VACCIREVIEW

Maternal RSVPreF3-Mat Vaccine: Efficacious but Halted After Preterm Birth Safety Signal

Bibliography

Banooni P, Gonik B, Epalza C, et al; GRACE Study Group. Efficacy, immunogenicity, and safety of an investigational maternal respiratory syncytial virus prefusion F protein–based vaccine. Clin Infect Dis. 2026;82(1):e146-e155.

Summary

This phase 3, randomized, double-blind, placebo-controlled trial evaluated the efficacy, immunogenicity, and safety of an investigational unadjuvanted maternal RSV prefusion F protein–based vaccine (RSVPreF3-Mat) in pregnant women and their infants across 24 countries, including both low- and middle-income countries (LMICs) and high-income countries (HICs). Women aged 18–49 years with singleton uncomplicated pregnancies at $24^0/_7$–$34^0/_7$ weeks' gestation were randomized 2:1 to receive a single intramuscular dose of RSVPreF3-Mat or placebo. The primary endpoints were efficacy against medically assessed RSV-associated lower respiratory tract disease (MA–RSV–LRTD) of any severity and severe MA–RSV–LRTD in infants up to 6 months after birth, and safety in infants up to 12 months of age. Immunogenicity in mothers and infants and additional efficacy endpoints (e.g., RSV hospitalization, all-cause LRTD) were secondary objectives.

A total of 5345 women were randomized, and 5328 received study intervention (3557 vaccine, 1771 placebo); 5235 infants were enrolled (3494 vaccine, 1741 placebo). Just over half of participants were from LMICs, and baseline characteristics were generally balanced between groups, apart from a higher proportion of preterm births later observed in the vaccine arm. Trial enrollment and vaccination were stopped prematurely in 2022 after a safety signal of increased preterm birth and neonatal death in the vaccine group was detected; however, follow-up continued to the planned end (6 months postpartum for mothers, 12 months postbirth for infants).

In infants born ≥4 weeks after maternal vaccination (primary efficacy population; 3426 vaccine, 1711 placebo), RSVPreF3-Mat showed substantial protection during the first 6 months of life. Vaccine efficacy (VE) against any MA–RSV–LRTD was 65.5% (95% credible interval [CrI], 37.5%–82.0%), and VE against severe MA–RSV–LRTD was 69.0% (95% CrI, 33.0%–87.6%). VE against RSV-associated hospitalization up to 6 months was 50.1% (95% CrI, −3.6% to 75.8%), with a wide CrI crossing zero owing to the limited number of events. Protection waned over time: cumulative VE against any MA–RSV–LRTD and severe MA–RSV–LRTD remained statistically supported (CrI lower bound >0) until approximately

9 and 7 months, respectively, but by 12 months VE estimates had declined to 23.0% and 14.8%, with CrIs including zero.

Regional analyses suggested higher efficacy in HICs than LMICs. VE against any MA–RSV–LRTD to 6 months was 75.9% (95% CrI, 46.1%–91.5%) in HICs and 47.8% (95% CrI, −25.8% to 77.3%) in LMICs, with similar patterns for severe disease. The authors note that these subgroup analyses were descriptive and not powered for formal comparisons; potential contributors to lower apparent VE in LMICs include differences in exposure intensity, co-morbidities, and factors influencing transplacental antibody transfer.

Immunogenicity data from a defined sub cohort (518 mothers, 571 infants in the vaccine group; 256 and 274, respectively, in the placebo group) showed robust boosting of maternal RSV-A neutralizing antibodies and efficient transplacental transfer. Maternal geometric mean titers (GMTs) rose from approximately 637 (ED_{60}) pre-vaccination to about 9200 one month post-vaccination (geometric mean ratio [GMR] ≈15), and remained ~5700 at delivery (GMR ≈9.6 vs baseline). In infants of vaccinated mothers, RSV-A neutralization GMTs at birth were markedly higher than in the placebo group (≈9500 vs 700), declining over 6 months but staying clearly above placebo values. The geometric mean transplacental transfer ratio of RSVPreF3-binding IgG was ~1.46 in the vaccine group, with ~87% of infants showing a transfer ratio ≥1, indicating active and generally efficient IgG transport. Transfer ratios were numerically lower in LMICs than HICs, but higher maternal titers in LMICs resulted in similar infant titers.

Safety analyses revealed acceptable reactogenicity: solicited local reactions (particularly injection-site pain) were more frequent with RSVPreF3-Mat than placebo, while solicited systemic reactions (fatigue, headache, fever) were broadly similar and usually mild or moderate. Unsolicited adverse events (AEs) within 30 days and serious adverse events (SAEs) up to 6 months postpartum in mothers and 12 months in infants occurred at similar frequencies in vaccine and placebo groups.

However, pregnancy-related AEs of special interest identified a higher rate of pathways to preterm birth (7.0% vs 5.3%) and a higher rate of preterm delivery (<37 weeks' gestation) in the vaccine group (6.8% vs 4.9%), corresponding to a relative risk of 1.37 (95% CI, 1.08–1.75). Neonatal deaths were also more frequent in the vaccine arm (13 vs 3), predominantly in LMICs, and largely among preterm infants; investigators considered most infant deaths related to prematurity rather than directly to vaccination. No maternal or infant deaths were judged vaccine related. Despite extensive investigation, no clear biological mechanism linking RSVPreF3-Mat to preterm birth was identified. Given the

observed imbalance and its clinical significance, the sponsor terminated further development of this maternal RSV vaccine candidate.

Comment

This publication has long been awaited as the reasons for the end of the trial had emerged. Thus, it illustrates a classic late-stage vaccine development paradox: a biologically plausible, immunogenic maternal vaccine with promising efficacy against infant RSV-LRTD fails because of a safety signal—in this case, a statistically significant excess of preterm birth, consistent with the high overall attrition rate of vaccine and drug candidates in advanced development. At the same time, the trial reinforces two key messages: preF-based maternal immunization can meaningfully reduce RSV disease in early infancy, but any signal suggesting harm in pregnancy—even with an unclear mechanism—appropriately triggers a very conservative regulatory and ethical response.

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