Respiratory Syncytial Virus (RSV) long-acting human recombinant monoclonal antibody, nirsevimab: GRADE tables

and

Respiratory Syncytial Virus (RSV) pre-F maternal vaccine: GRADE tables

for consideration by the Strategic Advisory Group of Experts (SAGE) on Immunization

Respiratory Syncytial Virus (RSV) long-acting human recombinant monoclonal antibody, nirsevimab: GRADE tables for consideration by the Strategic Advisory Group of Experts (SAGE) on Immunization

Overarching question: The overarching question to be addressed when preparing the evidence to recommendations table is proposed below:

Should a single dose (50 mg for infants <5 kg and 100 mg for infants ≥5 kg) of the RSV long-acting human recombinant monoclonal antibody (mAb) (nirsevimab) be recommended for infants aged <12 months born during or entering their first RSV season to prevent RSV-associated morbidity and mortality?

Contents

Table	Initial rating	Limitation in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias& confounding	Final rating
Part 1. GRADE questions on the efficacy of nirsevimab in infants										
1a. Efficacy of nirsevimab in preventing RSV-associated medically-attended lower respiratory tract illness (MA-LRTI) in infants during the first RSV season.	4	None	None serious	Serious	None serious	None serious	Applicable +1	Not applicable	Not applicable	High confidence ⊕⊕⊕⊕
1b: Efficacy of nirsevimab in preventing hospitalization with RSV-associated lower respiratory tract illness (LRTI) in infants during the first RSV season.	4	None	None serious	Serious	None serious	None serious	Applicable (+2)	Not applicable	Not applicable	High confidence ⊕⊕⊕⊕
1c: Efficacy of nirsevimab in preventing severe hospitalized RSV-associated lower respiratory tract illness (LRTI) in infants during the first RSV season.	4	None	None serious	Serious	None serious	None serious	Applicable +1	Not applicable	Not applicable	High confidence ⊕⊕⊕⊕
1d: Efficacy of nirsevimab in preventing RSV-associated lower respiratory tract illness (LRTI) with <90% SpO2 and/or supplemental oxygen in infants during the first season.	4	None	None serious	Serious	None serious	None serious	Applicable (+2)	Not applicable	Not applicable	High confidence ⊕⊕⊕⊕
1e: Efficacy of nirsevimab in preventing hospitalization for all-cause LRTI in infants during the first RSV season.	4	None	None serious	Serious	None serious	None serious	Not applicable	Not applicable	Not applicable	Moderate confidence ⊕⊕⊕
1f: Efficacy of nirsevimab in preventing all-cause severe hospitalized LRTI in infants during the first RSV season.	4	None	None serious	Serious	None serious	None serious	Not applicable	Not applicable	Not applicable	Moderate confidence ⊕⊕⊕
Part 2 – GRADE questions on the safety of nirsevimab in infants										
2a: Safety of nirsevimab with respect to serious adverse events in infants.	4	None	None serious	None serious	Serious	None serious	Not applicable	Not applicable	Not applicable	Moderate confidence ⊕⊕⊕

Part 1. GRADE questions on the efficacy of nirsevimab for preventing RSV disease in infants during the first RSV season.

GRADE TABLE 1a: Efficacy of nirsevimab in preventing RSV-associated medically-attended lower respiratory tract illness (MA-LRTI) in infants during the first RSV season.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: RSV-associated MA-LRTI in infants[1] during 150 days after administration.

What is the efficacy of a single dose of nirsevimab administered to infants before or during the first RSV season in preventing medically-attended RSV-associated LRTI in infants 150 days after administration?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-3]	4
	Factors decreasing	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1

[1] **Definition**: MA-RTI visit AND RSV-positive test result AND ≥1 of the following
- Rhonchi
- Rales
- Crackles
- Wheeze

AND ≥ 1 of the following
- Increased respiratory rate (*≥60 breaths/min for <2-month-old; ≥50 breaths/min for 2–6-month-old, ≥40 breaths/min for 6–24month-old
- Hypoxemia in room air: O2 <95% at ≤1800 m; O2 <92% at >1800 m
- Clinical signs of severe respiratory disease: New-onset apnoea; retractions; grunting, nasal flaring; acute hypoxic or ventilatory failure; dehydration due to respiratory distress requiring IV hydration; intercostal, subcostal, or supraventricular retractions

