Evidence to Recommendations Framework:

Pfizer Maternal RSVpreF Vaccine

Katherine 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
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Evidence to Recommendations (EtR) Framework
Policy Question

- Should vaccination with Pfizer RSVPreF vaccine (120µg antigen, 1 dose IM given 24–36 weeks gestation) be recommended for pregnant people to prevent RSV disease in infants?

RSVpreF is a bivalent recombinant stabilized prefusion F protein subunit vaccine

Evidence to Recommendations (EtR) Framework
PICO Question

Population	Pregnant people 24–36 weeks gestation
Intervention	Pfizer RSVPreF Vaccine
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

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 variability in how patients value the outcome?
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 in the impact of the intervention on health equity?

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]

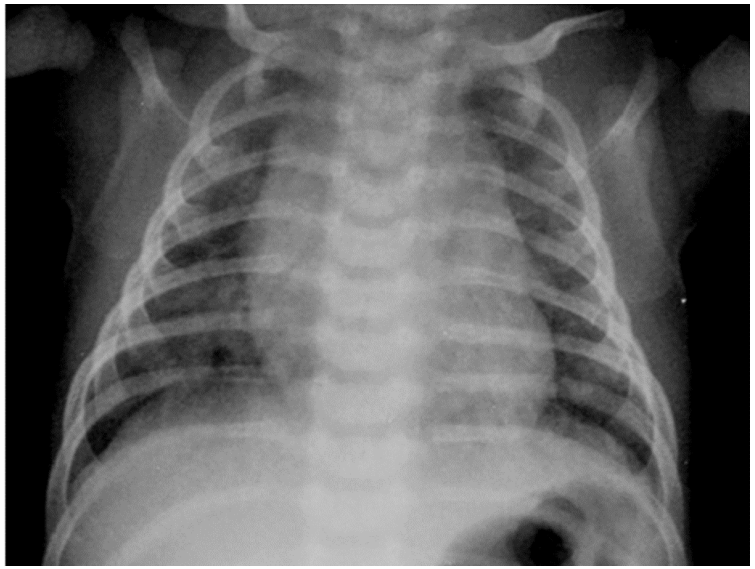
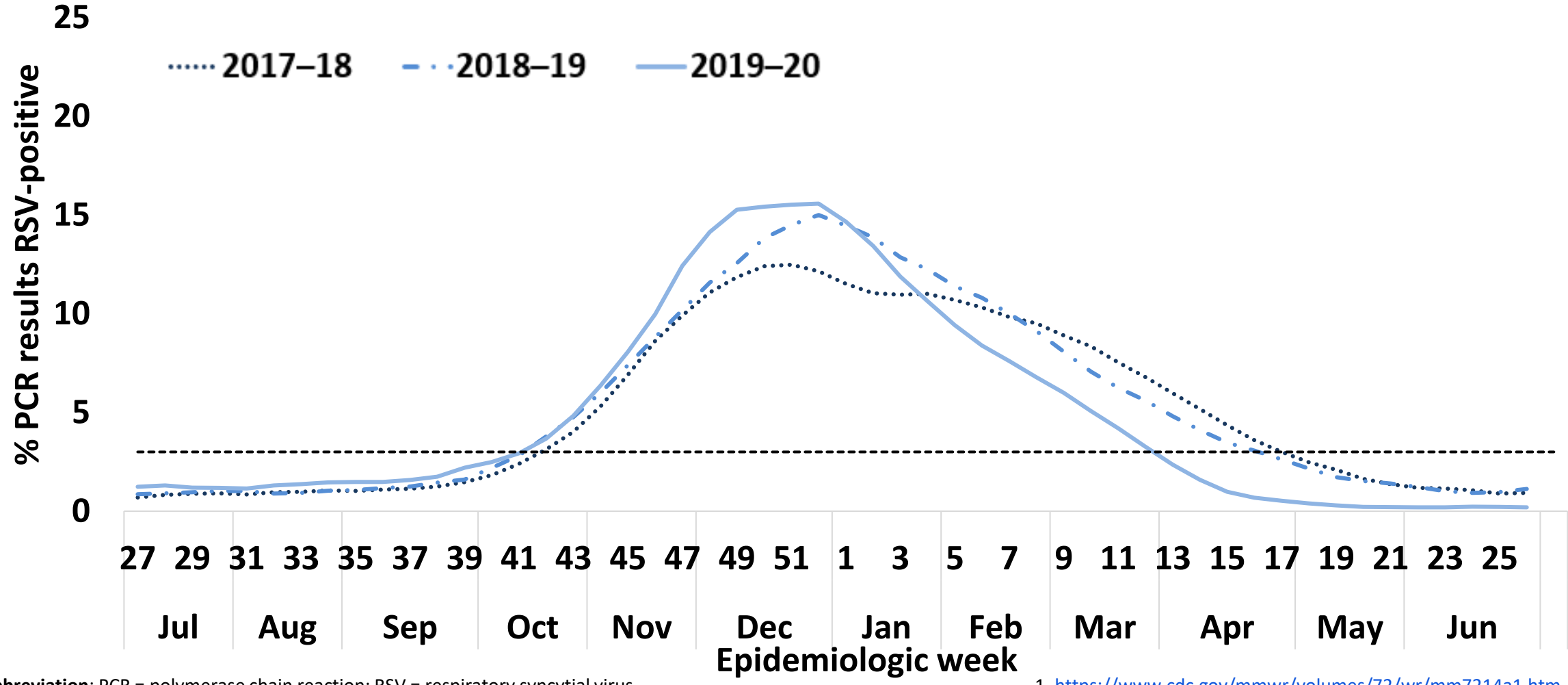


Image: Goncalves et al. Critical Care Research and Practice 2012

[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

Seasonality of RSV transmission — National Respiratory and Enteric Virus Surveillance System, NREVSS[1], 2017–2020

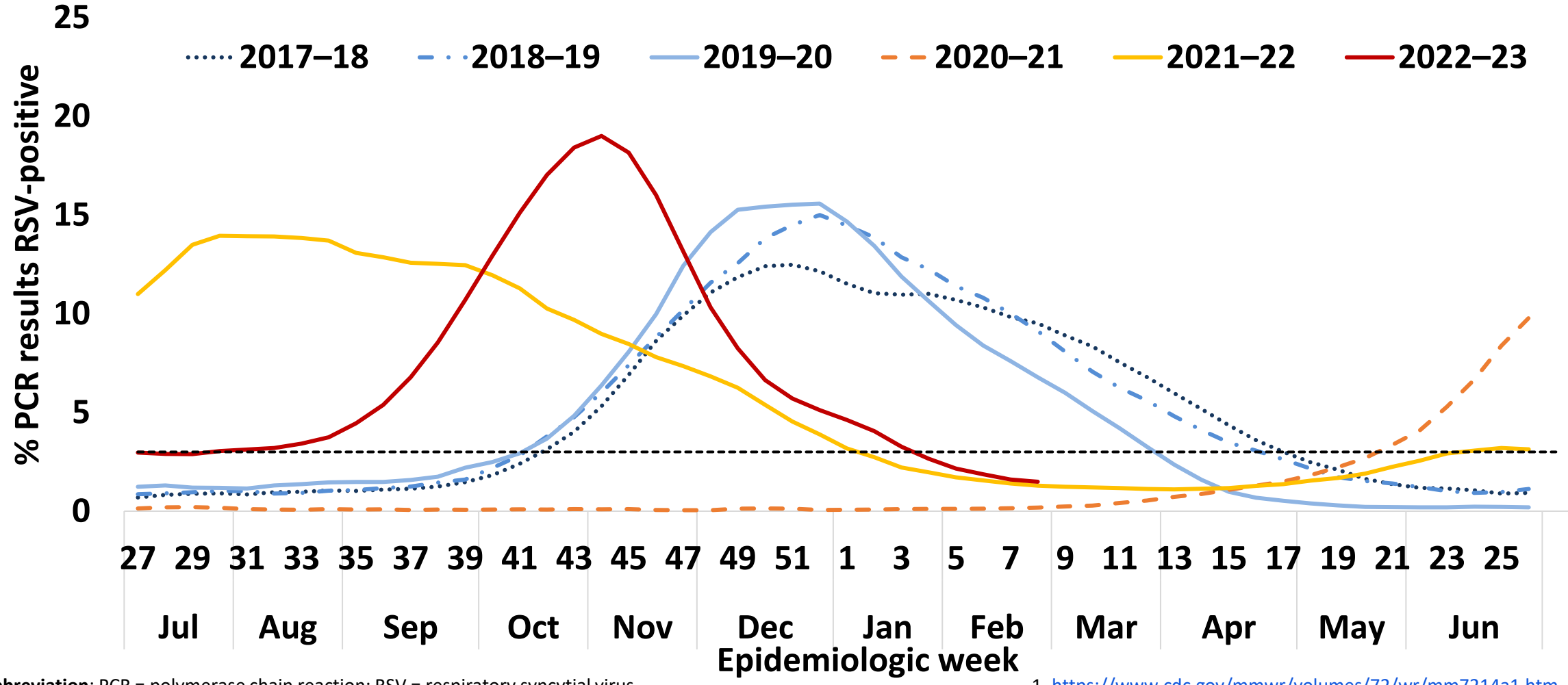


Abbreviation: PCR = polymerase chain reaction; RSV = respiratory syncytial virus.

1. https://www.cdc.gov/mmwr/volumes/72/wr/mm7214a1.htm

* 3-week centered moving averages of percentage of RSV-positive PCR results nationwide. The black dotted line represents the threshold for a seasonal epidemic (3% RSV-positive laboratory PCR results).

Changes in seasonality of RSV transmission following SARS-CoV2 introduction— NREVSS[1], 2017–2023



Abbreviation: PCR = polymerase chain reaction; RSV = respiratory syncytial virus.

1. https://www.cdc.gov/mmwr/volumes/72/wr/mm7214a1.htm

* 3-week centered moving averages of percentage of RSV-positive PCR results nationwide. The black dotted line represents the threshold for a seasonal epidemic (3% RSV-positive laboratory PCR results).

