GRADE tables: Comparison of Pfizer RSV Bivalent Pre-fusion F vaccine with placebo or no vaccine in pregnant women at 24 to 36 weeks gestation

NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making pilot results available on the Centre's website. Please read this material as a supplement to the Australian Immunisation Handbook respiratory syncytial virus (RSV) chapter.

Note: This GRADE includes published and unpublished data. Where unpublished data have been used, they have been redacted.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants

Patient or population: Pregnant women at 24–36 weeks gestation
Intervention: RSV Pfizer vaccine
Comparison: Placebo or no vaccine

Outcomes*	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITICAL OUTCOMES				
Vaccine efficacy (VE) against RSV-confirmed severe medically attended lower respiratory tract illness (MA-LRTI) in infants Follow-up: 90 days	Kampmann, et al 2023[1] n/N(vaccine)=6/3495 n/N(placebo)=33/3480 **VE=81.8% (99.5% CI: 40.6%–96.3%)**	6,975 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	90 days after birth, Pfizer RSV-Pre-Fusion F vaccine likely results in a large reduction in RSV-confirmed severe MA-LRTI in infants born to those who received maternal vaccination when compared with placebo.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants

Patient or population: Pregnant women at 24–36 weeks gestation
Intervention: RSV Pfizer vaccine
Comparison: Placebo or no vaccine

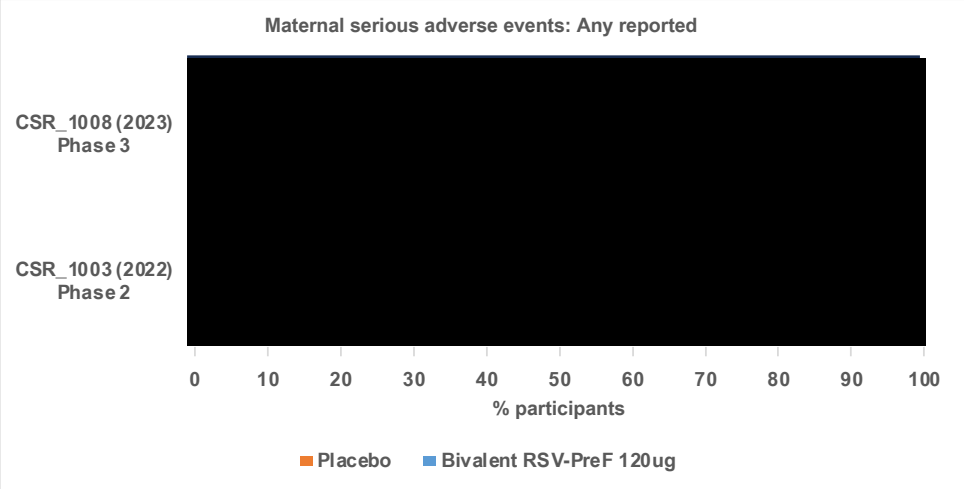
Outcomes*	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
VE against RSV-confirmed severe MA-LRTI in infants Follow-up: 180 days	Kampmann, et al 2023 n/N(vaccine)=19/3495 n/N(placebo)=62/3480 **VE=69.4 (97.58% CI: 44.3%–84.1%)**	6,975 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a]	180 days after birth, Pfizer RSV-Pre-Fusion F vaccine likely results in a moderate reduction in RSV-confirmed severe MA-LRTI in infants born to those who received maternal vaccination when compared with placebo.
VE against RSV-confirmed severe MA-LRTI in infants Follow-up: range 181 to 360 days	[redacted]	6,975 (1 RCT)[2]	⊕⊕◯◯ Low[b]	From 181 to 360 days after birth, there may be little to no reduction in RSV-confirmed severe MA-LRTI in infants born to those who received Pfizer RSV-Pre-Fusion F maternal vaccination when compared with placebo.

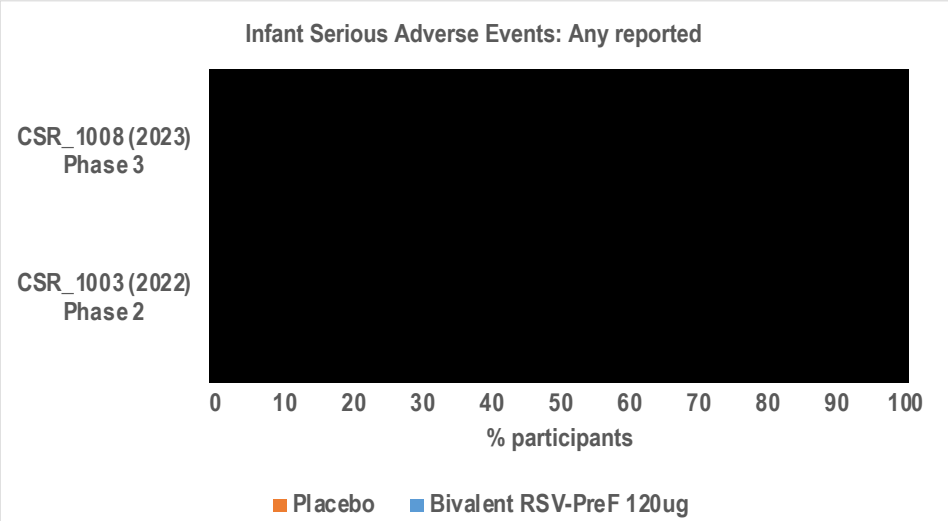
A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
VE against hospitalisation due to confirmed RSV in infants Follow-up: 90 days	Unpublished phase 3 data n/N(vaccine)=10/3495 n/N(placebo)=31/3480 **VE=67.7% (99.17% CI: 15.9%–89.5%)**	6,975 (1 RCT)[2,3]	⨁⨁◯◯ Low[b]	90 days after birth, Pfizer RSV-Pre-Fusion F vaccine may result in a moderate reduction in hospitalisation due to RSV in infants born to those who received maternal vaccination when compared with placebo.
VE against hospitalisation due to confirmed RSV in infants Follow-up: 180 days	Unpublished phase 3 data n/N(vaccine)=19/3495 n/N(placebo)=44/3480 **VE=56.8% (99.17% CI: 10.1%–80.7%)**	6,975 (1 RCT)[2,3]	⨁⨁◯◯ Low[b]	180 days after birth, Pfizer RSV-Pre-Fusion F vaccine may result in a moderate reduction in hospitalisation due to RSV in infants born to those who received maternal vaccination when compared with placebo.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
VE against hospitalisation due to confirmed RSV in infants Follow-up: 181 to 360 days	No data currently available	N/A	N/A	N/A