[2] Efficacy of nirsevimab in preventing RSV-associated LRTI in healthy preterm infants (n=1453, 29 weeks – 34 weeks 6 days gestational age) was evaluated in a Phase 2b study in 23 countries. Participants were assigned 2:1 to receive nirsevimab (50 mg IM) or placebo at the start of an RSV season.
Efficacy of nirsevimab in preventing RSV in term and late-preterm infants (gestational age of at least 35 weeks) was evaluated in a Phase 3 trial in 31 countries. Participants were randomized 2:1 to receive one dose of nirsevimab (at a dose of 50 mg if they weighed <5 kg or 100mg if they weighed ≥5 kg) or placebo. Phase 3 enrollment stopped after 1490 participants had been randomized due to the COVID-19 pandemic. After enrollment resumed, 3012 participants were randomized and dosed. In the pooled estimates, infants weighing ≥5 kg in the Phase 2b study were excluded, as the Phase 2b study demonstrated that infants ≥5 kg required a higher dose for sufficient efficacy and subsequent trials used a higher dose (100 mg) for infants ≥5 kg.
The final sample size for the pooled analysis was 3872 infants, 2579 in the nirsevimab group (570 in phase 2b and 2009 in phase 3) and 1293 in the placebo group (290 in phase 2b and 1003 in phase 3). The data from these analyses are not yet published but were made available by the manufacturer.
[3] The WHO RSV TAG reviewed the available evidence in meetings in May and June 2022 and concluded that, based on available data, there was no evidence that the pharmacokinetics (PK) of mAbs in malnourished children are likely to be different from those in healthy children. The MEDLEY study showed that the PK of nirsevimab in preterm infants 29-34 weeks and infants with chronic lung disease or congenital heart diseases was similar to term infants. There was no difference noted in the point estimates of efficacy among the different ethnic groups enrolled in the MELODY (phase 3)

	confidence	Imprecision	None serious[4]	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[5]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season demonstrates statistically significant moderately high efficacy in preventing RSV MA-LRTI during 150 days after administration.

trial. However, the seasonality of RSV in many low and low-middle-income countries is less well characterised, especially at subnational levels, and the capacity of national programmes to achieve the desired level of coverage at the appropriate time may be suboptimal. Hence, 1 point was deducted for indirectness since there was no representation from these countries in the trial.

[4] The distribution of cases of RSV MA-LRTI (RSV A and RSV B combined) was 31/2579 (1.2%) in the nirsevimab group and 80/1293 (6.2%) in the placebo group. Vaccine efficacy was 79% (95% CL 68.5-86.1%). The incidence rate (per 100,000 person-years (PY) was 12463 lower in the nirsevimab group (95% CL 8912 lower to 16014 lower).

[5] Efficacy of nirsevimab against medically attended RSV-associated LRTI was 79.0% (95% CI: 68.5% - 86.1%) and the risk ratio of medically attended RSV-associated LRTI was 0.21 (95% CI 0.14 – 0.31) with nirsevimab as compared to placebo in the pooled analysis. This is a moderately large effect size, so would warrant the addition of one point.

GRADE TABLE 1b: Efficacy of nirsevimab in preventing hospitalisation with RSV-associated lower respiratory tract illness (LRTI) in infants during the first RSV season.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: Hospitalisation with RSV-associated LRTI in infants[6] during 150 days following administration.

What is the efficacy of a single dose of RSV or nirsevimab administered before or during the first RSV season in preventing hospitalization with RSV-associated LRTI in infants during 150 days following administration?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-3]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[7]	(+2)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season demonstrates statistically significant high efficacy in preventing RSV MA-LRTI requiring hospitalization during 150 days after administration.

[6] **Definition**: Any RSV-associated MA-LRTI (trial definition) that required hospitalisation.
[7] Efficacy of nirsevimab against RSV-associated MA-LRTI requiring hospitalisation was 80.6% (95% CI: 62.3% - 90.1%) with an observed (risk ratio 0.19, 95% CI: 0.10 – 0.38). This is a large effect and would warrant the addition of two points; however, the total score cannot exceed four points so only 1 point was added. The incidence rate (per 100,000 PY) was 5217 lower in the nirsevimab group (95% CL 2943 lower to 7492 lower).

GRADE TABLE 1c: Efficacy of nirsevimab in preventing severe hospitalised RSV-associated lower respiratory tract illness (LRTI) in infants during the first RSV season.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: Severe hospitalised RSV-associated MA-LRTI[8] in infants during 150 days after administration.

What is the efficacy of a single dose of nirsevimab administered before or during the first RSV season in preventing severe RSV-associated MA-LRTI in infants during 150 days following administration?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-3]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[9]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season demonstrates statistically significant moderately large efficacy in preventing severe RSV MA-LRTI (protocol definition) during 150 days after administration.

[8] **Definition**: any confirmed RSV-associated MA-LRTI for which hospitalisation and supplemental oxygen (any level) or intravenous fluids are warranted (defined as very severe RSV MA-LRTI in the trial protocol). The WHO WG group felt that this outcome should be referred to as "severe", rather than "very severe".
[9] Efficacy against severe RSV-associated MA-LRTI was 78.6% (95% CI: 48.8% – 91.0%) in the pooled analysis. This is a moderately large effect size with a moderately wide confidence interval and warrants the addition of one point. The incidence rate (per 100,000 PY) was 4735 lower in the nirsevimab group (95% CL 2668 lower to 6803 lower).