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	No data
Mechanical ventilation from RSV hospitalization in infants	Important	No data
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	No data
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)	Critical	Phase 3 and phase 2b[2] RCT

RCT = Randomized-controlled trial

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 were included

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

Outcome	Importance[1]	Data sources	Manufacturer calculated vaccine efficacy (97.58% or 99.17% CI)[2]	Concerns in certainty assessment
Benefits				
Medically attended RSV-associated lower respiratory tract infection in infants (0–180 days)	Critical	Phase 3 RCT	51.3% (29.4, 66.8)	None
Hospitalization for RSV-associated lower respiratory tract infection in infants (0–180 days)	Critical	Phase 3 RCT	56.8% (10.1, 80.7)	Imprecision (serious)[3]
ICU admission from RSV hospitalization in infants	Important	No data		
Mechanical ventilation from RSV hospitalization in infants	Important	No data		
RSV-associated death in infants	Important	Phase 3 and phase 2b[4] 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% (-17.9, 19.4)	Imprecision (serious)[3]
All-cause hospitalization for lower respiratory tract infection in infants	Important	No data		

RCT = Randomized-controlled trial

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. 97.58% confidence interval used for medically attended RSV-associated lower respiratory tract infection in infants, 99.17% confidence interval used for other endpoints.

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

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

Efficacy 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[2] RCT	1.06 (0.95, 1.17)	Imprecision (serious)[3]
Reactogenicity (grade 3+) in pregnant people	Important	Phase 3 and phase 2b[2] RCT	0.97 (0.72, 1.31)	Indirectness (serious) [4]
Serious adverse events in infants	Critical	Phase 3 and phase 2b[2] RCT	1.01 (0.91, 1.11)	Imprecision (serious) [3]
Preterm birth (<37 weeks)	Critical	Phase 3 and phase 2b[2] RCT	1.20 (0.99, 1.46)	Imprecision (very serious) [5]

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

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

4 Serious concern for indirectness as these data only includes systemic reactions

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 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		No data	Not evaluated
Mechanical ventilation from RSV hospitalization in infants	Important		No data	Not evaluated
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		No data	Not evaluated
Harms				
Serious adverse events in pregnant people	Critical	RCT (2)	SAEs in pregnant people were balanced between vaccine and placebo groups	Moderate
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	Moderate
Preterm birth (<37 weeks)	Critical	RCT (2)	Preterm births were unbalanced between vaccine and placebo groups	Low

Summary of GRADE: Pfizer maternal RSVpreF vaccine

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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		No data	Not evaluated
Mechanical ventilation from RSV hospitalization in infants	Important		No data	Not evaluated
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		No data	Not evaluated
Harms				
Serious adverse events in pregnant people	Critical	RCT (2)	SAEs in pregnant people were balanced between vaccine and placebo groups	Moderate
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	Moderate
Preterm birth (<37 weeks)	Critical	RCT (2)	Preterm births were unbalanced between vaccine and placebo groups	Low

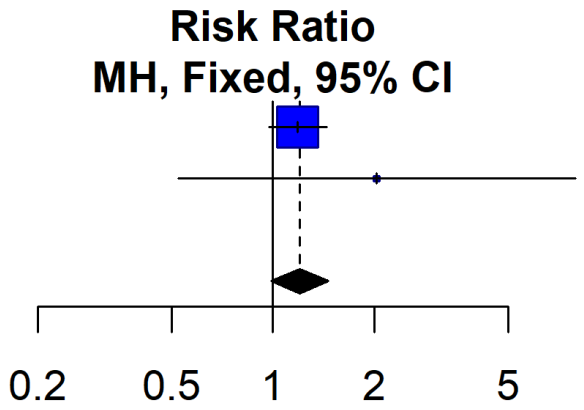
Overall evidence type: **Low**

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)

	Experimental		Control			Risk Ratio
Study	**Events**	**Total**	**Events**	**Total**	**Weight**	**MH, Fixed, 95% CI**
Phase 3, 2023	201	3568	169	3558	98.3%	1.19 [0.97; 1.45]
Phase 2b, 2022	6	115	3	117	1.7%	2.03 [0.52; 7.94]
Total (95% CI)		**3683**		**3675**	**100.0%**	**1.20 [0.99; 1.46]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0\%$



*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

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

- Measures of effect
  - Relative risk: 1.20 (0.99, 1.46)
  - Absolute risk*: 9 more per 1,000 (from 0 fewer to 22 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
- 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.

Preterm birth rates in maternal RSV vaccine clinical trials: GSK

- 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

Outcome	Vaccine group, n (%) N=3,496	Placebo group, n (%) N=1,739	Relative Risk (95% CI)
Preterm birth <37 weeks	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 rates in maternal RSV vaccine clinical trials: Novavax

- Phase 3 clinical trial in 4,636 women randomized 2:1, vaccine to placebo
- Vaccine formulation: 120µg of recombinant RSV F protein nanoparticle vaccine adsorbed to 0.4mg of aluminum (Novavax vaccine was not stabilized in the prefusion form)
- Maternal vaccine did not reach primary efficacy endpoints and thus did not move forward, but there were no safety concerns (preterm births or other) in this trial

Preterm Birth Definition	Preterm Birth in Vaccine group, n (%) N=2,986	Preterm Birth in Placebo, n (%) N=1,554
<37 weeks among infants*	175 (5.9%)	96 (6.2%)

*Study vaccine given at ≥28 through 36 weeks and 0 days gestation. Data from Table 1 among infants for whom the protocol-mandated dating ultrasonography result was available for calculating gestational age.

1. Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. N Engl J Med 2020;383:426-39. DOI: 10.1056/NEJMoa1908380

Preterm birth and low birth weight outcomes in maternal RSV vaccine clinical trials: Pfizer RSVpreF vaccine phase 3 trial data

	RSVpreF vaccine group N=3,568	Placebo group N=3,558
Preterm birth (<37 weeks)	**5.7%** (95% CI: 4.9%, 6.5%)	**4.7%** (95% CI: 4.1%, 5.5%)
Late preterm birth (≥34 to <37 weeks)	**5.0%***	**4.4%***
Low birth weight (≤2500g)	**5.1%** (95% CI: 4.4%, 5.8%)	**4.4%** (95% CI: 3.7%, 5.0%)

*Confidence intervals not reported for these estimates.

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)

Infant deaths in maternal RSV vaccine clinical trials: Pfizer RSVpreF vaccine phase 3 trial data

- **Infant deaths (all-cause) through 24 months of age:** 5 (0.1%) in the RSVpreF group vs 12 (0.3%) in placebo group
- Among infant deaths in the RSVpreF group
  - 4 of 5 deaths were considered unrelated to the investigational product by FDA
  - 1 death was in an infant with extreme prematurity (27 weeks) and prematurity-related complications, and FDA was unable to exclude possibility of relationship to investigational product

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)

Time from Vaccination to Birth Among Preterm and Term Births, Infant Participants, Safety Population: Pfizer RSVpreF vaccine phase 3 trial data

- Median gestational age at vaccination in trial was 31 weeks

Days from Vaccination to Birth	RSVpreF 120 µg (N=3568) n (%)	Placebo (N=3558) n (%)	Total (N=7126) n (%)
Preterm deliveries	201	169	370
≤7 days[a]	11 (5.5)	13 (7.7)	24 (6.5)
>7 days to ≤30 days[a]	69 (34.3)	58 (34.3)	127 (34.3)
>30 days[a]	121 (60.2)	98 (58.0)	219 (59.2)
At term deliveries	3364	3386	6750
≤7 days[a]	1 (<0.1)	2 (<0.1)	3 (<0.1)
>7 days to ≤30 days[a]	516 (15.3)	498 (14.7)	1014 (15.0)
>30 days[a]	2847 (84.6)	2886 (85.2)	5733 (84.9)

Source: Pfizer CSR 1008

Abbreviations: N=number of participants having birth date in the specified vaccine group. This value is the denominator for the percentage calculations; n = Number of participants in the specified category.

Note: Six participants have missing gestational age at birth in database, so are not included in counts above. Preterm/at term deliveries are determined based on gestational age at birth. Preterm=gestational age at birth less than 37 weeks. At term=gestational age at birth of 37 weeks or more. Number of days between vaccination and birth is calculated as birth date - vaccination date.

a. Percentages for this row are based on the number of preterm/at term deliveries, respectively.

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)

Subgroup analysis of gestational age at birth among live births by country income level: Pfizer RSVpreF vaccine phase 3 trial data

- In high-income countries, preterm birth rate was **5.1%** (126/2494) in RSVpreF recipients vs **5.1%** (126/2484) placebo recipients
- Imbalance was most prominent in upper middle income countries: **7.5%** (72/964) in RSVpreF recipients vs. **4.1%** (39/961) in placebo recipients

Country / Gestational Age at Birth	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
High income	2494	2484
≥24 weeks to <28 weeks	0	1 (<0.1)
≥28 weeks to <34 weeks	13 (0.5)	7 (0.3)
≥34 weeks to <37 weeks	113 (4.5)	118 (4.8)
≥37 weeks to <42 weeks	2360 (94.6)	2351 (94.6)
≥42 weeks	6 (0.2)	5 (0.2)
Upper middle income	964	961
≥24 weeks to <28 weeks	1 (0.1)	0
≥28 weeks to <34 weeks	7 (0.7)	4 (0.4)
≥34 weeks to <37 weeks	64 (6.6)	35 (3.5)
≥37 weeks to <42 weeks	882 (91.5)	906 (94.3)
≥42 weeks	9 (0.9)	15 (1.6)

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

Subgroup analysis of gestational age at birth among live births, South Africa and US: Pfizer RSVpreF vaccine phase 3 trial data

- In South Africa, preterm birth rate was **8.3%** (39/469) in RSVpreF recipients vs **4.0%** (19/471) placebo recipients
- In US, preterm birth rate was **5.7%** (94/1654) in RSVpreF recipients vs. **5.3%** (87/1644) in placebo recipients

Table 14. Live Birth Outcomes by Select Countries (US, South Africa)

Country	RSVpreF N=3568 n (%)	Placebo N=3558 n (%)
South Africa	**469**	**471**
≥24 weeks to <28 weeks	1 (0.2)	0
≥28 weeks to <34 weeks	4 (0.9)	3 (0.6)
≥34 weeks to <37 weeks	34 (7.2)	16 (3.4)
≥37 weeks to <42 weeks	420 (89.6)	439 (93.2)
≥42 weeks	9 (1.9)	12 (2.5)
United States	1654	1644
≥24 weeks to <28 weeks	0	1 (<0.1)
≥28 weeks to <34 weeks	11 (0.7)	5 (0.3)
≥34 weeks to <37 weeks	83 (5.0)	81 (4.9)
≥37 weeks to <42 weeks	1556 (94.1)	1553 (94.5)
≥42 weeks	2 (0.1)	2 (0.1)

Source: adapted from Pfizer CSR

Trial was conducted in 18 countries.

