Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

Evidence to Recommendations Framework Updates Pfizer Maternal RSVpreF Vaccine

Katherine E. Fleming-Dutra, MD

Co-lead, Respiratory Syncytial Virus Vaccines – Pediatric/Maternal Work Group

Coronavirus and Other Respiratory Viruses Division

National Center for Immunization and Respiratory Diseases

ACIP General Meeting

September 22, 2023

Policy question

- Should Pfizer RSVpreF vaccine be recommended for pregnant people to be given during 32 through 36 weeks gestation to prevent RSV lower respiratory tract infection in infants?

RSVpreF is a bivalent recombinant stabilized prefusion F protein subunit vaccine.

Key points that have been updated since the June ACIP presentation are highlighted on the slides.

FDA approval for RSVpreF vaccine

- On August 21, 2023, FDA approved Pfizer RSVpreF vaccine for use in pregnant people as a single dose to be given at 32 through 36 weeks gestation
- In the phase 2b and 3 trials, vaccination was given during 24 through 36 weeks gestation
- Throughout the presentation, these will be denoted as
  - Approved dosing interval (32–36 weeks gestation)
  - Trial dosing interval (24–36 weeks gestation)

FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in Infants | FDA

Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA

Same Pfizer RSV vaccine, formulation and dose approved for use in adults ages 60 years and older

Evidence to Recommendations (EtR) framework

PICO question

Population	Pregnant people
Intervention	Pfizer RSVpreF vaccine given at 32–36 weeks gestation
Comparison	No vaccine
Outcomes	▪ Medically attended RSV-associated lower respiratory tract infection in infants ▪ Hospitalization for RSV-associated lower respiratory tract infection in infants ▪ Intensive care unit (ICU) admission from RSV hospitalization in infants ▪ Mechanical ventilation from RSV hospitalization in infants ▪ RSV-associated death in infants ▪ All-cause hospitalization for lower respiratory tract infection in infants ▪ All-cause medically attended lower respiratory tract infection in infants ▪ Serious adverse events in pregnant people ▪ Reactogenicity (grade 3+) in pregnant people ▪ Serious adverse events in infants ▪ Preterm birth (<37 weeks gestation)

Evidence to Recommendations (EtR) framework

EtR Domain	Question(s)
Public Health Problem	▪ Is the problem of public health importance?
Benefits and Harms	▪ How substantial are the desirable anticipated effects? ▪ How substantial are the undesirable anticipated effects? ▪ Do the desirable effects outweigh the undesirable effects?
Values	▪ Does the target population feel the desirable effects are large relative to the undesirable effects? ▪ Is there important uncertainty about, or variability in, how much people value the main outcomes?
Acceptability	▪ Is the intervention acceptable to key stakeholders?
Feasibility	▪ Is the intervention feasible to implement?
Resource Use	▪ Is the intervention a reasonable and efficient allocation of resources?
Equity	▪ What would be the impact of the intervention on health equity?

ACIP Evidence to Recommendations Framework (cdc.gov)

EtR Domain: Public Health Problem

Is the problem of public health importance?

RSV is the leading cause of hospitalization in U.S. infants[1]

- Most (68%) infants are infected in the first year of life and nearly all (97%) by age 2 years[2]
- 2–3% of young infants will be hospitalized for RSV[3,4,5]
- RSV is a common cause of lower respiratory tract infection in infants
- Highest RSV hospitalization rates occur in first months of life and risk declines with increasing age in early childhood[3,5]
- 79% of children hospitalized with RSV aged <2 years had no underlying medical conditions[3]

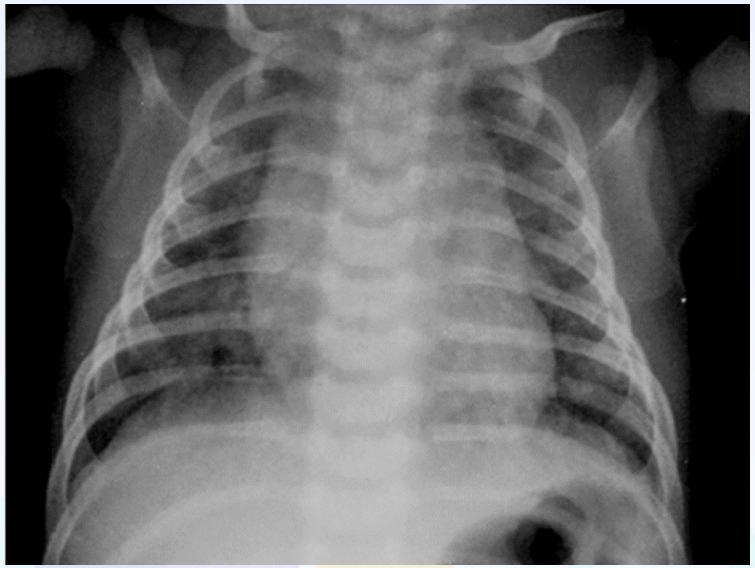


Image: Goncalves et al. Critical Care Research and Practice 2012

[1]Suh et al. JID 2022; [2]Glezen et al, Arch Dis Child, 1986; [3]Hall et al, Pediatrics, 2013; [4]Langley & Anderson, PIDJ, 2011; [5]CDC NVSN data

Public Health Problem: Work Group interpretation

- Is RSV among infants of public health importance?

No	Probably No	Probably Yes	**Yes**	Varies	Don't know

EtR Domain: Benefits and Harms

How substantial are the desirable anticipated effects?

How substantial are the undesirable anticipated effects?

Do the desirable effects outweigh the undesirable effects?

GRADE outcomes, importance, and data sources: Pfizer maternal RSVpreF vaccine

Outcome	Importance[1]	Data sources
Benefits		
Medically attended RSV-associated lower respiratory tract infection in infants	Critical	Phase 3 RCT
Hospitalization for RSV-associated lower respiratory tract infection in infants	Critical	Phase 3 RCT
ICU admission from RSV hospitalization in infants	Important	Phase 3 RCT
Mechanical ventilation from RSV hospitalization in infants	Important	Phase 3 RCT
RSV-associated death in infants	Important	Phase 3 and phase 2b[2] RCT
All-cause medically attended lower respiratory tract infection in infants	Important	Phase 3 RCT
All-cause hospitalization for lower respiratory tract infection in infants	Important	Phase 3 RCT
Harms		
Serious adverse events in pregnant people	Critical	Phase 3 and phase 2b[2] RCT
Reactogenicity (grade 3+) in pregnant people	Important	Phase 3 and phase 2b[2] RCT
Serious adverse events in infants	Critical	Phase 3 and phase 2b[2] RCT
Preterm birth (<37 weeks gestation)	Critical	Phase 3 and phase 2b[2] RCT

RCT = Randomized controlled trial; ICU= intensive care unit

1 Three options: Critical; Important but not critical; Not important for decision making

2 Among phase 2b trial participants, only those who received the vaccine formulation of the phase 3 trial or placebo were included

Data available for GRADE and Benefits and Harms

Trial phase	Dosing interval	Number of Participants*	Decision regarding use in GRADE
Phase 2b trial[1]	Trial dosing interval (24–36 weeks gestation)	Vaccine (received phase 3 dose and formulation): 115 Placebo: 117	Yes. Data for GRADE were limited to participants who received placebo or phase 3 vaccine formulation and only included for safety outcomes. Study was not designed to assess efficacy.
Phase 2b trial[1]	Approved dosing interval (32–36 weeks gestation)	Vaccine (received phase 3 dose and formulation): 45 Placebo: 44	No. Safety data are further limited by small sample size. Presented as supplemental data.
Phase 3 trial published analyses[1,2,3]	Trial dosing interval (24–36 weeks gestation)	Efficacy set / Safety set Vaccine: 3495 / 3682 Placebo: 3480 / 3675	Yes. Trial was designed and powered using a 24–36 weeks dosing interval.
Phase 3 trial, post-hoc analysis[1]	Approved dosing interval (32–36 weeks gestation)	Efficacy set / Safety set Vaccine: 1572 / 1653 Placebo: 1539 / 1632	No. Trial was not powered for this interval for efficacy, and safety data would be limited in power to detect harms. Presented as supplemental data.

*For phase 2b trial and phase 3 trial safety set, number of maternal participants are listed. For phase 3 trial efficacy set, number of infants participants are listed.

1 Data provided by Pfizer

2 Kampmann et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants - PubMed (nih.gov)

3 Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA

Effect estimates and concerns in certainty of assessment, benefits: Pfizer maternal RSVpreF vaccine

Outcome	Importance[1]	Data sources	Manufacturer calculated vaccine efficacy	Concerns in certainty assessment
Benefits				
Medically attended RSV-associated lower respiratory tract infection in infants (0–180 days)	Critical	Phase 3 RCT	51.3% (97.58% CI: 29.4, 66.8)[2]	None
Hospitalization for RSV-associated lower respiratory tract infection in infants (0–180 days)	Critical	Phase 3 RCT	56.8% (99.17% CI: 10.1, 80.7) [2]	Imprecision (serious)[3]
ICU admission from RSV hospitalization in infants (0–180 days)	Important	Phase 3 RCT	42.9% (95% CI: -124.8, 87.7)[4]	Imprecision (very serious)[5]
Mechanical ventilation from RSV hospitalization in infants (0–180 days)	Important	Phase 3 RCT	100% (95% CI: -9.1, 100)[4]	Imprecision (very serious)[5]
RSV-associated death in infants	Important	Phase 3 and phase 2b[6] RCT	1 RSV-associated death occurred in the placebo arm of the phase 3 trial that was recorded at day 120 after birth. No RSV-associated deaths were recorded in the phase 2b trial.	
All-cause medically attended lower respiratory tract infection in infants (0–180 days)	Important	Phase 3 RCT	2.5% (99.17% CI: -17.9, 19.4)[2]	Imprecision (serious)[3]
All-cause hospitalization for lower respiratory tract infection in infants (0–180 days)	Important	Phase 3 RCT	28.9% (95% CI: -2.0, 50.8)[4]	Imprecision (serious)[3]

1 Three options: Critical; Important but not critical; Not important for decision making

2 Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using the Bonferroni procedure and accounting for the primary endpoints results. Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

3 Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered

4 Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

5 Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and fragility of the estimate

6 Among phase 2b trial participants, only those who received the vaccine formulation of the phase 3 trial or placebo were included

Effect estimates and concerns in certainty of assessment, harms: Pfizer maternal RSVpreF vaccine

Outcome	Importance[1]	Data sources	Relative Risk[2] (95% confidence interval)	Concerns in certainty assessment
Harms				
Serious adverse events in pregnant people	Critical	Phase 3 and phase 2b RCT	1.06 (0.95, 1.17)	Indirectness (serious)[3] and Imprecision (serious)[4]
Reactogenicity (grade 3+) in pregnant people	Important	Phase 3 and phase 2b RCT	0.97 (0.72, 1.31)	Indirectness (serious)[5]
Serious adverse events in infants	Critical	Phase 3 and phase 2b RCT	1.01 (0.91, 1.11)	Indirectness (serious)[3] and Imprecision (serious)[4]
Preterm birth (<37 weeks gestation)	Critical	Phase 3 and phase 2b RCT	1.20 (0.99, 1.46)	Indirectness (serious)[3] and Imprecision (very serious)[6]

RCT = Randomized-controlled trial

1 Three options: Critical; Important but not critical; Not important for decision making

2 Pooled relative risk estimates were independently calculated using counts of events and participants in the phase 3 trial interim analysis, and phase 2b trial among those who received the phase 3 vaccine formulation or placebo.

3 Serious concern for indirectness as 55% of the Phase 3 RCT and 62% of the Phase 2b RCT did not receive vaccine or placebo in the approved dosing interval (32–36 weeks gestation). In the approved dosing interval, there is less opportunity for serious adverse events, including preterm birth/delivery, compared to the trial dosing interval (24–36 weeks gestation).

4 Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered

5 Serious concern for indirectness as these data only include systemic reactions. When selecting the *a priori* harm outcomes, the Work Group defined reactogenicity as both local and systemic reactions.

6 Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and not meeting optimal information size requirements

Summary of GRADE: Pfizer maternal RSVpreF vaccine

Outcome	Importance	Design (# of studies)	Findings	Evidence Type
Benefits				
Medically attended RSV-associated lower respiratory infection in infants	Critical	RCT (1)	Pfizer RSVpreF maternal vaccine is effective in preventing medically attended RSV-associated lower respiratory infection in infants	High
Hospitalization for RSV-associated lower respiratory tract infection in infants	Critical	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing hospitalization for RSV-associated lower respiratory tract infection in infants	Moderate
ICU admission from RSV hospitalization in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing ICU admission for RSV hospitalization in infants	Low
Mechanical ventilation from RSV hospitalization in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing mechanical ventilation for RSV hospitalization in infants	Low
RSV-associated death in infants	Important	RCT (2)	1 event observed in a placebo recipient among both trials	Not evaluated
All-cause medically attended lower respiratory tract infection in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine is not effective in preventing all-cause medically attended lower respiratory tract infection in infants	Moderate
All-cause hospitalization for lower respiratory tract infection in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing all-cause hospitalization for lower respiratory tract infection in infants	Moderate
Harms				
Serious adverse events in pregnant people	Critical	RCT (2)	SAEs in pregnant people were balanced between vaccine and placebo groups	Low
Reactogenicity (grade 3+) in pregnant people	Important	RCT (2)	Reactogenicity in pregnant people was balanced between vaccine and placebo groups	Moderate
Serious adverse events in infants	Critical	RCT (2)	SAEs in infants were balanced between vaccine and placebo groups	Low
Preterm birth (<37 weeks gestation)	Critical	RCT (2)	Preterm births were unbalanced between vaccine and placebo groups	Very low

RCT = Randomized-controlled trial

Summary of GRADE: Pfizer maternal RSVpreF vaccine

Outcome	Importance	Design (# of studies)	Findings	Evidence Type
Benefits				
Medically attended RSV-associated lower respiratory infection in infants	Critical	RCT (1)	Pfizer RSVpreF maternal vaccine is effective in preventing medically attended RSV-associated lower respiratory infection in infants	High
Hospitalization for RSV-associated lower respiratory tract infection in infants	Critical	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing hospitalization for RSV-associated lower respiratory tract infection in infants	Moderate
ICU admission from RSV hospitalization in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing ICU admission for RSV hospitalization in infants	Low
Mechanical ventilation from RSV hospitalization in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing mechanical ventilation for RSV hospitalization in infants	Low
RSV-associated death in infants	Important	RCT (2)	1 event observed in a placebo recipient among both trials	Not evaluated
All-cause medically attended lower respiratory tract infection in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine is not effective in preventing all-cause medically attended lower respiratory tract infection in infants	Moderate
All-cause hospitalization for lower respiratory tract infection in infants	Important	RCT (1)	Pfizer RSVpreF maternal vaccine may be effective in preventing all-cause hospitalization for lower respiratory tract infection in infants	Moderate
Harms				
Serious adverse events in pregnant people	Critical	RCT (2)	SAEs in pregnant people were balanced between vaccine and placebo groups	Low
Reactogenicity (grade 3+) in pregnant people	Important	RCT (2)	Reactogenicity in pregnant people was balanced between vaccine and placebo groups	Moderate
Serious adverse events in infants	Critical	RCT (2)	SAEs in infants were balanced between vaccine and placebo groups	Low
Preterm birth (<37 weeks gestation)	Critical	RCT (2)	Preterm births were unbalanced between vaccine and placebo groups	Very low

Overall evidence type:

Very Low

The overall evidence type is driven by the lowest quality of evidence for critical outcomes, and here is driven by the evidence rating for the critical harm of preterm birth being very low.

Effect estimates, benefits: Pfizer maternal RSVpreF vaccine comparing trial vs approved dosing interval

Outcome	Trial dosing interval (24–36 weeks gestation)	Approved dosing interval (32–36 weeks gestation)
	Manufacturer calculated vaccine efficacy (CI)[1]	Manufacturer calculated vaccine efficacy (95% CI)[2]
Benefits		
Medically attended RSV-associated lower respiratory tract infection in infants (0–180 days)	51.3% (97.58% CI: 29.4, 66.8)	57.3% (95% CI: 29.8, 74.7)
Hospitalization for RSV-associated lower respiratory tract infection in infants (0–180 days)	56.8% (99.17% CI: 10.1, 80.7)	48.2% (95% CI: -22.9, 79.6)
ICU admission from RSV hospitalization in infants (0–180 days)	42.9% (95% CI: -124.8, 87.7)	1 event in the vaccine group 2 events in the placebo group
Mechanical ventilation from RSV hospitalization in infants (0–180 days)	100% (95% CI: -9.1, 100)	0 events in the vaccine group 2 events in the placebo group
All-cause medically attended lower respiratory tract infection in infants (0–180 days)	2.5% (99.17%: -17.9, 19.4)	7.3% (95% CI: -15.7, 25.7)
All-cause hospitalization for lower respiratory tract infection in infants (0–180 days)	28.9% (95% CI: -2.0, 50.8)	34.7% (95% CI: -18.8, 64.9)

CI= confidence interval; ICU=Intensive care unit

1 Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. Confidence intervals that are not 95% were adjusted using the Bonferroni procedure and accounting for the primary endpoints results.