GRADE TABLE 1d: Efficacy of nirsevimab in preventing RSV-associated MA-LRTI with <90% SpO_2 and/or supplemental oxygen in infants during the first RSV season.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: RSV-associated MA-LRTI with <90% SpO_2 and/or supplemental oxygen[10] in infants during 150 days following administration

What is the efficacy of a single dose of nirsevimab administered before or during the first RSV season preventing RSV-associated LRTI with <90% SpO_2 and/or supplemental oxygen in infants during 150 days following administration?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-3]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[11]	(+2)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season demonstrates statistically significant high efficacy in preventing RSV MA-LRTI (protocol definition) with SpO2 <90% and/or requiring supplemental oxygen during 150 days after administration.

[10] In the nirsevimab trial, data were not collected on the level of supplemental oxygen. Hence, in this definition, supplemental oxygen refers to any level of oxygen supplementation. This definition differs from that used in the trial evaluating the RSV maternal pre-F vaccine.
[11] Efficacy against RSV-associated MA-LRTI (protocol defined) with SpO2 <90% and/or supplemental oxygen (any level) was 87.8% (95% CI: 70.2% - 95.0%) in the pooled analysis. This is a large effect size with the lower limit of the 95% CL over 70% and would warrant the addition of 2 points; however, the total score cannot exceed four points, so only one additional points was added. The incidence rate (per 100,000 PY) was 4639 lower in the nirsevimab group (95% CL 2615 lower to 6662 lower).

GRADE TABLE 1e: Efficacy of nirsevimab in preventing hospitalisation for all-cause MA-LRTI in infants during the first RSV season.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: Hospitalisation for all-cause MA-LRTI in infants during 150 days following administration[12]

What is the efficacy of a single dose of nirsevimab administered before or during the first RSV season in preventing all-cause hospitalization for LRTI in infants during 150 days after administration?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-3]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[13]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season demonstrates statistically significant efficacy in preventing all-cause MA-LRTI requiring hospitalization during 150 days after administration.

[12] **Definition**: Any MA-LRTI (trial definition) requiring hospitalization.
[13] Efficacy against all-cause LRTI-associated hospitalisation was 44.9% (95% CI: 24.9% - 59.6%). The incidence of all-cause hospitalised LRTI (per 100,000 PY) was 6360 lower in the nirsevimab group (95% CI. 2733 lower to 9987 lower). This is not a large effect size, so no additional points were added.

GRADE TABLE 1f: Efficacy of nirsevimab in preventing hospitalised all-cause severe MA- LRTI in infants during the first RSV season.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: Hospitalised all-cause severe MA-LRTI in infants during the first RSV season[14]

What is the efficacy of a single dose of nirsevimab administered before or during the first RSV season in preventing all-cause hospitalization for LRTI in infants during 150 days following administration?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-3]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[3]	-1
		Imprecision	None serious[15]	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[16]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season demonstrates statistically significant efficacy in preventing all-cause severe MA-LRTI during 150 days after administration.

[14] **Definition**: any MA-LRTI for which hospitalization and supplemental oxygen(any level) or intravenous fluids are warranted (referred to as very severe LRTI in the MELODY trial).
[15] Efficacy against all-cause severe MA-LRTI was 51.1% (95% CI: 26.3% - 67.5%). No deductions were made for imprecision because recommendations would still remain valid if the lower limit of the 95% CL represented the truth. The incidence of all-cause hospitalized LRTI (per 100,000 PY) was 4532 lower in the nirsevimab group (95% CI. 1701 lower to 7363 lower).
[16] Though the point estimate of efficacy was above 50%, given the moderately wide 95% CL with a lower limit of 26.3%, no additional points were added.

Part 2. GRADE questions on the safety of nirsevimab

GRADE TABLE 2a: Safety of nirsevimab with respect to serious adverse events in infants.

Population: Infants aged <12 months entering their first RSV season
Intervention: One dose of nirsevimab administered before or during the first RSV season
Comparison: Placebo
Outcome: Serious adverse events in infants receiving nirsevimab

What is the safety of nirsevimab with respect to serious adverse events in infants?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[2] [1-4]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[17]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[18]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			Nirsevimab administered to infants before or during the first RSV season did not demonstrate a statistically significant increase in severe adverse events during 150 days after administration.

[17] Trials were underpowered to detect rare serious adverse events, e.g., anaphylaxis.
[18] The risk ratio of severe adverse events in the nirsevimab group was 0.73 (95% CI: 0.59 – 0.89) as compared to the placebo group in the pooled analysis. The incidence of SAEs in infants (per 100,000 PY) was 2694 lower in the nirsevimab group (95% CL 4845 lower to 542 lower).

References

1. Muller, W.J., et al., *Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants.* New England Journal of Medicine, 2023. **388**(16): p. 1533-1534.
2. Hammitt, L.L., et al., *Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants.* New England Journal of Medicine, 2022. **386**(9): p. 837-846.
3. Griffin, M.P., et al., *Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants.* New England Journal of Medicine, 2020. **383**(5): p. 415-425.
4. Mankad, V.S., et al., *Comprehensive Summary of Safety Data on Nirsevimab in Infants and Children from All Pivotal Randomized Clinical Trials.* Pathogens, 2024. **13**(6): p. 503.

