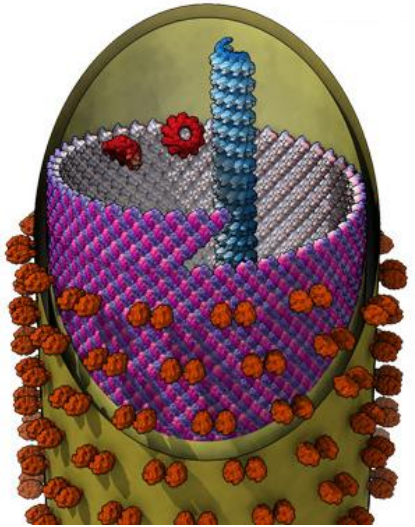
ACIP Adult RSV Work Group Considerations

Michael Melgar, MD
ACIP Adult RSV WG Lead



Conley MJ, et al. Helical ordering of envelope-associated proteins and glycoproteins in respiratory syncytial virus. EMBO J. 2022 Feb 1;41(3):e109728.

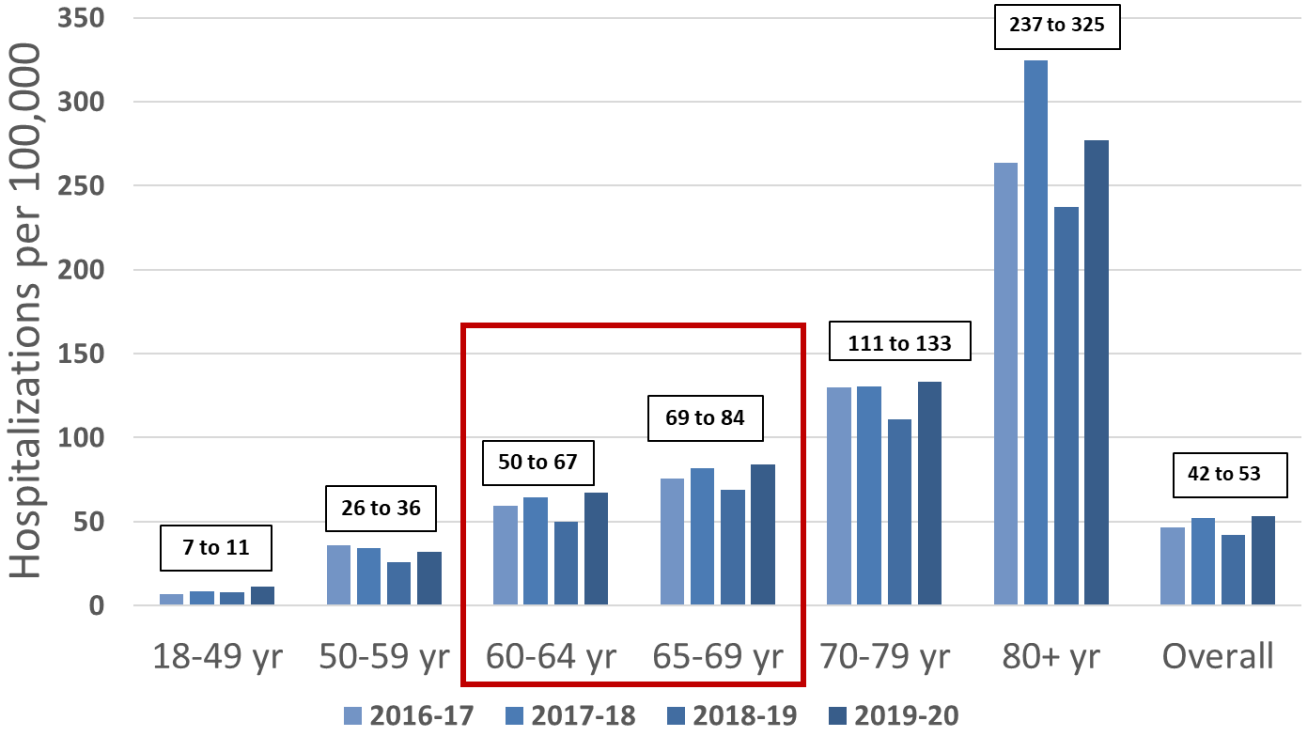
Policy questions being considered by the work group

- Should vaccination with GSK RSVpreF3 vaccine (120 µg antigen + $AS01_E$ adjuvant, 1 dose IM) be recommended for all older adults*?