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants

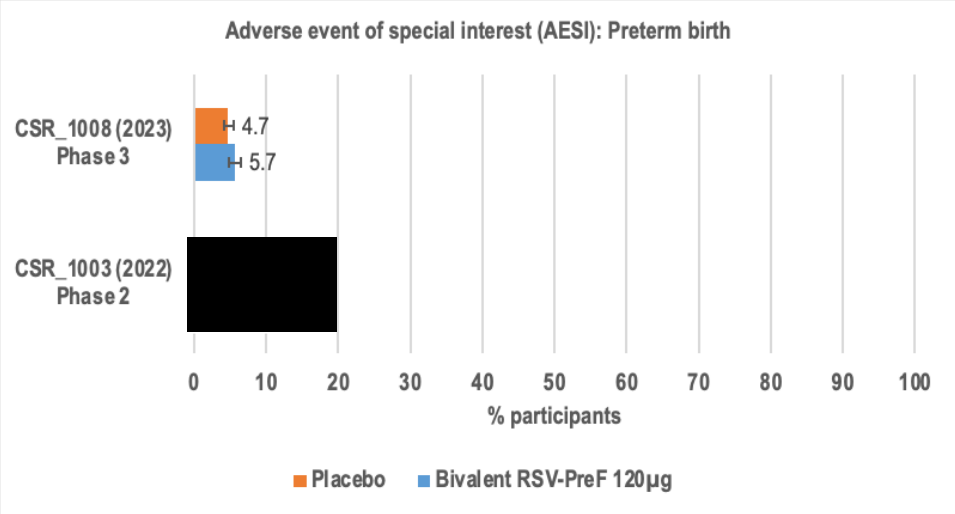
Patient or population: Pregnant women at 24–36 weeks gestation
Intervention: RSV Pfizer vaccine
Comparison: Placebo or no vaccine

Outcomes*	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Maternal serious adverse events (SAEs) Assessed with: any reported SAE	 **Maternal SAEs: Related** Unpublished phase 2 data:[4] **No SAE assessed as related to the intervention.** Kampmann, et al:[1,2] **n=4/3682** vaccine arm and **n=1/3675** placebo arm (*NCIRS-calculated Fisher's exact test* ***p=0.3748***).	7,589 (2 RCTs)[2-5]	⊕⊕⊕◯ Moderate[c]	Pfizer RSV-Pre-Fusion F vaccine likely results in little to no difference in any SAEs in pregnant women when compared with placebo, noting that clinical trials are not powered to detect rare events.

Infant SAEs Assessed with: any reported SAE	 **Infant SAEs: Related** Unpublished phase 2 data:[4] **No SAE assessed as related to the intervention.** Unpublished phase 3 data:[2] **No SAEs in infant participants were considered related to maternal vaccination by the sponsor. It is noted, however, a significantly premature infant whose mother received the intervention, died from prematurity-related complications, for which causality could be uncertain.**	7,356 (2 RCTs)[2-5]	⊕⊕⊕◯ Moderate[c]	Pfizer RSV-Pre-Fusion F vaccine likely results in little to no difference in SAEs in infants born to those who received maternal vaccination when compared with placebo, noting that clinical trials are not powered to detect rare events.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants

Patient or population: Pregnant women at 24–36 weeks gestation
Intervention: RSV Pfizer vaccine
Comparison: Placebo or no vaccine