Respiratory Syncytial Virus (RSV) pre-F maternal vaccine: GRADE tables for consideration by the Strategic Advisory Group of Experts (SAGE) on Immunization

Overarching question: The overarching question to be addressed when preparing the evidence to recommendations table is proposed below:

Should the RSV pre-F vaccine (Abrysvo®, Pfizer) be recommended for use in pregnant people in a single-dose schedule at 24-36 weeks of gestation to prevent RSV disease in infants during the first 180 days of life?

Contents

Summary

Table 1: GRADE Questions of the efficacy of maternal RSV pre-F vaccine

Table	Initial rating	Limitations in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias & confounding	Final rating
1a: Efficacy of maternal pre-F vaccine in preventing RSV-associated medically-attended lower respiratory tract illness (MA-LRTI) in infants during the first 180 days of life	4	None	None serious	Serious	None serious	None serious	N/A	N/A	N/A	Moderate confidence ⊕⊕⊕
1b: Efficacy of maternal pre-F vaccine in preventing hospitalisation with RSV-associated lower respiratory tract illness (LRTI) in infants during the first 180 days of life.	4	None	None serious	Serious	None serious	None serious	N/A	N/A	N/A	Moderate confidence ⊕⊕⊕
1c: Efficacy of maternal pre-F vaccine in preventing severe RSV-associated MA-LRTI in infants during the first 180 d of life.	4	None	None serious	Serious	None serious	None serious	Applicable	N/A	N/A	High confidence ⊕⊕⊕⊕

Table	Initial rating	Limitations in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias & confounding	Final rating
1d: Efficacy of maternal pre-F vaccine in preventing RSV-associated LRTI with <90% SpO2 and/or supplemental oxygen in infants during the first 180 d of life.	4	None	None serious	Serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕
1e: Efficacy of maternal pre-F vaccine in deaths adjudicated to be due to RSV in infants during the first 180 d of life.	4	None	None serious	Very serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕
1f: Efficacy of maternal pre-F vaccine in preventing all-cause hospitalisation for LRTI in infants during the first 180 d of life.	4	None	None serious	Serious	Serious	None serious	N/A	N/A	N/A	Limited confidence ⊕⊕
1g: Efficacy of maternal pre-F vaccine in preventing all-cause severe MA-LRTI in infants during the first 180 d of life.	4	None	None serious	Serious	Serious	None serious	N/A	N/A	N/A	Limited confidence ⊕⊕

The final scores are interpreted as follows:

***4** (⊕⊕⊕⊕) = Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on health outcome.*

***3** (⊕⊕⊕) = Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on health outcome.*

***2** (⊕⊕) = Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on health outcome.*

***1** (⊕) = Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on health outcome.*

Table 2: GRADE questions on the safety of maternal RSV pre-F vaccine

Table	Initial rating	Limitations in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias & confounding	Final rating
2a: Safety of RSV pre-F vaccine with respect to serious adverse events in pregnant people.	4	None	None serious	Serious	Serious	None serious	N/A	N/A	N/A	Limited confidence ⊕⊕
2b: Safety of RSV pre-F vaccine with respect to systemic reactogenicity (grade 3+) in pregnant people.	4	None	None serious	Serious	Serious	None serious	N/A	N/A	N/A	Limited confidence ⊕⊕
2c: Safety of RSV pre-F vaccine with respect to serious adverse events in infants.	4	None	None serious	None serious	Serious	None serious	N/A	N/A	N/A	Moderate confidence ⊕⊕⊕
2d: Safety of RSV pre-F vaccine with respect to all pre-term births (< 37 weeks gestation).	4	None	Serious	Serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕
2e: Safety of RSV pre-F vaccine with respect to moderate, very, and extremely pre-term births (< 34 weeks gestation).	4	None	Serious	Serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕
2f: Safety of RSV pre-F vaccine with respect to very and extremely pre-term births (< 32 weeks gestation).	4	None	None serious	Serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕

Table	Initial rating	Limitations in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias & confounding	Final rating
2g: Safety of RSV pre-F vaccine with respect to low birth weight (<2500 grams) in infants.	4	None	None serious	Serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕
2h: Safety of RSV pre-F vaccine with respect to very low birth weight (<1500 grams) in infants.	4	None	None serious	Serious	Very serious	None serious	N/A	N/A	N/A	Very low confidence ⊕

The final scores are interpreted as follows:
***4** (⊕⊕⊕⊕) = Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on health outcome.*
***3** (⊕⊕⊕) = Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on health outcome.*
***2** (⊕⊕) = Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on health outcome.*
***1** (⊕) = Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on health outcome.*

Part 1. GRADE questions on the efficacy of the maternal RSV pre-F vaccine for preventing RSV disease in infants during the first 180 days of life.

