RSV Vaccines for Adults

Kathryn M. Edwards MD
Professor of Pediatrics Emerita
Vanderbilt University Medical Center
Nashville, TN

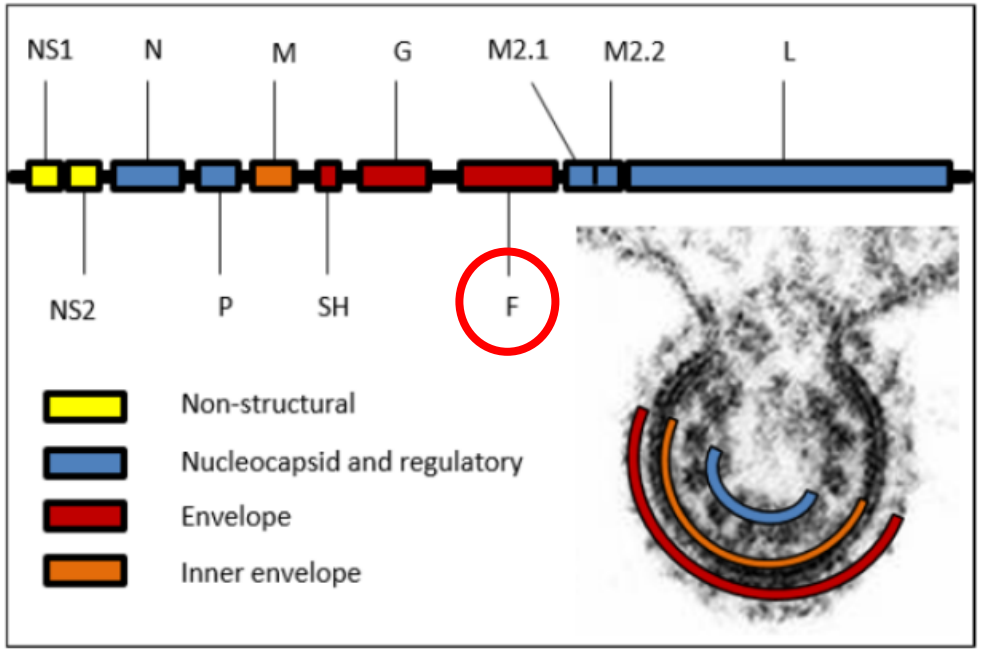
Disclosures

Affiliation / Financial Interest	Organization
Grant Recipient	CDC (Vaccine Safety with COVID vaccines)
Grant Recipient	NIH (Mentoring young investigators in vaccine sciences)
Consultant	BioNet and Dynavax (pertussis vaccines)
Consultant	IBM (vaccine safety networks)
Consultant	Data Safety and Monitoring Boards: Sanofi, X-4 Pharma, Seqirus, Moderna, Pfizer, Merck, Roche,

Objectives of Presentation

- Review the Structural Basis of Immunity to RSV
- Review the Impact of RSV on Older Adults
- Discuss 2 New Vaccines for RSV prevention
  - GlaxoSmithKline (GSK)
  - Pfizer
- Outline efficacy and safety of each vaccine
- Review recommendations for Adult vaccine use in the US
- Review recommendations for RSV prevention in infants