- Should vaccination with Pfizer RSVpreF vaccine (120 µg antigen, 1 dose IM) be recommended for all older adults*?

*Age ≥60 years? Age ≥65 years? Other?

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



RSV-NET: unpublished data. Rates are adjusted for the frequency of RSV testing during recent prior seasons and the sensitivity of RSV diagnostic tests

Evidence reviewed by the work group includes (but is not limited to):

- Epidemiology and burden of RSV in U.S. adults
  - RSV seasonality
  - Population-based rates of RSV-associated outpatient visits, hospitalizations, and deaths
- RSV virology, immunology
- Safety and efficacy of GSK RSVpreF3
  - Pivotal phase 3 study in adults aged ≥60 years, earlier phase studies
- Safety and efficacy of Pfizer RSVpreF
  - Pivotal phase 3 study in adults aged ≥60 years, earlier phase studies

Work group interpretation of data presented

Both clinical trials showed significant efficacy against lower respiratory tract disease/illness caused by RSV

- Efficacy point estimates against the primary outcomes in both trials exceeded 60%

GSK		Pfizer	
Outcome	**Efficacy (%), 96.95% CI**	**Outcome**	**Efficacy (%), 95% CI**
RSV LRTD[a]	**82.6** (57.9–94.1)	RSV LRTI ≥2 symptoms[b]	**66.7** (32.5–84.8)
		RSV LRTI ≥3 symptoms[b]	**85.7** (37.9–98.4)

[a] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours

[b] Lower respiratory tract illness: ≥2 or ≥3 lower respiratory signs/symptoms lasting more than 1 day

Both clinical trials showed significant efficacy against lower respiratory tract disease/illness caused by RSV

- Efficacy point estimates against the primary outcomes in both trials exceeded 60%
- Based on a small number of total events (<50 in each trial)

GSK			Pfizer		
Outcome	**n/N, vaccine**	**n/N, placebo**	**Outcome**	**n/N, vaccine**	**n/N, placebo**
RSV LRTD[a]	**7**/12,466	**40**/12,494	RSV LRTI ≥2 symptoms[b]	**11**/16,306	**33**/16,308
			RSV LRTI ≥3 symptoms[b]	**2**/16,306	**14**/16,308

[a] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours

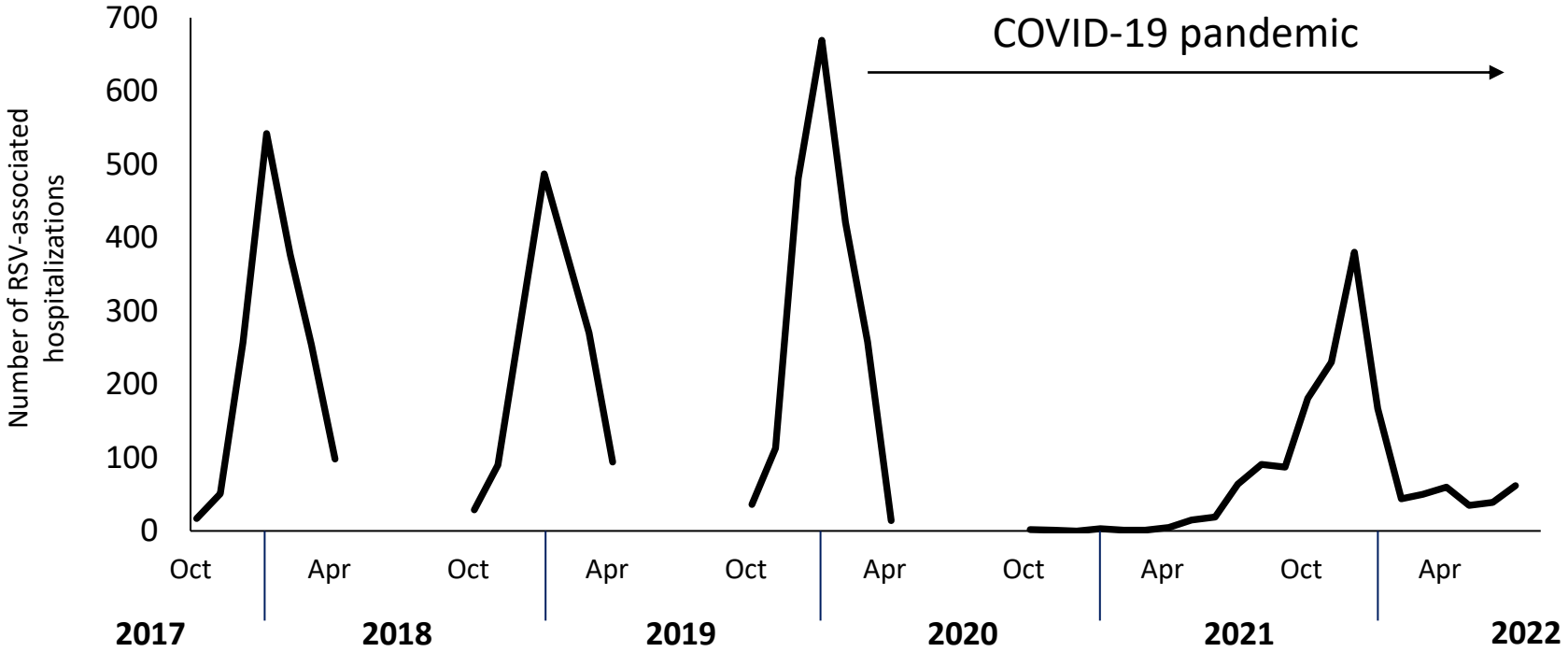
[b] Lower respiratory tract illness: ≥2 or ≥3 lower respiratory signs/symptoms lasting more than 1 day