GRADE TABLE 1a: Efficacy of maternal pre-F vaccine in preventing RSV-associated medically-attended lower respiratory tract illness (MA-LRTI) in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: RSV-associated MA-LRTI in infants during the first 180 days of life[19]

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing medically-attended RSV-associated LRTI in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[20][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious[21]	0
		Indirectness	Serious[22] [2-6]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0

[19] **Definition**: MA-RTI visit AND RSV-positive test result AND
• Fast breathing (RR ≥60 bpm for <2 months of age [<60 days of age], ≥50 bpm for 2–<12 months of age, or ≥40 bpm for 12–24 months of age)
OR
• SpO2 <95%
OR
• Chest wall indrawing

[20] Efficacy of the Pfizer bivalent RSV prefusion F protein-based (RSVpreF) vaccine was evaluated in a phase 3, double-blind, randomized controlled trial conducted in 18 countries in which pregnant women at 24 through 36 weeks' gestation were randomized (1:1) to receive a single intramuscular dose of RSVpreF or placebo. The primary efficacy endpoints were medically attended severe RSV-associated LRTI and medically attended RSV-associated LRTI in infants within 90, 120, 150, and 180 days after birth.

[21] The VE was consistent to those observed in the main analyses; clinically meaningful differences between subgroups (gestational age, country, country income level, exclusive breast feeding, duration of breast feeding, maternal smoking, maternal age at vaccination and number of household members) were generally not observed. However, these were limited by the numbers of cases in the subgroups and should be interpreted with caution. Source: presentation to US FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC), May 2023. (Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Presentation- Review of Efficacy and Safety of Respiratory Syncytial Virus Vaccine (ABRYSVO) (fda.gov) ; accessed 08/06/2024)

[22] 1 point was deducted because of low representation from low-income and low-middle-income countries (276 of 7357 [3.75%] of pregnant women enrolled in the study). There is evidence for lower rates of transfer of maternal antibody in these countries, associated with higher rates of hypergammaglobuliaemia.

	Factors increasing confidence	Large effect	Not applicable[23]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			**3**
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation demonstrates statistically significant efficacy against MA-LRTI in their infants during the first 180 days of life.

[23] The effect size did not merit an addition of a point as vaccine efficacy against medically attended RSV-associated LRTI in infants 180 days after birth was 49.2% (67 cases in RSVpreF group as compared to 132 cases in placebo group), with a moderately wide confidence interval (95% confidence interval [CI] 31.4 % - 62.8%) in the final analysis. The incidence rate (per 100,000 PY) was 3672 lower in the vaccine group (95% CL 2123 lower to 5221 lower).

GRADE TABLE 1b: Efficacy of maternal pre-F vaccine in preventing hospitalisation with RSV-associated LRTI in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Hospitalization with RSV-associated LRTI in infants[24] during the first 180 days of life

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing medically-attended RSV ALRTI requiring hospitalisation in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[2][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious[3]	0
		Indirectness	Serious[4]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[25]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			**3**
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation demonstrates statistically significant efficacy against MA-LRTI requiring hospitalization in their infants during the first 180 days of life.

[24] **Definition**: Any medically-attended RSV LRTI (see footnote 1) that requires hospitalization.
[25] Vaccine efficacy was 54.8% against RSV-associated LRTI hospitalization 180 days after birth (19 hospitalizations in RSVpreF group as compared to 42 cases in placebo group), which is consistent with a moderate effect size; because of the relatively wide confidence interval (95% CI 20.5% - 75.2%), no additional point was awarded. The incidence rate (per 100,000 PY) was 1298 lower in the vaccine group (95% CL 440 lower to 2155 lower). No deductions were made for imprecision because recommendations would still remain valid if the lower limit of the 95% CL represented the truth.

GRADE TABLE 1c: Efficacy of maternal pre-F vaccine in preventing severe RSV-associated MA-LRTI in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Severe RSV-associated MA-LRTI[26] in infants during the first 180 days of life

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing severe medically-attended RSV-associated LRTI in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[2][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious[3]	0
		Indirectness	Serious[4]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[27]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			**4**
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation demonstrates statistically significant efficacy against severe MA-LRTI in their infants during the first 180 days of life.

[26] **Definition**: medically attended LRTI visit AND RSV-positive test result* AND ≥1 of the following
• Fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for 2–<12 months of age, or ≥ 50 bpm for 12–24 months of age)
• SpO_2 <93%
• High-flow nasal cannula or mechanical ventilation (i.e., invasive or noninvasive)
• ICU admission for >4 hours
• Failure to respond/unconscious

[27] A moderate effect size was noted, as vaccine efficacy against medically attended severe RSV-associated LRTI in infants was 70.0% (95% CI: 50.6% – 82.5%) within 180 days of birth, so one point was added. The incidence rate (per 100,000 PY) was 2758 lower in the vaccine group (95% CL 1710 lower to 3806 lower).