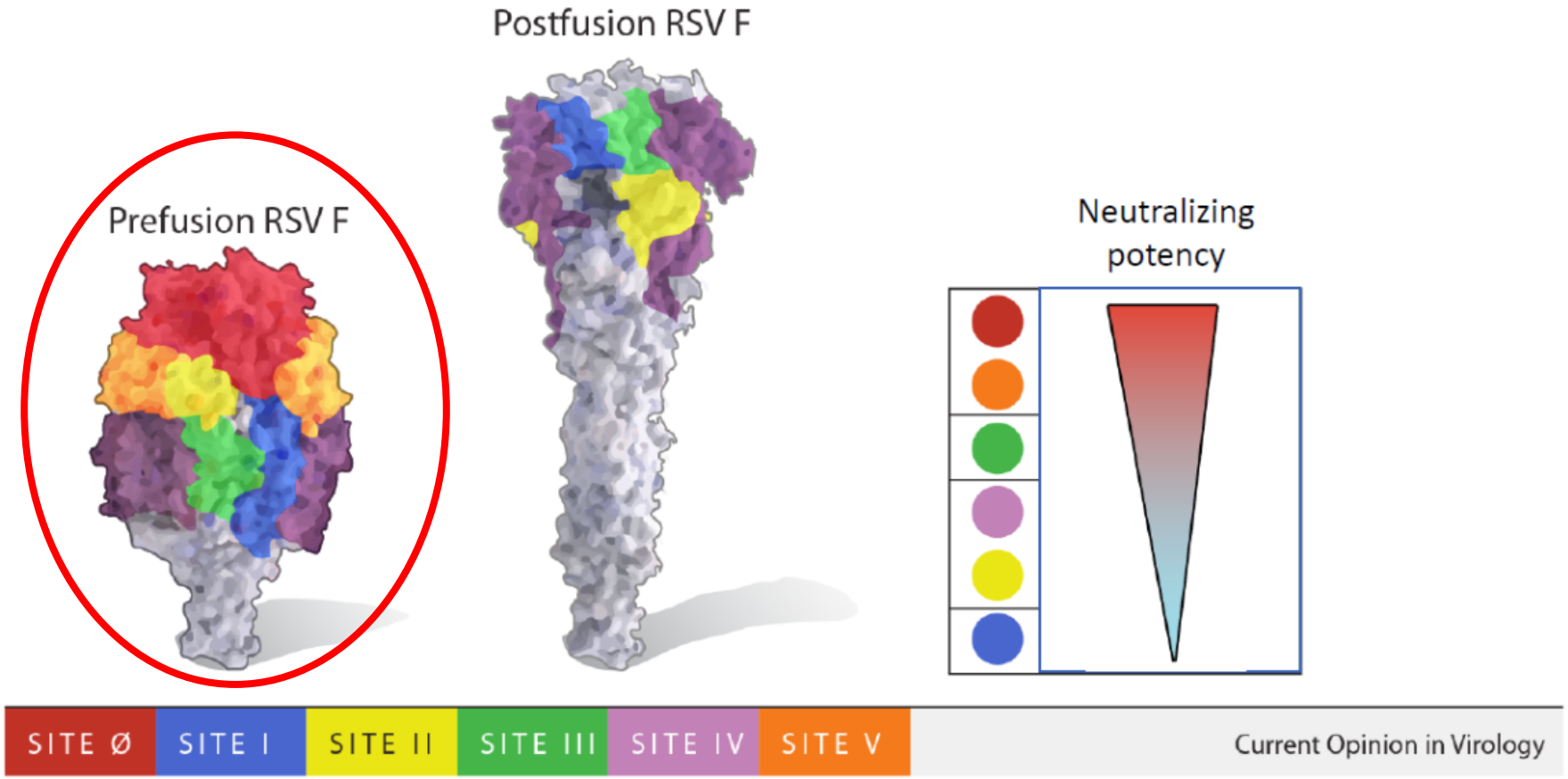
RSV genome



Respiratory Syncytial Virus (RSV) | British Society for Immunology

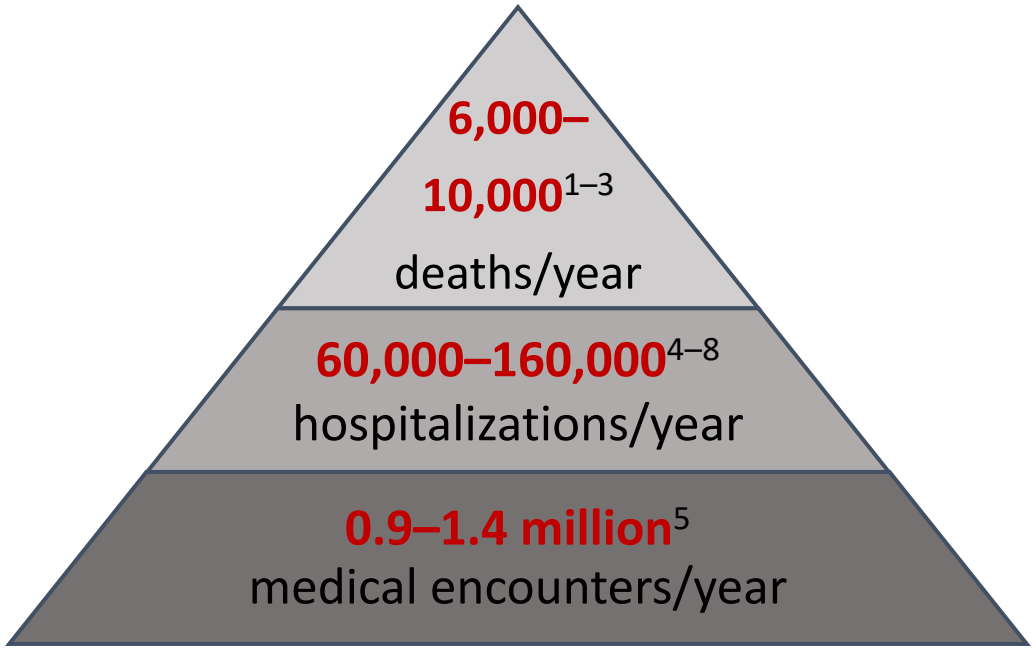
- Filamentous *Orthopneumovirus*
- 15.2 kbp genome
- Single stranded negative sense
- 11 viral proteins
- Divided into two subgroups / serotypes A and B
- RSV A and B co-circulate

The fusion (F) protein exists in two or more structural forms exposes different antigenic regions



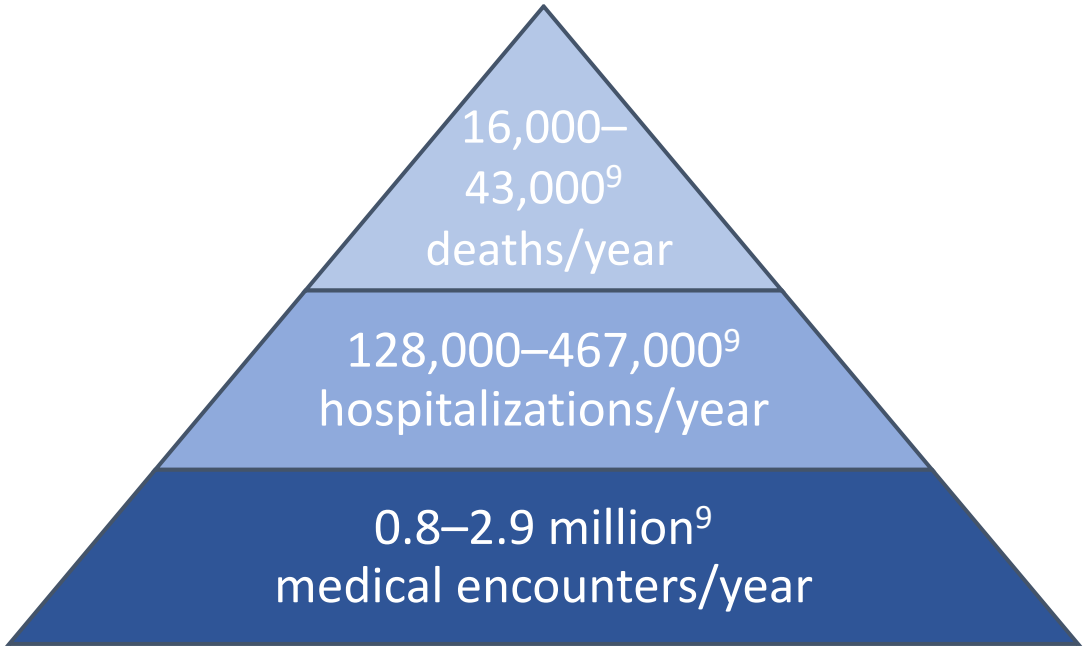
Graham B. Current Opinion in Virology. 23: 107-112. 2017.