Incidence of symptomatic RSV infection was low in both trials

Why?

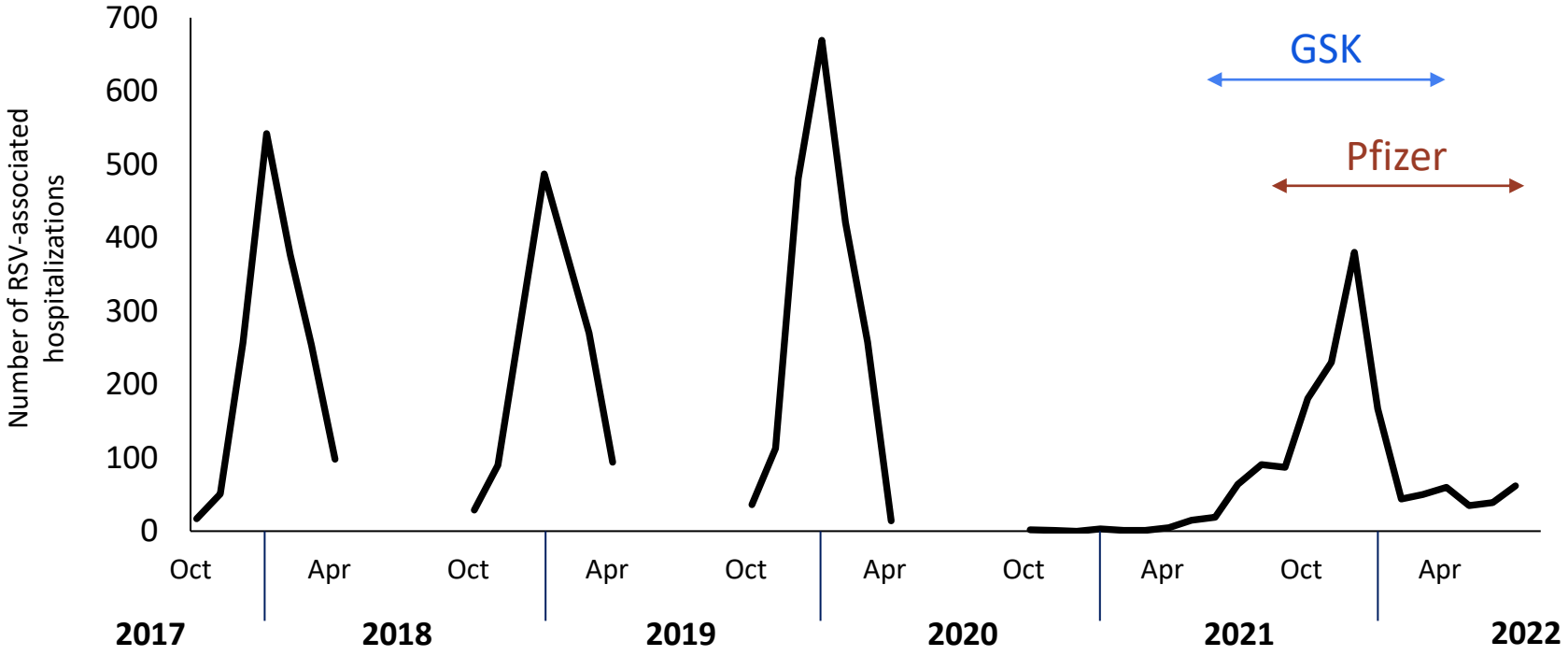
- Clinical trials may enroll a healthier population, compared with the general U.S. population
- Both trials were conducted during periods of atypical RSV seasonality in the United States, attributable to the COVID-19 pandemic