2 Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.

Severe medically attended RSV-associated lower respiratory tract infection (LRTI), co-primary trial endpoint

- As defined in the Pfizer trial, this outcome was **not** included by the Work Group as an *a priori* critical or important outcome for GRADE for vaccine policy decisions
- Severe medically-attended RSV-associated LRTI* required at least 1 of the following signs/ symptoms:
  - Fast breathing (respiratory rate ≥70 (<2 month of age [60 days]) or ≥60 (≥2 to 12 months of age) breaths per minute
  - SpO2 measured in room air <93%
  - High-flow nasal cannula or mechanical ventilation
  - ICU admission for >4 hours
  - Unresponsive/unconscious
- Included by the Work Group as an *a priori* critical outcome for GRADE for vaccine policy decisions
- Medically-attended RSV-associated LRTI* required at least 1 of the following signs/symptoms:
  - Fast breathing: respiratory rate ≥60 (<2 months of age [60 days]) or ≥50 (≥2 to 12 months of age) breaths per minute
  - SpO2 measured in room air <95%
  - Chest wall indrawing

*Medically attended visit includes inpatient and outpatient encounters. Additionally, definition also required RT-PCR or nucleic acid amplification (NAAT) test positive for RSV. Blue text denotes differences between the two definitions. SpO2= Peripheral capillary oxygen saturation

1. Kampmann et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants - PubMed (nih.gov)
2. Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA

Phase 3 trial vaccine efficacy against severe medically attended RSV-associated LRTI, co-primary trial endpoint

Time period after birth	Trial dosing interval (24–36 weeks gestation) Vaccine efficacy[1] (99.5% or 97.58% CI)	Approved dosing interval (32–36 weeks gestation) Vaccine efficacy[2] (95% CI)
0–90 days after birth	81.8% (40.6, 96.3)	91.1% (38.8, 99.8)
0–180 days after birth	69.4% (44.3, 84.1)	76.5% (41.3, 92.1)

Within 0-180 days after birth

- Among 81 infants with severe medically attended RSV LRTI, 50 (62%) were hospitalized
- Among 63 infants hospitalized with RSV, 50 (79%) had severe medically attended RSV LRTI

1 Vaccine efficacy was calculated as 1−(P/[1−P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness. At 90 days, 99.5% confidence intervals (CIs) were used (determined by the alpha-spending function and adjusted with the use of the Bonferroni procedure), and at later intervals, 97.58% CIs were used (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure).

2 Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.

1. Kampmann et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants - PubMed (nih.gov)
2. Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA

Effect estimates, harms: Pfizer maternal RSVpreF vaccine comparing trial vs approved dosing interval

Outcome	Trial dosing interval[1] (24–36 weeks)	Approved dosing interval[1] (32–36 weeks)
	Relative Risk[2] (95% CI)	Relative Risk[2] (95% CI)
Harms		
Serious adverse events in pregnant people	1.06 (0.95, 1.17)	1.02 (0.87, 1.20)
Reactogenicity (grade 3+) in pregnant people	0.97 (0.72, 1.31)	0.98 (0.62, 1.54)
Serious adverse events in infants	1.01 (0.91, 1.11)	1.04 (0.90, 1.20)
Preterm birth (<37 weeks gestation)	1.20 (0.99, 1.46)	1.15 (0.82, 1.61)

CI= confidence interval

1 Phase 3 and 2b trials

2 Pooled relative risk estimates were independently calculated using counts of events and participants in the phase 3 trial interim analysis, and phase 2b trial among those who received the phase 3 vaccine formulation

Effect estimates, harms: Pfizer maternal RSVpreF vaccine comparing trial vs approved dosing interval

Outcome	Trial dosing interval[1] (24–36 weeks)	Approved dosing interval[1] (32–36 weeks)
	Relative Risk[2] (95% CI)	Relative Risk[2] (95% CI)
Harms		
Serious adverse events in pregnant people	1.06 (0.95, 1.17)	1.02 (0.87, 1.20)
Reactogenicity (grade 3+) in pregnant people	0.97 (0.72, 1.31)	0.98 (0.62, 1.54)
Serious adverse events in infants	1.01 (0.91, 1.11)	1.04 (0.90, 1.20)
Preterm birth (<37 weeks gestation)	1.20 (0.99, 1.46)	1.15 (0.82, 1.61)

CI= confidence interval

1 Phase 3 and 2b trials

2 Pooled relative risk estimates were independently calculated using counts of events and participants in the phase 3 trial interim analysis, and phase 2b trial among those who received the phase 3 vaccine formulation

GSK maternal RSV vaccine clinical trial and preterm birth

- Trial of a similar GSK maternal RSV vaccine (stabilized prefusion F protein vaccine without an adjuvant) was halted due to an imbalance of preterm births with higher numbers in the vaccine vs placebo group

Outcome	Vaccine group, n (%) N=3,496	Placebo group, n (%) N=1,739	Relative Risk (95% CI)
Preterm birth (<37 weeks gestation)	238 (6.81%)	86 (4.95%)	1.38 (1.08, 1.75)
Neonatal death	13 (0.37%)	3 (0.17%)	2.16 (0.62, 7.55)

- Imbalance of neonatal deaths was a consequence of preterm birth imbalance
- Imbalance in preterm births was seen in low and middle-income countries (RR: 1.57, 95% CI: 1.17, 2.10) but not high-income countries (RR: 1.04, 95% CI: 0.68, 1.58)
- Imbalance was observed from April–December 2021, but not consistently after December 2021
- Reason for the imbalance remains unclear

Study vaccine given at 24 0/7 to 34 0/7 weeks gestation

Vaccines and Related Biological Products Advisory Committee February 28 - March 1, 2023 Meeting Briefing Document- Sponsor GSK (fda.gov)

Preterm birth in Pfizer RSVpreF vaccine phase 3 trial data, comparing trial vs approved dosing interval

	Trial dosing interval (24–36 weeks gestation)[1]				Approved dosing interval (32–36 weeks gestation)[1,2]			
	RSVpreF vaccine group N=3,568		Placebo group N=3,558		RSVpreF vaccine group N=1,628		Placebo group N=1,604	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Preterm birth (<37 weeks gestation)	202	**5.7%** (4.9%, 6.5%)	169	**4.7%** (4.1%, 5.5%)	68	**4.2%** (3.3%, 5.3%)	59	**3.7%** (2.8%, 4.7%)

1. Package Insert - ABRYSVO (STN 125768) (fda.gov)

2. Pfizer response to ACIP, unpublished data, August 2023. In package insert, approved dosing interval reported as: 4.2% (68/1,631) in the RSVpreF group and 3.7% (59/1,610) in the placebo group.

Low birth weight and neonatal jaundice outcomes in Pfizer RSVpreF vaccine phase 3 trial data, trial vs approved dosing interval

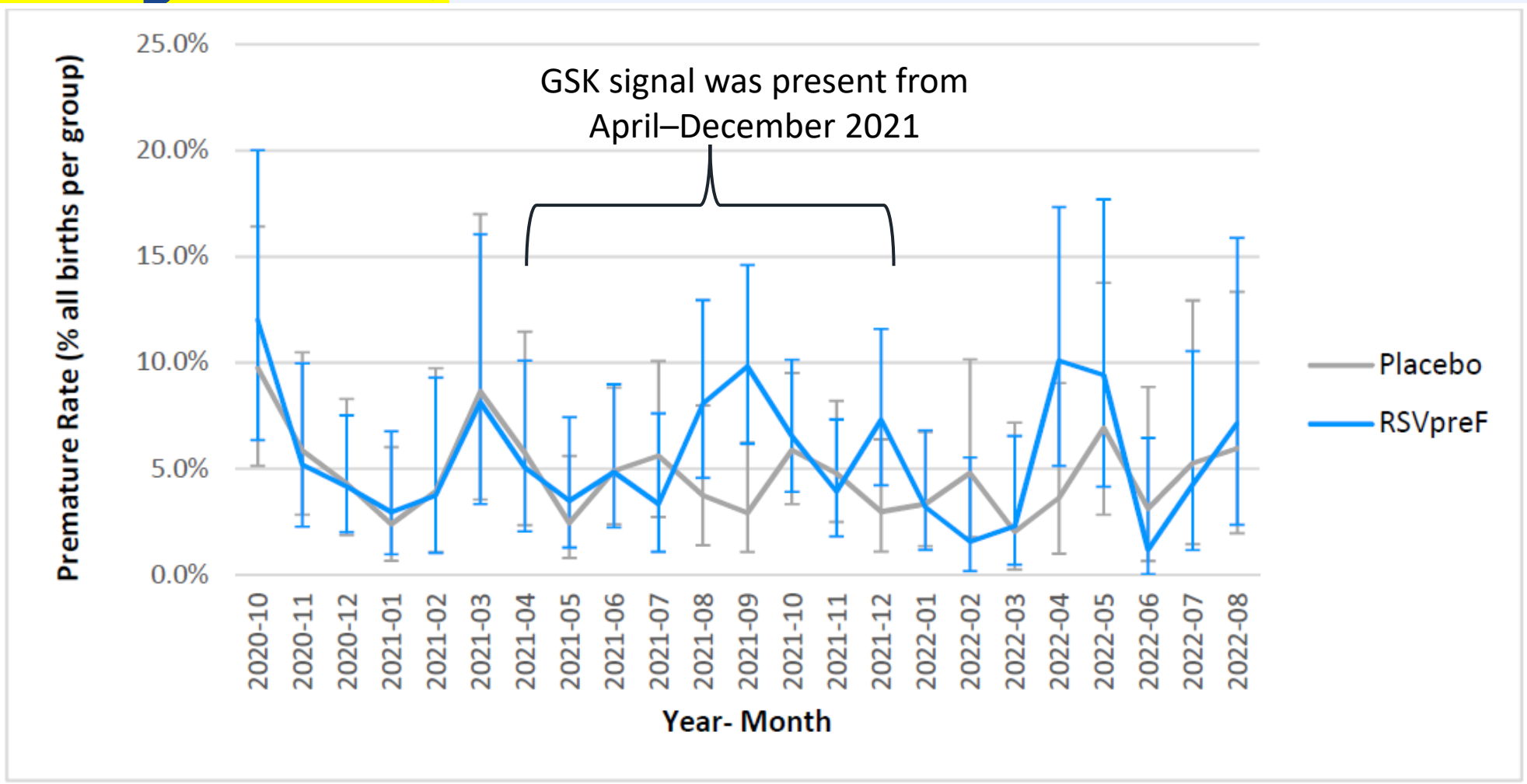
	Trial dosing interval (24–36 weeks gestation) [1,2]				Approved dosing interval (32–36 weeks gestation) [3]			
	RSVpreF vaccine group N=3,568		Placebo group N=3,558		RSVpreF vaccine group N=1,628		Placebo group N=1,604	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Low birth weight (≤2500 g)	181	**5.1%** (4.4%, 5.8%)	155	**4.4%** (3.7%, 5.1%)	67	**4.1%** (3.2%, 5.2%)	54	**3.4%** (2.5%, 4.4%)
Neonatal jaundice	257	**7.2%** (6.4%, 8.1%)	240	**6.7%** (5.9%, 7.6%)	102	**6.3%** (5.1%, 7.6%)	107	**6.7%** (5.5, 8.0%)

1. 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)
2. Package Insert - ABRYSVO (STN 125768) (fda.gov)
3. Pfizer response to ACIP, unpublished data, August 2023

In June, ACIP requested additional data regarding the Pfizer maternal RSV vaccine

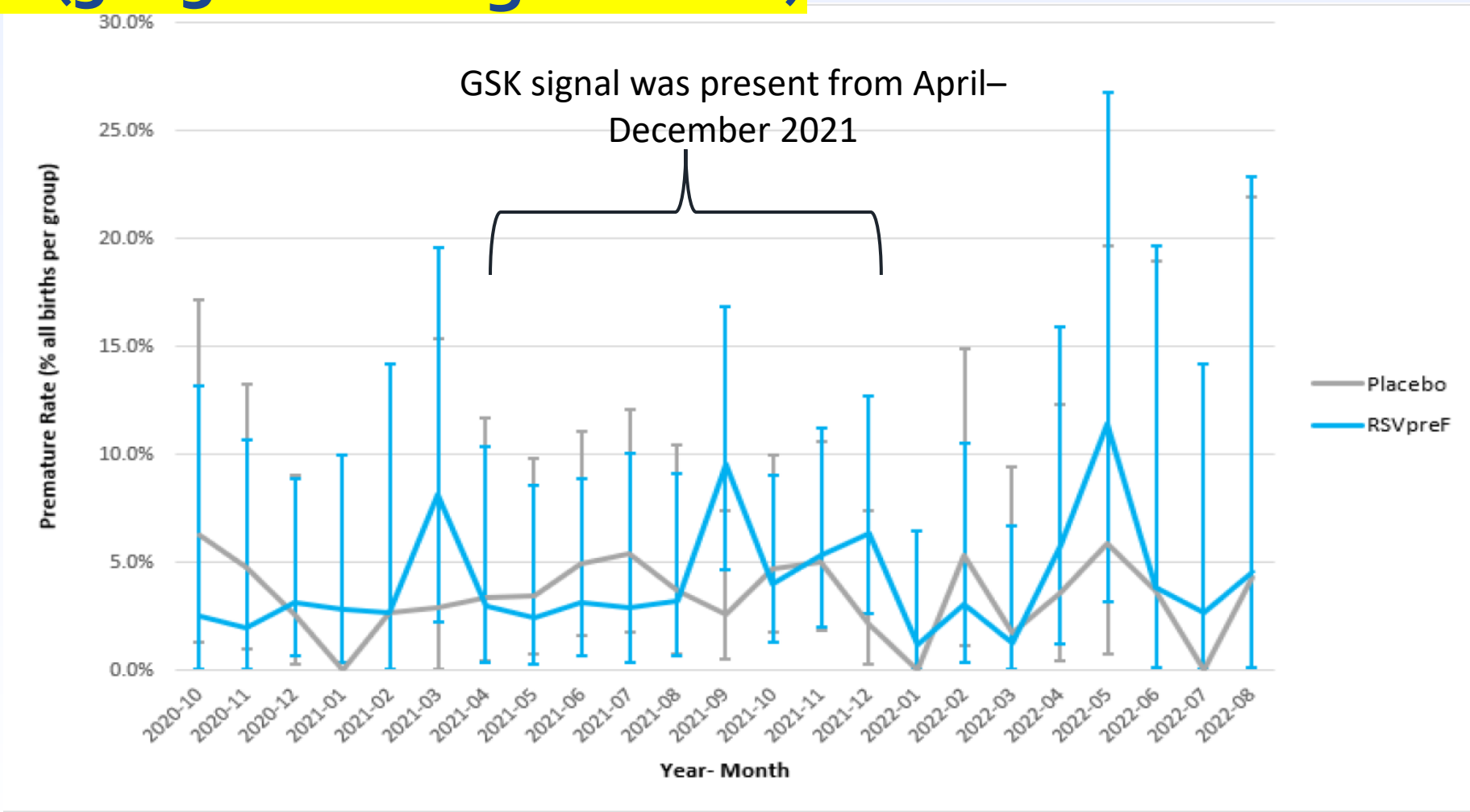
- Rate of preterm birth by calendar month of birth
- Birth by week of gestational age
- Percent of births that were preterm by country
- Adverse pregnancy outcomes

Preterm birth rate for vaccine and placebo recipients by calendar time—Pfizer Phase 3 trial, trial dosing interval (24–36 weeks gestation)