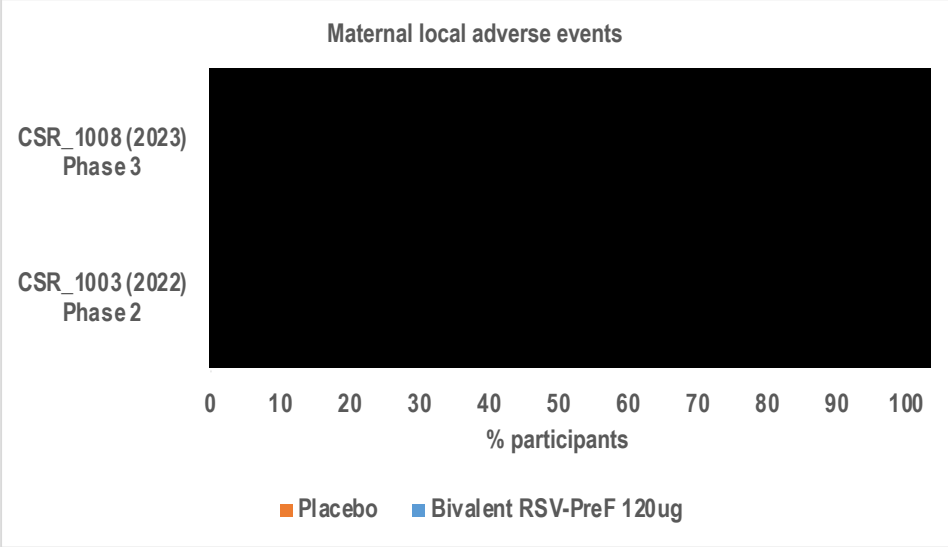
Outcomes*	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Infant adverse event of special interest (AESI) – Preterm birth (born at <37 weeks gestational age)	 Phase 3 study: *NCIRS-calculated p value using chi-squared test = 0.083285.* Phase 2 study: *NCIRS-calculated p value using Fisher's exact test = 0.3308.*	7,356 (2 RCTs)[2-4]	⊕⊕⊕◯ Moderate[d]	Pfizer RSV-Pre-Fusion F vaccine likely results in little to no difference in preterm births in infants born to those who received maternal vaccination when compared with placebo. Note: clinical trials were not powered to detect rare SAEs.

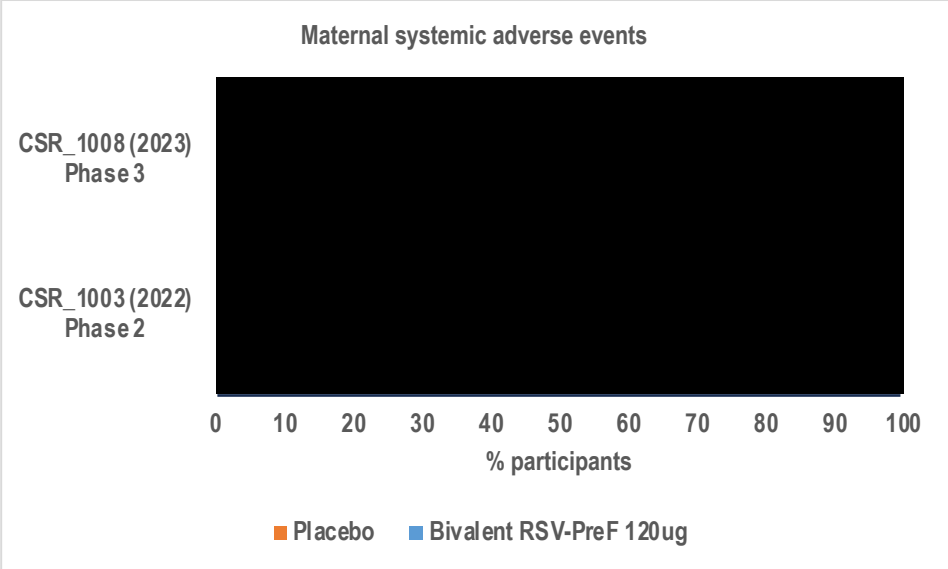
A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
IMPORTANT OUTCOMES				
VE against RSV-confirmed MA-LRTI in infants Assessed with: confirmation from Endpoint Adjudication Committee (EAC) Follow-up: 90 days	Kampmann, et al 2023[1] n/N(vaccine)=24/3495 n/N(placebo)=56/3480 **VE=57.1% (99.5% CI: 14.7%–79.8%)** p=0.0058	6,975 (1 RCT)[1]	⨁⨁◯◯ Low[b]	90 days after birth, Pfizer RSV-Pre-Fusion F vaccine may result in a moderate reduction in RSV-confirmed MA-LRTI in infants born to those who received maternal vaccination when compared with placebo

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
VE against RSV-confirmed MA-LRTI in infants Assessed with: confirmation from EAC Follow-up: 180 days	Kampmann, et al 2023[1] n/N(vaccine)=57/3495 n/N(placebo)=117/3480 **VE=51.3% (97.58% CI: 29.4, 66.8)** p=0.0011	6,975 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	180 days after birth, Pfizer RSV-Pre-Fusion F vaccine likely results in a moderate reduction in RSV-confirmed MA-LRTI in infants born to those who received maternal vaccination when compared with placebo.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
VE against RSV-confirmed MA-LRTI in infants Follow-up: range 181 to 360 days	Kampmann, et al 2023[1] n/N(vaccine)=130 (3.7%) n/N(placebo)=112 (3.2) **VE=−16.1% (95% CI: −50.8, 10.5)**	6,975 (1 RCT)[1]	⨁⨁◯◯ Low[b]	From 181 to 360 days after birth, there may be little to no reduction in RSV-confirmed MA-LRTI in infants born to those who received Pfizer RSV-Pre-Fusion F maternal vaccination when compared with placebo.
VE against RSV-A confirmed severe MA-LRTI in infants Follow-up: 180 days	Kampmann, et al 2023[1] n/N (vaccine)=7/3495 (0.2%) n/N(placebo)=14/3480 (0.4%) **VE=50.0% (95% CI: −32.4, 82.9)**	6,975 (1 RCT)[1]	⨁⨁◯◯ Low[b]	180 days after birth, Pfizer RSV-Pre-Fusion F vaccine may result in a moderate reduction in severe MA-LRTI due to RSV-A in infants born to those who received maternal vaccination when compared with placebo.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
VE against RSV-B confirmed severe MA-LRTI in infants Follow-up: 180 days	Kampmann, et al 2023[1] n/N(vaccine)=11/3495 (0.3%) n/N(placebo)=44/3480 (1.3%) **VE=75.0% (95% CI: 50.8, 88.4)**	6,975 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	180 days after birth, Pfizer RSV-Pre-Fusion F vaccine results in a moderate reduction in severe MA-LRTI due to RSV-B in infants born to those who received maternal vaccination when compared with placebo.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Maternal local AEs Follow-up: 7 days		7,533 (2 RCTs)[2-4]	⨁⨁⨁⨁ High	Pfizer RSV-Pre-Fusion F vaccine results in a large increase in local AEs in pregnant women when compared with placebo