RSV and influenza burden, compared



RSV

Adults aged ≥65 years

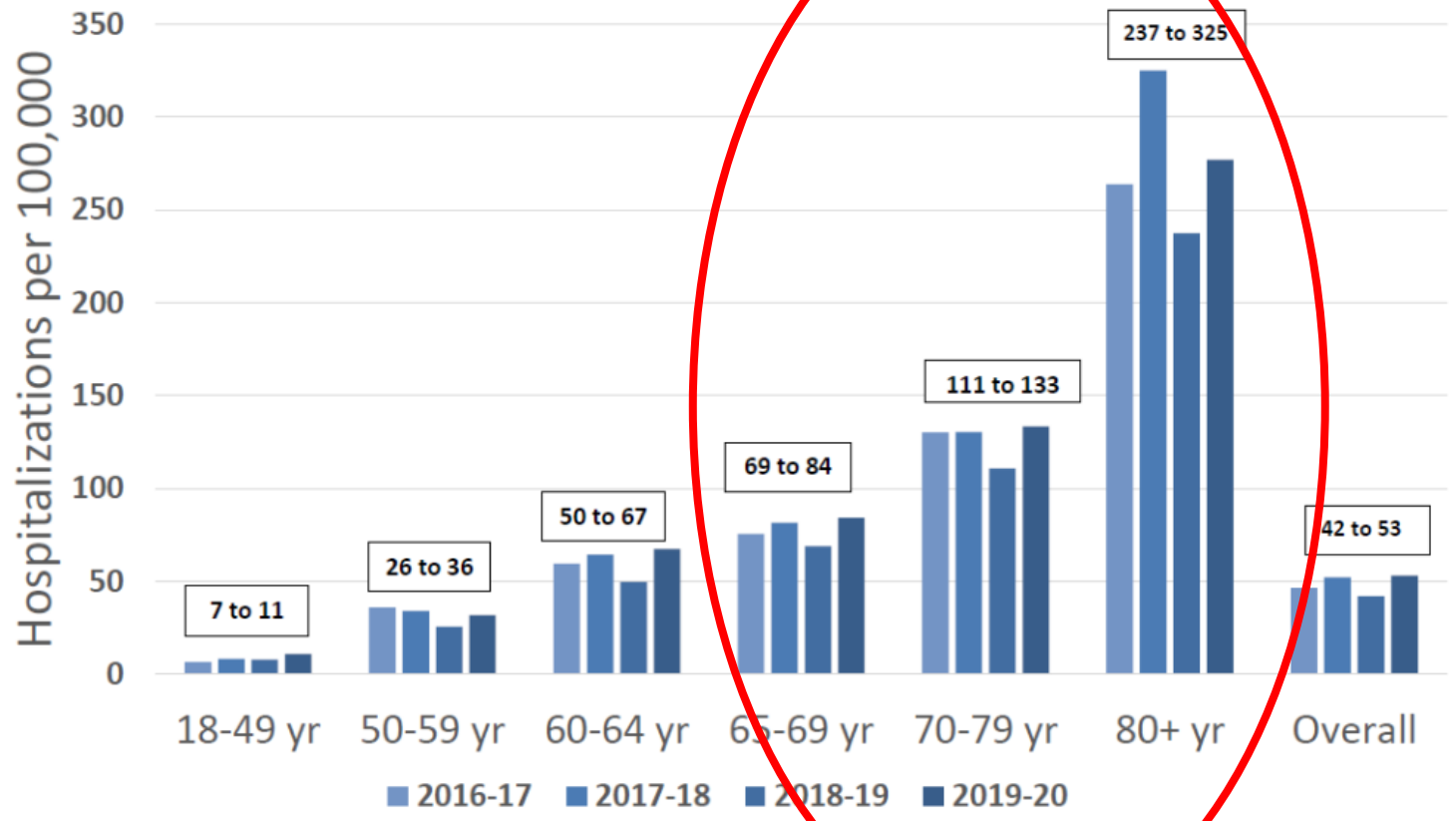


Influenza

Adults aged ≥65 years

1. Thompson et al, JAMA (2003): https://doi.org/10.1001/jama.289.2.179
2. Matias et al, Influenza Other Respi Viruses (2014): https://doi.org/10.1111/irv.12258
3. Hansen et al, JAMA Network Open (2022): https://doi.org/10.1001/jamanetworkopen.2022.0527
4. Widmer et al, JAMA Network Open (2012): https://doi.org/10.1093/infdis/jis309
5. McLaughlin et al, Open Forum Infect Dis (2022): https://doi.org/10.1093/ofid/ofac300
6. Zheng et al, Pneumonia (2022): https://doi.org/10.1186/s41479-022-00098-x
7. Branche et al, Clinical Infect Dis (2022): https://doi.org/10.1093/cid/ciab595
8. CDC RSV-NET data 2016–2020 (unpublished)
9. CDC Influenza Burden 2015-2020: https://www.cdc.gov/flu/about/burden/past-seasons.html

RSV-associated hospitalization rates by adult age group, RSV-NET 2016–2020



RSV-NET: unpublished data; https://www.cdc.gov/rsv/research/rsv-net/overview-methods.html.
Rates are adjusted for the frequency of RSV testing during recent prior seasons and the sensitivity of RSV diagnostic tests..