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

VRBPAC discussion regarding preterm births: Pfizer RSVpreF vaccine

- An imbalance was seen in preterm births in both phase 2b and phase 3 trials, but the imbalance was not statistically significant
- Preterm birth rate in trials was lower than background incidence rate of preterm birth (~10% in US), but the trial had multiple exclusion criteria selecting for a population at lower risk of preterm birth
- Trial was underpowered to detect a 20% relative increase in preterm birth

181st Meeting of the Vaccines and Related Biological Products Advisory Committee – YouTube
Preterm Birth | Maternal and Infant Health | Reproductive Health | CDC

VRBPAC discussion regarding preterm births: Pfizer RSVpreF vaccine (cont.)

- Imbalance was still present but less pronounced when comparing prevalence of low birth weight
- Most preterm births were late preterm (≥34 to <37 weeks)
- Most preterm births were >30 days after vaccination
- Preterm birth imbalance was most prominent in a single country, South Africa
- VRBPAC voted 14-0 that the data supported effectiveness of Pfizer maternal RSVpreF and voted 10-4 that data supported safety

181st Meeting of the Vaccines and Related Biological Products Advisory Committee - YouTube

Other considerations: Inflammatory neurologic events Pfizer RSVPreF Vaccine

- Same Pfizer RSV vaccine, formulation and dose approved for use in older adults
- Within the main phase 3 trial for this product among adults ages ≥ 60 years (RENOIR) a *potential* neurologic safety signal was identified
- **A total of 3 cases** of potential inflammatory neurologic events were recorded among 20,255 investigational vaccine recipients across all clinical trials. No cases were observed among placebo recipients.

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/06-RSV-Adults-Melgar-508.pdf)

Other considerations: Inflammatory neurologic events 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

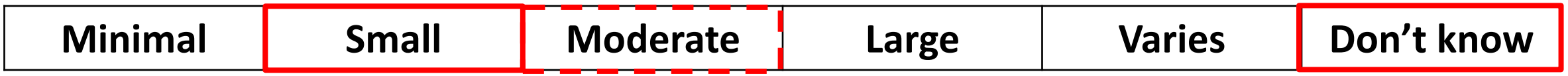
Benefits and Harms Pfizer Maternal RSVPreF Vaccine

- 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

Minimal	Small	Moderate	Large	Varies	Don't know

Benefits and Harms Pfizer Maternal RSVPreF Vaccine

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



Minority Opinion

Benefits and Harms Pfizer Maternal RSVPreF Vaccine

- 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

EtR Domain: Values

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

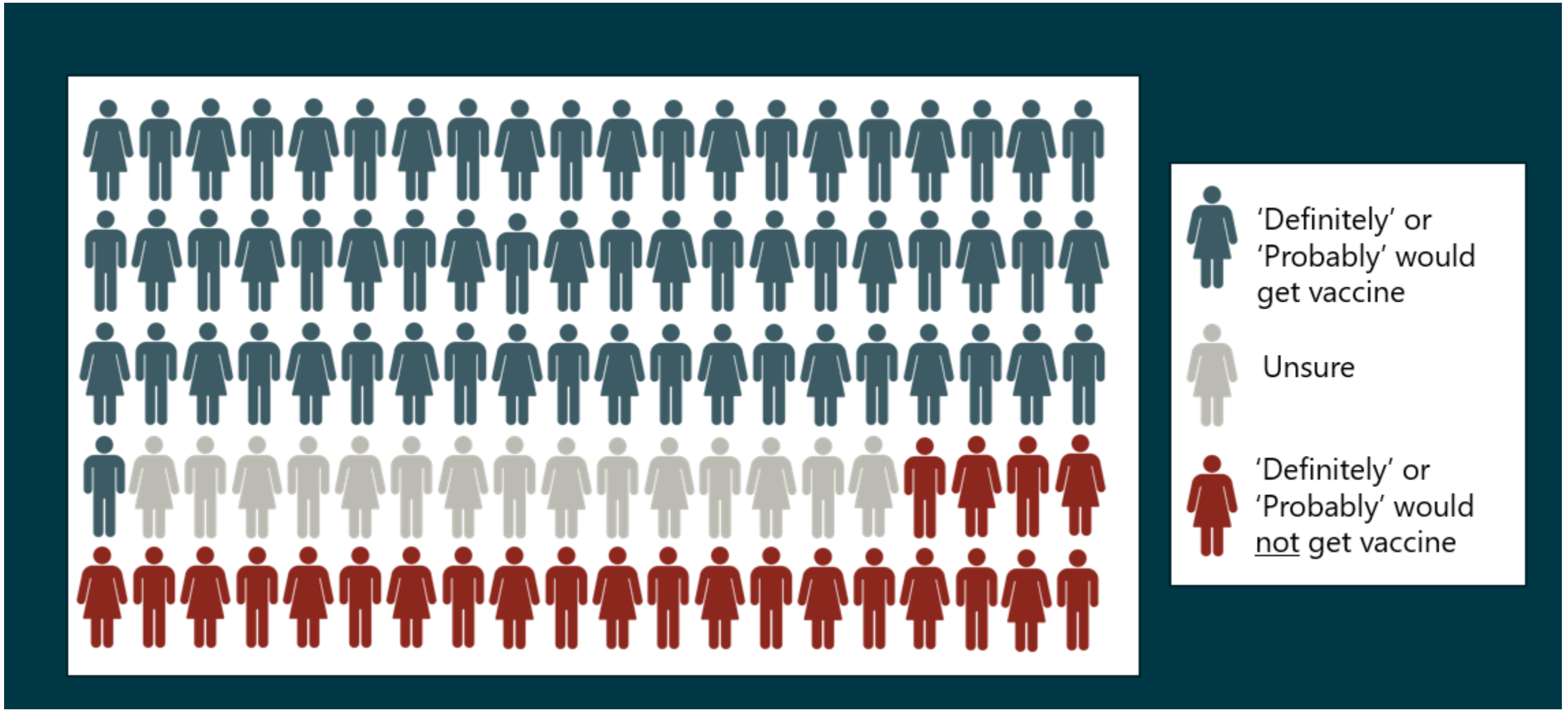
Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

University of Iowa, RAND, and CDC Values Survey, December 21, 2022-January 2, 2023

- 523 participants
  - Pregnancy status:*
    - 58.1% currently pregnant
    - 44.9% given birth in the last 12 months
  - Race and Ethnicity:*
    - 66.0% Non-Hispanic White
    - 16.5% Non-Hispanic Black
    - 9.8% Hispanic
    - 7.7% Other Race/Ethnicity
- 68% of respondents had knowledge of RSV prior to taking survey

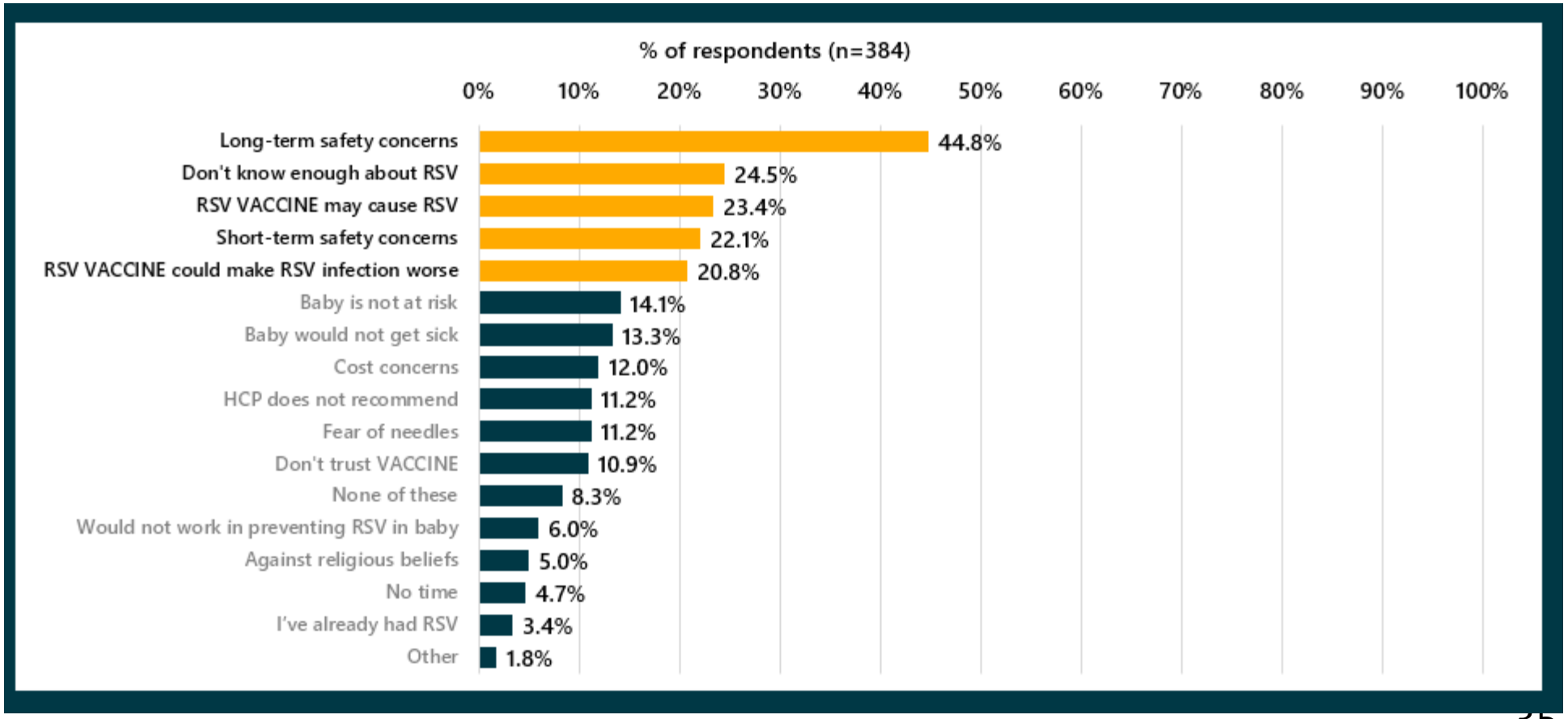
*Participants were able to select all applicable answer choices.
CDC and University of Iowa/RAND survey, unpublished

61% of respondents said they ‘definitely’ or ‘probably’ would get an RSV vaccine while pregnant