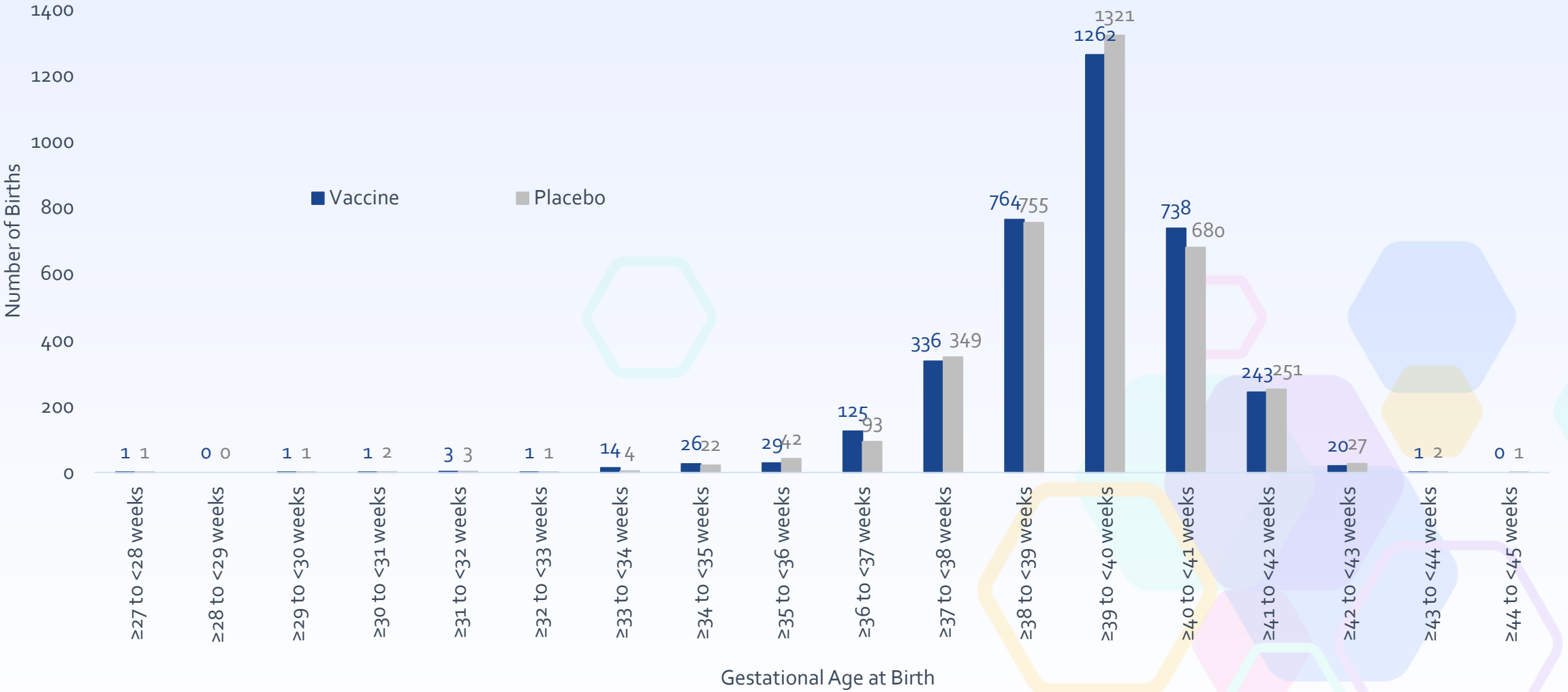
Data source: Pfizer response to ACIP, unpublished data, July 2023

Preterm birth rate for vaccine and placebo recipients by calendar time—Pfizer Phase 3 trial, approved dosing interval (32–36 weeks gestation)



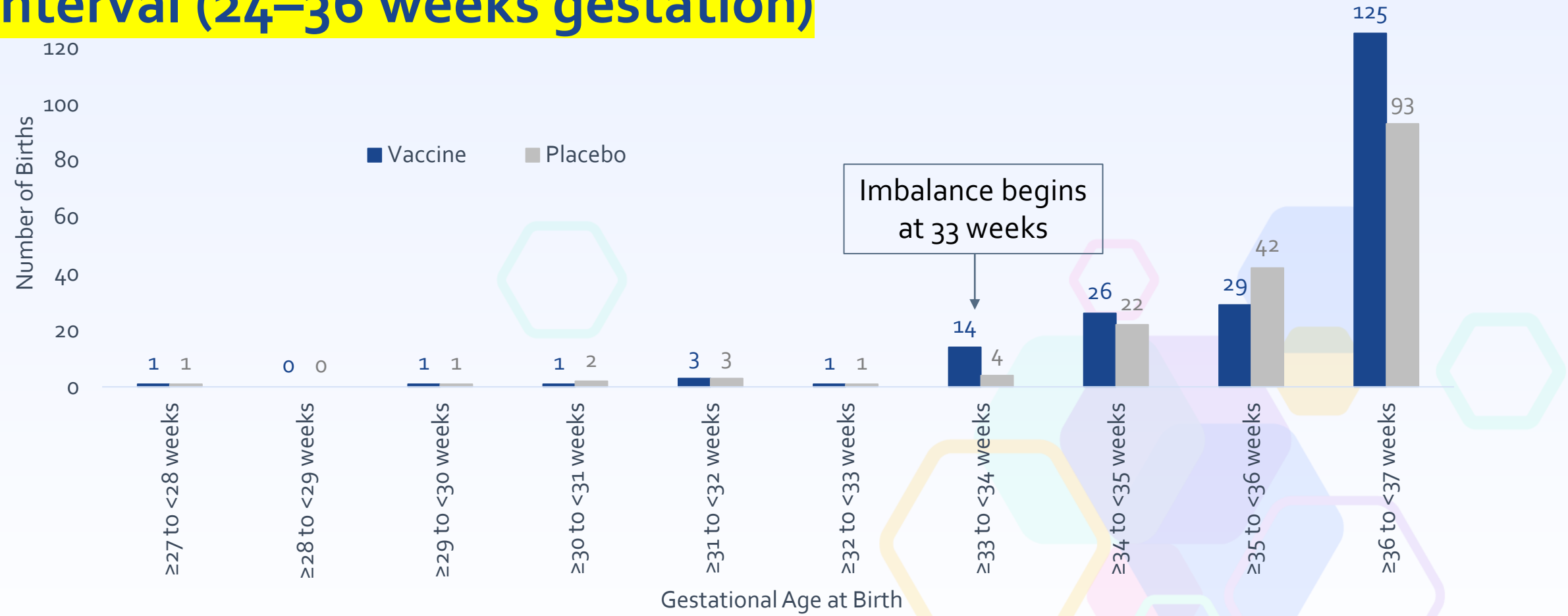
Data source: Pfizer response to ACIP, unpublished data, September 2023

Number of births by gestational age: Pfizer phase 3 trial, trial dosing interval (24–36 weeks gestation)



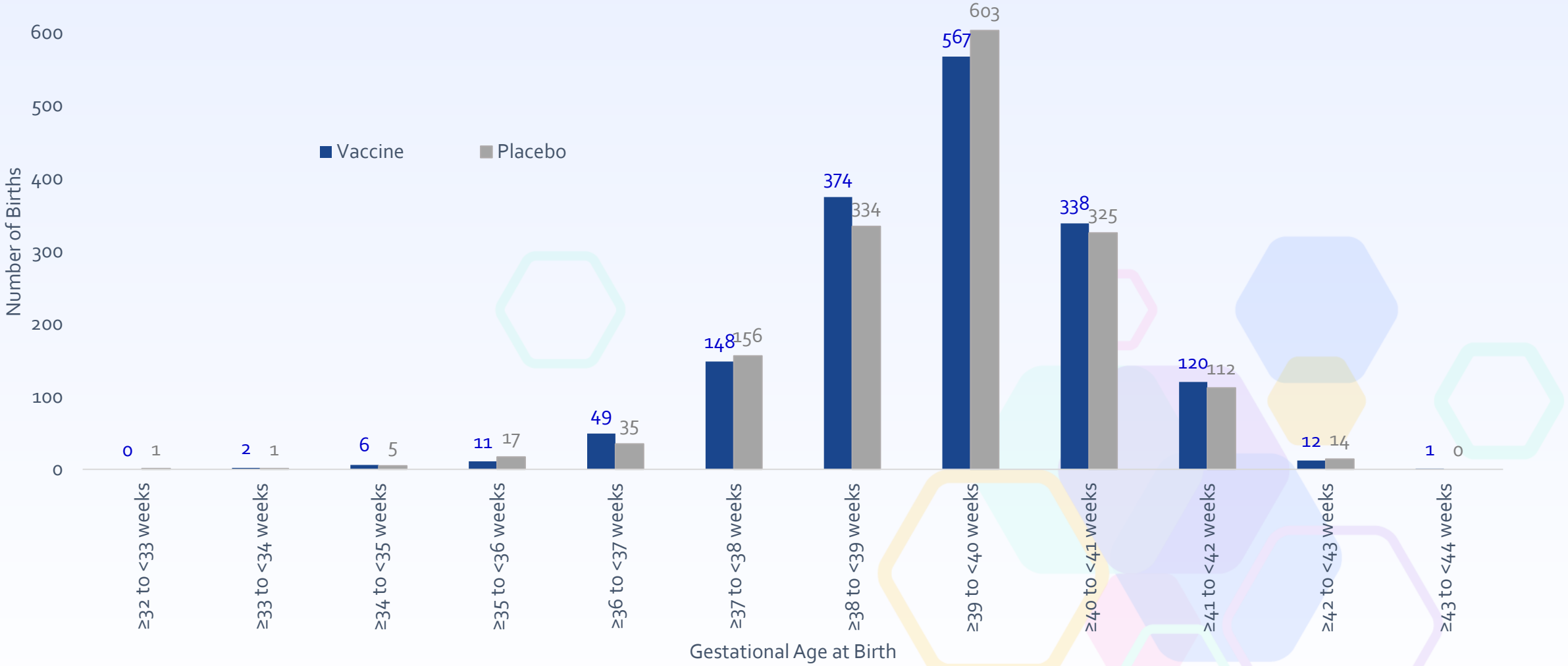
Preterm birth: <37 weeks gestation
Data source: Pfizer response to ACIP, unpublished data, July 2023

Number of births by gestational age, preterm births (<37 weeks gestation) only: Pfizer phase 3 trial, trial dosing interval (24–36 weeks gestation)



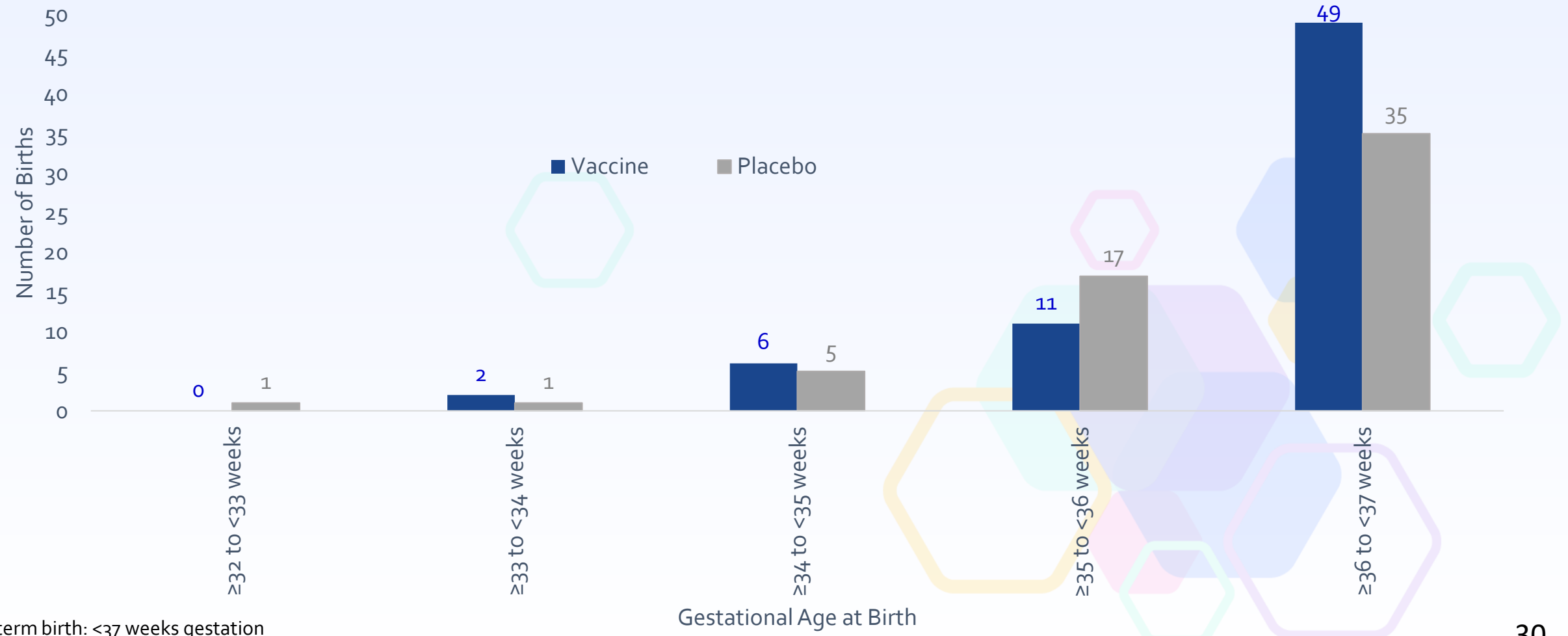
Preterm birth: <37 weeks gestation
Data source: Pfizer response to ACIP, unpublished data, July 2023

Number of births by gestational age: Pfizer phase 3 trial, approved dosing interval (32–36 weeks gestation)



Preterm birth: <37 weeks gestation
Data source: Pfizer unpublished data, August 2023

Number of births by gestational age, preterm births (<37 weeks gestation) only: Pfizer Phase 3 trial, approved dosing interval (32–36 weeks gestation)



Preterm birth: <37 weeks gestation
Data source: Pfizer unpublished data, August 2023

Number births and percent preterm by country–Pfizer phase 3 trial

	Trial dosing interval (24–36 weeks gestation)				Approved dosing interval (32–36 weeks gestation)			
	RSVpreF recipients N=3568		Placebo recipients N=3558		RSVpreF recipients N=1628		Placebo recipients N=1604	
Country	No. births	% preterm	No. births	% preterm	No. births	% preterm	No. births	% preterm
Argentina	423	6.4%	416	4.1%	230	4.8%	230	4.3%
Australia	11	0.0%	13	7.7%	8	0.0%	8	12.5%
Brazil	35	8.6%	37	2.7%	22	9.1%	23	4.3%
Canada	27	0.0%	28	3.6%	20	0.0%	27	3.7%
Chile	86	8.1%	85	7.1%	47	6.4%	50	2.0%
Denmark	30	3.3%	31	0.0%	21	4.8%	17	0.0%
Finland	75	2.7%	73	1.4%	44	0.0%	40	2.5%
Gambia	78	2.6%	79	2.5%	32	3.1%	24	0.0%
Japan	218	3.2%	216	6.0%	111	2.7%	94	2.1%
Korea	7	0.0%	4	25.0%	6	0.0%	1	100.0%
Mexico	37	8.1%	37	5.4%	13	7.7%	13	0.0%
Netherlands	97	3.1%	95	3.2%	43	2.3%	44	0.0%
New Zealand	49	4.1%	47	6.4%	29	3.4%	28	3.6%
Philippines	32	3.1%	34	5.9%	0	0.0%	1	0.0%
South Africa	469	8.3%	471	4.0%	150	6.7%	127	2.4%
Spain	117	3.4%	123	2.4%	73	2.7%	88	3.4%
Taiwan	123	4.9%	125	5.6%	58	5.2%	57	3.5%
United States	1654	5.7%	1644	5.3%	721	4.0%	732	4.4%

Data source: Pfizer response to ACIP, unpublished data, July and August 2023. Trial included 480 sites across 18 countries. Number of births is the total number of births regardless of gestational age. Blue indicates higher percent of preterm birth among RSVpreF vs. placebo in trial dosing interval, red in approved dosing interval, and purple in both dosing intervals. Black indicates either balanced preterm birth rates or a higher percent of preterm births among placebo vs RSVpreF recipients. Caution should be used in interpreting rates based on small numbers; some differ by very small counts.

Number births and percent preterm by country–Pfizer phase 3 trial

	Trial dosing interval (24–36 weeks gestation)				Approved dosing interval (32–36 weeks gestation)			
	RSVpreF recipients N=3568		Placebo recipients N=3558		RSVpreF recipients N=1628		Placebo recipients N=1604	
Country	No. births	% preterm	No. births	% preterm	No. births	% preterm	No. births	% preterm
Argentina	423	6.4%	416	4.1%	230	4.8%	230	4.3%
Australia	11	0.0%	13	7.7%	8	0.0%	8	12.5%
Brazil	35	8.6%	37	2.7%	22	9.1%	23	4.3%
Canada	27	0.0%	28	3.6%	20	0.0%	27	3.7%
Chile	86	8.1%	85	7.1%	47	6.4%	50	2.0%
Denmark	30	3.3%	31	0.0%	21	4.8%	17	0.0%
Finland	75	2.7%	73	1.4%	44	0.0%	40	2.5%
Gambia	78	2.6%	79	2.5%	32	3.1%	24	0.0%
Japan	218	3.2%	216	6.0%	111	2.7%	94	2.1%
Korea	7	0.0%	4	25.0%	6	0.0%	1	100.0%
Mexico	37	8.1%	37	5.4%	13	7.7%	13	0.0%
Netherlands	97	3.1%	95	3.2%	43	2.3%	44	0.0%
New Zealand	49	4.1%	47	6.4%	29	3.4%	28	3.6%
Philippines	32	3.1%	34	5.9%	0	0.0%	1	0.0%
South Africa	469	8.3%	471	4.0%	150	6.7%	127	2.4%
Spain	117	3.4%	123	2.4%	73	2.7%	88	3.4%
Taiwan	123	4.9%	125	5.6%	58	5.2%	57	3.5%
United States	1654	5.7%	1644	5.3%	721	4.0%	732	4.4%

Data source: Pfizer response to ACIP, unpublished data, July and August 2023. Trial included 480 sites across 18 countries. Number of births is the total number of births regardless of gestational age. Blue indicates higher percent of preterm birth among RSVpreF vs. placebo in trial dosing interval, red in approved dosing interval, and purple in both dosing intervals. Black indicates either balanced preterm birth rates or a higher percent of preterm births among placebo vs RSVpreF recipients. Caution should be used in interpreting rates based on small numbers; some differ by very small counts.

