth
- At end of trial, unsolicited AEs generally balanced except:

Adverse event	RSV MAT No.	RSV MAT % (95% CI)	Placebo No.	Placebo % (95% CI)
Maternal participants	3557		1771	
Pathways to preterm birth	248	7.0 (6.2-7.9)	93	5.3 (4.3-6.4)
Hypertensive disorders of pregnancy	209	5.9 (5.1-6.7)	99	5.6 (4.6-6.8)
Infant participants	3494		1741	
Neonatal death	13	0.4 (0.2-0.6)	3	0.2 (0.0-0.5)
Preterm birth (<37 wk gestation)	237	6.8 (6.0-7.7)	86	4.9 (4.0-6.1)
Small for gestational age	253	7.2 (6.4-8.2)	161	9.2 (7.9-10.7)

End of trial vaccine efficacy (descriptive only*)

Infants up to 6 months of age

Outcome	RSVPreF3 (N=3426)		Placebo (N=1711)		Vaccine Efficacy (95% credible interval)
	No. events	Incidence (per 1000 person-yr)	No. events	Incidence (per 1000 person-yr)	
Any medically assessed RSV-associated LRTD	16	9.7	24	29.2	65.5 (37.5 – 82.0)
Severe medically assessed RSV-associated LRTD	8	4.8	14	17.0	69.0 (33.0 – 87.6)
RSV hospitalization	14	8.5	14	17.0	50.1 (-3.6 – 75.8)

*After signal of preterm birth confirmed and treatment groups unblinded, protocol was amended to replace hypothesis testing with descriptive analysis for evaluation of vaccine efficacy

RSV MAT-015 follow-up descriptive, observational cohort study

- Objective: to further monitor and describe any potential impact on subsequent pregnancies (within 2 years after study vaccination) and neonatal outcomes (up to 6 weeks post-delivery) for women who received unadjuvanted RSVPreF3 maternal vaccine candidate (any dose) or a control vaccine in seven prior Phase 1-3 clinical trials
- Data retrospectively (medical records) and prospectively (medical records and scheduled participant contact timepoints) collected to maximize enrollment
- No new safety signals or risks were identified
  - Numerically higher incidence of preterm births (RR 1.57, 95% CI 0.69–3.58; p=0.28) in subsequent pregnancies after RSVPreF3 maternal vaccination versus control vaccination
  - Limitations:
    - Small number of live births (n=399: 266 in RSVPreF3 Mat and 133 in control)
    - Potential for selection bias: majority of women had participated in RSV MAT-009
    - Potential for recall bias in retrospective data

Conclusions

- In the Phase 3 GRACE study, 37% greater risk of preterm birth among maternal participants that received unadjuvanted RSVPreF3 candidate vaccine as compared with placebo
- Numerical imbalance in neonatal deaths in RSVPreF3 group, likely attributable to imbalance in preterm births and degree of prematurity
- Risk of preterm birth in both groups was below background rates, but greater in LMIC than HIC and had distinctive temporal distribution
- No plausible explanation for the signal was identified in post-hoc analyses

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