GRADE TABLE 1d: Efficacy of maternal pre-F vaccine in preventing RSV-associated LRTI with <90% SpO_2 and/or supplemental oxygen in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: RSV-associated LRTI with <90% SpO_2 and/or supplemental oxygen[28] in infants during the first 180 days of life

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing RSV-associated LRTI with <90% SpO_2 and/or supplemental oxygen in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[2][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious[29]	0
		Indirectness	Serious[4]	-1
		Imprecision	Very serious[30]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			**1**
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate statistically significant (with a very low level of confidence) efficacy against MA-LRTI with SpO2 <90% or requiring supplemental oxygen in their infants

[28] i.e., requiring high-flow nasal cannula or higher level.
[29] Results from stratified analysis by subgroups were not available to assess inconsistency.
[30] Vaccine efficacy (VE) against RSV-associated LRTI with <90% SpO_2 **or** supplemental oxygen 180 days after birth was 48.0% but with a wide confidence interval that crosses zero (-5.6% to 75.6%). The incidence rate (per 100,000 PY) was 678 lower in the vaccine group (95% CL 1 lower to 1355 lower).
VE against RSV-associated LRTI with <90% SpO_2 180 days after birth was 55.0% and VE against RSV-associated LRTI with supplemental oxygen 180 days after birth was 41.7% , but also with very wide confidence intervals crossing zero (-3.4% – 82.0%) and (-60.7% – 80.5%), respectively. Thus, two points would have been deducted for very serious imprecision.

		during the first 180 days of life.

GRADE TABLE 1e: Efficacy of maternal pre-F vaccine in preventing any death adjudicated to be due to RSV infection in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: RSV LRTI deaths[31] in infants during the first 180 days of life

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing any death adjudicated to be due to RSV infection in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[2][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Very serious[32]	-2
		Imprecision	Very serious[33]	(-2)
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			**1**
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate statistically significant efficacy against death adjudicated to RSV infection in their infants during the first 180 days of life. Since over 90% of RSV deaths occurred in low and low-middle-income countries that contributed to only 3.75% of the study population,

[31] **Definition**: Any death adjudicated to be due to RSV infection in infants during 180 days of follow up.
[32] Two points deducted for indirectness because over 90% of RSV deaths occurred in low-income and low-middle-income countries, which represented only 3.75% of the study population.
[33] There was only 1 RSV-associated death in a placebo recipient within the follow-up period in the phase 3 trial and no RSV-associated deaths in the Phase 2b trial; therefore, the study was not powered to assess vaccine efficacy against RSV-associated LRTI in infants in the first 180 days of life. Two points would have been deducted for imprecision, but the final numerical grading cannot be below one, so only one point was deducted.

		no firm conclusions about the impact of the vaccine on mortality can be drawn from the available evidence.

GRADE TABLE 1f: Efficacy of maternal pre-F vaccine in preventing all-cause hospitalisation for LRTI in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: All-cause hospitalisation for LRTI in infants during the first 180 days of life[34]

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing all-cause hospitalization for LRTI in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[2][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[4]	-1
		Imprecision	Serious[35][7]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			**2**
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a limited level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation demonstrates statistically significant (with limited level of confidence) efficacy against all-cause hospitalization for LRTI in their infants during the first 180 days of life.

[34] **Definition**: Any medically-attended LRTI requiring hospitalization.
[35] Vaccine efficacy against all-cause hospitalization for LRTI in infants was 31.0% (95% CI: 2.4% - 51.5%). This estimate is low and the confidence interval is wide. The incidence rate (per 100,000 PY) was 1479 lower in the vaccine group (95% CL 172 lower to 2787 lower). The score was downgraded by 1 point because of imprecision.

GRADE TABLE 1g: Efficacy of maternal pre-F vaccine in preventing all-cause severe MA-LRTI in infants during the first 180 days of life.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: All-cause severe medically attended LRTI in infants during the first 180 days of life[36]

What is the efficacy of a single dose of RSV pre-F vaccine administered to pregnant women in preventing all-cause severe medically attended for LRTI in infants during the first 180 days of life?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[2][1]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[4]	-1
		Imprecision	Serious[37]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a limted level of confidence** that the true effect lies close to the estimate of the effect on health outcome.

[36] **Definition**: all-cause medically attended LRTI visit AND ≥1 of the following
• Fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for 2–<12 months of age, or ≥ 50 bpm for 12–24 months of age)
• SpO2 <93%
• High-flow nasal cannula or mechanical ventilation (i.e., invasive or noninvasive)
• ICU admission for >4 hours
• Failure to respond/unconscious

[37] Vaccine efficacy against all-cause severe LRTI 180 days after birth was 23.3% (95% CI: 3.2% – 39.3%). This is a low VE estimate with a somewhat wide confidence interval. The incidence rate (per 100,000 PY) was 2291 lower in the vaccine group (95% CL 378 lower to 4204 lower). The score was downgraded by 1 point for imprecision because of the width of the confidence interval for the difference in incidence, containing estimates for which different policy decisions might be considered.

	Conclusion	RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation demonstrates statistically significant (with a limited level of confidence) efficacy against all-cause severe LRTI in their infants during the first 180 days of life.