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants				
Patient or population: Pregnant women at 24–36 weeks gestation **Intervention:** RSV Pfizer vaccine **Comparison:** Placebo or no vaccine				
Outcomes*	**Impact**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Maternal systemic AEs Follow-up: 7 days		7,507 (2 RCTs)[2-4]	⨁⨁⨁⨁ High	Pfizer RSV-Pre-Fusion F vaccine results in little to no difference in systemic AEs in pregnant women when compared with placebo.

A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants

Patient or population: Pregnant women at 24–36 weeks gestation
Intervention: RSV Pfizer vaccine
Comparison: Placebo or no vaccine

Outcomes*	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

Explanations

a. Wide CI (≥20 percentage points)
b. Very wide CI (≥50 percentage points)
c. Downgraded for inconsistency across studies
d. Downgraded for imprecision due to population size being too small to detect rare events

*Case definitions for all efficacy outcomes are provided in Appendix A

Abbreviations: AE=adverse event; AESI = adverse event of special interest; CI=confidence interval; RCT=randomised controlled trial; SAE=serious adverse event; VE=vaccine efficacy

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: We have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE evidence profile

Evidence profile: A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women for the prevention of severe RSV disease in infants

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine efficacy against RSV-confirmed severe medically attended lower respiratory tract illness (MA-LRTI) in infants (follow-up: 90 days)									
1	Randomised trial	Not serious	N/A	Not serious	Serious[a]	None	In the phase 3 study, vaccine efficacy against RSV-confirmed severe MA-LRTI in infants from 72 hours to 90 days after birth was **81.8% (99.5% CI: 40.6, 96.3)**, with 6/3,495 cases in those born to mothers who received the vaccine and 33/3,480 cases in those born to mothers who received placebo.[1]	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine efficacy against RSV-confirmed severe MA-LRTI in infants (follow-up: 180 days)									
1	Randomised trials	Not serious	N/A	Not serious	Serious[a]	None	In the phase 3 study, vaccine efficacy against RSV-confirmed severe MA-LRTI in infants from 72 hours to 180 days after birth was **69.4 (97.58% CI: 44.3, 84.1)**, with 19/3,495 cases in those born to mothers who received the vaccine and 62/3,480 cases in those born to mothers who received placebo.[1]	⊕⊕⊕◯ Moderate	CRITICAL
Vaccine efficacy against RSV-confirmed severe MA-LRTI in infants (follow-up: range 181 days to 360 days)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	In the phase 3 study, vaccine efficacy against RSV-confirmed severe MA-LRTI in infants from 181 to 360 days after birth was [redacted], with [redacted] cases in those born to mothers who received the vaccine and [redacted] cases in those born to mothers who received placebo.[2]	⊕⊕◯◯ Low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine efficacy against hospitalisation due to confirmed RSV in infants (follow-up: 90 days)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	In the phase 3 study, vaccine efficacy against hospitalisation due to RSV in infants from 72 hours to 90 days after birth was **67.7% (99.17% CI: 15.9, 89.5)**, with 10/3,495 cases in those born to mothers who received the vaccine and 31/3,480 cases in those born to mothers who received placebo.[2,3]	⨁⨁◯◯ Low	CRITICAL
Vaccine efficacy against hospitalisation due to confirmed RSV in infants (follow-up: 180 days)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	In the phase 3 study, vaccine efficacy against hospitalisation due to RSV in infants from 72 hours to 180 days after birth was **56.8 (99.17% CI: 10.1, 80.7)**, with 19/3,495 cases in those born to mothers who received the vaccine and 44/3,480 cases in those born to mothers who received placebo.[2,3]	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Maternal serious adverse events (SAEs) (assessed with: any reported SAE)									
2	Randomised trials	Not serious	Serious[c]	Not serious	Not serious	None	Throughout the phase 2 study, 7/115 **(6.1%** [redacted]**)** SAEs occurred in the 120 µg vaccine arm compared with 14/117 **(12.0%** [redacted]**)** in the placebo arm.[4,5] In the phase 3 study, from vaccination to 6 months post-delivery 598/3682 **(16.2%** [redacted]**)** SAEs occurred in the vaccination arm compared with 558/3,675 **(15.2%** [redacted]**)** in the placebo arm.[2,3] For maternal SAEs that the assessor considered to be related to the intervention, none were reported in the phase 2 study,[3] while 4/3,682 and 1/3,675 were reported in the vaccine arm and placebo arm, respectively, of the phase 3 study[2] *NCIRS-calculated Fisher's exact test p=0.3748.*	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Infant SAEs (assessed with: any reported SAE)									
2	Randomised trials	Not serious	Serious[c]	Not serious	Not serious	None	Throughout the phase 2 study,[4,5] 41/114 **(36.0%** [redacted]**)** SAEs occurred in the 120 µg vaccine arm compared with 38/116 **(32.8%** [redacted]**)** in the placebo arm. The majority of SAEs for both study arms were congenital abnormalities, familial and genetic disorders. In the phase 3 study,[2,3] from birth to 24 months after birth, [redacted] **(17.5%** [redacted]**)** SAEs occurred in infants born to mothers who received the vaccine and [redacted] **(17.5%** [redacted]**)** SAEs in infants who were born to mothers who received placebo. No SAEs reported in infants were assessed as related to the maternal vaccination in either the phase 2[4,5] or phase 3[2,3] studies.	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Infant adverse events of special interest (AESI) – preterm birth (<37 weeks)									
2	Randomised trials	Not serious	Not serious	Not serious	Serious[d]	None	For infant AESI of preterm birth, there were cases in the vaccine and placebo arms for both the phase 2 and 3 studies. In the phase 2 study,[3,4] the AESI of preterm birth was measured from birth to 1 month post-delivery; 6/114 **(5.3%)** [redacted] cases occurred in infants born to mothers who received the 120 µg vaccine dose compared with 3/116 **(2.6%)** [redacted] cases in infants born to mothers who received placebo. The difference between vaccine and placebo was 2.7 percentage points (95% CI: –2.9, 9.0) *NCIRS-calculated p value using Fisher's exact test* = 0.3308.	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Infant AESI – preterm birth (<37 weeks) *continued*									
							In the phase 3 study,[2,3] the AESI of preterm birth was measured from birth to 24 months of age; 202/3,568 **(5.7%)** (95% CI: 4.9, 6.5) cases occurred in infants born to mothers who received the vaccine and 169/3,558 **(4.7%)** (95%CI: 4.1, 5.5) cases occurred in infants born to mothers who received placebo. The difference between vaccine and placebo was 0.91 percentage points (95%CI: −0.12, 1.95) *NCIRS-calculated p value using chi-squared test = 0.083285.* Despite non-statistical significance of preterm births in trials, these studies were not powered to detect differences in rare events.		