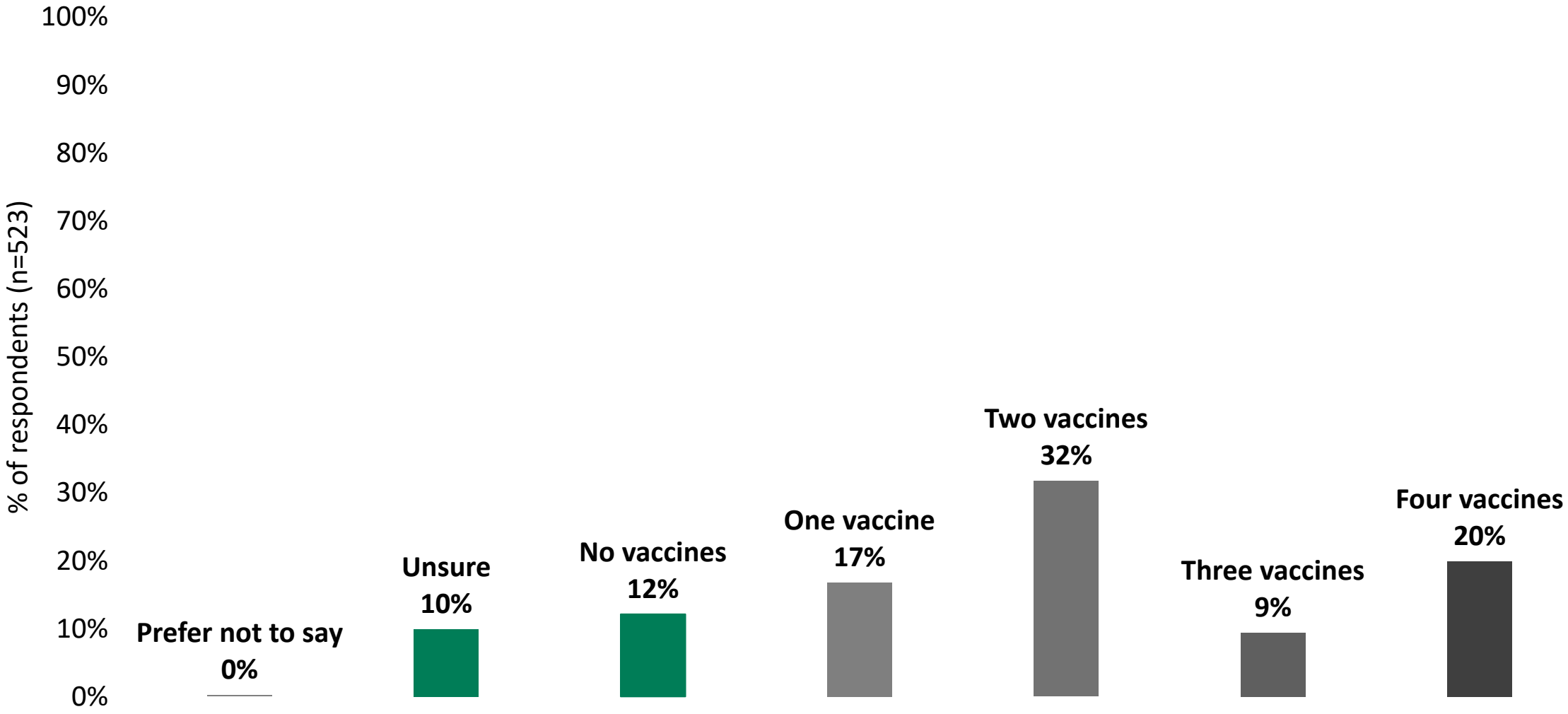
CDC and University of Iowa/RAND survey, unpublished

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



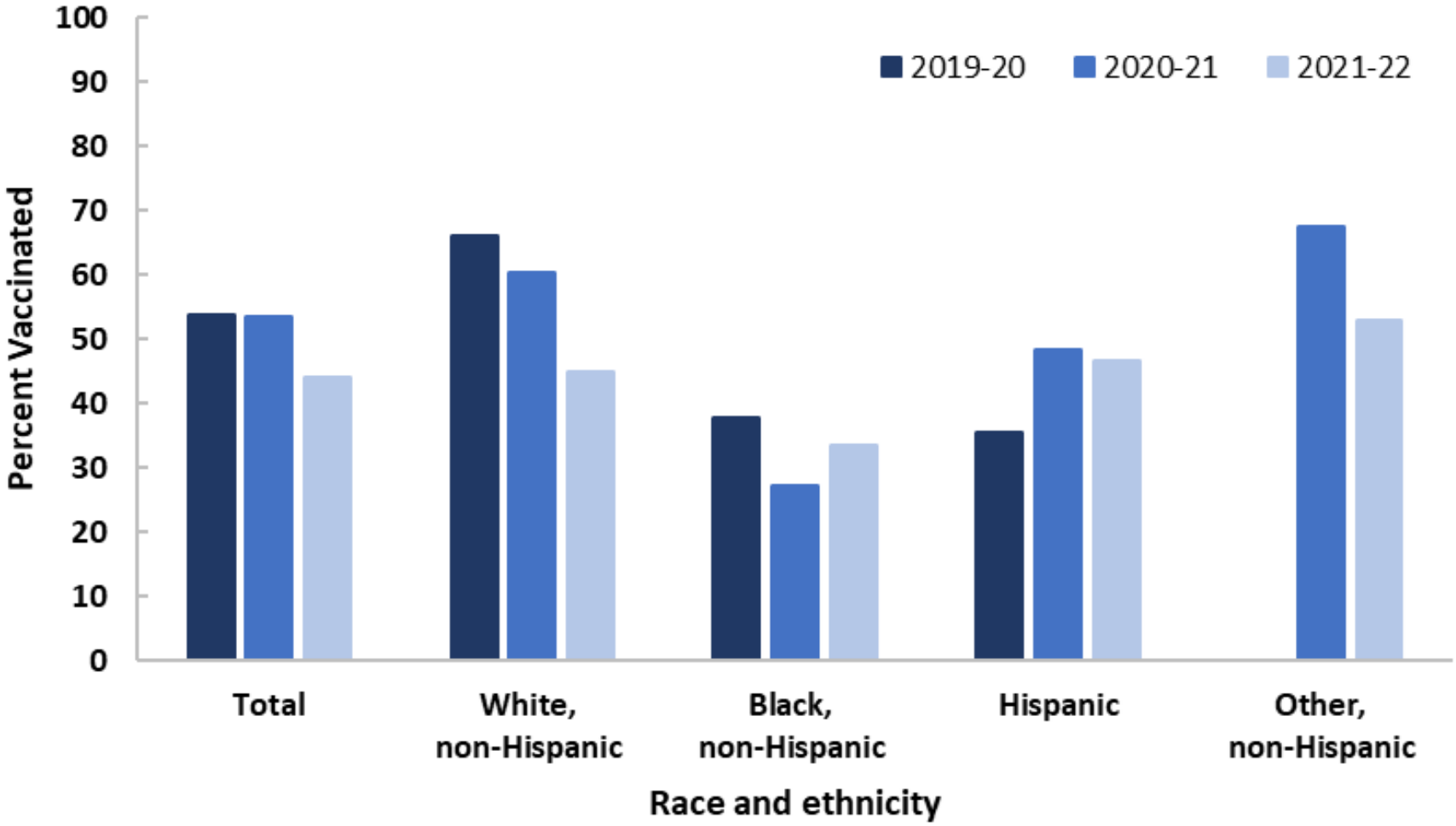
CDC and University of Iowa/RAND survey, unpublished

22% of respondents did not want any vaccines or were unsure about how many vaccines they would be willing to get in the same healthcare visit during pregnancy



CDC and University of Iowa/RAND survey, unpublished

Tdap vaccine coverage among pregnant women (n=838), by race and ethnicity — Internet Panel Survey, United States, April 2020 – April 2022



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

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

– – – – – – Minority Opinion

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 38(9):p 944-951, September 2019. | DOI: 10.1097/INF.0000000000002384

Acceptability

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

No	Probably No	Probably Yes	Yes	Varies	Don’t know

EtR Domain: Feasibility

Is the intervention feasible to implement?

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

ShowLabeling.aspx (pfizer.com) and Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Presentation- Bivalent RSV Prefusion F Vaccine for Maternal Immunization to Protect Infants (fda.gov)

Timing of RSVPreF vaccination during pregnancy

- Trial dosing was between 24 through 36 weeks gestation
- Median gestational age at vaccination in phase 3 trial was 31 weeks[1]
- Administration of maternal RSVPreF vaccine during regularly scheduled prenatal visits and bundling with recommended screening tests and other recommended vaccinations could also improve feasibility
  - Tdap recommended every pregnancy, preferably during the early part of gestational weeks 27 through 36[2]
  - Glucose challenge test recommended at 26-28 weeks gestation[3]

1. FDA. 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. CDC, https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html
3. US HHS OASH, https://www.womenshealth.gov/pregnancy/youre-pregnant-now-what/prenatal-care-and-tests#:~:text=Typically%2C%20routine%20checkups%20occur%3A,for%20weeks%2036%20to%20birth

Efficacy against medically attended RSV-associated lower respiratory tract disease by gestational age at vaccination

Subgroup Gestational Age at Vaccination	RSVpreF (N= 3495) n	RSVpreF (N= 3495) # cases (%)	Placebo (N=3480) n	Placebo (N=3480) # cases (%)	VE (%) (95% CI)
Interim analysis at 180 days	--	--	--	--	--
≥24 weeks to <28 weeks	890	22 (2.5)	866	27 (3.1)	20.7 (-44.6, 57.0)
≥28 weeks to <32 weeks	1030	11 (1.1)	1070	35 (3.3)	67.4 (34.2, 85.0)
≥32 weeks to ≤36 weeks	1572	24 (1.5)	1539	55 (3.6)	57.3 (29.8, 74.7)

Source: adapted from Pfizer 1008 CSR
Abbreviations: RSV= respiratory syncytial virus; VE= vaccine efficacy; CI= confidence interval
Note: this subgroup analysis did not appear in the FDA Briefing Document

Potential considerations for timing of RSV vaccine dosing during the year

- RSV vaccine dosing could be implemented for pregnant people as a seasonal campaign or year-round
- Year-round dosing
  - Simplify implementation and potentially increase vaccine uptake
  - Protect infants in the event of atypical RSV seasonality
  - Is less cost-effective
- Limited benefit for doses given during March-May changes benefit/risk calculation

Potential considerations for timing of RSV vaccine dosing during the year (cont.)