Monthly RSV-associated hospitalizations among adults aged ≥65 years reported to RSV-NET, 2017–2022



RSV-NET: unpublished data. Data are preliminary and subject to change.

Monthly RSV-associated hospitalizations among adults aged ≥65 years reported to RSV-NET, 2017–2022



RSV-NET: unpublished data. Data are preliminary and subject to change.

Trials were underpowered to estimate efficacy against more severe RSV outcomes (e.g., hospitalization, death)

- There were <5 RSV hospitalizations in each trial, and no RSV-associated deaths
- However, the burden of RSV-associated hospitalizations is high among older adults in the United States

Trials were underpowered to estimate efficacy against more severe RSV outcomes (e.g., hospitalization, death)

- There were <5 RSV hospitalizations in each trial, and no RSV-associated deaths
- However, the burden of RSV-associated hospitalizations is high among older adults in the United States

RSV season (October–April)	Estimated U.S. Hospitalizations in adults aged ≥60 years	95% confidence interval
2016-17	64,428	44,382 to 117,495
2017-18	80,652	58,778 to 128,458
2018-19	66,548	50,851 to 96,264
2019-20	84,941	64,105 to 125,848

CDC unpublished data from RSV-NET (https://www.cdc.gov/rsv/research/rsv-net.html). Note that rates are adjusted for test sensitivity (using 95% for rRT-PCR testing) and undertesting for RSV among patients with acute respiratory illnesses. Data are preliminary and subject to change.

Estimates for 2018-19 and 2019-20:
Havers et al. Hospitalization rates and outcomes for RSV-associated hospitalizations in adults ≥18 years in the United States during two respiratory seasons, October 2018 - April 2020. Presentation at: 12th International RSV Symposium; 2022 Sep 29 – Oct 2; Belfast, United Kingdom.

Trials were underpowered to estimate efficacy against more severe RSV outcomes (e.g., hospitalization, death)

- There were <5 RSV hospitalizations in each trial, and no RSV-associated deaths
- However, the burden of RSV-associated hospitalizations is high among older adults in the United States
- Industry-sponsored 2022 meta-analysis* estimated ≥**106,165** annual RSV hospitalizations among adults aged ≥65 years

RSV season (October–April)	Estimated U.S. Hospitalizations in adults aged ≥60 years	95% confidence interval
2016-17	**64,428**	**44,382 to 117,495**
2017-18	**80,652**	**58,778 to 128,458**
2018-19	**66,548**	**50,851 to 96,264**
2019-20	**84,941**	**64,105 to 125,848**

CDC unpublished data from RSV-NET (https://www.cdc.gov/rsv/research/rsv-net.html). Note that rates are adjusted for test sensitivity (using 95% for rRT-PCR testing) and undertesting for RSV among patients with acute respiratory illnesses. Data are preliminary and subject to change.

Estimates for 2018-19 and 2019-20:
Havers et al. Hospitalization rates and outcomes for RSV-associated hospitalizations in adults ≥18 years in the United States during two respiratory seasons, October 2018 - April 2020. Presentation at: 12th International RSV Symposium; 2022 Sep 29 – Oct 2; Belfast, United Kingdom.