Select pregnancy-related serious adverse events at any time following vaccination[1,2]: Pfizer phase 3 trial, trial dosing interval (24–36 weeks gestation)

	RSVpreF Vaccine N= 3,682		Placebo N= 3,675	
Serious Adverse Reaction	**n (%)**	**95% CI**	**n (%)**	**95% CI**
All Maternal Serious Adverse Events (SAEs)	**598 (16.2)**	**(15.1, 17.5)**	**558 (15.2)**	**(14.0, 16.4)**
Pre-eclampsia	68 (1.8)	(1.4, 2.3)	53 (1.4)	(1.1, 1.9)
Gestational hypertension	41 (1.1)	(0.8, 1.5)	38 (1.0)	(0.7, 1.4)
Premature rupture of membranes	15 (0.4)	(0.2, 0.7)	16 (0.4)	(0.2, 0.7)
Preterm premature rupture of membranes	15 (0.4)	(0.2, 0.7)	10 (0.3)	(0.1, 0.5)
Hypertension	13 (0.4)	(0.2, 0.6)	6 (0.2)	(0.1, 0.4)
Maternal death[3]	1 (<0.1)	(0.0, 0.2)	0	(0.0, 0.1)
Fetal death[4]	10 (0.3)	(0.1, 0.5)	8 (0.2)	(0.1, 0.4)

1 Table 3 ABRYSVO package insert Package Insert - ABRYSVO (STN 125768) (fda.gov)

2 Includes all SAEs from vaccination to 6 months post-delivery (up to approximately 10 months, depending on the gestational age at the time of vaccination). In the phase 3 RCT, eclampsia occurred in 5 participants (3 in the RSVpreF group and 2 in the placebo group) and HELLP syndrome occurred in 5 participants (2 in the RSVpreF group and 3 in the placebo group).

3 There was one maternal death in the vaccine group due to postpartum hemorrhage that was not likely to be associated with vaccination.

4 A total of 18 intrauterine deaths were reported for the index pregnancy: 10 intrauterine deaths in the vaccine group (0.3%) and 8 intrauterine deaths in the placebo group (0.2%). The intrauterine deaths represented various clinical conditions and presentations resulting in fetal demise without clear evidence of a common pathophysiology.

Other considerations: Inflammatory neurologic events and Pfizer RSVpreF Vaccine

- Same Pfizer RSV vaccine, formulation and dose approved for use in adults ages 60 years and older
- Within the trials for this product among adults ages 60 years and older, a *potential* safety signal of inflammatory neurologic events was identified
- **A total of 3 cases** of interest were recorded among 20,255 investigational vaccine recipients aged 60 years and older. No cases were observed among placebo recipients.
  - 1 case of Guillain-Barré Syndrome (GBS)
  - 1 case of Miller Fisher syndrome (a GBS variant)
  - 1 case of undifferentiated motor-sensory axonal polyneuropathy (with worsening of preexisting symptoms)

Melgar et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)

Other considerations: Inflammatory neurologic events and Pfizer RSVpreF Vaccine (cont.)

- No Guillain-Barré syndrome (GBS) or other demyelinating events were reported in the phase 2b or 3 trials among pregnant people[1]
- Background rate of GBS in pregnant people is much lower than among older adults[2,3]
  - Incidence rate of GBS in pregnant people in the Vaccine Safety Datalink during 2004–2015: 2.8 (95% CI 0.5–9.3) per million person-years (based on 2 cases)[2]

1. Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA
2. Myers TR, McCarthy NL, Panagiotakopoulos L, Omer SB. Estimation of the Incidence of Guillain-Barré Syndrome During Pregnancy in the United States. Open Forum Infect Dis. 2019 Mar 15;6(3):ofz071. doi: 10.1093/ofid/ofz071.
3. Sejvar JJ, Baughman AL, Wise M, Morgan O. Population Incidence of Guillain-Barré Syndrome: A Systematic Review and Meta-Analysis. Neuroepidemiology 2011;36:123–133

Summary of Benefits and Harms

- Efficacious vaccine that can prevent RSV lower respiratory tract infection in young infants
- No consensus among Work Group regarding clinical importance of preterm birth imbalance observed in clinical trials

Work Group members found the following points concerning regarding preterm birth

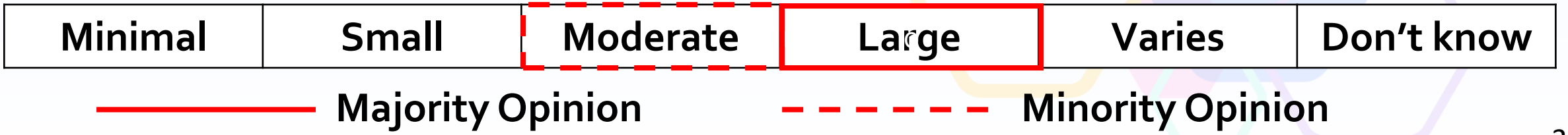
- Though not statistically significant, imbalance in preterm births was seen in the full trial population
- Trial powered for efficacy outcomes and not designed or powered to detect 20% increase in preterm birth
- There may have been less precise dating of gestational age in some sites and countries in the trial, but there is no reason this should bias towards a preterm birth imbalance among vaccinated compared to placebo participants
- Preterm birth signal in the GSK maternal RSV vaccine trial (also a stabilized prefusion F protein vaccine) adds to concern

Work Group members found the following data reassuring regarding preterm birth imbalance

- When using the full trial dosing interval (24–36 weeks gestation), most preterm births (60%) were >30 days after vaccination, and no known biologic mechanism for vaccines to cause preterm birth, particularly >30 days after vaccination
- When assessed among those vaccinated during the approved interval (32–36 weeks gestation), data on preterm birth were reassuring to the Work Group
  - Imbalance in preterm birth was still present but lessened
  - Most infants born preterm in the vaccine group (72%, 49/68) were born at 36 weeks
  - In the United States (largest contributing country in the trial), imbalance in preterm births reversed:
    - Trial dosing interval: 5.7% in vaccine vs. 5.3% in placebo recipients
    - Approved dosing interval: 4.0% in vaccine vs. 4.4% in placebo recipients
- Majority of the Work Group felt the approved dosing interval (32–36 weeks gestation) reduces the potential risk of preterm birth and the potential for complications from preterm birth, which is their major safety concern

Benefits and Harms - Pfizer maternal RSVpreF vaccine, given as a single dose at 32–36 weeks gestation

- How substantial are the desirable anticipated effects?
  - How substantial are the anticipated effects for:
    - Medically attended RSV-associated lower respiratory infection in infants
    - Hospitalization for RSV-associated lower respiratory tract infection in infants
    - ICU admission from RSV hospitalization in infants
    - Mechanical ventilation from RSV hospitalization in infants
    - RSV-associated death in infants
    - All-cause hospitalization for lower respiratory tract infection in infants
    - All-cause medically attended lower respiratory tract infection in infants



Benefits and Harms - Pfizer maternal RSVpreF vaccine, given as a single dose at 32–36 weeks gestation

- How substantial are the undesirable anticipated effects?
  - How substantial are the anticipated effects for:
    - Serious adverse events in pregnant people
    - Reactogenicity (3+ or higher) in pregnant people
    - Serious adverse events in infants
    - Preterm birth

Minimal	Small	Moderate	Large	Varies	Don't know

Majority Opinion

Benefits and Harms - Pfizer maternal RSVpreF vaccine, given as a single dose at 32–36 weeks gestation

- Do the desirable effects outweigh the undesirable effects?
  - What is the balance between the desirable effects relative to the undesirable effects?

Favors intervention (Pfizer Maternal RSVpreF Vaccine)
Favors comparison (No intervention)
Favors both
Favors neither
Unclear

Majority Opinion

EtR Domain: Values

Criterion 1: Does the target population feel that the desirable effects are large relative to undesirable effects?

Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

Summary of values domain

- Values survey of pregnant and recently pregnant people conducted from December 21, 2022–January 2, 2023 by University of Iowa, RAND, and CDC[1]
  - 68% of respondents had knowledge of RSV prior to taking survey
  - 61% of respondents said they 'definitely' or 'probably' would get an RSV vaccine while pregnant
  - Among those who did not respond that they "definitely would" get an RSV vaccine while pregnant, **safety concerns, lack of RSV knowledge, and concerns about vaccination causing or intensifying RSV infection** were the top reasons for not wanting an RSV vaccine during pregnancy

- In the US, coverage for recommended vaccines among pregnant people has decreased during the pandemic and varies by race and ethnicity[2]
  - Tdap vaccination coverage was 53.5% in 2020–21 season and 45.8% in 2021–22 season
  - Rates of Tdap coverage were higher in White, non-Hispanic women than among Black, non-Hispanic women during the 2020–21 and 2021–22 seasons

1 CDC and University of Iowa/RAND survey, unpublished

2 Flu, Tdap, and COVID-19 Vaccination Coverage Among Pregnant Women – United States, April 2022 | FluVaxView | Seasonal Influenza (Flu) | CDC

Values

- Criterion 1: Do pregnant people feel that the desirable effects are large relative to undesirable effects?

No	Probably No	Probably Yes	Yes	Varies	Don't know

Majority Opinion

Values

- Criterion 2: Is there important uncertainty about, or variability in, how much pregnant people value the main outcomes?

Important uncertainty or variability
Probably important uncertainty or variability
Probably not important uncertainty or variability
No important uncertainty or variability
No known undesirable outcomes

Most common answers

EtR Domain: Acceptability

Is the intervention acceptable to key stakeholders?

Maternity healthcare professionals survey—England, 2019

- Obstetrician and midwife support of RSV vaccine, if it was routinely recommended:
  - 47% definitely
  - 34% likely
  - 14% not sure
  - 4% unlikely
  - 0.5% very unlikely

Wilcox CR, Calvert A, Metz J, et al. Attitudes of Pregnant Women and Healthcare Professionals Toward Clinical Trials and Routine Implementation of Antenatal Vaccination Against Respiratory Syncytial Virus: A Multicenter Questionnaire Study. The Pediatric Infectious Disease Journal. 2019 Sept;38(9):944-951. DOI: 10.1097/INF.0000000000002384

Acceptability

- Is RSV prevention with Pfizer maternal RSVpreF vaccine acceptable to key stakeholders?

Majority Opinion

Minority Opinion

EtR Domain: Feasibility

Is the intervention feasible to implement?

Storage and handling

- Storage and handling requirements
  - Supplied as single 0.5 mL dose, or as a 5-pack or 10-pack of single-dose kits
  - Reconstitution required: single dose vial of lyophilized powder, reconstitution supplies included in kit
  - Product should be refrigerated (2–8°C) in original container, protected from light
  - After reconstitution, the product should be administered within 4 hours, otherwise discarded
- Most pregnant patients receive Tdap vaccine in an obstetrician's or midwife's office
  - Likely pregnant patients would also most often receive RSV vaccine at their prenatal care provider's office

Package Insert - ABRYSVO (STN 125769/26) (fda.gov)
Flu, Tdap, and COVID-19 Vaccination Coverage Among Pregnant Women – United States, April 2022 | FluVaxView | Seasonal Influenza (Flu) | CDC

Simultaneous administration of RSV vaccine with other vaccines in pregnant people

- Pregnant people may potentially be eligible to receive RSV, Tdap, COVID-19, and influenza vaccines at same visit
- Pfizer Phase 2b study in healthy non-pregnant women ages 18–49 years on simultaneous administration of Tdap and Pfizer RSVpreF found decreased immune response to pertussis components (i.e., non-inferiority criteria were not met)[1]
- Given lack of correlates of protection for pertussis, it is unclear how this might impact protection against pertussis from maternal Tdap when simultaneously administered with RSVpreF vaccine

1 Peterson et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F Vaccine When Coadministered With a Tetanus, Diphtheria, and Acellular Pertussis Vaccine. The Journal of Infectious Diseases. 2022 June 15; 225(12): 2077–2086. doi: 10.1093/infdis/jiab505

RSV vaccine and Tdap dosing timing

- Tdap recommended every pregnancy, preferably during the early part of gestational weeks 27 through 36[1]
- Tdap would be preferably given before 32 weeks (based on recommendation) and RSV vaccine would be given at or after 32 weeks
- In MarketScan data from 2018–2021, about half of captured Tdap doses were given before 32 weeks gestation[2]

1 CDC, https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html
2 MarketScan data, 2018-2021

RSVpreF vaccine is one of two available preventive products for RSV in infants

- Either RSV vaccination during pregnancy or nirsevimab administration for the infant can be used to prevent RSV lower respiratory tract infection in infants
- Work Group felt both products are not needed for most infants
- Pregnant person and prenatal care provider will need to make the decision during pregnancy regarding which RSV prevention product to use
- Many prenatal care providers may not have time to discuss options for RSV prevention with their patients
- Prenatal care providers may not feel equipped to discuss nirsevimab, as this product will be given to the infant after birth

Work Group unanimously supported use of a seasonal dosing strategy for maternal RSV vaccine

- Maximizes cost-effectiveness
- Maximizes benefits for infants
- Targets dosing to infants who will be in the first months of life during RSV season
- Another product (nirsevimab) is available for infants who are born out of season— for whom maternal vaccine protection would have waned by RSV season

Seasonal dosing for RSVpreF vaccine

- Work Group supported seasonal dosing during **September through January** in most of the continental US based on typical (pre-pandemic) RSV seasonality
  - Aligns with implementation of influenza vaccine and thus would simplify implementation for prenatal care providers
- Work Group felt that jurisdictions in which RSV seasonality differs from most of the continental US should have flexibility regarding start and stop of administration of RSVpreF vaccine in pregnant people
  - Alaska
  - Tropical climates: parts of Florida, Puerto Rico, U.S. Virgin Islands, Hawaii, Guam, and U.S.-affiliated Pacific Islands

Feasibility

- Is Pfizer Maternal RSVpreF vaccine feasible to implement among pregnant people at 32–36 weeks gestation?

No	Probably No	Probably Yes	Yes	Varies	Don't know

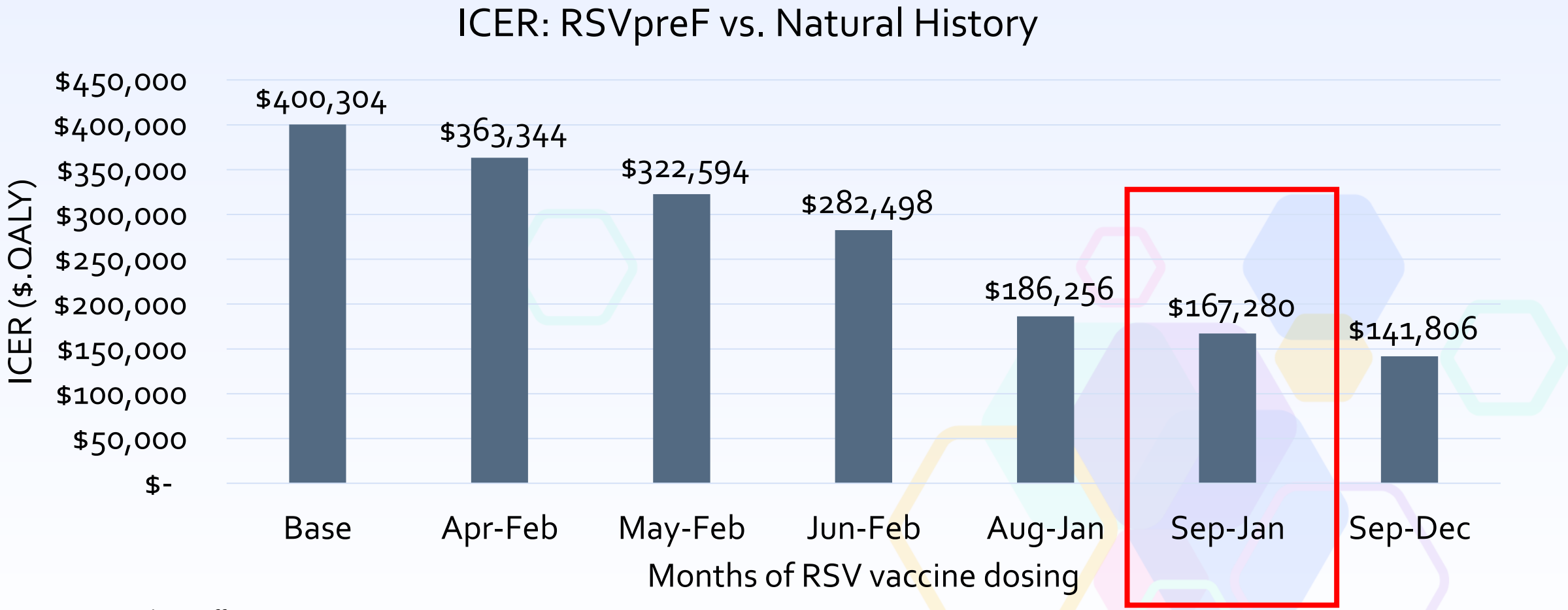
Majority Opinion

Minority Opinion

EtR Domain: Resource Use

Is the intervention a reasonable and efficient allocation of resources?

Scenarios for cost-effectiveness by months of RSVpreF vaccine dosing during the calendar year



ICER: Incremental cost-effectiveness ratio

QALY: Quality-Adjusted Life-Year

Cost-effectiveness model assumes typical RSV seasonality (based on pre-pandemic years) in most of the continental United States.