Slide credit: Fiona Havers

Underlying medical conditions among adults ≥18 years hospitalized for RSV: RSV-NET 2014-2018

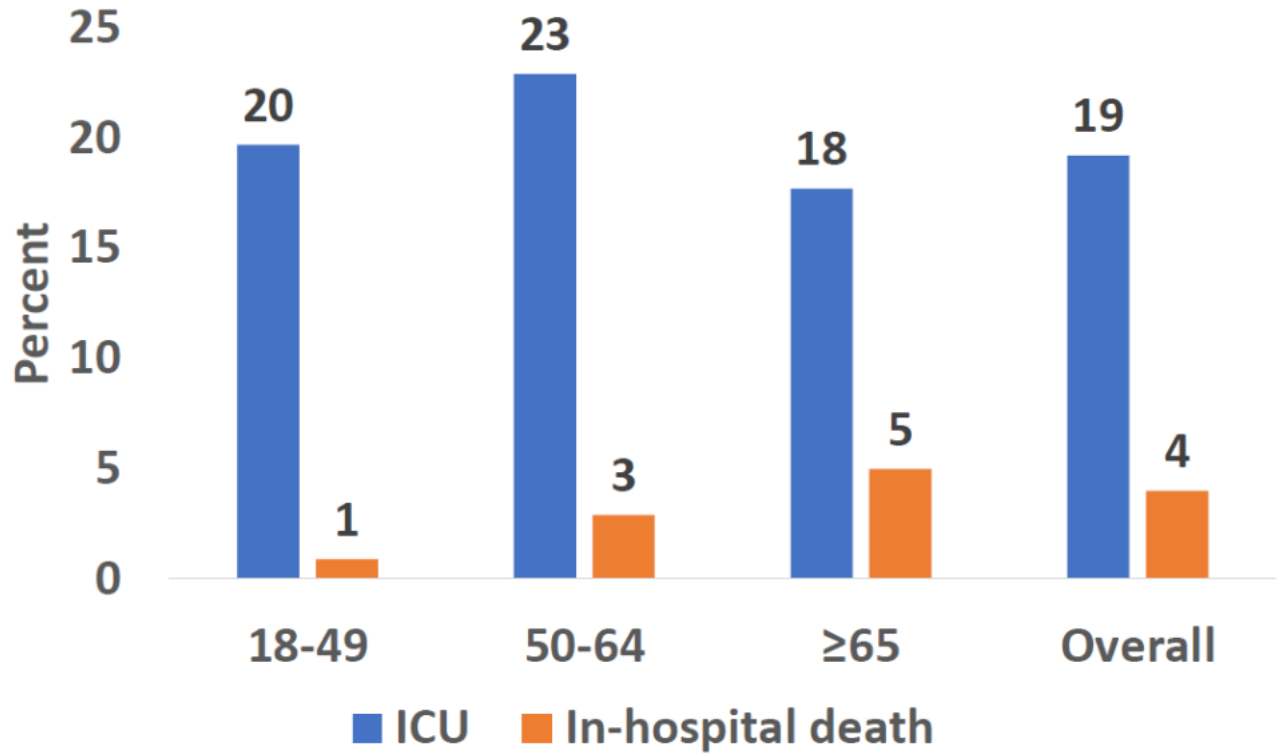
Major underlying condition categories (n=4,970)	N=4,970	%
Cardiovascular disease	2833	57.0
Chronic lung disease	2486	50.0
Diabetes mellitus	1692	34.0
Renal disease	1378	27.7
Immunocompromised condition	1126	22.7
Neurologic disorder	1041	21.0
Chronic metabolic disease (except diabetes)	934	18.8
Liver disease	332	6.7
Blood disorders/ hemoglobinopathy	132	2.7
Other disease or condition	429	8.7

Source: CDC unpublished data.

94% of hospitalized adults have underlying medical conditions:

- **46%: 1-2 conditions**
- **48%: ≥3 conditions**

Outcomes among adults ≥18 years hospitalized for RSV: RSV-NET 2017-18 to 2019-20 seasons (n=8,214)



Severe outcomes frequent among adults hospitalized for RSV of all ages

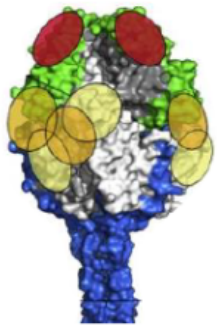
Source: CDC unpublished data.

GSK's RSV older adult vaccine

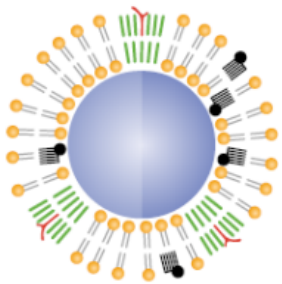
The combination of RSVPreF3 (120 µg) and AS01$_E$ is designed to induce a robust humoral and cellular immune response, to help protect older adults and those with underlying comorbidities

RSVPreF3 OA Vaccine

RSVPreF3 Antigen (120 µg) + **AS01$_E$ Adjuvant System**



Antigen engineered to preferentially maintain the pre-fusion conformation and display potent neutralizing epitopes to boost humoral immune response in older adults[1,2]



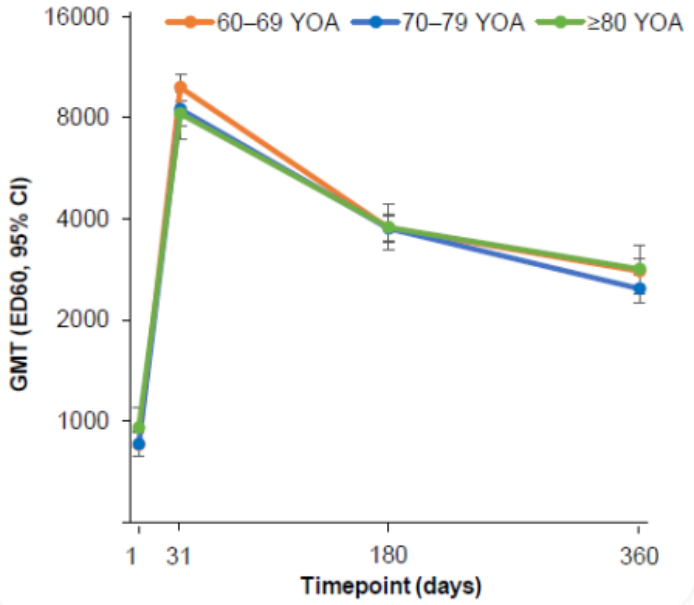
Boosts cellular immune response and restores the RSVPreF3 CD4+ T-cell level in older adults[2]