- Some U.S. jurisdictions have different or less predictable RSV seasonality, and recommendations for RSV vaccine dosing in those jurisdictions would need to account for that
  - Tropical climates: parts of Florida, Puerto Rico, U.S. Virgin Islands, Hawaii, Guam, and U.S.-affiliated Pacific Islands
  - Alaska: RSV seasonality is less predictable, and the duration of RSV activity is often longer than the national average

Simultaneous administration of RSV vaccines in pregnant people

- Pregnant people may potentially be eligible to receive RSV, Tdap, COVID-19, and influenza vaccines at same visit
- No available data on simultaneous administration of RSVpreF vaccine in pregnant people and limited data in non-pregnant people
- According to CDC's immunization general best practices, age-appropriate vaccinations can be administered simultaneously, with two specific exceptions[1,2]

1. In persons with anatomic or functional asplenia and/or HIV infection, quadrivalent meningococcal conjugate vaccine (MCV4)-D (MenACWY-D, Menactra) and pneumococcal conjugate vaccine (PCV)13 (PCV13, Prevnar 13) should not be administered simultaneously. In patients recommended to receive both PCV13 and PPSV23, the 2 vaccines should not be administered simultaneously. ACIP Timing and Spacing Guidelines for Immunization | CDC

Available data on simultaneous administration with Pfizer RSVpreF vaccine

- Pfizer Phase 2b study in healthy **non-pregnant** women ages 18-49 on coadministration of Tdap and Pfizer RSVpreF [1]
  - Coadministration of Tdap and Pfizer RSVpreF led to decreased immune response to pertussis components (i.e. non-inferiority criteria were not met)
- Phase 3 study in **non-pregnant** adults ages ≥65 years on coadministration of RSVpreF and adjuvanted seasonal quadrivalent influenza vaccine[2]
  - Non-inferiority criteria were met for antibody titers against all 4 influenza strains, as well as RSV-A and RSV-B
- No safety concerns in either trial
- Neither trial evaluated efficacy (not powered)

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, Volume 225, Issue 12, 15 June 2022, Pages 2077–2086, https://doi.org/10.1093/infdis/jiab505

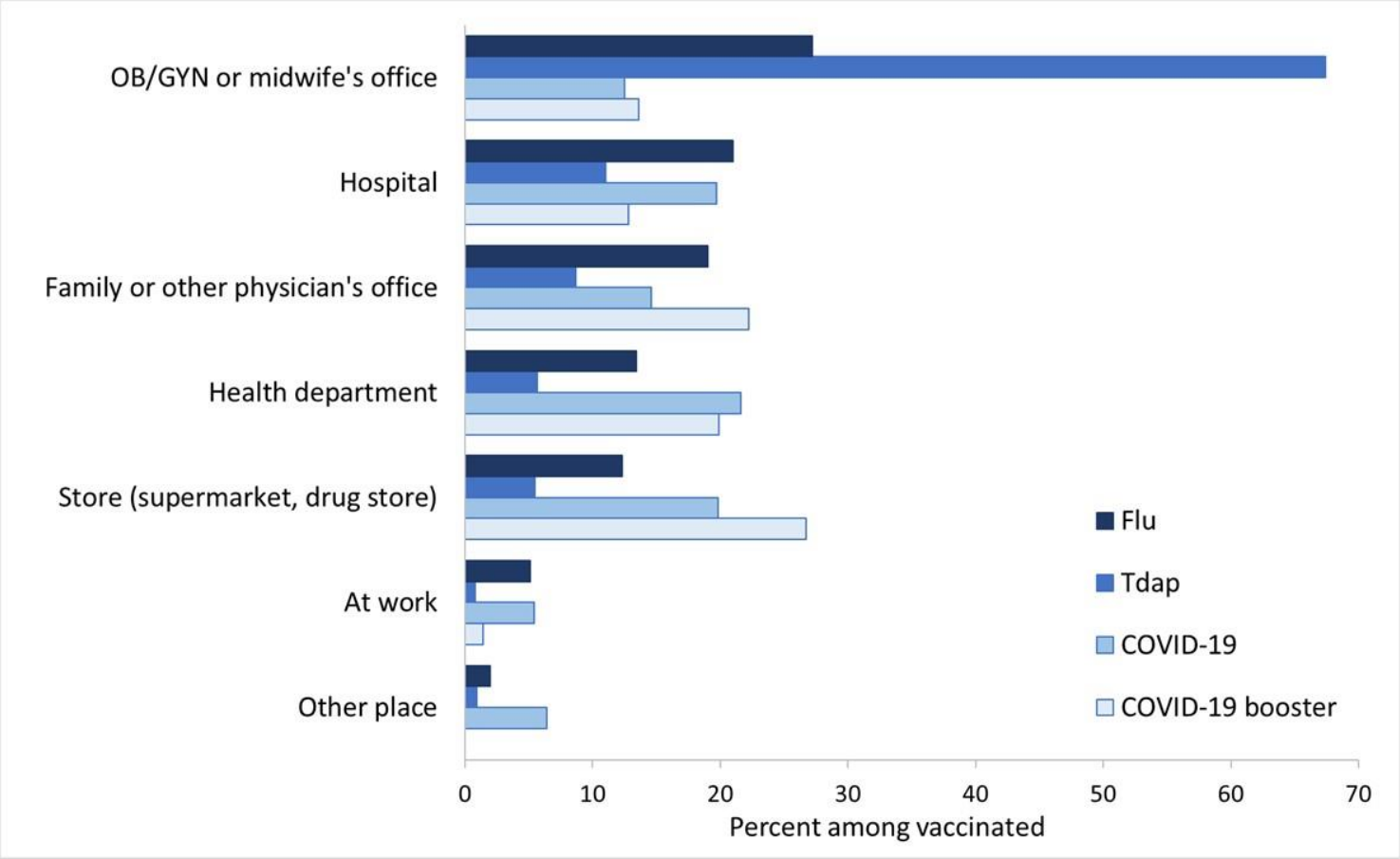
2. Safety and Immunogenicity of RSVpreF Coadministered With SIIV in Adults ≥65 Years of Age - Full Text View - ClinicalTrials.gov

Pertussis immunogenicity and co-administration in adolescents and adults

- There is no accepted correlate of protection for pertussis vaccination
  - In the absence of a correlate of protection, non-inferiority is used to assess immunogenicity of co-administration
  - Clinical significance of failing to meet non-inferiority for pertussis is unclear
- Some studies in adolescents and adults looking at Tdap coadministration with other vaccines, including meningococcal and influenza vaccines, failed to demonstrate non-inferiority against at least one pertussis antibody, but coadministration is still recommended
- Unclear how this might impact protection against pertussis from maternal Tdap when co-administered with RSVpreF

Liang JL, Tiwari T, Moro P, et al. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2018;67(No. RR-2):1–44. DOI: http://dx.doi.org/10.15585/mmwr.rr6702a1external icon

Place of Flu, Tdap, COVID-19 Vaccination among Pregnant Women, United States, Internet Panel Survey, April 2022



"Other place" includes other medical or non-medical place, including school or special site for COVID-19 vaccination

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

Availability of vaccines to pregnant people by practice type

- Survey of health care providers conducted in Fall 2022

Proportion of practices that offer or administer vaccinations on site to pregnant patients

		Provider type (%)			
	Total (n=1,538)	**Family Practitioner/ Internist**	**Pediatrician**	**OB/GYN**	**NP/PA**
Tdap	72%	73%	79%	74%	58%
COVID-19	53%	56%	66%	40%	49%
Influenza	81%	85%	83%	74%	67%

Ob/Gyn = Obstetrician-Gynecologist; NP/PA: Nurse Practitioner or Physician's Assistant
Unpublished data, Fall 2022 DocStyles

Feasibility

- Is Pfizer Maternal RSVPreF vaccine feasible to implement among pregnant people at 24-36 weeks gestation?

Minority Opinion

EtR Domain: Resource Use

Is the intervention a reasonable and efficient allocation of resources?

Summary of Economic Analysis of RSVPreF in Pediatric Populations

- RSVPreF has the potential to be cost-effective
  - Base case ICER: $214,087/QALY
- Results sensitive to:
  - Rate of prematurity
  - Cost per dose
  - Efficacy
  - QALYs lost
  - Timing of vaccination: year-round vs seasonal (e.g., June-February)

ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year

Resource Use

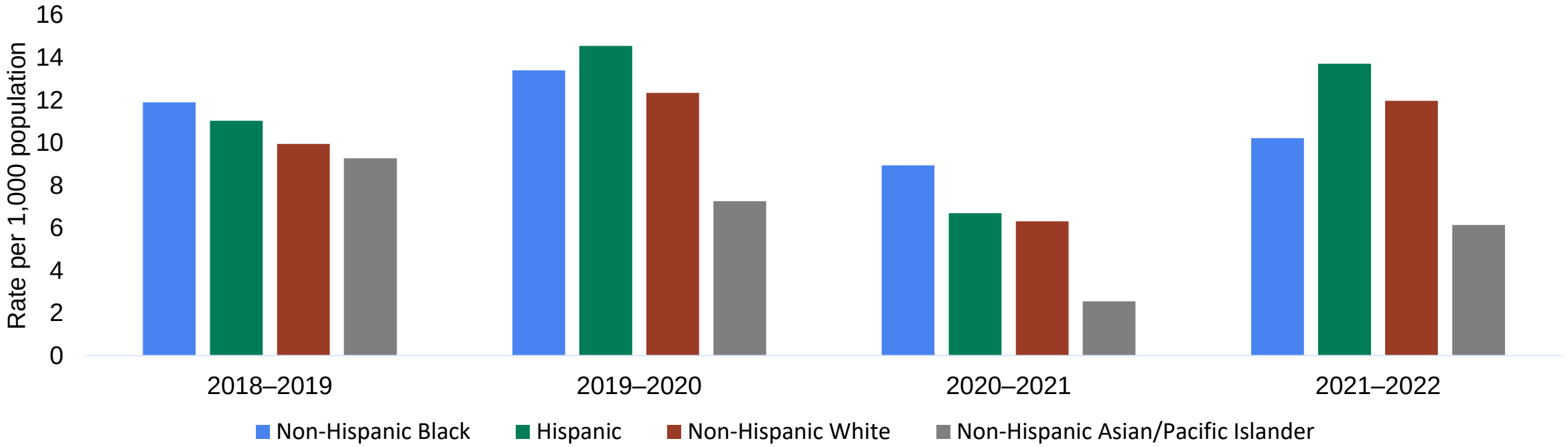
- Is Pfizer Maternal RSVPreF vaccine use among pregnant people at 24–36 weeks gestation a reasonable and efficient allocation of resources?