WG interpretations: Resource Use

- RSVpreF vaccine may improve RSV outcomes but will also increase costs
  - Base case incremental cost-effectiveness (ICER) ratio : $400,304/QALY
    - Year-round dosing
    - Typical RSV seasonality (based on pre-pandemic years) in most of the continental United States
  - Work group felt that this vaccine would not be cost-effective under the base case conditions
- Cost-effectiveness would improved by using a seasonal dosing strategy
  - **September through January** in most of the continental US based on typical (pre-pandemic) RSV seasonality
- Work Group unanimously supported use of a seasonal dosing strategy

QALY: Quality-Adjusted Life-Year

Cost-effectiveness model assumes typical RSV seasonality (based on pre-pandemic years) in most of the continental United States.

Resource Use

- Is Pfizer Maternal RSVpreF vaccine use among pregnant people at 32–36 weeks gestation a reasonable and efficient allocation of resources?
- Work Group responses were based on seasonal dosing for RSVpreF vaccine (i.e., September-January in most of the continental United States)

No	Probably No	Probably Yes	Yes	Varies	Don't know

Majority Opinion

Minority Opinion

EtR Domain: Equity

What would be the impact of the intervention on health equity?

Equity summary: Incidence of RSV disease by race and ethnicity in infants and children

- National studies of death certificates found higher rates of RSV-associated deaths among non-Hispanic Black children compared with non-Hispanic White infants and children aged 1–4 years[1]
- ICU admission rates for RSV among Non-Hispanic Black infants <6 months old were 1.2–1.6x higher than among Non-Hispanic White infants[2]
- RSV hospitalization rates 4–10x higher among Alaska Native and American Indian children ages <24 months than the rate in the general population[3]
  - This study was limited to specific populations and might not be broadly representative of risk in all Alaska Native and American Indian children

1. Hansen et al. The Use of Death Certificate Data to Characterize Mortality Associated With Respiratory Syncytial Virus, Unspecified Bronchiolitis, and Influenza in the United States, 1999-2018 J Infect Dis. 2022 Aug 15;226(Supplement 2): S255–S266.

2 Unpublished data from RSV-NET, CDC.

3 Atwell et al. RSV Among American Indian and Alaska Native Children: 2019 to 2020 Pediatrics. 2023 Aug 1;152(2):e2022060435

Equity summary: Medicaid coverage for pregnant people and vaccines during pregnancy

- By federal law, all states provide Medicaid coverage for pregnancy-related services to pregnant women with incomes up to 138% of the federal poverty level[1]
- In 2021, 41.0% of mothers had Medicaid at the time of birth[2]
- If recommended, ACIP will vote on a Vaccines for Children resolution for the Pfizer RSV vaccine for pregnant people <19 years of age
- After October 1, 2023, when the Inflation Reduction Act provisions become effective, state Medicaid agencies will be required to cover vaccines and their administration without cost-sharing for nearly all full-benefit adult beneficiaries covered under traditional Medicaid, if the CDC/ACIP recommendations apply

1 Medicaid Coverage for Women | KFF

2 2023 Medicaid and CHIP Beneficiary Profile: Enrollment, Expenditures, Characteristics, Health Status, and Experience

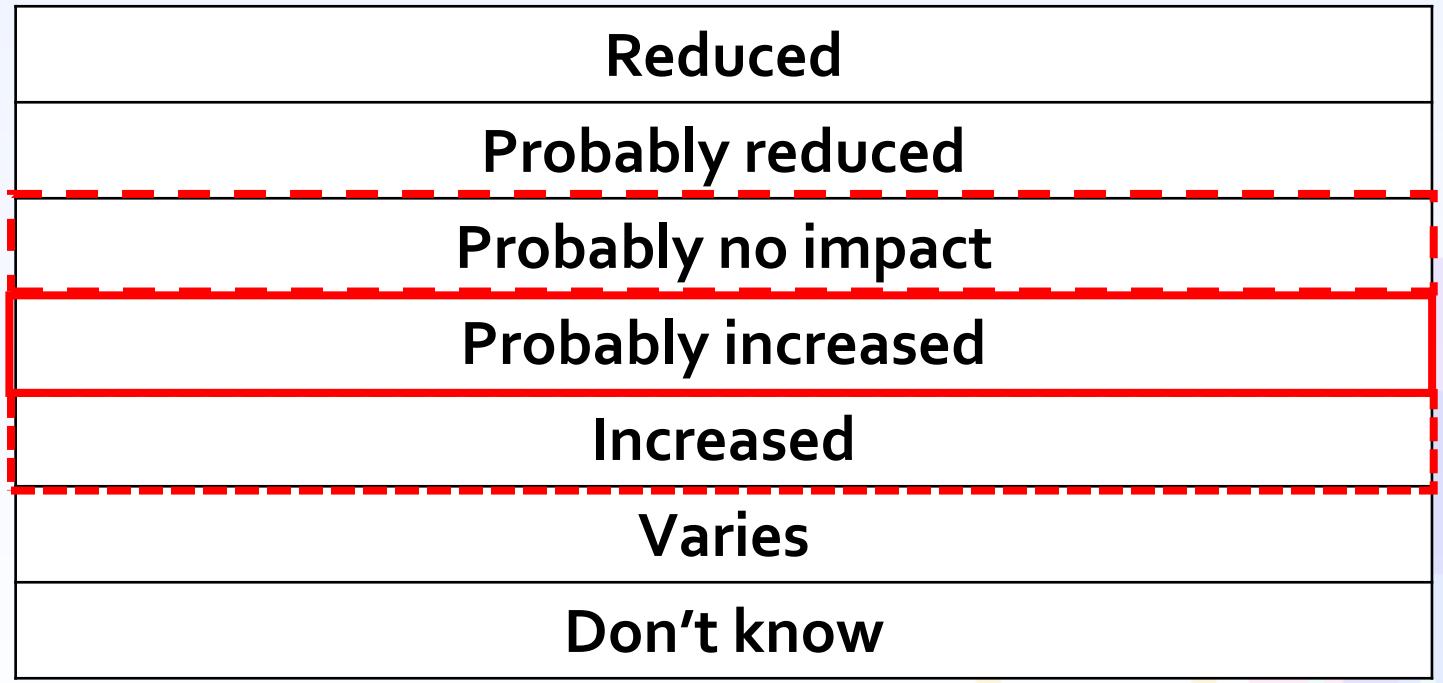
Equity summary: Other insurance coverage for vaccines during pregnancy

- Under the Affordable Care Act and its implementing regulations, ACIP recommendations that have been adopted by CDC "with respect to the individual involved" and are "listed on the Immunization Schedules of the Centers for Disease Control and Prevention" generally are required to be covered by group health plans and health insurance issuers offering group or individual health insurance coverage without imposing any cost-sharing requirements (such as a copayment, coinsurance, or deductible)

ACIP Shared Clinical Decision-Making Recommendations | CDC

Equity

- What would be the impact of Pfizer Maternal RSVpreF vaccine on health equity? Answers ranged, no majority



Summary

Evidence to Recommendations (EtR) framework

EtR Domain	Question(s)	Work Group Judgements
Public Health Problem	Is the problem of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Large
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Probably yes
	Is there important uncertainty about, or variability in, how much people value the main outcomes?	Probably not important uncertainty or variability/ Probably important uncertainty or variability
Acceptability	Is the intervention acceptable to key stakeholders?	Yes
Feasibility	Is the intervention feasible to implement?	Yes
Resource Use	Is the intervention a reasonable and efficient allocation of resources?	Probably yes, with seasonal dosing
Equity	What would be the impact of the intervention on health equity?	Ranged from probably no impact to increased

Evidence to Recommendations framework

Summary: Work Group interpretations

Balance of Consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

Majority Opinion **Minority Opinion**

Evidence to Recommendations framework
Summary: Work Group interpretations

Type of Recommendation	We do not recommend the intervention	We recommend the intervention for individuals based on shared clinical decision-making	We recommend the intervention

Majority Opinion — — — — — **Minority Opinion**

Work Group considerations: Benefit and harms

- Majority of Work Group was supportive of intervention with Pfizer maternal RSVpreF vaccine for pregnant people with dosing during the approved dosing interval (32–36 weeks gestation)
  - Found the data on preterm birth when assessed among those vaccinated during the approved dosing interval (32–36 weeks gestation) to be reassuring
  - Felt the approved dosing interval (32–36 weeks gestation) reduces the potential risk of preterm birth and the potential for complications from preterm birth, which is their major safety concern
- All Work Group members endorsed the importance of post-introduction vaccine safety monitoring

Work Group considerations: Seasonal dosing

- Unanimously supported use of a seasonal dosing strategy which would maximize benefits and cost-effectiveness
- Supported that RSVpreF vaccine dosing should occur during September–January in most of the continental United States
- Felt that jurisdictions in which RSV seasonality differs from most of the continental US should have flexibility regarding start and stop of administration of RSVpreF vaccine in pregnant people

Work Group considerations: RSVpreF vaccine is one of two available preventive products for RSV in infants

- Pregnant people should have options for RSV prevention
  - Nirsevimab may not be readily available in all settings
  - Pregnant people and their providers may have preferences regarding these two products
- Pregnant people should be made aware that they can either receive RSVpreF vaccine during pregnancy or nirsevimab can be given to the infant, but most infants will not need both
- Pregnant people should be informed regarding the risks and benefits of both products before making a decision

Work Group considerations: Full vs shared clinical decision making (SCDM) recommendation for Pfizer maternal RSVpreF vaccine during the approved dosing interval (32–36 weeks gestation)

- Most work group members support a full recommendation
  - Approved dosing interval (32–36 weeks) reduces the potential risk of and complications from preterm birth
  - Importance of clear vaccine recommendations
  - Providers who will help pregnant people decide which product to receive generally have less familiarity with the data than ACIP
  - SCDM can be confusing to providers, hard to implement for providers, can lead to lower vaccine confidence and uptake of vaccination, and could potentially influence support for the vaccine in lower and middle income countries
- Minority supported a recommendation with SCDM
  - Without SCDM, a full recommendation could result in some providers recommending RSVpreF vaccine during pregnancy without discussing with pregnant patients that nirsevimab is an option
  - Potential risk for preterm birth (and neuroinflammatory events)
  - Same vaccine is recommended under SCDM for adults ages 60 years and older
- ACIP generally makes SCDM recommendations when individuals may benefit from vaccination, but broad vaccination of people in that group is unlikely to have population-level impacts

Work Group considerations: Additional vaccine doses in subsequent pregnancies

- Currently there are no data available on:
  - Efficacy of the first lifetime dose during subsequent pregnancies
  - Safety of additional doses given in subsequent pregnancies

- Work Group felt that it was too early to decide whether additional doses should be given in subsequent pregnancies given the lack of data

- Additional data are needed to inform whether additional doses in subsequent pregnancies would be indicated, and recommendations can be updated in the future

Proposed voting language

- Maternal RSV vaccine is recommended for pregnant people during 32 through 36 weeks gestation, using seasonal administration, to prevent RSV lower respiratory tract infection in infants

Acknowledgements

Jefferson Jones

Lauren Roper

Meredith McMorrow

Mila Prill

Monica Godfrey

Michael Melgar

Amadea Britton

Amanda Payne

Megan Wallace

Danielle Moulia

Morgan Najdowski

David Hutton

Jamison Pike

Andrew Leidner

Ismael Ortega-Sanchez

Karen Broder

Naomi Tepper

Heidi Moline

Amber Winn

Monica Patton

Jenny Milucky

Fiona Havers

Rebecca Morgan

Doug Campos-Outcalt

Patricia Wodi

Sascha Ellington

Megan Lindley

Fangjun Zhou

Sarah Meyer

David Hutton

Barbara Mahon

Aron Hall

Coronavirus and Other Respiratory Viruses Division

Immunization Services Division

Note

- We acknowledge that not every person who can become pregnant identifies as a woman. Although we try to use gender-neutral language as often as possible, much of the research available currently refers only to “women” when discussing the ability to become pregnant. When citing research, we refer to the language used in the study. In these cases, “woman” refers to someone who was assigned female at birth. For clarity in terminology, “maternal” is used to identify the person who is pregnant or postpartum throughout this presentation; the authors are aware that pregnancy is not equated with the decision to parent nor do all parents who give birth identify as mothers.

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

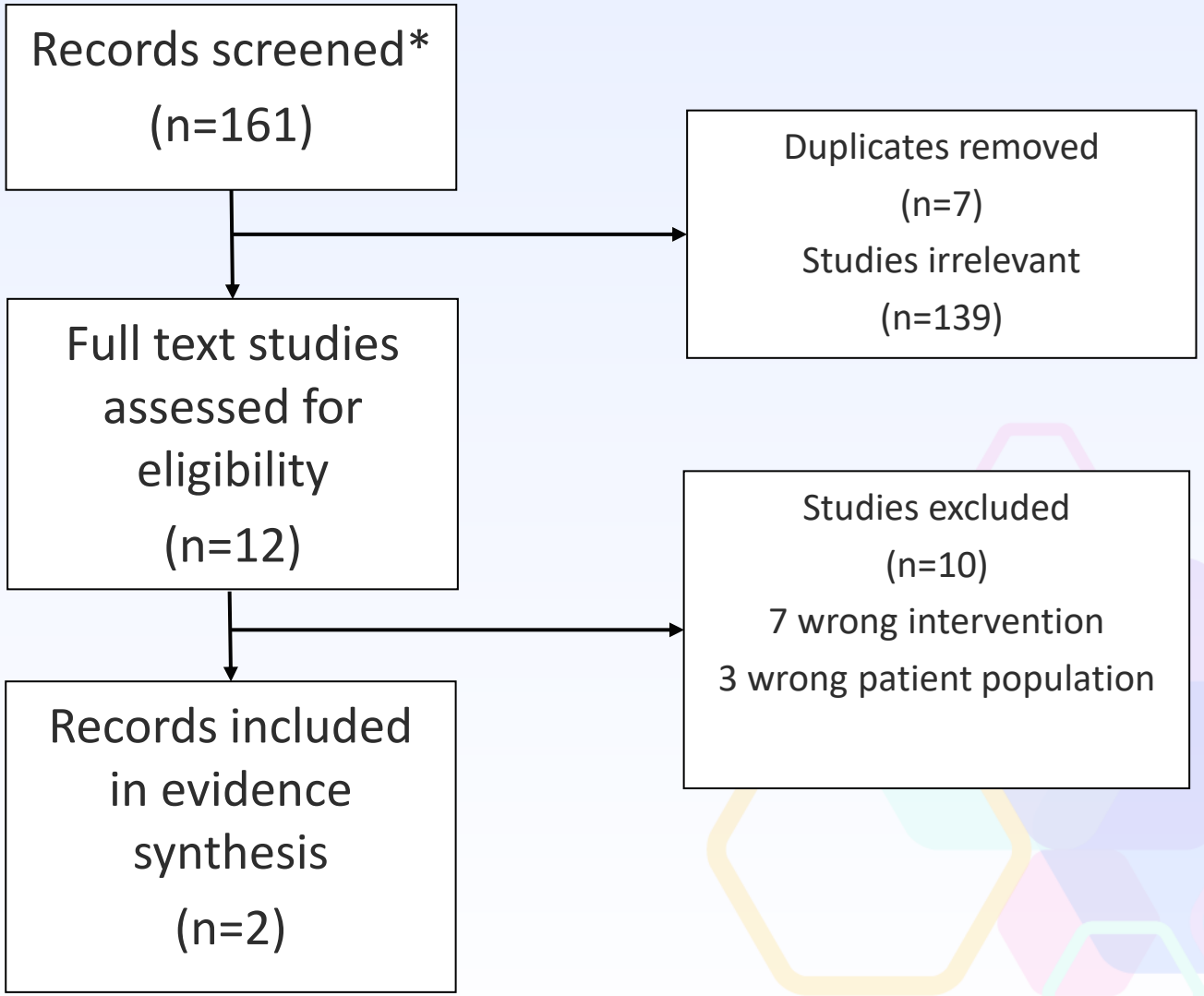
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer Maternal RSVpreF Vaccine

Update: September 6, 2023

Evidence Retrieval, conducted as of April 10, 2023



*Medline (OVID), Embase (OVID), Cochrane Library, CINAHL (EbscoHost), Scopus, clinicaltrials.gov

GRADE Evidence Type

- **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:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the effect estimate.
- **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 the effect.