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine efficacy against RSV-confirmed MA-LRTI in infants (follow-up: 90 days; assessed with: confirmation from EAC)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	In the phase 3 study,[1] vaccine efficacy against RSV-confirmed MA-LRTI in infants from 72 hours to 90 days after birth was **57.1% (99.5% CI: 14.7, 79.8; p=0.0058)**, with 24/3,495 cases in infants born to mothers who received the vaccine and 56/3,480 cases in those born to mothers who received placebo.	⨁⨁◯◯ Low	IMPORTANT
Vaccine efficacy against RSV-confirmed MA-LRTI in infants (follow-up: 180 days; assessed with: confirmation from EAC)									
1	Randomised trials	Not serious	N/A	Not serious	Serious[a]	None	In the phase 3 study,[1] vaccine efficacy against RSV-confirmed MA-LRTI in infants from 72 hours to 180 days after birth was **51.3% (97.58% CI: 29.4, 66.8; p=0.0011)**, with 57/3,495 cases in infants born to mothers who received the vaccine and 117/3,480 cases in those born to mothers who received placebo.	⨁⨁⨁◯ Moderate	IMPORTANT
Vaccine efficacy against RSV-confirmed MA-LRTI in infants (follow-up: range 181 days to 360 days)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	In the phase 3 study,[2] vaccine efficacy against RSV-confirmed MA-LRTI in infants from 181–360 days after birth was **−16.1 (95% CI: −50.8, 10.5)**, with 130/3,495 cases in infants born to mothers who received the vaccine and 112/3,480 cases in those born to mothers who received placebo.	⨁⨁◯◯ Low	IMPORTANT
Vaccine efficacy against RSV-A confirmed severe MA-LRTI in infants (follow-up: 180 days)									
1	Randomised trials	Not serious	N/A	Not serious	Very serious[b]	None	In the phase 3 study,[1] vaccine efficacy against RSV-A confirmed severe MA-LRTI in infants from 72 hours to 180 days after birth was **50.0% (95% CI: −32.4, 82.9)**, with 7/3,495 cases in infants born to mothers who received the vaccine and 14/3,480 cases in those born to mothers who received placebo.	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							Impact		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Vaccine efficacy against RSV-B confirmed severe MA-LRTI in infants (follow-up: 180 days)										
1	Randomised trials	Not serious	N/A	Not serious	Serious[a]	None	In the phase 3 study,[1] vaccine efficacy against RSV-B confirmed severe MA-LRTI in infants from 72 hours to 180 days after birth was **75.0% (95% CI: 50.8, 88.4)**, with 11/3,495 cases in infants born to mothers who received the vaccine and 44/3,480 cases in those born to mothers who received placebo.	⨁⨁⨁◯ Moderate[2]	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Maternal local adverse events (AEs) (follow-up: 7 days)									
2	Randomised trials	Not serious	N/A	Not serious	Not serious	None	Local AEs were more common in women who received the vaccine than in those who received placebo in both the phase 2[4] and phase 3[2,3] studies. Between [redacted] **42.5%** [redacted] of women experienced any local AE within 7 days of receiving the 120µg vaccine dose compared with **10.4%** [redacted] of women in the placebo arm. The most common AE was injection site pain. In the phase 2 study, no AEs were classified as severe in either the vaccine or placebo arms; in the phase 3 study, no AEs were classified as severe in the placebo arm and 0.3% were classified as severe in the vaccine arm.	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Maternal systemic AEs (follow-up: 7 days)									
2	Randomised trials	Not serious	N/A	Not serious	Not serious	None	There was little to no difference in the rate of systemic AEs in those who received the vaccine compared with placebo in both the phase 2[4] and phase 3[2,3] studies. Rates of any systemic AE experienced within 7 days from vaccination ranged from [redacted] **63.2%** [redacted] in those who received the 120µg vaccine dose compared with **59.2%** [redacted] in those who received placebo. The most common event was fatigue. Severe systemic AEs were reported in [redacted] 2.3% [redacted] 2.3% [redacted] in the placebo arm.	⊕⊕⊕⊕ High	IMPORTANT