AS01$_E$, Adjuvant System 01$_E$ (25 µg *Quillaja saponaria* Molina, fraction 21, 25 µg 3-Odesacyl-4'- monophosphoryl lipid A); OA, older adults.
Image of F protein reproduced from Graham BS, et al. *Curr Opin Immunol* 2015;35:30–38, Copyright 2015, with permission from Elsevier.
1. Graham BS, et al. *Curr Opin Immunol.* 2015;35:30–38; 2. Leroux-Roels I, et al. *J Infect Dis*. 2022:jiac327.

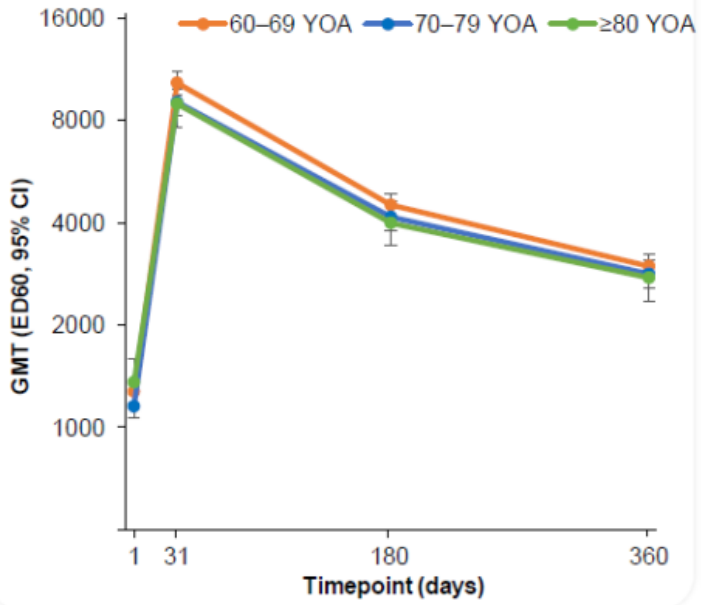
Durable RSV-A, RSV-B neutralizing antibody and CD4+ T-cell responses across all age groups, 12 months post vaccination

AReSVi-004

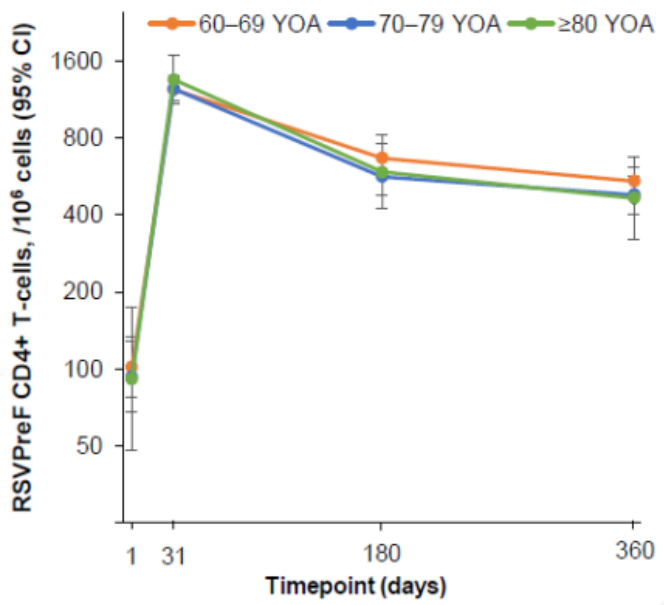
RSV-A NAb



RSV-B NAb



RSVPreF3-specific CD4+ T-cells*



*CD4+ T-cells expressing ≥2 activation markers including ≥1 cytokine among CD40L, 4-1BB, IL-2, TNF-α, IFN-γ, IL-13, IL-17 (events/10^6 cells; by intracellular staining). Data at each timepoint for all 3 groups combined: Day 1 N=985 for RSV A, N=986 for RSV B, and N=471 for RSVPreF-specific CD4+ T-cells; Day 31 N=937 for RSV A and B, and N=408 for RSVPreF-specific CD4+ T-cells; Month 6=924 for RSV A and B and N=436 for RSVPreF-specific CD4+ T-cells; Month 12 N=870 for RSV A and B, and N=438 for RSVPreF-specific CD4+ T-cells; NCT0473287. CD, cluster of differentiation; CI, confidence interval; ED, Estimated Dilution; ED60, serum dilution inducing 60% inhibition in plaque-forming units; GMT, geometric mean titer; IL, interleukin; NAb, neutralizing antibody; TNF, tumor necrosis factor; YOA, years of age.

1. https://clinicaltrials.gov/ct2/show/NCT04732871 (accessed October 2022).

GSK pivotal phase 3 trial

- GSK phase III randomized controlled trial (RCT) (unpublished, data obtained from manufacturer)
- Persons aged ≥60 years in Australia, Belgium, Canada, Estonia, Finland, Germany, Italy, Japan, Republic of Korea, Mexico, New Zealand, Poland, Russian Federation, South Africa, Spain, United Kingdom, United States
  - 32% from United States; 92% from Northern Hemisphere
- Data evaluated: data cut-off April 11, 2022; median follow-up 6.7 months
  - Enrollment and efficacy follow up: May 2021–April 2022
- Exposed set: 12,467 participants in vaccine arm; 12,499 in placebo arm
  - Per-protocol set: 1 excluded from vaccine arm; 5 from placebo arm
  - 8.2% aged ≥80 years, 1.5% with gait speed <0.4 m/s, 1.2% long term care facility residents

TABLE 1. Efficacy of 1 dose of GSK respiratory syncytial virus RSVpreF3 vaccine against respiratory syncytial virus–associated disease among adults aged ≥60 years — multiple countries, 2021–2023

Efficacy evaluation period	Vaccine efficacy against outcome*	
	RSV-associated LRTD†	RSV-associated medically attended LRTD§
Season 1¶	82.6 (57.9–94.1)**	87.5 (58.9–97.6)††
Season 2§§	56.1 (28.2–74.4)††	—¶¶
Combined seasons 1 and 2 (Interim)***	74.5 (60.0–84.5)†††	77.5 (57.9–89.0)††

Abbreviations: LRTD = lower respiratory tract disease; RSV = respiratory syncytial virus.