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

GRADE Evidence Type

- Initial evidence type (certainty level) determined by study design
  - Initial evidence high certainty: A body of evidence from randomized controlled trials
  - Initial evidence low certainty: A body of evidence from observational studies
- The certainty of evidence may be downgraded due to risk of bias, inconsistency, indirectness, imprecision, or publication bias. For non-randomized studies, the certainty may be rated up for presence of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

Benefits

Vaccine efficacy methods

Dosing interval	Number of Participants	VE Formula	Outcomes	Reference
Phase 3 trial, Trial dosing interval (24–36 weeks)*	Vaccine: 3495 Placebo: 3480	1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases	• Medically attended RSV-associated lower respiratory tract infection in infants • Hospitalization for RSV-associated lower respiratory tract infection in infants • All-cause medically attended lower respiratory tract infection in infants	Kampmann et al. and VRBPAC briefing document
Phase 3 trial, Trial dosing interval (24–36 weeks)*	Vaccine: 3495 Placebo: 3480	1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases	• ICU admission from RSV hospitalization in infants • Mechanical ventilation from RSV hospitalization in infants • All-cause hospitalization for lower respiratory tract infection in infants	Post-hoc analysis, data provided by the manufacturer for GRADE
Phase 3 trial, Approved dosing interval (32–36 weeks)	Vaccine: 1572 Placebo: 1539	1-(hP/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group	All efficacy outcomes	Post-hoc analysis, data provided by the manufacturer

*8 participants (3 in the vaccine group and 5 in the placebo group) received injection at >36 weeks gestation and were included in the analysis

Outcome 1: Medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

- Pfizer phase 3 randomized controlled trial (RCT), MATISSE[1]
- Trial locations: Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, United States
  - 45% of participants from United States
- Study enrollment and efficacy follow-up occurred June 17, 2020, to October 2, 2022
- Data evaluated: data cut-off September 30, 2022; mean follow-up in infant participants 11.97 months after birth (range: 0.0, 24.3)
- Infant evaluable efficacy set: 3,495 in vaccine arm; 3,480 in placebo arm
- Exclusion criteria of certain conditions may not represent all pregnant people and their infants in the United States
- Placebo was not a saline placebo, but a lyophile match to the vaccine consisting of excipients matched to those used in the RSVpreF vaccine formulation, minus the active ingredients

[1] Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023 Apr 5. doi: 10.1056/NEJMoa2216480.

Outcome 1: Medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

- Medically attended visit (inclusive of inpatient and outpatient encounters) and ≥1:
  - Fast breathing: respiratory rate ≥60 bpm (<2 months of age [60 days]) or ≥50 bpm (≥2 to 12 months of age)
  - SpO2 measured in room air <95%
  - Chest wall indrawing
- RSV RT-PCR–positive test result by Pfizer central laboratory or by certified laboratory with NAAT for RSV
- Confirmed by endpoint adjudication committee (EAC)

Outcome 1: Medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.5% or 97.58% CI)
0–90 days after birth[2]	24/3495	56/3480	57.3% (31.3, 73.5)	57.1% (14.7, 79.8)
0–120 days after birth	35/3495	81/3480	57.0% (36.2, 71.0)	56.8% (31.2, 73.5)
0–150 days after birth	47/3495	99/3480	52.7% (33.3, 66.5)	52.5% (28.7, 68.9)
0–180 days after birth	57/3495	117/3480	51.5% (33.7, 64.5)	51.3% (29.4, 66.8)

RR= relative risk, CI=confidence interval

[1] Vaccine efficacy was calculated as 1−(P/[1−P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness. At 90 days, 99.5% confidence intervals (CIs) were used (determined by the alpha-spending function and adjusted with the use of the Bonferroni procedure), and at later intervals, 97.58% CIs were used (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure). Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

[2] This outcome did not meet success criterion using manufacturer calculated VE (lower bound of CI was <20%)

Outcome 1: Severe medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

- Medically attended visit (inclusive of inpatient and outpatient encounters) and ≥1:
  - Fast breathing (respiratory rate ≥70 (<2 month of age [60 days]) or ≥60 (≥2 to 12 months of age)
  - SpO2 measured in room air <93%
  - High-flow nasal cannula or mechanical ventilation
  - ICU admission for >4 hours
  - Unresponsive/unconscious
- RSV RT-PCR–positive test result by Pfizer central laboratory or by certified laboratory with NAAT for RSV
- Confirmed by EAC

SpO2= Peripheral capillary oxygen saturation; RT-PCR = Real-time polymerase chain reaction; NAAT= nucleic acid amplification technology; EAC= endpoint adjudication committee

Blue text denotes differences between definitions of severe medically attended RSV-associated lower respiratory tract infection and medically attended RSV-associated lower respiratory tract infection.

Outcome 1: Severe medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.5% or 97.58% CI)
0–90 days after birth	6/3495	33/3480	81.9% (56.8, 92.4)	81.8% (40.6, 96.3)
0–120 days after birth	12/3495	46/3480	74.0% (51.1, 86.2)	73.9% (45.6, 88.8)
0–150 days after birth	16/3495	55/3480	71.0% (49.6, 83.4)	70.9% (44.5, 85.9)
0–180 days after birth	19/3495	62/3480	69.5% (49.1, 81.7)	69.4% (44.3, 84.1)

RR= relative risk, CI= confidence interval

[1] Vaccine efficacy was calculated as 1−(P/[1−P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness. At 90 days, 99.5% confidence intervals (CIs) were used (determined by the alpha-spending function and adjusted with the use of the Bonferroni procedure), and at later intervals, 97.58% CIs were used (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure).

Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

GRADE: Medically attended RSV-associated lower respiratory infection in infants (n=1 study)

- Measures of effect
  - Relative Risk: 0.487 (97.58% CI: 0.332, 0.706)
  - Absolute Risk[1]: 1,725 fewer per 100,000 (988 to 2,246 fewer); NNV: 58 (45, 101)
  - Absolute Risk[2]: 11,850 fewer per 100,000 (6,791 to 15,431 fewer); NNV: 8 (6, 15)
  - Absolute Risk[3]: 5,643 fewer per 100,000 (3,234 to 7,348 fewer); NNV: 18 (14, 31)
- Concerns in certainty assessment:
  - None
- Evidence type: High

[1] Calculated using the observed outcomes in the placebo arm during the clinical trial follow-up (3.4%)

[2] Calculated using rate from Lively 2019 JPIDS, 2004-2009 from 3 New Vaccine Surveillance Network (NVSN) sites from Nov-Apr season, included if with acute respiratory infection (ARI), not restricted to lower respiratory tract infection (LRTI).

[3] Calculated assuming 47.5% of ARI from Lively et al paper were LRTI (Rainisch 2020 Vaccine)

NNV= Number needed to vaccinate

Outcome 2: Hospitalization for RSV-associated lower respiratory tract infection in infants (n=1 study)

- Phase 3 RCT, MATISSE[1]
- A respiratory tract infection due to RSV that results in hospitalization
- Confirmed by endpoint adjudication committee (EAC)

[1] Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023 Apr 5. doi: 10.1056/NEJMoa2216480.

Outcome 2: Hospitalization for RSV-associated lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.17% CI)
0–90 days after birth	10/3495	31/3480	67.9% (34.6, 84.2)	67.7% (15.9, 89.5)
0–120 days after birth	15/3495	37/3480	59.6% (26.6, 77.8)	59.5% (8.3, 83.7)
0–150 days after birth	17/3495	39/3480	56.6% (23.4, 75.4)	56.4% (5.2, 81.5)
0–180 days after birth	19/3495	44/3480	57.0% (26.5, 74.8)	56.8% (10.1, 80.7)
0–360 days after birth[2]	38/3495	57/3480	33.6% (0.2, 55.8)	33.3% (-17.6, 62.9)

RR= relative risk, CI= confidence interval

[1] Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using the Bonferroni procedure and accounting for the primary endpoints results. As a secondary endpoint, the criterion for vaccine efficacy was a lower bound of the confidence interval >0%.

[2] This outcome did not meet success criterion using manufacturer calculated VE (lower bound of CI was <0%)

Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

GRADE: Hospitalization for RSV-associated lower respiratory tract infection in infants (n=1 study)

- Measures of effect
  - Relative risk: 0.432 (99.17% CI: 0.193, 0.899)
  - Absolute risk[1]: 718 fewer per 100,000 (128 to 1,020 fewer); NNV: 139 (98, 781)
  - Absolute risk[2]: 1,051 fewer per 100,000 (187 to 1,493 fewer); NNV: 95 (67, 535)
- Concerns in certainty assessment:
  - Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered
- Evidence type: Moderate

[1] Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up.

[2] Calculated using the rate of acute respiratory infection (ARI) hospitalizations for infants 0-5 months (2016-2020 NVSN, unpublished)

Outcome 3: ICU admission from RSV hospitalization in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (95% CI)
0–90 days after birth	2/3495	6/3480	66.8% (-64.3, 93.3)	66.7% (-86.4, 96.7)
0–150 days after birth	4/3495	6/3480	33.6% (-135, 81.3)	33.3% (-181.1, 86.2)
0–180 days after birth	4/3495	7/3480	43.1% (-94.2, 83.3)	42.9% (-124.8, 87.7)

RR= relative risk, CI= confidence interval

[1] Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

Outcome 3: ICU admission from RSV hospitalization in infants (n=1 study)

- Measures of effect
  - Relative risk: 0.571 (95% CI: 0.123, 2.248)
  - Absolute risk[1]: 86 fewer per 100,000 (from 176 fewer to 251 more)
  - Absolute risk[2]: 285 fewer per 100,000 (from 583 fewer to 830 more)
- Concerns in certainty assessment:
  - Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and fragility of the estimate
- Evidence type: Low

[1] Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up.

[2] Calculated using the rate of ICU admissions in hospitalizations from Arriola 2019 JPIDS and acute respiratory infection (ARI) hospitalizations for infants 0-5 months (2016-2020 NVSN, unpublished)

Outcome 4: Mechanical ventilation[1] from RSV hospitalization in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy[2] (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[3] (95% CI)
0–90 days after birth	0/3495	4/3480	88.9% (-105.4, 99.4)	100% (-51.5, 100)
0–150 days after birth	0/3495	4/3480	88.9% (-105.4, 99.4)	100% (-51.5, 100)
0–180 days after birth	0/3495	5/3480	90.0% (-63.6, 99.5)	100% (-9.1, 100)

RR= relative risk, CI= confidence interval

Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation)

1 Invasive or non-invasive mechanical ventilation

2 Using 0.5 offset to account for zero events in the vaccine arm

3 Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases

Outcome 4: Mechanical ventilation from RSV hospitalization in infants (n=1 study)

- Measures of effect
  - Relative risk: 0.001 (95% CI: 0.001, 1.091)
  - Absolute risk[1]: 144 fewer per 100,000 (144 fewer to 13 more)
  - Absolute risk[2]: 209 fewer per 100,000 (209 fewer to 19 more)
- Concerns in certainty assessment:
  - Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and fragility of the estimate
- Evidence type: Low

[1] Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up

[2] Calculated using the rate of mechanical ventilations in hospitalizations from Arriola 2019 JPIDS and acute respiratory infection (ARI) hospitalizations for infants 0-5 months (2016-2020 NVSN, unpublished)

Outcome 5: RSV-associated death in infants (n=2 studies)

- Phase 3 RCT, MATISSE and Phase 2b RCT (unpublished, data obtained from manufacturer)
- Phase 2b RCT[1,2]
  - Pregnant people ages 18–49 in Argentina, Chile, South Africa and United States
    - Infant safety set: 114 in vaccine arm (phase 3 formulation); 116 in placebo arm
- 1 RSV-associated death occurred in an infant in the placebo group recorded at day 120 after birth in the Phase 3 study, no RSV-associated deaths occurred in the RSVpreF group
- No RSV-associated deaths were recorded in the Phase 2b study among those who received the phase 3 formulation or placebo
- Outcome not included in GRADE

[1] Simões EAF, Center KJ, Tita ATN, et al. Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy. N Engl J Med. 2022 Apr 28. doi: 10.1056/NEJMoa2106062.

[2] https://www.clinicaltrials.gov/ct2/show/study/NCT04032093

Outcome 6: All-cause medically attended lower respiratory tract infection in infants (n=1 study)

- Phase 3 RCT, MATISSE[1]
- Infant with any medically attended-RTI visit (inpatient or outpatient) AND
  - Fast breathing (respiratory rate ≥60 bpm for <2 months of age [<60 days of age] or ≥50 bpm for ≥2 to <12 months of age) OR
  - SpO2 <95% OR
  - Chest wall indrawing

Outcome 6: All-cause medically attended lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.17% CI)
0–90 days after birth[2]	186/3495	200/3480	7.4% (-12.4, 23.7)	7.0% (-22.3, 29.3)
0–120 days after birth[2]	261/3495	278/3480	6.5% (-10, 20.5)	6.1% (-18.3, 25.5)
0–150 days after birth[2]	331/3495	349/3480	5.6% (-8.9, 18.1)	5.2% (-16.5, 22.8)
0–180 days after birth[2]	392/3495	402/3480	2.9% (-10.7, 14.8)	2.5% (-17.9, 19.4)
0–360 days after birth[2]	504/3495	531/3480	5.5% (-5.8, 15.5)	5.1% (-12.1, 19.6)

RR= relative risk, CI= confidence interval

[1] Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using the Bonferroni procedure and accounting for the primary endpoints results. As a secondary endpoint, the criterion for vaccine efficacy was a lower bound of the confidence interval >0%. Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

[2] This outcome did not meet success criterion (lower bound of CI was <0%)

GRADE: All-cause medically attended lower respiratory tract infection in infants (n=1 study)

- Measures of effect
  - Relative risk: 0.975 (99.17% CI: 0.806, 1.179)
  - Absolute risk*: 289 fewer per 100,000 (2,241 fewer to 2,068 more)
- Concerns in certainty assessment
  - Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered
- Evidence type: Moderate

*Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute risk estimates should be interpreted in this context.

Outcome 7: All-cause hospitalization for lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (95% CI)
0–90 days after birth	35/3495	55/3480	36.6% (3.4, 58.4)	36.4% (1.0, 59.6)
0–150 days after birth	47/3495	67/3480	30.2% (-1.10, 51.8)	29.9% (-3.4, 52.7)
0–180 days after birth	54/3495	76/3480	29.3% (0, 49.9)	28.9% (-2.0, 50.8)

RR= relative risk, CI= confidence interval

1 Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

Outcome 7: All-cause hospitalization for lower respiratory tract infection in infants (n=1 study)

- Measures of effect
  - Relative risk: 0.711 (95% CI: 0.492, 1.020)
  - Absolute risk*: 631 fewer per 100,000 (from 1,109 fewer to 44 more)
- Concerns in certainty assessment
  - Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered
- Evidence type: Moderate

*Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute risk estimates should be interpreted in this context.

Harms

Outcome 8: Serious adverse events in pregnant people (n=2 studies)

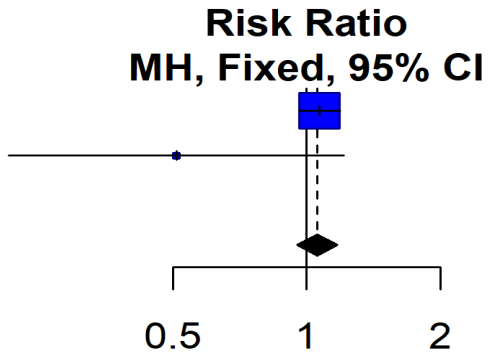
- Phase 3 RCT, MATISSE (unpublished, data obtained directly from manufacturer)
  - Maternal safety set: 3,682 participants in vaccine arm; 3,675 in placebo arm
- Phase 2b RCT (unpublished, data obtained directly from manufacturer)
  - Maternal safety set: 115 participants in vaccine arm (phase 3 formulation); 117 in placebo arm
- Follow up times for serious adverse events reported by maternal participants were from vaccination through 6 months after delivery (Phase 3) or throughout the study (Phase 2b)

Outcome 8: Serious adverse events in pregnant people (n=2 studies)

Trial	Events/Vaccine (n/N)	Events/Placebo (n/N)	Relative Risk (95% CI)
Phase 3	598/3682 (16.2%)	558/3675 (15.1%)	1.07 (0.96, 1.19)
Phase 2b	7/115 (6.1%)	14/117 (12.0%)	0.51 (0.21, 1.21)

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio MH, Fixed, 95% CI
Phase 3, 2023	598	3682	558	3675	97.6%	1.07 [0.96; 1.19]
Phase 2b, 2022	7	115	14	117	2.4%	0.51 [0.21; 1.21]
Total (95% CI)		**3797**		**3792**	**100.0%**	**1.06 [0.95; 1.17]**

Heterogeneity: $Tau^2 = 0.1762$; $Chi^2 = 2.76$, df = 1 (P = 0.10); $I^2 = 64\%$



Serious adverse events in four vaccine recipients (pain in an arm followed by bilateral lower extremity pain, premature labor, systemic lupus erythematosus, and eclampsia) and in one placebo recipient (premature placental separation) were assessed by the investigator as being related to the injection. Based on review of the event narratives and temporal association of these events to vaccination, FDA agreed with the investigator's assessments that there was a reasonable possibility that these events were related to the study intervention.