* Where N/A = 1 study and inconsistency cannot be assessed

Explanations

a. Wide confidence interval (≥20 percentage points)
b. Very wide confidence interval (≥50 percentage points)
c. Downgraded for inconsistency across studies
d. Downgraded for imprecision due to population size being too small to detect rare events

Abbreviations: AE=adverse event; AESI=adverse event of special interest; CI=confidence interval; EAC=Endpoint Adjudication Committee; SAE=severe adverse event

Evidence to Decision framework: A single dose of Pfizer RSV Pre-fusion F vaccine compared with placebo or no vaccine in pregnant women at 24 to 36 weeks gestation for the prevention of severe RSV disease in infants

PICO Question	
Population	Pregnant women at 24–36 weeks gestation
Intervention	Abrysvo (recombinant respiratory syncytial virus bivalent pre-fusion F protein vaccine)
Comparison	Placebo or no vaccine
Main outcomes	*Critical* • Vaccine efficacy (VE) against RSV-confirmed severe medically attended lower respiratory tract illness (MA-LRTI) in infants follow-up: 90 days • VE against RSV-confirmed severe MA-LRTI in infants follow-up: 180 days • VE against RSV-confirmed severe MA-LRTI in infants follow-up: 181–360 days • VE against hospitalisation due to confirmed RSV in infants follow-up: 90 days • VE against hospitalisation due to confirmed RSV in infants follow-up: 180 days • VE against hospitalisation due to confirmed RSV in infants follow-up: 181–360 days • Maternal serious adverse events (SAEs), assessed with any reported SAE • Infant SAEs assessed with any reported SAE • Infant adverse event of special interest (AESI) – preterm birth (born at <37 weeks gestational age) *Important* • VE against RSV-confirmed MA-LRTI in infants follow-up: 90 days • VE against RSV-confirmed MA-LRTI in infants follow-up: 180 days • VE against RSV-confirmed MA-LRTI in infants follow-up: 180–360 days • VE against RSV-A confirmed severe MA-LRTI in infants follow-up: 180 days • VE against RSV-B confirmed severe MA-LRTI in infants follow-up: 180 days • Maternal local AEs follow-up: 7 days • Maternal SAEs follow-up: 7 days
Setting	USA, Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Most children are infected with RSV, a respiratory infection, within the first few years of life.
- Infants with RSV infection often develop lower respiratory tract infection, which may require hospitalisation and supplementary oxygen and/or respiratory ventilatory support.
- RSV hospitalisation rates are highest in the 0–5-month age group. Between 2016–2019, data on hospitalisations among infants <6 months of age from the Australian Institute of Health and Welfare (AIHW) National Hospitalisation and Morbidity database showed a hospitalisation rate of 3,100 per 100,000 (RSV-specific coded principal and additional diagnoses)(AIHW, unpublished NCIRS analysis). As this is a conservative estimate based only on RSV-specific coded hospitalisation, it is likely to underestimate the true disease burden due to not accounting for some diagnoses with unspecified causes where a substantial proportion are likely to be RSV-attributable, such as acute unspecified bronchiolitis. Nonetheless, the relative disease burden remains particularly significant in this age group.
- Aboriginal and Torres Strait Islander infants have an increased burden of RSV hospitalisation with an incidence rate ratio of 2.0 from 0 to <12 months and 1.5 from 12 months to <5 years of age compared with non-indigenous children (AIHW, unpublished NCIRS analysis).

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- In phase 2 and 3 clinical trials for Abrysvo, there were large to moderate reductions in severe and medically attended RSV-confirmed lower respiratory tract infection (LRTI), and RSV-related hospitalisation in infants to 6 months (180 days) after birth.
- The certainty of evidence for protection against any clinical outcome beyond 6 months, was low. Point estimates suggested little to no protection against severe and medically attended RSV-confirmed LRTI beyond 6 months, and there was no data provided on protection against hospitalisation beyond 6 months.
- There was evidence of moderate protection against both RSV A and B subtypes although this is of low certainty for RSV A and moderate certainty for RSV B.

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Abrysvo resulted in a large increase in maternal local adverse events (AEs) compared with placebo. There was little to no difference in maternal systemic AEs. Both local and systemic AEs were brief and mild to moderate in severity.
- SAEs in infants born to women who received Abrysvo were very rare and comparable with those in infants born to women who received a placebo. Serious maternal AEs were also comparable between vaccine and placebo arms.