TABLE 2. Safety* of 1 dose of GSK respiratory syncytial virus RSVPreF3 vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event		
	RSVPreF3 recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	549/12,570 (4.4)	540/12,604 (4.3)	1.02 (0.91–1.15)
Severe reactogenicity events††	37/979 (3.8)	9/976 (0.9)	4.10 (1.99–8.45)
Inflammatory neurologic events§§	3 events in trials without placebo recipients¶¶	—¶¶	—¶¶

Abbreviations: AE = adverse event; GBS = Guillain-Barré syndrome.

PFIZER RSV Vaccine

Bivalent RSV Prefusion F Vaccine

Proposed Indication:

Prevention of acute respiratory disease and lower respiratory tract disease caused by respiratory syncytial virus (RSV)

Individuals 60 years of age and older

DOSE LEVEL

- 120 µg without an adjuvant
- Dose contains 60 µg dose of each prefusion protein antigen, in a 0.5 mL injection

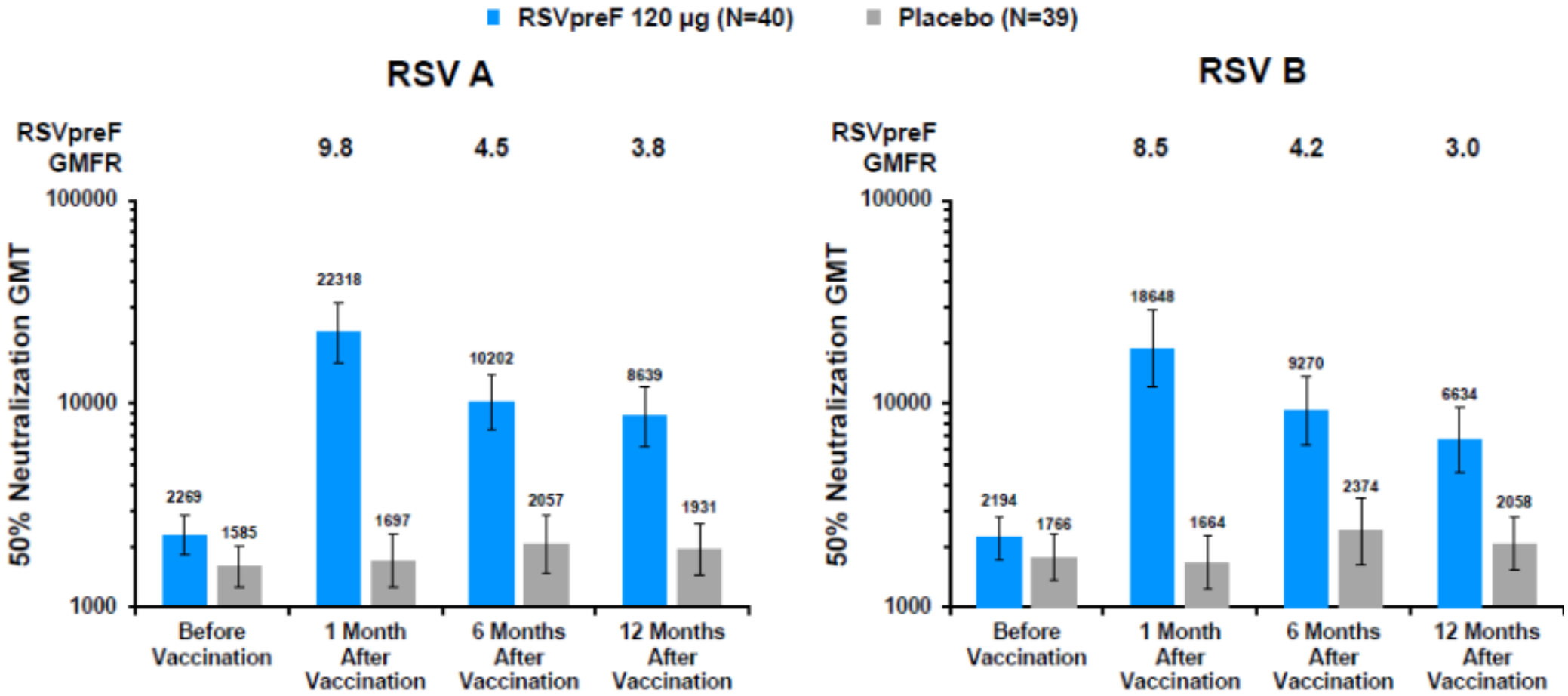
PRESENTATION

- Single dose 2 mL vial
- 1 mL Pre-filled syringe
- Vial adaptor

STORAGE

- Refrigeration at 2°C to 8°C (36°F to 46°F)
- After reconstitution: 15ºC to 30ºC (used within 4 hours of reconstitution)

RSV Neutralizing Titer GMFRs at 1, 6, and 12 months After Vaccination Compared with Pre-vaccination for RSV Subgroups A and B in Participants 65–85 Years of Age