CI= confidence interval

Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA

GRADE: Serious adverse events in pregnant people (n=2 studies)

- Measures of effect
  - Relative risk: 1.06 (95% CI: 0.95, 1.17)
  - Absolute risk*: 905 more per 100,000 (754 fewer to 2,564 more)
- Concerns in certainty assessment
  - Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered
  - Serious concern for indirectness as 55% of the Phase 3 RCT and 62% of the Phase 2b RCT did not receive vaccine or placebo in the approved dosing interval (32–36 weeks gestation). In the approved dosing interval, there is less opportunity for serious adverse events, including preterm birth/delivery, compared to the trial dosing interval (24–36 weeks gestation).
- Evidence type: Low

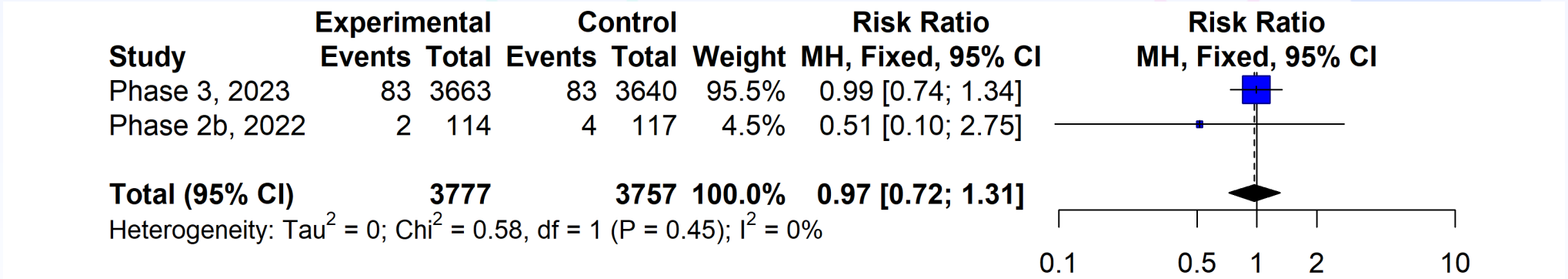
*Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute risk estimates should be interpreted in this context. CI= confidence interval

Outcome 9: Reactogenicity (grade 3+) in pregnant people (n=2 studies)

- Phase 3 RCT, MATISSE and Phase 2b (unpublished, data obtained directly from manufacturer)
- Participants reported local and systemic reactions up to 7 days after vaccination

Outcome 9: Reactogenicity (grade 3+) in pregnant people

Trial	Outcome	Events/Vaccine (n/N)	Events/Placebo (n/N)	Relative Risk (95% CI)
Phase 3	Local events (grade 3+)	11/3663 (0.3%)	0/3639 (0%)	21.86 (1.29, 371.74)
	Systemic events (grade 3+)	83/3663 (2.3%)	83/3640 (2.3%)	0.99 (0.74, 1.34)
Phase 2b	Local events (grade 3+)	0/114 (0%)	0/117 (0%)	1.03 (0.02, 51.28)*
	Systemic events (grade 3+)	2/114 (1.8%)	4/117 (3.4%)	0.51 (0.10, 2.75)



Grade 3: prevents daily routine activity. For redness or swelling is >10 cm. For vomiting, requires intravenous hydration. For diarrhea, includes 6 or more loose stools in 24 hours. Grade 4: requires emergency room visit or hospitalization; for redness included necrosis or exfoliative dermatitis; for swelling included necrosis.

*Using 0.5 offset to account for zero events

CI= confidence interval

Outcome 9: Reactogenicity (grade 3+) in pregnant people (n=2 studies)

- Measures of effect
  - Relative risk: 0.97 (95% CI: 0.72, 1.31)
  - Absolute risk*: 69 fewer per 100,000 (648 fewer to 718 more)
- Concerns in certainty assessment:
  - Serious concern for indirectness as this data only includes systemic reactions. When selecting the *a priori* harm outcomes, the Work Group defined reactogenicity as both local and systemic reactions.
- Evidence type: Moderate

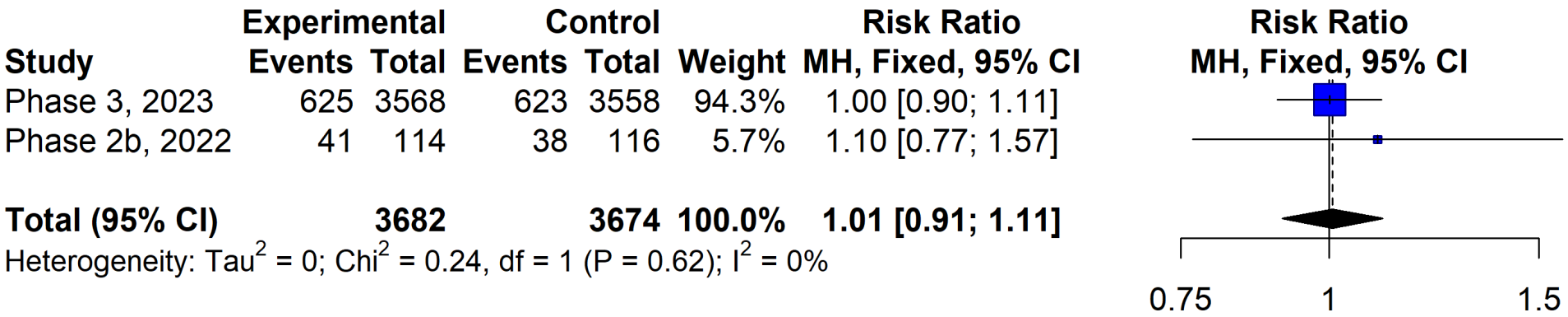
*Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute risk estimates should be interpreted in this context. CI= confidence interval

Outcome 10: Serious adverse events in infants (n=2 studies)

- Phase 3 RCT, MATISSE (unpublished, data obtained directly from manufacturer)
  - Infant safety set: 3,568 in vaccine arm; 3,558 in placebo arm
- Phase 2b RCT (unpublished, data obtained directly from manufacturer)
  - Infant safety set: 114 in vaccine arm (phase 3 formulation); 116 in placebo arm

Outcome 10: Serious adverse events in infants (n=2 studies)

Trial	Events/Vaccine (n/N)	Events/Placebo (n/N)	Relative Risk (95% CI)
Phase 3	625/3568 (17.5%)	623/3558 (17.5%)	1.00 (0.90, 1.11)
Phase 2b	41/114 (36.0%)	38/116 (32.8%)	1.10 (0.77, 1.57)



No serious adverse events in infants were considered by the investigators to be related to the vaccine. For infant deaths in the RSVpreF group, the FDA agreed with the investigator's conclusions for 4 out of 5 of the infant deaths; however, for 1 case of extreme prematurity in an infant born to an 18-year-old mother at 10 days after vaccination who died from prematurity-related complications, FDA was unable to exclude the possibility of the extreme prematurity and subsequent death being related to receipt of the investigational product. No non-fatal SAEs in infant participants were considered related to maternal vaccination by FDA.

Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA, CI= confidence interval

GRADE: Serious adverse events in infants (n=2 studies)

- Measures of effect
  - Relative risk: 1.01 (95% CI: 0.91, 1.11)
  - Absolute risk*: 180 more per 100,000 (1,619 fewer to 1,979 more)
- Concerns in certainty assessment
  - Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered
  - Serious concern for indirectness as 55% of the Phase 3 RCT and 62% of the Phase 2b RCT did not receive vaccine or placebo in the approved dosing interval (32–36 weeks gestation). In the approved dosing interval, there is less opportunity for serious adverse events, including preterm birth/delivery, compared to the trial dosing interval (24–36 weeks gestation)
- Evidence type: Low

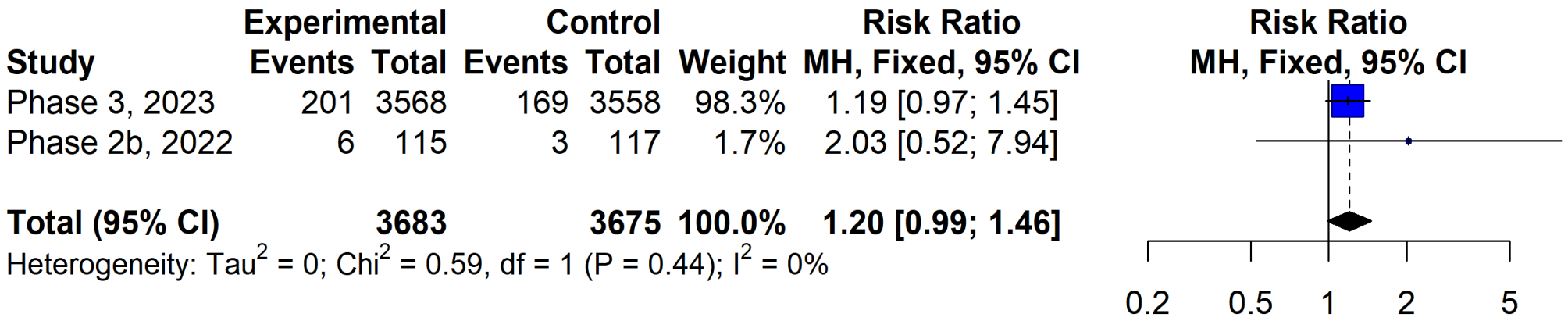
CI= confidence interval

Outcome 11: Preterm births (n=2 studies)

- Phase 3 RCT, MATISSE and Phase 2b (unpublished, data obtained directly from manufacturer)
  - Gestational age at birth <37 weeks and <34 weeks

Outcome: Preterm births (n=2 studies), Pfizer maternal RSVpreF vaccine

Publication	Definition	Events/Vaccine (n/N)	Events/Placebo (n/N)	Relative Risk (95% CI)
Phase 3	<34 weeks	21/3568	12/3558	1.75 (0.86, 3.54)
	<37 weeks	201*/3568	169/3558	1.19 (0.97, 1.45)
Phase 2b	<34 weeks	0/115	1/117	0.34 (0.01, 8.24)**
	<37 weeks	6/115	3/117	2.03 (0.52, 7.94)



*When reported as an adverse event of special interest, 202 preterm births occurred in the vaccine arm; the relative risk is minimally changed at 1.19 (0.98, 1.45) when using this count

**Using 0.5 offset to account for zero events in the vaccine arm

CI= confidence interval

Outcome: Preterm births (n=2 studies)

- Measures of effect
  - Relative risk: 1.20 (0.99, 1.46)
  - Absolute risk*: 936 more per 100,000 (from 47 fewer to 2,153 more)
- Concerns in certainty assessment:
  - Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and not meeting optimal information size requirements
  - Serious concern for indirectness as 55% of the Phase 3 RCT and 62% of the Phase 2b RCT did not receive vaccine or placebo in the approved dosing interval (32–36 weeks gestation). In the approved dosing interval, there is less opportunity for serious adverse events, including preterm birth/delivery, compared to the trial dosing interval (24–36 weeks gestation)
- Evidence type: Very low

*Absolute risk was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute risk estimates should be interpreted in this context. CI= confidence interval

GRADE additional slides

Inclusion/exclusion criteria for pregnant people-Phase 3 Trial

Inclusion	Exclusion
Healthy women ≤49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Receiving prenatal standard of care based on country requirements. Had a fetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed. Determined by medical history, physical examination, and clinical judgment to be appropriate for inclusion in the study. Documented negative HIV antibody test, syphilis test, and hepatitis B virus (HBV) surface antigen test during this pregnancy and prior to randomization (Visit 1). Intention to deliver at a hospital or birthing facility where study procedures can be obtained. Expected to be available for the duration of the study and can be contacted by telephone during study participation. Participant is willing to give informed consent for her infant to participate in the study. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol OR If the maternal participant is illiterate, a thumbprinted informed consent must be obtained, which must be signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant has been informed of all pertinent aspects of the study.	Prepregnancy body mass index (BMI) of >40 kg/m2. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the investigational product or any related vaccine. Current pregnancy resulting from in vitro fertilization. Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following: Preeclampsia, eclampsia, or uncontrolled gestational hypertension. Placental abnormality. Polyhydramnios or oligohydramnios. Significant bleeding or blood clotting disorder. Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism. This also includes disorders of glucose intolerance (e.g., diabetes mellitus type 1 or 2) antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent. Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth. Prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following: Prior preterm delivery ≤34 weeks' gestation. Prior stillbirth or neonatal death. Previous infant with a known genetic disorder or significant congenital anomaly. Major illness of the maternal participant or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the maternal or infant participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response (includes positive serologic testing for regional endemic conditions assessed during routine maternal care, as per local standards of care and obstetric recommendations). Congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrollment. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. Participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation. Receipt of monoclonal antibodies within the year prior to enrollment or the use of systemic corticosteroids for >14 days within 28 days prior to study enrollment. Permitted treatments include the receipt of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies, prednisone doses of <20 mg/day for ≤14 days and, inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids. Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales. Receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (e.g., RhoGAM), which can be given at any time. Previous vaccination with any licensed or investigational RSV vaccine or planned. Note: Licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary or emergency use will not be prohibited during the course of this study. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study. Participants who are breastfeeding at the time of enrollment.

Inclusion/exclusion criteria for infants-Phase 3 Trial

Inclusion	Exclusion
Evidence of a signed and dated informed consent document signed by the parent(s)/legal guardian(s) OR If the infant participant's maternal participant/parent(s)/legal guardian(s) is illiterate, a thumbprinted informed consent must have been obtained, which must have been signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant/parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study for herself (maternal participant) and her fetus/infant prior to taking part in the study. Parent(s)/legal guardian(s) willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.	Infant who is a direct descendant (e.g., child or grandchild) of the study personnel.

Inclusion/exclusion criteria for pregnant people-Phase 2b

Inclusion-Pregnant people	Exclusion-Pregnant people
Healthy women 18 to 49 years of age between 24 and 36 weeks of gestation on the day of planned vaccination, with an uncomplicated pregnancy, who are at no known increased risk for complications, and whose fetus has no significant abnormalities observed on ultrasound. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Receiving prenatal standard of care. Had an ultrasound performed at >=18 weeks of pregnancy. Had a negative urinalysis for protein and glucose at the screening visit. Trace protein in the urine is acceptable if the blood pressure is also normal. Determined by medical history, physical examination, screening laboratory assessment, and clinical judgment to be appropriate for inclusion in the study. Documented negative human immunodeficiency virus antibody, hepatitis B virus surface antigen, hepatitis C virus antibody, and syphilis tests at the screening visit. Body mass index of </=40 kg/m2 at the time of the screening visit. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent document and in this protocol. Expected to be available for the duration of the study and willing to give informed consent for her infant to participate in the study.	Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the investigational product or any related vaccine. History of latex allergy. History of any severe allergic reaction. Participants with known or suspected immunodeficiency. Current pregnancy resulting from in vitro fertilization or other assisted reproductive technology. A prior history of or known current pregnancy complications or abnormalities that will increase the risk associated with the participant's participation in and completion of the study. Major illness of the mother or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response. Participant with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1). Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. Participation in other studies involving investigational drug(s) within 28 days prior to study entry and/or during study participation. Participants who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids (such as for cancer or an autoimmune disease), or planned receipt of such treatment or agents during study participation. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before investigational product administration. Inhaled/nebulized, intra articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted. Current alcohol abuse or illicit drug use. Receipt of blood or plasma products or immunoglobulin, from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (eg, RhoGAM), which can be given at any time. Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation. Laboratory test results at the screening visit outside the normal reference value for pregnant women according to their trimester in pregnancy. Participants who are breastfeeding at the time of the screening visit.

Inclusion/exclusion criteria for infants-Phase 2b

Inclusion-Infants	Exclusion-Infants
Evidence of a signed and dated informed consent document signed by the parent(s). Parent(s) willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.	Infant who is a direct descendant (eg, child or grandchild) of the study personnel.