- There was no conclusive evidence of a difference in preterm births in the vaccine group compared with the placebo group in both Abrysvo clinical trials. In the phase 3 trial, the proportion of preterm births that occurred <7 days, 7–30 days and >30 days following vaccination was not statistically different between vaccine and placebo groups. However, neither the phase 2 nor phase 3 trial were powered to detect a difference in preterm births.
- Another maternal RSV vaccine candidate[6] was noted to have an imbalance in the number of neonatal deaths in low- and middle-income countries during a clinical trial, which was attributed to an imbalance in the number of preterm births. A trial of a third maternal RSV vaccine candidate in which pregnant women were vaccinated between 28–36 weeks, did not find any imbalance in preterm births in either low-middle income countries or high-income countries.[7]
- In both the phase 2 and 3 Abrysvo trials, despite a non-statistically significant imbalance in preterm births, mainly seen in upper-middle income countries but not in high income countries, no imbalance in neonatal deaths was observed. There were no deaths of maternal or infant participants reported during the phase 2 study. There were 5 neonatal deaths in the vaccine arm and 12 in the placebo arm in the phase 3 study, of which one baby died due to prematurity in each of the vaccine and placebo arms. The calculated relative risk of preterm birth (<37 weeks) in those who received the vaccine was 1.20 (95%CI: 0.99–1.46) compared with placebo.[8]

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't Know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention

- The balance of effects favours maternal vaccination with Abrysvo.
- Phase 2 and 3 clinical trials demonstrated a large to moderate reduction in RSV LRTI and RSV-related hospitalisation compared with placebo for infants aged up to 6 months.
- Infants aged ≤6 months will benefit significantly from maternal vaccination due to the high disease burden for this cohort in Australia and large to moderate vaccine efficacy demonstrated in the Abrysvo clinical trials.
- The undesirable effects from vaccination were typical post-vaccination local and systemic AEs in the vaccinated mother and were brief and mild to moderate in severity. Infant and maternal SAEs were comparable between vaccine and placebo arms.
- The rare AESI of preterm birth requires further investigation to assess if there is a true association with vaccination.

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- The overall certainty of evidence was moderate. There were 2/15 outcomes that were assessed as high certainty, 7/15 outcomes were assessed as moderate, 5/15 outcomes assessed as low and 1/15 was assessed as very low.
- Low certainty outcomes included those measuring vaccine efficacy beyond 180 days.
- Evidence was downgraded due to imprecision from wide and very wide confidence intervals and small population numbers to detect rare events. Some outcomes were also downgraded due to inconsistency of results across studies.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

- There is unlikely to be important uncertainty in how people value protection against RSV disease in infants aged 0–6 months.
- 80%–90% of current and future parents are aware of RSV and around 50%–60% are aware that it causes pneumonia and bronchiolitis.[9]
- Attitudes towards RSV vaccines in pregnancy may mirror those for pertussis vaccine, for which studies have shown that pregnant women may place greater value on vaccines which they perceive to protect their newborn infants over themselves.[10]

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Maternal RSV vaccination during pregnancy may be acceptable to key stakeholders (pregnant women, immunisation providers) based on good uptake of pertussis vaccine, another maternal vaccine intended to protect infants after birth. For pertussis vaccine, uptake of 70%–89% has been reported across jurisdictions in Australia.[11]
- A survey of current and future parents on RSV prevention strategies suggests high-level acceptance of maternal vaccination.[9]
- However, pregnant women may consider the addition of RSV vaccine in pregnancy on top of the currently recommended maternal vaccines (dTpa [pertussis], influenza) to be excessive.
- Some stakeholders may have safety concerns which affect acceptability in pregnant women, highlighting the importance of post marketing vaccine safety surveillance.
- Behavioural and social drivers may impact on uptake of a new vaccine in pregnant women[12] or Aboriginal and Torres Strait Islander people[13] as was seen initially with COVID-19 vaccines.
- Some stakeholders may prefer alternative strategies to protect infants against severe RSV, such as long-acting monoclonal antibodies against RSV.

Equity

What would be the impact on health inequities?

Don't know	Varies	Increased	Probably increased	Probably no impact	Probably reduced	Reduced

- Aboriginal and Torres Strait Islander infants have increased burden of RSV hospitalisation with an incidence rate ratio of 2.3–2.4 from 0 to <12 months and 1.3–2.0 from 12 months to <5 years of age compared with non-indigenous children.
- Current uptake of vaccines during pregnancy is lower in Aboriginal and Torres Strait Islander women, being 5%–20% lower for maternal pertussis vaccine than among non-Indigenous pregnant women.[11]

- Health inequity could be decreased if high vaccine uptake is achieved in high-risk populations. Strategies to achieve high vaccine uptake may include communications, resources and initiatives targeted to and co-designed with high-risk populations such as pregnant Aboriginal and Torres Strait Islander women. A universal program with comparatively lower vaccine uptake among high-risk populations could increase health inequities.

Feasibility
Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Abrysvo should be feasible to implement as there is already a vaccine delivery system for maternal vaccination in Australia including through primary care, antenatal clinics, and pharmacist vaccination.
- A year-round vaccination program and suitability for co-administration with other maternal vaccines are likely to aid feasibility.
- Potential challenges include training requirements for a new vaccine on the National Immunisation Program, and the need to schedule the maternal RSV vaccine into limited antenatal visits within the allowed gestational period for vaccination.