MFR=Geometric Mean Fold Rise, GMT=Geometric Mean Titer

Pfizer pivotal phase 3 trial

- Pfizer phase 3 randomized controlled trial (RCT), RENOIR, (unpublished, data obtained from manufacturer)
- Persons aged ≥60 years in Argentina, Canada, Finland, Japan, Netherlands, South Africa, and United States
  - 60% from United States; 76% from Northern Hemisphere
- Data evaluated: data cut-off July 8, 2022; mean follow-up 6.8 months per participant
  - Enrollment and efficacy follow up: August 2021–July 2022
- Exposed set: 17,214 participants in vaccine arm; 17,069 in placebo arm
  - Per protocol set: 908 participants excluded from vaccine arm; 761 from placebo
    - <15 days of follow up, ineligibility for study, incorrect intervention, major protocol deviations

TABLE 3. Efficacy of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine against respiratory syncytial virus–associated disease among adults aged ≥60 years — multiple countries, 2021–2023

Efficacy evaluation period	Vaccine efficacy against outcome, % (95% CI)*	
	RSV-associated LRTD†	RSV-associated medically attended LRTD§
Season 1¶	88.9 (53.6–98.7)	84.6 (32.0–98.3)
Season 2 (Interim)**	78.6 (23.2–96.1)	—††
Combined seasons 1 and 2 (Interim)§§	84.4 (59.6–95.2)	81.0 (43.5–95.2)

Abbreviations: LRTD = lower respiratory tract disease; LRTI = lower respiratory tract illness; RSV = respiratory syncytial virus.

TABLE 4. Safety* of 1 dose of Pfizer respiratory syncytial virus RSVpreF vaccine in adults aged ≥60 years — multiple countries, 2021–2023

Safety event	Risk for event		
	RSVpreF recipients no./No. (%)†	Placebo recipients no./No. (%)§	Relative risk (95% CI)¶
Serious AE**	792/18619 (4.3%)	749/18334 (4.1%)	1.04 (0.94–1.15)
Severe reactogenicity events††	36/3673 (1.0%)	24/3491 (0.7%)	1.43 (0.85–2.39)
Inflammatory neurologic events§§	3/18622 (—)¶¶	0/18335 (—)	—¶¶

Abbreviations: AE = adverse events; GBS = Guillain-Barré syndrome.

Cases of Guillain Barré syndrome (GBS) were reported after vaccination with both investigational vaccines

- All cases had onset during the 42-day risk window post-vaccination used in CDC surveillance
- The significance of 1–2 cases in safety databases of 15,000–26,000 persons is unclear
- Population-based rates of GBS increase with age[a]
- RSV infection has also been associated with GBS in case reports and case series[b,c], but causal link has not been established
- The work group continues to review and interpret safety evidence

[a] Sejvar JJ, Baughman AL, Matthew Wise, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33.
[b] Helgeson SA, Heckman AJ, Harris DM. First Reported Case of Respiratory Syncytial Virus Infection Causing Guillain-Barré Syndrome. Indian J Crit Care Med. 2018 Apr;22(4):309-310.
[c] Munayco CV, Gavilan RG, Ramirez G, et al. Large Outbreak of Guillain-Barré Syndrome, Peru, 2019. Emerg Infect Dis. 2020 Nov;26(11):2778-2780.

Background incidence of GBS increases with increasing age

Meta-analysis[a], 13 studies, North America & Europe

Age group, years	Annual rate per 100,000 population (95% CI)
0–9	0.62 (0.52–0.75)
10–19	0.75 (0.60–0.92)
20–29	0.90 (0.67–1.19)
30–39	1.07 (0.74–1.56)
40–49	1.29 (0.80–2.06)
50–59	1.54 (0.87–2.74)
60–69	1.85 (0.94–3.64)
70–79	2.22 (1.01–4.86)
80–89	2.66 (1.09–6.48)

Vaccine safety datalink, United States, 2000–2009[b]

Age group, years	Annual rate per 100,000 population (95% CI)	
	Female	Male
0–4	0.51 (0.24–0.78)	0.39 (0.16–0.61)
5–17	0.43 (0.29–0.57)	0.62 (0.46–0.79)
18–24	0.64 (0.39–0.89)	0.75 (0.47–1.03)
25–49	1.00 (0.85–1.15)	1.39 (1.20–1.57)
50–64	2.19 (1.90–2.50)	2.85 (2.49–3.21)
≥65	4.68 (4.14–5.21)	7.06 (6.31–7.81)

[a] Sejvar JJ, et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33. https://doi.org/10.1159/000324710
[b] Shui IM, et al. Guillain-Barré syndrome incidence in a large United States cohort (2000-2009). Neuroepidemiology. 2012;39(2):109-15. https://doi.org/10.1159/000339248

Deliberations of the Advisory Committee on Immunization Practices: CDC

Work Group interpretation

- GSK's adjuvanted RSVpreF3 and Pfizer's bivalent RSVpreF vaccines both have demonstrated significant efficacy against lower respiratory tract illness caused by RSV among older adults
  - Trials underpowered to show efficacy against RSV hospitalization
  - Groups at highest risk of severe RSV disease were under-represented in clinical trials
- At least one case of inflammatory neuropathy has been observed among recipients of each investigational vaccine
- If licensed, post licensure surveillance for both safety and vaccine effectiveness will be critical

Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

Michael Melgar, MD[1]; Amadea Britton, MD[1]; Lauren E. Roper, MPH[1]; H. Keipp Talbot, MD[2]; Sarah S. Long, MD[3]; Camille N. Kotton, MD[4]; Fiona P. Havers, MD[1]

Recommendations for Use of RSV Vaccines in Older Adults

On June 21, 2023, ACIP recommended that adults aged ≥60 years may receive a single dose of RSV vaccine, using shared clinical decision-making.[§§§§]

BOX. Underlying medical conditions and other factors associated with increased risk for severe RSV disease

Chronic underlying medical conditions associated with increased risk

- Lung disease (such as chronic obstructive pulmonary disease and asthma)
- Cardiovascular diseases (such as congestive heart failure and coronary artery disease)
- Moderate or severe immune compromise*
- Diabetes mellitus
- Neurologic or neuromuscular conditions
- Kidney disorders
- Liver disorders
- Hematologic disorders
- Other underlying conditions that a health care provider determines might increase the risk for severe respiratory disease

Other factors associated with increased risk

- Frailty†
- Advanced age§
- Residence in a nursing home or other long-term care facility
- Other underlying factors that a health care provider determines might increase the risk for severe respiratory disease

Abbreviation: RSV = respiratory syncytial virus.