No	Probably No	Probably Yes	Yes	Varies	Don’t know

EtR Domain: Equity

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

Population-based *hospitalization* rates among infants <6 months old with laboratory-confirmed RSV by race and ethnicity, RSV-NET, 2018–2019 to 2021–2022

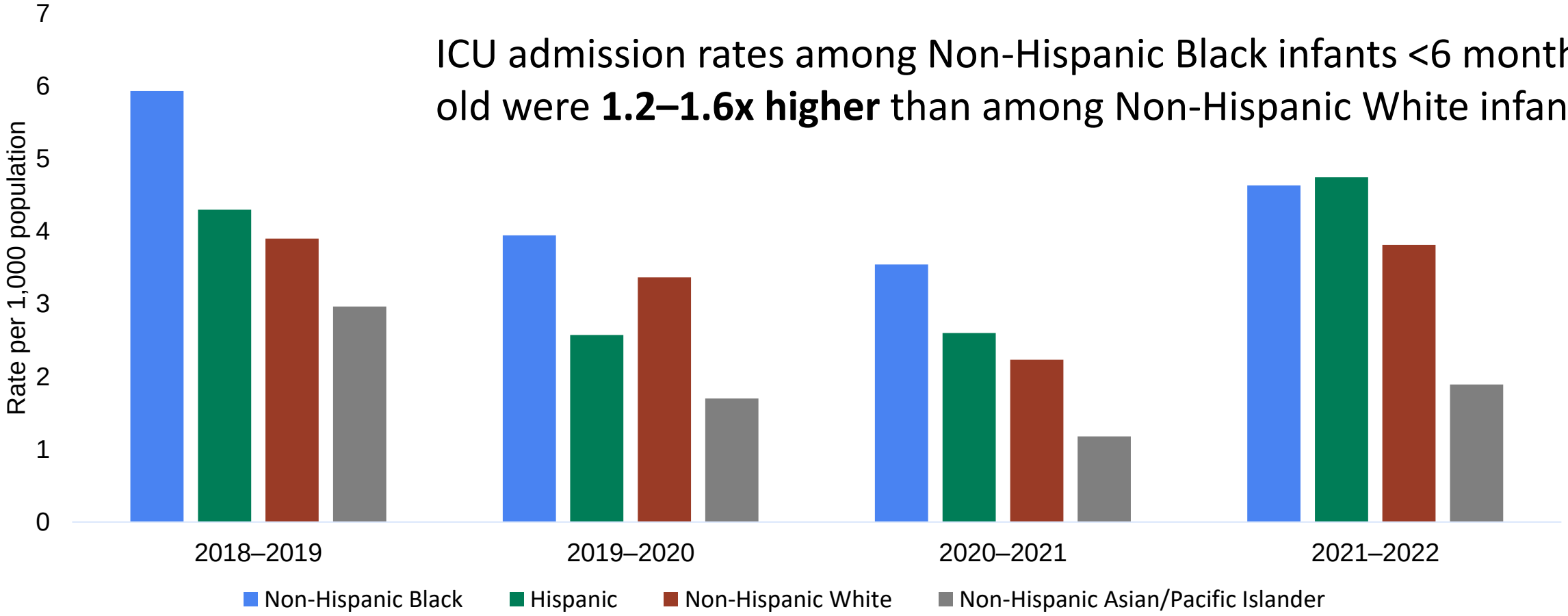


- Hospitalization rates among infants <6 months old differ by race and ethnicity but vary by season
- Rates were not adjusted for RSV testing practices and thus may underrepresent RSV hospitalization rates but should not affect distributions by race and ethnicity

RSV-NET: unpublished data. Surveillance was conducted from October–April for the 2018–19 and 2019–20 seasons, October–September for the 2020–21 season, and October–September excluding May–June for the 2021–22 season. Rates were not adjusted for RSV testing practices; testing practices may differ by racial and ethnic groups and may have changed over time. Black, White, Asian/Pacific Islander children were categorized as non-Hispanic; Hispanic children could be of any race.

Population-based *ICU admission* rates among infants <6 months old with laboratory-confirmed RSV by race and ethnicity, RSV-NET, 2018–2019 to 2021–2022

ICU admission rates among Non-Hispanic Black infants <6 months old were **1.2–1.6x higher** than among Non-Hispanic White infants



RSV-NET: unpublished data. Surveillance was conducted from October–April for the 2018–19 and 2019–20 seasons, October–September for the 2020–21 season, and October–September excluding May–June for the 2021–22 season. Rates were not adjusted for RSV testing practices; testing practices may differ by racial and ethnic groups and may have changed over time. Black, White, and Asian/Pacific Islander children were categorized as non-Hispanic; Hispanic children could be of any race.

Seasonal rate of RSV-associated hospitalizations per 1,000 children among American Indian and Alaska Native children <5 years of age, Nov 2019- May 2020 (SuNA)*

Age	Chinle, Arizona	Whiteriver, Arizona	Anchorage, Alaska	Yukon-Kuskokwim Delta, Alaska	NVSN** for comparison
0-5 Months	83.0 (52.0, 132.5)	70.4 (36.3, 136.6)	35.7 (20.4, 62.6)	132.3 (98.2, 178.1)	21.6 (20.0, 23.3)
6-11 Months	61.6 (35.9, 105.8)	90.1 (50.0, 162.3)	0.0 (0.0, 10.8)	91.6 (64.0, 131.0)	8.2 (7.1, 9.3)
0-11 Months	**71.8 (50.4, 102.4)**	**80.6 (51.9, 125.2)**	**19.2 (11.2, 33.0)**	**112.2 (89.3, 141.0)**	**14.9 (13.9, 16.0)**
12-23 Months	**42.1 (27.2, 65.3)**	**38.7 (22.0, 68.1)**	**15.6 (8.7, 27.7)**	**26.4 (16.6, 41.8)**	**4.5 (3.9, 5.2)**
24-59 Months	10.9 (6.8, 17.4)	8.2 (4.2, 16.0)	1.1 (0.3, 3.8)	5.9 (3.2, 10.9)	1.2 (1.2, 1.5)
0-59 Months	27.2 (21.4, 34.4)	25.4 (18.7, 34.5)	7.7 (5.3, 11.1)	32.7 (26.9, 39.7)	4.6 (4.3, 4.8)

*Hartman et al, RSV2022 12th International Symposium, Belfast 9/29/2022-10/2/2022; Atwell et al. RSV among American Indian and Alaska Native children: 2019-20 (manuscript in press) SuNA = RSV Surveillance among Native American Persons

**Incidence of RSV-associated hospitalization in 2019-2020 included for comparison. NVSN = New Vaccine Surveillance Network.

Insurance coverage for vaccinations among pregnant people

- All ACIP-recommended vaccinations are covered without cost-sharing for adults in the Affordable Care Act (ACA) adult group who receive all essential health benefits[1]
- Beginning on October 1, 2023, coverage of all approved ACIP-recommended adult vaccines and vaccine administration, without cost sharing, will be mandatory for both Medicaid and the Children's Health Insurance Program under section 11405 of the Inflation Reduction Act (IRA) (Pub. L. 117-169).
- Currently, most state Medicaid agencies cover at least some ACIP-recommended adult immunizations for those not subject to essential health benefits, but may not cover all recommended vaccines.

1 Quality of Care Vaccines | Medicaid

Medicaid coverage among pregnant people

- 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 2020, 42.0% of mothers had Medicaid at the time of birth[2]
- In 2020, about 1 in 9 (11.6%) women of childbearing age (aged 15-44 years) was uninsured in the United States[3]

1 Medicaid Coverage for Women | KFF
2 Medicaid coverage of births: United States, 2020 | PeriStats | March of Dimes
3 Uninsured women: United States, 2010-2020 | PeriStats | March of Dimes

Equity

- What would be the impact of Pfizer Maternal RSVPreF vaccine on health equity?

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

Summary

Evidence to Recommendations (EtR) Framework

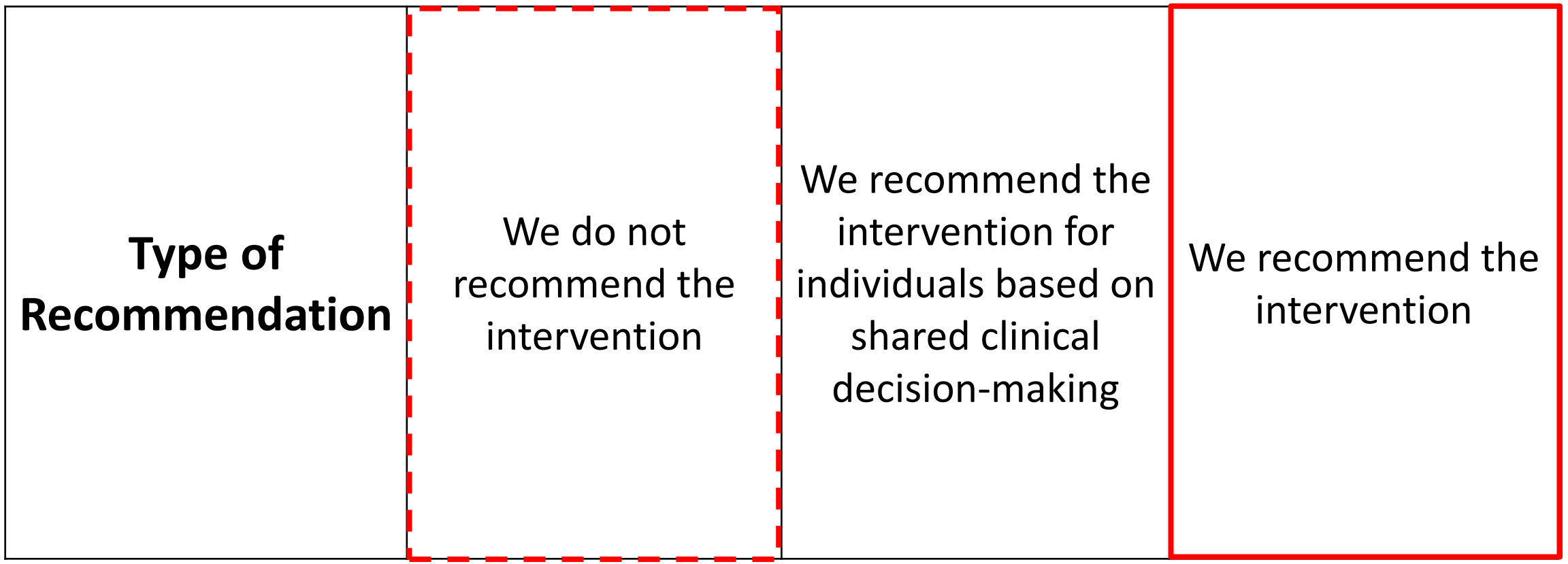
EtR Domain	Question(s)	Work Group Judgements
Public Health Problem	Is the problem of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate to large
	How substantial are the undesirable anticipated effects?	Small vs Don't Know
	Do the desirable effects outweigh the undesirable effects?	Favors intervention vs Unclear
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Probably Yes
	Is there important variability in how patients value the outcome?	Probably important uncertainty or variability
Acceptability	Is the intervention acceptable to key stakeholders?	Probably yes or Yes
Feasibility	Is the intervention feasible to implement?	Probably yes
Resource Use	Is the intervention a reasonable and efficient allocation of resources?	Probably yes
Equity	What would be in the impact of the intervention on health equity?	Probably 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

Minority Opinion

Evidence to Recommendations Framework
Summary: Work Group Interpretations



Minority Opinion

Summary of WG interpretations

- Efficacious vaccine that can prevent RSV lower respiratory tract infection in young infants
- WG expressed concern that the Pfizer trial was underpowered to detect a 20% difference in preterm births between vaccine and placebo recipients
- Interpretation of these overarching themes varied:
  - Some members of the WG expressed concern that the data were insufficient to determine the safety of this vaccine
  - Others stressed this vaccine can provide benefit by preventing RSV lower respiratory tract infection in infants and the difference in preterm births was not statistically significant

Summary of WG interpretations (cont.)