Part 2. GRADE questions on the safety of the maternal RSV pre-F vaccine

GRADE TABLE 2a: Safety of RSV pre-F vaccine with respect to serious adverse events in pregnant people.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Serious adverse events in pregnant people

What is the safety of the RSV pre-F vaccine with respect to serious adverse events in pregnant people?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[38][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[39]	-1
		Imprecision	Serious[40]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2

[38] Safety and efficacy of the Pfizer bivalent RSV prefusion F protein-based (RSVpreF) vaccine were evaluated in a phase 3, double-blind, randomized controlled trial conducted in 18 countries in which pregnant women at 24 through 36 weeks' gestation were randomized (1:1) to receive a single intramuscular dose of RSVpreF or placebo. Safety and immunogenicity were evaluated in a phase 2b trial, in which pregnant women at 24 through 36 weeks' gestation were randomised to receive either 120 or 240 µg of RSVpreF vaccine (with or without aluminum hydroxide) or placebo. In the final analysis, 3698 and 3687 mothers and 3659 and 3646 infants were evaluated in the RSVpreF 120 µg and placebo groups, respectively.

[39] Deducted 1 point because stringent study exclusion criteria contribute to indirectness. Participants were excluded if they had: conditions leading to prolonged bleeding or severe adverse reactions to vaccines, major maternal or fetal illnesses increasing study risk or complicating evaluation (including positive serologic testing for regional endemic conditions assessed during routine maternal care, as per local standards of care and obstetric recommendations), current pregnancy via in vitro fertilization or pregnancy complications like preeclampsia or placental abnormalities, prior pregnancies with risks like preterm delivery, stillbirth, or genetic anomalies, immunodeficiency or rheumatologic disorders requiring immunosuppressants, recent suicidal behavior, recent use of investigational drugs, certain monoclonal antibodies, systemic corticosteroids, alcohol abuse, or illicit drug use, or if they had received or planned to receive blood products or RSV vaccines during the study.

[40] The risk ratio of serious adverse events among pregnant people was 1.15 (95%CI 0.92 – 1.43) after vaccination to 1 month post vaccination, and 1.05 (95% CI: 0.95 – 1.17) after vaccination to six months after delivery. The incidence rate (per 100,000 PY) was 818 higher in the vaccine group (95% CL 1016 lower to 2653 higher). The score was downgraded by 1 point for imprecision because the width of the confidence interval in the difference in incidence of SAEs, containing estimates for which different policy decisions might be considered. In addition, the study was underpowered to detect rare serious adverse events, e.g., anaphylaxis.

Summary of Findings	Statement on the certainty of evidence	Evidence supports a **limited level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion	RSV pre-F vaccine administered at 24-36 weeks of gestation did not demonstrate a statistically significant risk of serious adverse events in pregnant people.

GRADE TABLE 2b: Safety of RSV pre-F vaccine with respect to systemic reactogenicity (grade 3+) in pregnant people.

Population: Pregnant persons 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Reactogenicity (grade 3 or more) in pregnant people

What is the safety of the RSV pre-F vaccine with respect to systemic reactogenicity (grade 3+) in pregnant people?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[21]	-1
		Imprecision	Serious[41]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[7]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **limited level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant increase in grade ≥ 3 reactogenicity compared to placebo.

[41] Grade ≥3 systemic reactogenicity events in pregnant people were reported by 2.3% of vaccine recipients and 2.3% of placebo recipients (RR: 0.97; 95% CI: 0.72 - 1.31) across Ph2b and Ph3 trials (85/3777 among RSVpreF recipients and 87/3757 among placebo recipients). The incidence rate (per 100,000 PY) was 65 lower in the vaccine group (95% CL 748 lower to 617 higher).There were no grade 4 reactions in the study. The score was downgraded by 1 point for imprecision because the width of the confidence interval in the difference in incidence of SAEs, containing estimates for which different policy decisions might be considered.

GRADE TABLE 2c: Safety of RSV pre-F vaccine with respect to serious adverse events in infants.

Population: Pregnant women 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Serious adverse events in infants

What is the safety of the RSV pre-F vaccine with respect to serious adverse events in infants?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[42]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			**3**
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant increase in serious adverse events in their infants up to 24 months after birth.

[42] Over the duration of study follow up (birth to 24 months of age), the risk ratio of severe adverse events in infants was 1.01 (95%. CI 0.92 – 1.11). The incidence rate (per 100,000 PY) was 76 higher in the vaccine group (95% CL 923 lower to 1075 higher). One point was deducted for imprecision due to the width of the confidence interval in the difference in incidence of SAEs, containing estimates for which different policy decisions. In addition, the study was underpowered to detect rare serious adverse events, e.g., anaphylaxis.

GRADE TABLE 2d: Safety of RSV pre-F vaccine with respect to all pre-term births (< 37 weeks gestation).