Both nirsevimab and maternal RSV vaccine provide passive immunity

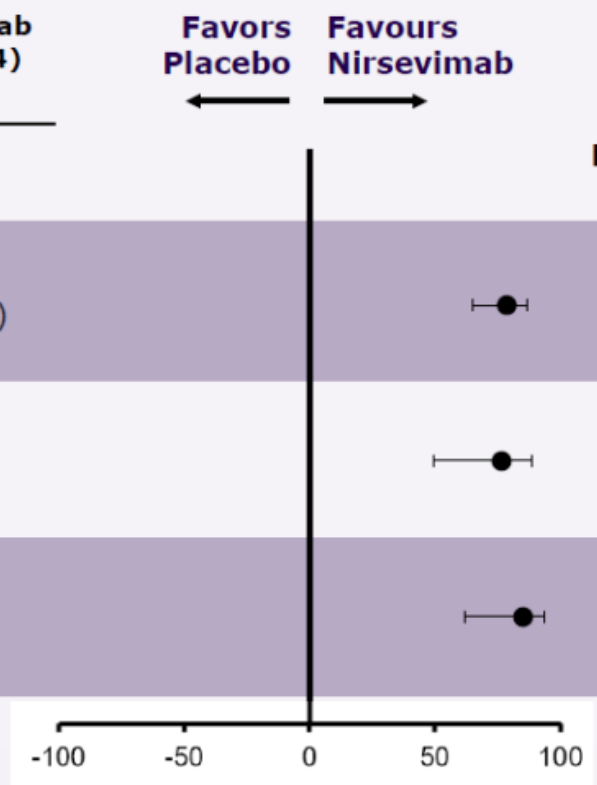
- A person develops active immunity from infection or vaccination
  - Triggers an immune response
  - Immunologic memory provides prolonged protection that may be lifelong

- Passive immunity is transfer of preformed antibody produced externally to provide protection to the recipient
  - From mother to baby through transplacental or breastmilk transfer
  - Direct administration of antibodies, such as IVIG or monoclonal antibodies
  - Provides temporary protection that wanes with time

IVIG= Intravenous Immunoglobulin Therapy
https://www.cdc.gov/vaccines/vac-gen/immunity-types.htm

Consistent efficacy across MA RSV LRTI of different severities

	Placebo (N=786) n (%)	Nirsevimab (N=1564) n (%)	Efficacy (%)	95% CI†	p-value†
Medically attended RSV LRTI‡	51 (6.5)	19 (1.2)	79.5	65.9, 87.7	<0.0001
Medically attended RSV LRTI with hospitalization‡	21 (2.7)	9 (0.6)	77.3	50.3, 89.7	0.0002
Medically attended RSV LRTI (very severe)#	18 (2.3)	5 (0.3)	86.0	62.5, 94.8	<0.0001



†Estimated based on Poisson regression with robust variance (including study as a covariate); not corrected for multiplicity. ‡Included imputation of missing data. #Defined as those cases requiring supplemental oxygen or intravenous fluids (exploratory endpoint). CI, confidence interval; ITT, intent-to-treat

1. Eric AF Simões1, et al (9-12th of May 2022) [Conference Presentation] ESPID 2022 Meeting, Athens, Greece & Online. https://espidmeeting.org/

Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

Jefferson M. Jones, MD[1]; Katherine E. Fleming-Dutra, MD[1]; Mila M. Prill, MSPH[1]; Lauren E. Roper, MPH[1]; Oliver Brooks MD[2]; Pablo J. Sánchez, MD[3]; Camille N. Kotton, MD[4]; Barbara E. Mahon, MD[1]; Sarah Meyer, MD[5]; Sarah S. Long, MD[6]; Meredith L. McMorrow, MD[1]

Summary

What is already known about this topic?

In July 2023, the Food and Drug Administration approved nirsevimab, a long-acting monoclonal antibody, for prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in infants.

What is added by this report?

On August 3, 2023, the Advisory Committee on Immunization Practices recommended nirsevimab for infants aged <8 months born during or entering their first RSV season and for infants and children aged 8–19 months who are at increased risk of severe RSV disease entering their second RSV season.

What are the implications for public health practice?

Nirsevimab can prevent severe RSV disease among infants and children aged <20 months at increased risk for severe RSV disease.

Primary Endpoints:

Vaccine Efficacy by Cumulative Days after Birth for Two Primary Endpoints

	Maternal Vaccine Group (as Randomized)		
RSV-Positive Severe MA-LRTI	RSVpreF 120 µg (N[a]=3495)	Placebo (N[a]=3480)	
Time Interval	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (%) (CI*)**
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6, 96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6, 88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5, 85.9)
180 Days after birth	19 (0.5)	62 (1.8)	69.4 (44.3, 84.1)
RSV-Positive MA-LRTI			
Time Interval	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (%) (CI*)**
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7, 79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2, 73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7, 68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4, 66.8)

*99.5% CI for 90 days, 97.58% CI for 120/150/180 days. CI LB >20% for all time points.

Abbreviations: RSV = respiratory syncytial virus. a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations. b. 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 Bonferroni procedure and accounting for the primary endpoints results.

Final Vote Language

On September 22, 2023, members of the Advisory Committee on Immunization Practices (ACIP) voted, 11-1, to recommend maternal RSV vaccine for pregnant people during 32 through 36 weeks gestation, using seasonal administration, to prevent RSV lower respiratory tract infection in infants. They also voted to approve Pfizer's bivalent RSVpreF vaccine for the Vaccines for Children Program (applying to pregnant people under 19 years of age).