ATAGI recommendation

- ATAGI recommends a single dose of Abrysvo (recombinant respiratory syncytial virus bivalent pre-fusion F protein vaccine) in all pregnant women from 28 to 36 weeks gestation, to prevent severe RSV disease in infants aged 0 to <6 months. Administration beyond 36 weeks is acceptable if a pregnant woman has not been vaccinated.

Justification and considerations

Additional considerations

- Abrysvo is likely to be most effective in infants soon after birth when transplacental antibody levels are at their highest.
- As a precaution, ATAGI recommends maternal vaccination from 28 weeks gestation while awaiting further data on AESIs, particularly the risk of preterm birth. The advice regarding gestational age at vaccination may be updated (i.e. recommended at an earlier gestation) as further data becomes available.
- If pregnant women are not vaccinated between 28- and 36-weeks' gestation, they should receive RSV vaccine as soon as possible and at any time up to delivery.
- Two weeks post-vaccination are required for adequate transplacental transfer of maternal antibodies against RSV.
- Women are recommended to receive the vaccine at the 28–36 weeks gestation, regardless of the season/month they are due to give birth.
- It is anticipated, based on first principles and use of other vaccines in pregnancy, that a dose of Abrysvo will be required for subsequent pregnancies to maximise transplacental transfer of antibodies and to protect each infant. However, as the vaccine is new, data on immunogenicity, efficacy and safety of vaccination with Abrysvo in subsequent pregnancies are not yet available. ATAGI will review this data as it becomes available and provide a recommendation regarding vaccination in subsequent pregnancies.

- Alternative prevention strategies such as monoclonal antibodies may also be considered to protect infants against severe RSV disease.
- Pregnant women can receive Abrysvo at the same time as, or separate to, other maternal vaccines. Data on co-administration in pregnant women are still emerging; however, there are no theoretical safety concerns based on data in non-pregnant women.
- Co-administration of Abrysvo with influenza or dTpa was demonstrated to be safe and immunogenic in non-pregnant women.[14,15] There was a small reduction in anti-pertussis antibodies in non-pregnant women co-administered Abrysvo and dTpa vaccine; however, the clinical significance of this is uncertain.
- Post-marketing surveillance is recommended after introduction of RSV maternal vaccine onto the National Immunisation Program (NIP) to monitor for both vaccine effectiveness and safety signals including AESIs such as preterm birth.

Justification

- A national maternal RSV vaccination program is likely to have substantial clinical benefit due to infants aged 0 to <6 months having the highest burden of RSV disease and the lack of a current vaccine.
- Abrysvo given to pregnant women in clinical trials had high to moderate efficacy against severe RSV disease in infants aged up to 6 months.
- Efficacy in the clinical trials in infants beyond 6 months of age appeared minimal and was based on limited low certainty data.
- Local and systemic AEs in pregnant women who received Abrysvo in the clinical trials were reasonably common but brief and mild to moderate in severity.
- Infant and maternal SAEs were comparable between vaccine and placebo.
- The AESI of preterm birth in the Abrysvo clinical trials is noted but the relationship to vaccination is not certain. Post-marketing surveillance studies will be required to establish if any links exist between preterm birth and Abrysvo vaccination.
- The body of evidence suggests that in comparison to no vaccine, the benefits of Abrysvo outweigh the potential undesirable effects following immunisation.

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Appendix A

Table S1. Case definitions used for infant participants in the study

Case	Definition
MA visit	Infant participant has been taken to or seen by a healthcare provider (eg, outpatient, inpatient visit, emergency room, urgent care, or home visit)
MA-RTI visit	A medically-attended visit AND ≥1 of the following RTI signs and symptoms: • Nasal discharge for ≥24 hours • Difficulty breathing, labored breathing, or rapid breathing (any duration) • Cough • Inability to feed for any duration because of respiratory symptoms • Apnea • Any other respiratory symptom of concern
RSV-MA-RTI	An MA-RTI visit AND **RSV-positive test result***
MA-LRTI due to any cause	MA-RTI visit AND ≥1 of the following: • 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) • SpO_2 <95% • Chest wall indrawing
RSV-MA-LRTI	MA-RTI visit AND **RSV-positive test result*** AND ≥1 of the following • 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) • SpO_2 <95% • Chest wall indrawing
Hospitalized RSV-RTI†	RTI due to RSV that results in hospitalization
Severe RSV-MA-LRTI†	MA-RTI 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 (ie, invasive or noninvasive) • ICU admission for >4 hours • Failure to respond/unconscious

bpm=breaths per minute; ICU=intensive care unit; LRTI=lower respiratory tract illness; MA=medically-attended; NAAT=nucleic acid amplification technology; RR=respiratory rate; RSV=respiratory syncytial virus; RTI=respiratory tract illness; RT-PCR=reverse transcription-polymerase chain reaction; SpO_2=oxygen saturation.

* RSV RT-PCR–positive test result by Pfizer central laboratory or by certified laboratory with NAAT for RSV, which was conducted on a sample obtained during the medically-attended visit or within 10 days (where Day 1 is the day of the MA-RTI visit).

† An endpoint adjudication committee determined if the endpoint criteria were met upon review of the site source documentation from the MA-RTI visit and RTI study visits, including all available RSV test results.

Figure 1: Supplementary table 1 from published phase 3[1] study detailing case definitions for key efficacy outcomes