*McLaughlin JM, et al. Rates of Medically Attended RSV Among US Adults: A Systematic Review and Meta-analysis. Open Forum Infect Dis. 2022 Jun 17;9(7):ofac300.

Expect efficacy against more severe outcomes to be at least as high as efficacy against lower respiratory tract disease/illness

Increasing severity

GSK		Pfizer	
Outcome	**Efficacy**	**Outcome**	**Efficacy**
RSV acute respiratory illness[a]	71.7%	RSV acute respiratory illness[b]	62.1%
RSV lower respiratory tract disease[c]	82.6%	RSV lower respiratory tract illness ≥2 symptoms[d]	66.7%
		RSV lower respiratory tract illness ≥3 symptoms[d]	85.7%
RSV lower respiratory tract disease with ≥2 lower respiratory **signs** or assessed as '**severe**' by investigator	94.1%		

[a] Acute respiratory illness: ≥2 respiratory symptoms/signs for ≥24 hours OR ≥1 respiratory symptom/sign +1 systemic sign for ≥24 hours
[b] Acute respiratory illness: ≥1 respiratory symptom lasting more than 1 day
[c] Lower respiratory tract disease: ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign OR ≥3 lower respiratory symptoms for ≥24 hours
[d] Lower respiratory tract illness: ARI with ≥2 or ≥3 lower respiratory signs/symptoms

Efficacy beyond one RSV season is unknown

- Both trials are ongoing, with multiple years of follow up planned
- However, data from only the first year will be available for consideration of the first policy recommendations
- There is no established immunologic correlate of protection for RSV
- Need for revaccination, and the time interval, are yet to be determined

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

GSK	Pfizer
No cases of GBS observed in main phase 3 trial (N=24,966 participants, 12,467 received investigational vaccine) 1 case of GBS was reported in a randomized open-label study evaluating safety & long-term immunogenicity of different revaccination schedules (N=1,650 participants) • Onset 9 days after receipt of investigational vaccine	2 cases of GBS (1 case Miller-Fisher syndrome) observed in main phase 3 trial (N=34,283 participants, 17,214 received investigational vaccine) • Onset 8 and 11 days after receipt of investigational vaccine No cases of GBS observed in any other trials of this investigational vaccine
Total: 1 case of GBS / ~15,000 persons who received the investigational vaccine	**Total: 2 cases of GBS / ~26,000 persons who received the investigational vaccine**

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.

Uptake of a novel RSV vaccine among older adults will depend on patient and clinician education

- Adult immunization schedule is becoming more complex
  - Primary series only: pneumococcal vaccine, recombinant zoster vaccine
  - Revaccination: influenza vaccine, COVID-19 vaccine, Td/Tdap, **RSV**?
- RSV is likely less well known as a pathogen in adults, compared with influenza and SARS-CoV-2
- Safety and efficacy of coadministration of influenza, COVID-19, and RSV vaccines must be established

Next steps for the work group

- Review GRADE of evidence for GSK RSVpreF3
- Review GRADE of evidence for Pfizer RSVpreF
- Review cost effectiveness analysis (CEA)
- Review Evidence to Recommendations
  - Public health problem, benefits and harms, values and preferences, equity, resource use (cost effectiveness), acceptability, feasibility
- All of these will inform age threshold for an RSV vaccine recommendation
  - Both trials enrolled adults aged ≥60 years
  - There may be other considerations that inform an age threshold for a recommendation

Acknowledgements

Coronavirus and Other Respiratory Viruses Division (proposed)

- Katherine Fleming-Dutra
- Fiona Havers
- Jefferson Jones
- Meredith McMorrow
- Tamara Pilishvili
- Mila Prill
- Lauren Roper
- Diya Surie

Immunization Safety Office

- Anne Hause
- Christine Olson
- David Shay
- Tom Shimabukuro

Questions for ACIP

1. Are there additional data needed prior to ACIP voting on recommendations for the use of either of these investigational vaccines in older adults?
2. What additional data would ACIP like to see to determine an age threshold for an adult RSV vaccine recommendation?
3. Other questions from ACIP?

Thank you

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