- Imbalance in preterm birth was most prominent in a single country, South Africa
- Imbalance in preterm births was not seen in high-income countries
- Imbalance was still present but less pronounced when comparing prevalence of low birth weight
- Most preterm births were >30 days after vaccination

Summary of WG interpretations (cont.)

- WG discussed considering a narrower recommended dosing window
  - Some expressed support for starting dosing at a later gestational age within 24–36-week window used in the trial as this could mitigate potential risk of early preterm birth until additional safety data are available
  - Others expressed concern that this could leave preterm infants who are at higher risk of severe RSV disease unprotected
- Aligning RSVpreF vaccine dosing during pregnancy with Tdap administration could improve feasibility
- All WG members endorsed the importance of post-introduction vaccine safety monitoring

ACIP Policy Question

- Should vaccination with Pfizer RSVPreF vaccine (120µg antigen, 1 dose IM given 24–36 weeks gestation) be recommended for pregnant people to prevent RSV disease in infants?

Summary of proposed clinical considerations for use of Pfizer RSVpreF vaccine during pregnancy

Proposed clinical considerations: Timing of dosing during pregnancy and simultaneous administration

- Proposed dosing interval for RSVpreF vaccine is 24–36 weeks (aligned with trials)
- Healthcare providers could consider aligning RSVpreF vaccine dosing during pregnancy with Tdap administration for feasibility of implementation
- RSVpreF vaccine can be administered with other recommended vaccines (e.g., influenza, COVID-19) without regards to timing, including simultaneous vaccination on same clinic day

Proposed clinical considerations: Timing of dosing during the year

- RSVpreF vaccine should be offered to pregnant people during June-February in the continental United States

- Healthcare providers can consider offering RSVpreF vaccine year-round
  - For ease of implementation
  - If RSV seasonality is unpredictable
  - In jurisdictions with different RSV seasonality than continental U.S.

Proposed clinical 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
- WG felt that it was too early 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

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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.

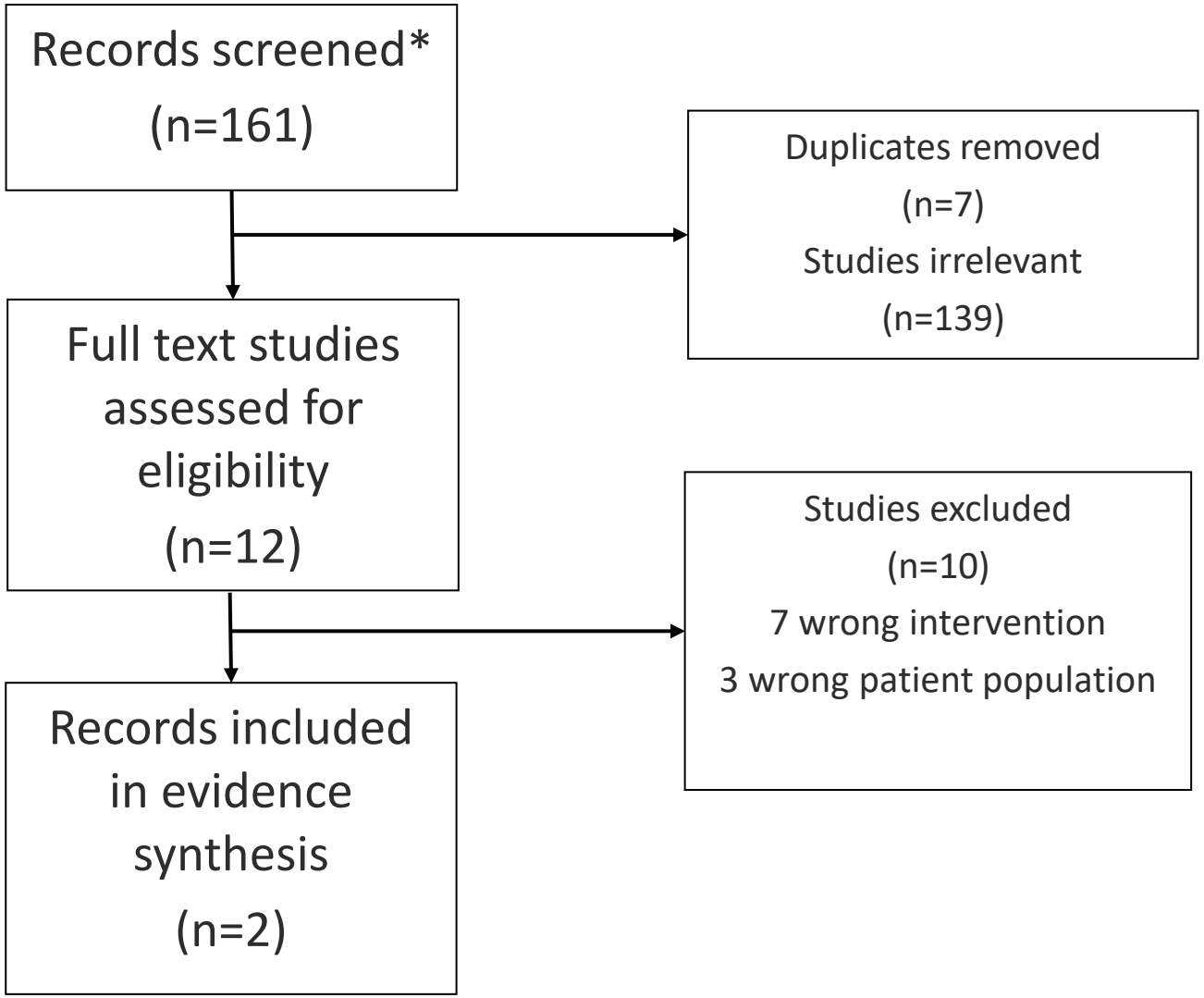
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Extra slides for GRADE

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

Update: May 19, 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

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
- Positive validated RT-PCR in central laboratory
- Confirmed by endpoint adjudication committee (EAC)

SpO2= Peripheral capillary oxygen saturation

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)

[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] 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
- Positive validated RT-PCR in central laboratory
- Confirmed by endpoint adjudication committee (EAC)

SpO2= Peripheral capillary oxygen saturation

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)

[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).

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

- Measures of effect
  - Relative Risk: 0.487 (0.332, 0.706)
  - Absolute Risk[1]: 17 fewer per 1,000 (10 to 22 fewer); NNV: 59 (45, 100)
  - Absolute Risk[2]: 119 fewer per 1,000 (68 to 154 fewer); NNV: 8 (6, 15)
  - Absolute Risk[3]: 56 fewer per 1,000 (32 to 73 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 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)

[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%)

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

- Measures of effect
  - Relative risk: 0.432 (0.193, 0.899)
  - Absolute risk[1]: 7 fewer per 1,000 (1 to 10 fewer); NNV: 143 (100, 1,000)
  - Absolute risk[2]: 11 fewer per 1,000 (2 to 15 fewer); NNV: 91 (67, 500)
- 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 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

SpO2= Peripheral capillary oxygen saturation

[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 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)

[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 (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 (0.806, 1.179)
  - Absolute risk*: 3 fewer per 1,000 (22 fewer to 21 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)

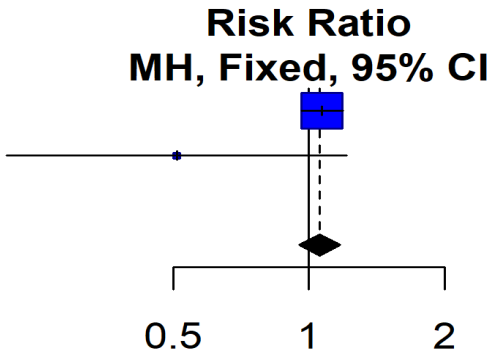
- Phase 3 RCT, MATISSE (unpublished, data obtained directly from manufacturer)
  - Maternal safety set: 3,682 participants in vaccine arm; 3,675 in placebo arm
- Phase 2b RCT (unpublished, data obtained directly from manufacturer)
  - Maternal safety set: 115 participants in vaccine arm (phase 3 formulation); 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.

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

- Measures of effect
  - Relative risk: 1.06 (0.95, 1.17)
  - Absolute risk*: 9 more per 1,000 (8 fewer to 26 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 9: Reactogenicity (grade 3+) in pregnant people (n=2 studies)

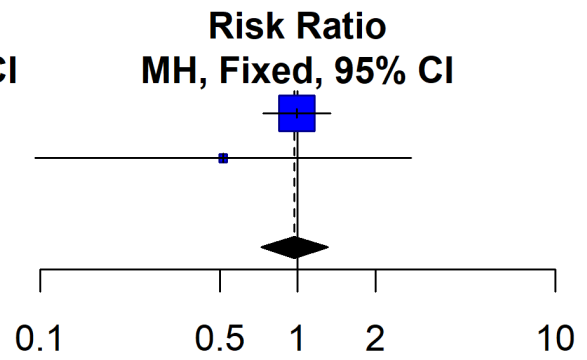
- Phase 3 RCT, MATISSE and Phase 2b (unpublished, data obtained directly from manufacturer)
- Participants reported local and systemic reactions up to 7 days after vaccination

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+)	11/3660 (0.3%)	0/3639 (0%)	22.87 (1.35, 387.94)
	Systemic events (grade 3+)	83/3663 (2.3%)	83/3640 (2.3%)	0.94 (0.70, 1.28)
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)

	Experimental		Control			Risk Ratio
Study	**Events**	**Total**	**Events**	**Total**	**Weight**	**MH, Fixed, 95% CI**
Phase 3, 2023	83	3663	83	3640	95.5%	0.99 [0.74; 1.34]
Phase 2b, 2022	2	114	4	117	4.5%	0.51 [0.10; 2.75]
Total (95% CI)		**3777**		**3757**	**100.0%**	**0.97 [0.72; 1.31]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0\%$



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.