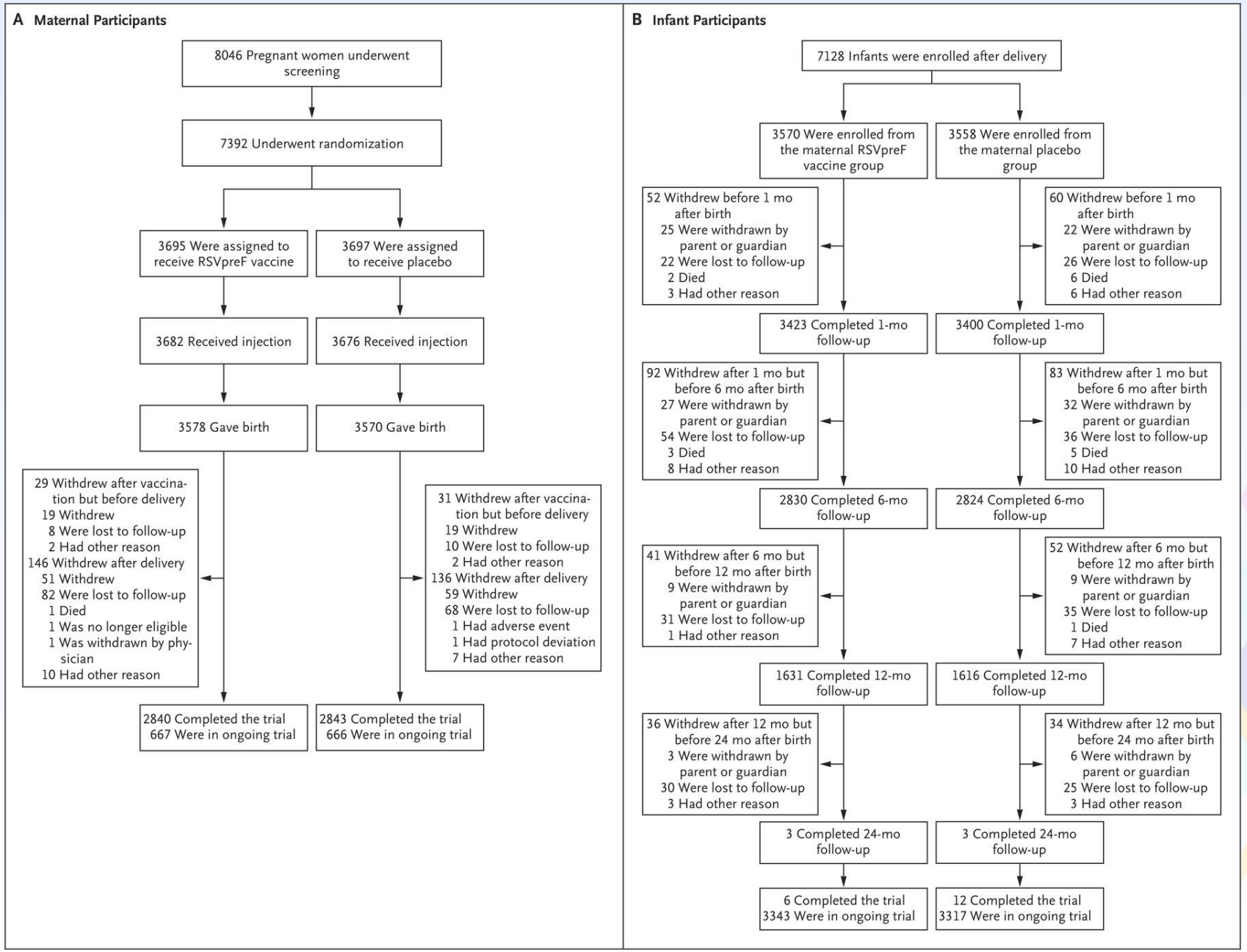


Figure 1. Enrollment, Randomization, Administration of Vaccine or Placebo, and Follow-up

Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023 Apr 5. doi: 10.1056/NEJMoa2216480.

Table 1. Demographics of phase 3 trial

Table 1. Demographic and Clinical Characteristics of the Maternal and Infant Participants in the Safety Population.*

Characteristic	RSVpreF Vaccine	Placebo	Total
Maternal participants			
Age at injection — yr			
Mean	29.1±5.6	29.0±5.7	29.0±5.7
Median (range)	29 (16–45)	29 (14–47)	29 (14–47)
Gestation at injection — wk			
Mean	30.8±3.5	30.8±3.6	30.8±3.5
Median (range)	31.3 (24.0–36.6)	31.3 (24.0–36.9)	31.3 (24.0–36.9)
Race or ethnic group — no./total no. (%)†			
White	2383/3682 (64.7)	2365/3675 (64.4)	4748/7357 (64.5)
Black	720/3682 (19.6)	723/3675 (19.7)	1443/7357 (19.6)
Asian	454/3682 (12.3)	464/3675 (12.6)	918/7357 (12.5)
Multiracial	30/3682 (0.8)	21/3675 (0.6)	51/7357 (0.7)
Race not reported	41/3682 (1.1)	45/3675 (1.2)	86/7357 (1.2)
Race unknown	7/3682 (0.2)	8/3675 (0.2)	15/7357 (0.2)
Hispanic or Latinx	1049/3682 (28.5)	1075/3675 (29.3)	2124/7357 (28.9)
Not Hispanic or Latinx	2603/3682 (70.7)	2567/3675 (69.8)	5170/7357 (70.3)
American Indian or Alaska Native	38/3682 (1.0)	37/3675 (1.0)	75/7357 (1.0)
Native Hawaiian or other Pacific Islander	9/3682 (0.2)	12/3675 (0.3)	21/7357 (0.3)
Ethnic group not reported or unknown	30/3682 (0.8)	33/3675 (0.9)	63/7357 (0.9)
Infant participants			
Sex — no./total no. (%)			
Male	1816/3568 (50.9)	1793/3558 (50.4)	3609/7126 (50.6)
Female	1752/3568 (49.1)	1765/3558 (49.6)	3517/7126 (49.4)
Gestational age at birth — no./total no. (%)			
24 to <28 wk	1/3568 (<0.1)	1/3558 (<0.1)	2/7126 (<0.1)
28 to <34 wk	20/3568 (0.6)	11/3558 (0.3)	31/7126 (0.4)
34 to <37 wk	180/3568 (5.0)	157/3558 (4.4)	337/7126 (4.7)
37 to <42 wk	3343/3568 (93.7)	3356/3558 (94.3)	6699/7126 (94.0)
≥42 wk	21/3568 (0.6)	30/3558 (0.8)	51/7126 (0.7)
Apgar score, 5 min			
<4 — no./total no. (%)	8/3528 (0.2)	5/3517 (0.1)	13/7045 (0.2)
4 to <7 — no./total no. (%)	29/3528 (0.8)	27/3517 (0.8)	56/7045 (0.8)
7 to 10 — no./total no. (%)	3491/3528 (99.0)	3485/3517 (99.1)	6976/7045 (99.0)
Median (range)	9 (1–10)	9 (2–10)	9 (1–10)
Outcome — no./total no. (%)			
Normal	3172/3568 (89.9)	3149/3558 (88.5)	6321/7126 (88.7)
Congenital malformation or anomaly	174/3568 (4.9)	203/3558 (5.7)	377/7126 (5.3)
Other neonatal problems	219/3568 (6.1)	200/3558 (5.6)	419/7126 (5.9)
Extremely low birth weight, ≤1000 g — no./total no. (%)	1/3568 (<0.1)	2/3558 (<0.1)	3/7126 (<0.1)
Very low birth weight, >1000 to 1500 g — no./total no. (%)‡	3/3568 (<0.1)	6/3558 (0.2)	9/7126 (0.1)
Low birth weight, >1500 to 2500 g — no./total no. (%)‡	177/3568 (5.0)	147/3558 (4.1)	324/7126 (4.5)
Developmental delay — no./total no. (%)‡	12/3568 (0.3)	10/3558 (0.3)	22/7126 (0.3)

* Plus–minus values are means ±SD. The safety population consisted of all the maternal participants who underwent randomization and received vaccine or placebo and all their infants (except one maternal infant and two infant participants, who did not meet eligibility criteria). Percentages may not total 100 because of rounding. RSVpreF denotes respiratory syncytial virus prefusion F protein–based vaccine.
† Race or ethnic group was reported by the maternal participants.
‡ This outcome was an adverse event of special interest reported at any time after birth during the trial period.

Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023 Apr 5. doi: 10.1056/NEJMoa2216480.

Severity scale for local reactions and systemic events (maternal participants)

Table S16. Severity scale for local reactions and systemic events (maternal participants)

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4*
Local reaction				
Redness†	>2.0–5.0 cm (5–10 measuring device units)	>5.0–10.0 cm (11–20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis or exfoliative dermatitis
Swelling†	>2.0–5.0 cm (5–10 measuring device units)	>5.0–10.0 cm (11–20 measuring device units)	>10 cm (>20 measuring device units)	Necrosis
Injection site pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	ER visit or hospitalization for severe pain at the injection site
Systemic event				
Fatigue	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization for severe fatigue
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization for severe headache
Vomiting	1–2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	ER visit or hospitalization for severe vomiting
Nausea	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization for severe nausea
Diarrhea	2–3 loose stools in 24 hours	4–5 loose stools in 24 hours	≥6 loose stools in 24 hours	ER visit or hospitalization for severe diarrhea
Muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization for severe muscle pain
Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	ER visit or hospitalization for severe joint pain
Fever	38.0°C–38.4°C	>38.4°C–38.9°C	>38.9°C–40.0°C	>40.0°C

AE=adverse event; ER=emergency room; IV=intravenous.

* Only an investigator or qualified designee was able to classify a participant's local reaction as grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, ER or hospital record) or, in the case of pain at the injection site only, contact with the participant. Grade 4 local reactions and systemic events (except fever) were collected on the AE case report form and assessed by the investigator using the AE intensity grading scale in the table above.

† Measured by the maternal participant, study staff or field worker and recorded in measuring device units (range, 1–20 and ≥21) and then categorized during analysis as mild, moderate, or severe based on the grading scale in the table. Measuring device units could be converted to centimeters according to the following scale: 1 measuring device unit=0.5 cm.

Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023 Apr 5. doi: 10.1056/NEJMoa2216480.

Studies Included in the Review of Evidence

Last name first author, Publication year	Study design	Country	Age mean (SD), years	Total Population	N intervention	N comparison	Outcomes	Funding Source
Kampmann B, et al. plus unpublished data obtained directly from the manufacturer	RCT	Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Philippines, South Africa, Spain, Taiwan, United States	29.0 (5.7)	7,357	3,682	3,675	Medically attended RSV-associated lower respiratory infection in infants; Hospitalization for RSV-associated lower respiratory tract infection in infants; RSV-associated death in infants; All cause medically attended lower respiratory tract infection in infants; Serious adverse events in pregnant people; Reactogenicity in pregnant people; Serious adverse events in infants; Preterm birth	Pfizer
Pfizer, Phase 2 Trial plus unpublished data obtained directly from the manufacturer	RCT	Argentina, Chile, South Africa and the United States	27.1 (5.2)	232	115 (phase 3 formulation)	117	RSV-associated death in infants; Serious adverse events in pregnant people; Reactogenicity in pregnant people; Serious adverse events in infants; Preterm birth;	Pfizer

Summary of Studies Reporting Outcome 1: Medically attended RSV-associated lower respiratory infection in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (97.58% CI)	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3495	3480	Placebo	1,725 fewer per 100,000 (988 to 2,246 fewer)	None

Absolute difference was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute difference estimates should be interpreted in this context.

Summary of Studies Reporting Outcome 2: Hospitalization for RSV-associated lower respiratory tract infection in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (99.17% CI)	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3495	3480	Placebo	718 fewer per 100,000 (128 to 1,020 fewer)	None

Absolute difference was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute difference estimates should be interpreted in this context.

Summary of Studies Reporting Outcome 3: ICU admission from RSV hospitalization in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (95% CI)	Study limitations (Risk of Bias)
Data received directly from the manufacturer	29.0 (5.7)	3495	3480	Placebo	86 fewer per 100,000 (176 fewer to 251 more)	None

Absolute difference was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute difference estimates should be interpreted in this context.

Summary of Studies Reporting Outcome 4: Mechanical ventilation from RSV hospitalization in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (95% CI)	Study limitations (Risk of Bias)
Data received directly from the manufacturer	29.0 (5.7)	3495	3480	Placebo	144 fewer per 100,000 (144 fewer to 13 more)	None

Absolute difference was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute difference estimates should be interpreted in this context.

Summary of Studies Reporting Outcome 5: RSV-associated death in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3495	3480	Placebo	Not estimable 1 death in a placebo recipient	None
Phase 2b RCT, unpublished	18-49 (range)	114	116	Placebo	Not estimable 0 deaths in trial	None

Summary of Studies Reporting Outcome 6: All-cause medically attended lower respiratory tract infection in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (99.17% CI)	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3495	3480	Placebo	289 fewer per 100,000 (2,241 fewer to 2,068 more)	None

Absolute difference was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute difference estimates should be interpreted in this context.

Summary of Studies Reporting Outcome 7: All-cause hospitalization for lower respiratory tract infection in infants

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (95% CI)	Study limitations (Risk of Bias)
Data received directly from the manufacturer	29.0 (5.7)	3495	3480	Placebo	631 fewer per 100,000 (1,109 fewer to 44 more)	None

Absolute difference was calculated using the observed outcomes in the placebo arm during the available clinical trial follow-up. Absolute difference estimates should be interpreted in this context.

Summary of Studies Reporting Outcome 8: Serious adverse events in pregnant people

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Relative difference/effect estimate	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3682	3675	Placebo	RR: 1.07 (0.96, 1.19)	None
Phase 2b RCT	27.1 (5.2)	115	117	Placebo	RR: 0.51 (0.21, 1.21)	None

Summary of Studies Reporting Outcome 9: Reactogenicity (grade 3+) in pregnant people

Last name first author, Publication year	Age mean (SD), years	N intervention	N comparison	Comparator Vaccine	Relative difference/effect estimate	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3663	3640	Placebo	RR: 0.99 (0.74, 1.34)	None
Phase 2b RCT	27.1 (5.2)	114	117	Placebo	RR: 0.51 (0.10, 2.75)	None

Summary of Studies Reporting Outcome 10: Serious adverse events in infants

Last name first author, Publication year	Age median (range)	N intervention	N comparison	Comparator Vaccine	Relative difference/effect estimate	Study limitations (Risk of Bias)
Kampmann B, et al.	11.97 months (0.0, 24.3)	3568	3558	Placebo	RR: 1.00 (0.90, 1.11)	None
Phase 2b RCT		114	116	Placebo	RR: 1.10 (0.77, 1.57)	None

Summary of Studies Reporting Outcome 11: Preterm birth

Last name first author, Publication year	Age mean (SD)	N intervention	N comparison	Comparator Vaccine	Relative difference/effect estimate	Study limitations (Risk of Bias)
Kampmann B, et al.	11.97 months (0.0, 24.3)	3568	3558	Placebo	RR: 1.19 (0.97, 1.45)	None
Phase 2b RCT		115	117	Placebo	RR: 2.03 (0.52, 7.94)	None

Grade Summary of Findings Table- Benefits

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (CI)	Absolute (CI)	Importance	Certainty
Medically attended RSV-associated lower respiratory infection in infants												
1	Randomized studies	Not serious	Not serious	Not serious	Not serious	None	57/3495 (1.6%)	117/3480 (3.4%)	0.487 (97.58% CI: 0.332, 0.706)	1,725 fewer per 100,000 (988 to 2,246 fewer)	Critical	High
								23.1%		11,850 fewer per 100,000 (6,791 to 15,431 fewer)		
								11.0%		5,643 fewer per 100,000 (3,234 to 7,348 fewer)		
Hospitalizations RSV-associated lower respiratory infection in infants												
1	Randomized studies	Not serious	Not serious	Not serious	Serious	None	19/3495 (0.5%)	44/3480 (1.3%)	0.432 (99.17% CI: 0.193, 0.899)	718 fewer per 100,000 (128 to 1,020 fewer)	Critical	Low
								1.9%		1,051 fewer per 100,000 (187 to 1,493 fewer)		
ICU admission from RSV hospitalization												
1	Randomized studies	Not serious	Not serious	Not serious	Very serious	None	4/3495 (0.1%)	7/3480 (0.2%)	0.571 (95% CI: 0.123, 2.248)	86 fewer per 100,000 (176 fewer to 251 more)	Important	Low
								0.7%		285 fewer per 100,000 (583 fewer to 830 more)		

Grade Summary of Findings Table- Benefits

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (CI)	Absolute (95% CI)	Importance	Certainty
Mechanical ventilation from RSV hospitalization												
1	Randomized studies	Not serious	Not serious	Not serious	Very serious	None	0/3495 (0.0%)	5/3480 (0.1%) 0.2%	0.001 (95% CI: 0.001, 1.091)	144 fewer per 100,000 (144 fewer to 13 more) 209 fewer per 100,000 (209 fewer to 19 more)	Important	Low
All-cause medically attended lower respiratory tract infection in infants												
1	Randomized studies	Not serious	Not serious	Not serious	Serious	None	392/3495 (11.2%)	402/3480 (11.6%)	0.975 (99.17% CI: 0.806, 1.179)	289 fewer per 100,000 (2,241 fewer to 2,068 more)	Important	Moderate
All-cause hospitalization for lower respiratory tract infection in infants												
1	Randomized studies	Not serious	Not serious	Not serious	Serious	None	54/3495 (1.5%)	76/3480 (2.2%)	0.711 (95% CI: 0.492, 1.010)	631 fewer per 100,000 (1,109 fewer to 44 more)	Important	Moderate

Grade Summary of Findings Table- Harms

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison	Relative (95% CI)	Absolute (95% CI)	Importance	Certainty
Serious adverse events in pregnant women												
2	Randomized studies	Not serious	Not serious	Serious	Serious	None	605/3797 (15.9%)	572/3792 (15.1%)	1.06 (0.95, 1.17)	905 more per 100,000 (754 fewer to 2,564 more)	Critical	Low
Reactogenicity (3+ or higher) in pregnant women												
2	Randomized studies	Not serious	Not serious	Serious	Not serious	None	85/3777 (2.3%)	87/3757 (2.3%)	0.97 (0.72, 1.31)	69 fewer per 100,000 (648 fewer to 718 more)	Important	Moderate
Serious adverse events in infants												
2	Randomized studies	Not serious	Not serious	Serious	Serious	None	666/3682 (18.1%)	661/3674 (18.0%)	1.01 (0.91, 1.11)	180 more per 100,000 (1,619 fewer to 1,979 more)	Critical	Low
Preterm birth												
2	Randomized studies	Not serious	Not serious	Serious	Very serious	None	207/3683 (5.6%)	172/3675 (4.7%)	1.20 (0.99, 1.46)	936 more per 100,000 (47 fewer to 2,153 more)	Critical	Very low