Population: Pregnant women 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: All pre-term births (< 37 weeks gestation)

What is the safety of the RSV pre-F vaccine with respect to all pre-term births (<37 weeks gestation) in pregnant people?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	Serious[43]	-1
		Indirectness	Serious[21]	-1
		Imprecision	Very serious[44]	(-2)
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant (with a very low level of confidence) increase in preterm births (<37 weeks gestation).

[43] The frequency of preterm births among trial participants varied between countries of different income levels; therefore, one point has been deducted for inconsistency.
[44] Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered. Risk ratio of preterm birth was 1.20 (95% CI: 0.98 – 1.46), with 207/3659 (5.7%) among RSVpreF recipients and 172/3646 (4.7%) among placebo recipients. The incidence rate of preterm birth was 1,880/100,000 higher (95% CI 209 lower to 3,969 higher) in the vaccine group. However, as the lowest possible final score is 1, only a 1 point deduction was made.

GRADE TABLE 2e: Safety of RSV pre-F vaccine with respect to moderate, very, and extreme pre-term births (< 34 weeks gestation).

Population: Pregnant women 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Moderate, very, and extreme pre-term births (< 34 weeks gestation)

What is the safety of the RSV pre-F vaccine with respect to moderate, very, and extremely pre-term births (<34 weeks gestation) in pregnant people?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	Serious[45]	-1
		Indirectness	Serious[21]	-1
		Imprecision	Very serious[46]	(-2)
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant (with a very low level of confidence) increase in moderate, very, and extreme preterm births (<34 weeks gestation).

[45] The frequency of extremely, very, and moderately preterm births among trial participants varied between countries of different income levels; therefore, one point has been deducted for inconsistency.
[46] The risk ratio of extremely, very, and moderately preterm births is 1.83 (22/3659 in vaccine groups vs 12/3646 in placebo group), with a 95% CI of 0.91-3.69. The incidence rate of preterm births <34 weeks was 544/100,000 higher (95%CI 81 lower to 1,170 higher) among vaccine recipients. Two points were deducted because of a very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered. However, one 1 point was deducted since the lowest possible score is 1.

GRADE TABLE 2f: Safety of RSV pre-F vaccine with respect to very and extreme pre-term births (< 32 weeks gestation).

Population: Pregnant women 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Very and extreme pre-term births (< 32 weeks gestation)

What is the safety of the RSV pre-F vaccine with respect to very and extremely pre-term births (<32 weeks gestation) in pregnant people?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious[47]	0
		Indirectness	Serious[21]	-1
		Imprecision	Very serious[48]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant (with a very low level of confidence) increase in very, and extreme preterm births (<32 weeks gestation).

[47] No deductions were made for inconsistency for this outcome since the number of events were too small to determine whether they were different by countries in different income groups.
[48] The risk ratio for very and extremely preterm births is 1.00; however, the 95% CI is wide (0.35 – 2.84) and the numbers are very small (7 in each group). The incidence rate of preterm births <32 weeks was 1/100,000 higher (95%CI 403 lower to 400 higher) in the vaccine group. Two points were deducted because of very serious concern for imprecision due to the confidence interval containing estimates for which different policy decisions might be considered..

GRADE TABLE 2g: Safety of RSV pre-F vaccine with respect to low birth weight (<2500 grams) in infants.

Population: Pregnant women 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Low birth weight (<2500 grams) in infants

What is the safety of the RSV pre-F vaccine with respect to low birth weight (<2500 grams) in infants?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious	0
		Indirectness	Serious[21]	-1
		Imprecision	Very serious[49]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant (with a very low level of confidence) increase in low birth weight (< 2500 G) in infants.

[49] The risk ratio of low birth weight (<2500g) was 1.17 (95% CI 0.94 – 1.44) in the final analysis. The incidence rate of low birth weight was 1,392/100,000 higher (95%CI 552 lower to 3,335 higher) in vaccine recipients. Two points were deducted because of very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered..

GRADE TABLE 2h: Safety of RSV pre-F vaccine with respect to very low birth weight (<1500 grams) in infants.

Population: Pregnant women 24-36 weeks of gestation
Intervention: One dose of RSV pre-F vaccine
Comparison: Placebo
Outcome: Very low birth weight (<1500 grams) in infants

What is the safety of the RSV pre-F vaccine with respect to very low birth weight (<1500 grams) in infants?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		2 RCTs[24][1, 8]	4
	Factors decreasing confidence	Limitation in study design	None	0
		Inconsistency	None serious[50]	0
		Indirectness	Serious[21]	-1
		Imprecision	Very serious[51]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion			RSV pre-F vaccine administered to pregnant people at 24-36 weeks of gestation did not demonstrate a statistically significant (with a very low level of confidence) increase in very low birth weight (< 1500 G) in infants.

[50] Since there were very few cases, it was not possible to assess whether there was any difference between the subjects in different country income levels.
[51] The risk ratio of very low birth weight (<1500g) was 0.50 (95% CI 0.15 – 1.65) in the final analysis. The incidence rate of very low birth weight was 220/100,000 lower (95%CI 592 lower to 152 higher) among vaccine recipients. Two points were deducted because of very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered.

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