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

- Measures of effect
  - Relative risk: 0.97 (0.72, 1.31)
  - Absolute risk*: 1 fewer per 1,000 (6 fewer to 7 more)
- Concerns in certainty assessment:
  - Serious concern for indirectness as this data only includes 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.

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

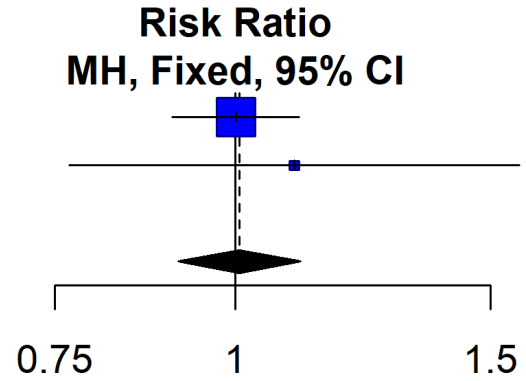
- Phase 3 RCT, MATISSE (unpublished, data obtained directly from manufacturer)
  - Infant safety set: 3,568 in vaccine arm; 3,558 in placebo arm
- Phase 2b RCT (unpublished, data obtained directly from manufacturer)
  - Infant safety set: 114 in vaccine arm (phase 3 formulation); 116 in placebo arm

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)

Study	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio MH, Fixed, 95% CI
Phase 3, 2023	625	3568	623	3558	94.3%	1.00 [0.90; 1.11]
Phase 2b, 2022	41	114	38	116	5.7%	1.10 [0.77; 1.57]
Total (95% CI)		**3682**		**3674**	**100.0%**	**1.01 [0.91; 1.11]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.24$, df = 1 (P = 0.62); $I^2 = 0\%$



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.

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

- Measures of effect
  - Relative risk: 1.01 (0.91, 1.11)
  - Absolute risk*: 2 more per 1,000 (16 fewer to 19 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 11: Preterm births (n=2 studies)

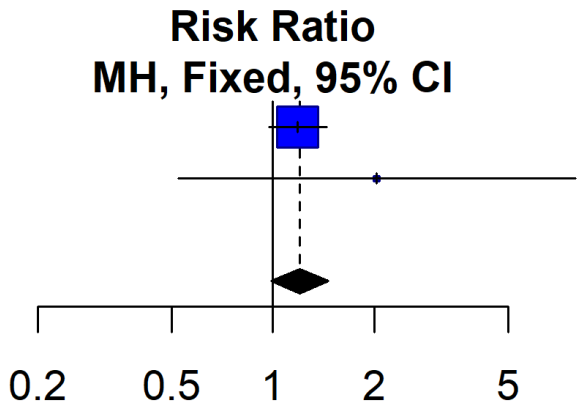
- Phase 3 RCT, MATISSE and Phase 2b (unpublished, data obtained directly from manufacturer)
  - Gestational age at birth <37 weeks and <34 weeks

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)

	Experimental		Control			Risk Ratio
Study	**Events**	**Total**	**Events**	**Total**	**Weight**	**MH, Fixed, 95% CI**
Phase 3, 2023	201	3568	169	3558	98.3%	1.19 [0.97; 1.45]
Phase 2b, 2022	6	115	3	117	1.7%	2.03 [0.52; 7.94]
Total (95% CI)		**3683**		**3675**	**100.0%**	**1.20 [0.99; 1.46]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0\%$



*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

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

- Measures of effect
  - Relative risk: 1.20 (0.99, 1.46)
  - Absolute risk*: 9 more per 1,000 (from 0 fewer to 22 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
- 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.

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 (eg, 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 (eg, 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 (eg, 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.

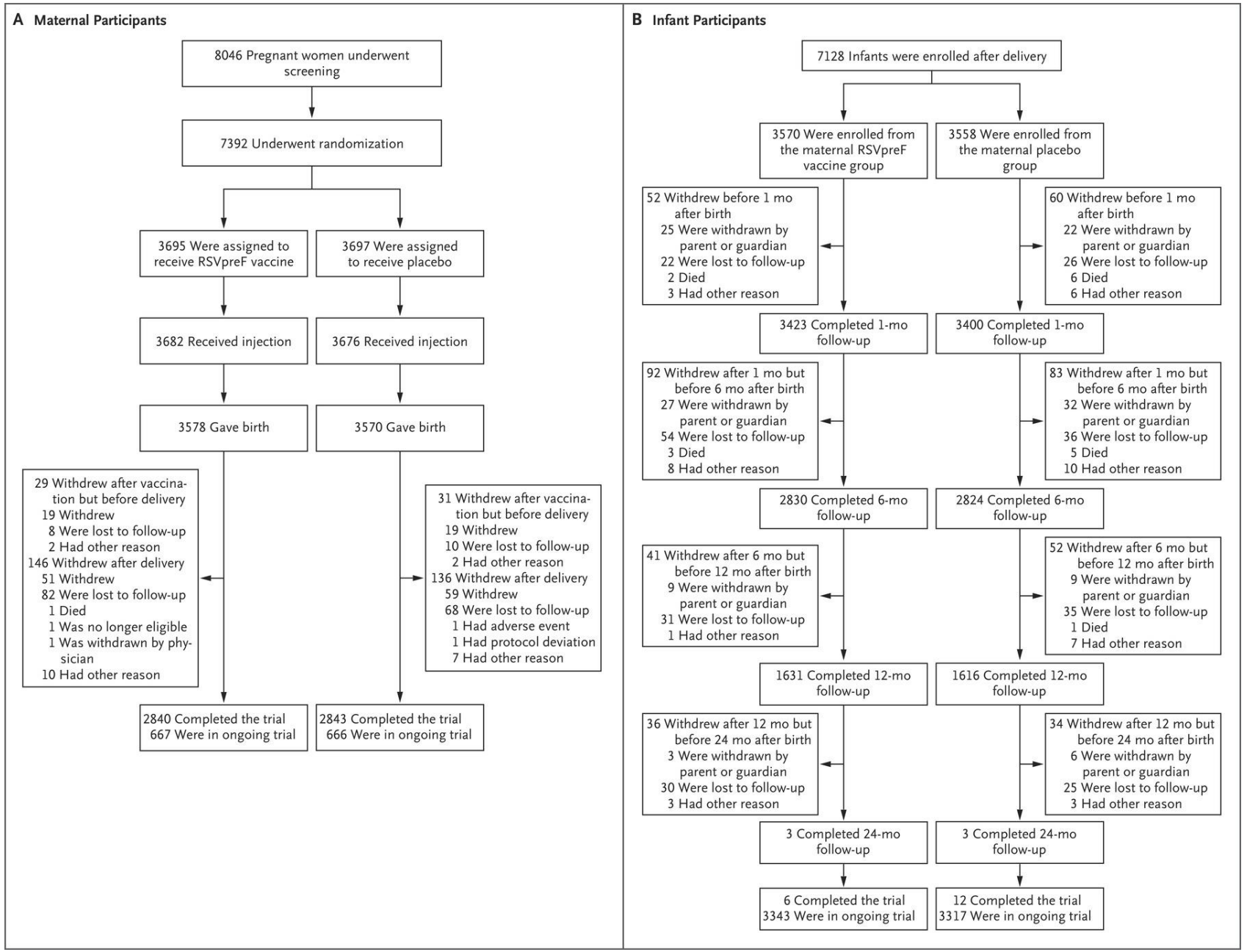


Figure 1. Enrollment, Randomization, Administration of Vaccine or Placebo, and Follow-up

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.

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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	38.0ºC–38.4ºC	>38.4ºC–38.9ºC	>38.9ºC–40.0ºC	>40.0ºC

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.

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Studies Included in the Review of Evidence

Last name first author, Publication year	Study design	Country	Age mean (SD)	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)	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate (99.58% CI)	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3495	3480	Placebo	17 fewer per 1,000 (10 to 22 fewer)	None

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)	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	7 fewer per 1,000 (1 to 10 fewer)	None

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

Last name first author, Publication year	Age mean (SD)	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	N/A
Phase 2b RCT, unpublished	18-49 (range)	114	116	Placebo	Not estimable 0 deaths in trial	N/A

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)	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	3 fewer per 1,000 (22 fewer to 21 more)	None

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

Last name first author, Publication year	Age mean (SD)	N intervention	N comparison	Comparator Vaccine	Absolute 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)	N intervention	N comparison	Comparator Vaccine	Absolute difference/effect estimate	Study limitations (Risk of Bias)
Kampmann B, et al.	29.0 (5.7)	3663	3640	Placebo	RR: 0.94 (0.70, 1.28)	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	Absolute 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	Absolute 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 (95% CI)	Absolute (95% 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 (0.332, 0.706)	17 fewer per 1,000 (10 to 22 fewer)	Critical	High
								23.1%		119 fewer per 1,000 (68 to 154 fewer)		
								11.0%		56 fewer per 1,000 (32 to 73 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 (0.193, 0.899)	7 fewer per 1,000 (1 to 10 fewer)	Critical	Moderate
								1.9%		11 fewer per 1,000 (2 to 15 fewer)		
All-cause medically attended lower respiratory infection in infants												
1	Randomized studies	Not serious	Not serious	Not serious	Serious	None	392/3495 (11.2%)	402/3480 (11.6%)	0.97 (0.85, 1.11)	3 fewer per 1,000 (22 fewer to 21 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	Not serious	Serious	None	605/3797 (15.9%)	572/3792 (15.1%)	1.06 (0.95, 1.17)	9 more per 1,000 (8 fewer to 26 more)	Critical	Moderate
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)	1 fewer per 1,000 (6 fewer to 7 more)	Important	Moderate
Serious adverse events in infants												
2	Randomized studies	Not serious	Not serious	Not serious	Serious	None	625/3568 (17.5%)	623/3558 (17.5%)	1.01 (0.91, 1.11)	2 more per 1,000 (16 fewer to 19 more)	Critical	Moderate
Preterm birth												
2	Randomized studies	Not serious	Not serious	Not serious	Very serious	None	207/3683 (5.6%)	172/3675 (4.7%)	1.20 (0.99, 1.46)	9 more per 1,000 (0 fewer to 22 more)	Critical	Low