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

Evidence to Recommendations Framework (EtR): RSV Vaccination in Adults Aged 50–59 years, 60–74 years, and 75 years and older

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Policy questions

- Should **all** adults aged **≥75** years be recommended to receive a single dose of RSV vaccination?
- Should adults aged **60–74** years **at increased risk of severe RSV disease** be recommended to receive a single dose of RSV vaccination?
- Should adults aged **50–59** years **at increased risk of severe RSV disease** be recommended to receive a single dose of RSV vaccination?

We will consider the first two questions together in EtR and then return to the 50–59 age group.

Evidence to Recommendations (EtR) framework

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

ACIP Evidence to Recommendations Framework (cdc.gov)

EtR Domain: Public Health Problem

Is the problem of public health importance **among adults aged ≥75 years?**

Is the problem of public health importance **among adults aged 60–74 years at increased risk of severe RSV disease?**

During 2016–2020, CDC estimates:

RSV was associated with[1]

90,000 – 140,000 *annual* **hospitalizations** in U.S. adults aged **65 years and older**

and

10,000 – 20,000 *annual* **hospitalizations** in U.S. adults aged **60–64 years**

Influenza* was associated with[2]

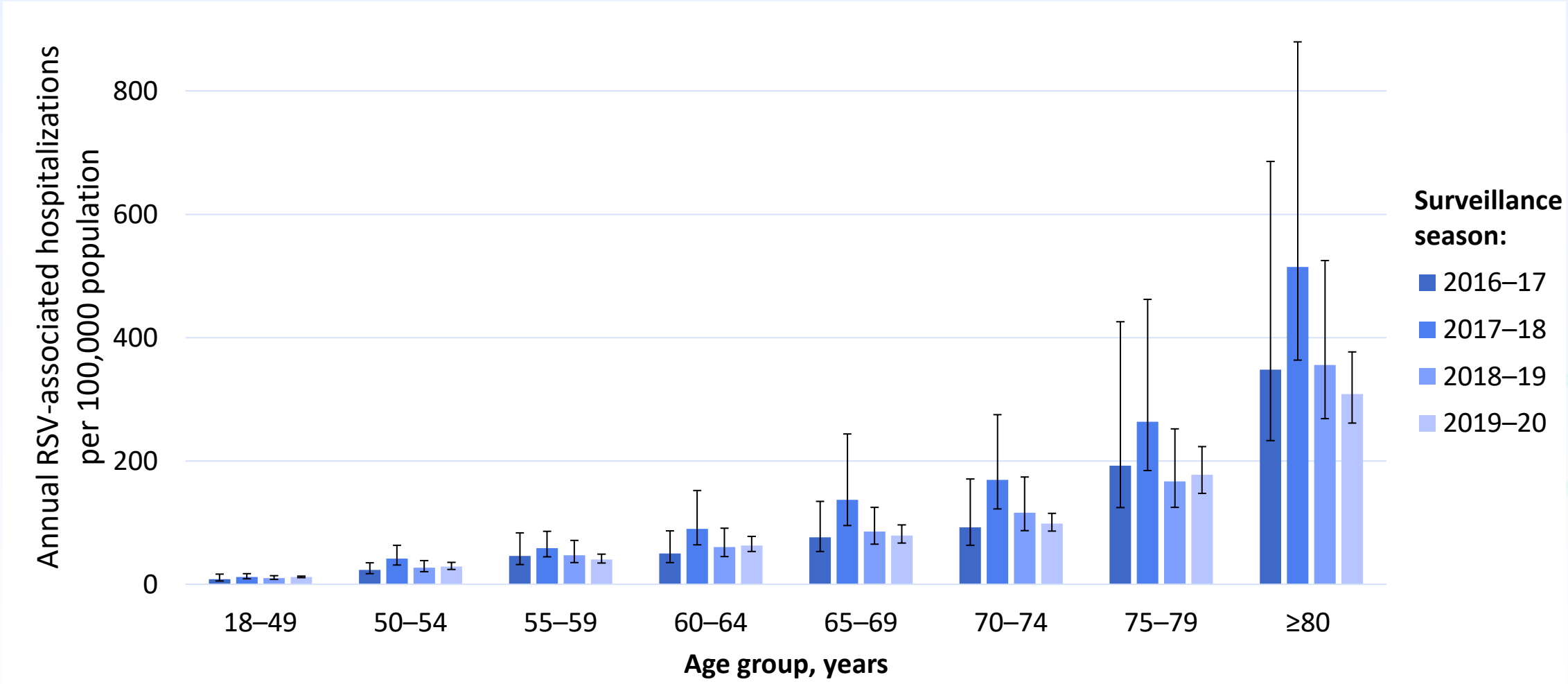
170,000 – 470,000 *annual* **hospitalizations** in U.S. adults aged **65 years and older**

*Annual influenza disease burden is attenuated by the routine vaccination program.

1. Preliminary CDC RSV-NET data 2016–2020 (unpublished). Updated from prior CDC estimates which are available at: https://www.cdc.gov/rsv/php/surveillance/index.html
Ranges reflect point estimates for individual seasons, but not uncertainty in those estimates

2. CDC Influenza Burden 2016–2020: https://www.cdc.gov/flu/about/burden/past-seasons.html

Estimated annual RSV-associated **hospitalization** rates per 100,000 adults* **≥18 years** by age group and year, RSV-NET, 2016–17 to 2019–20

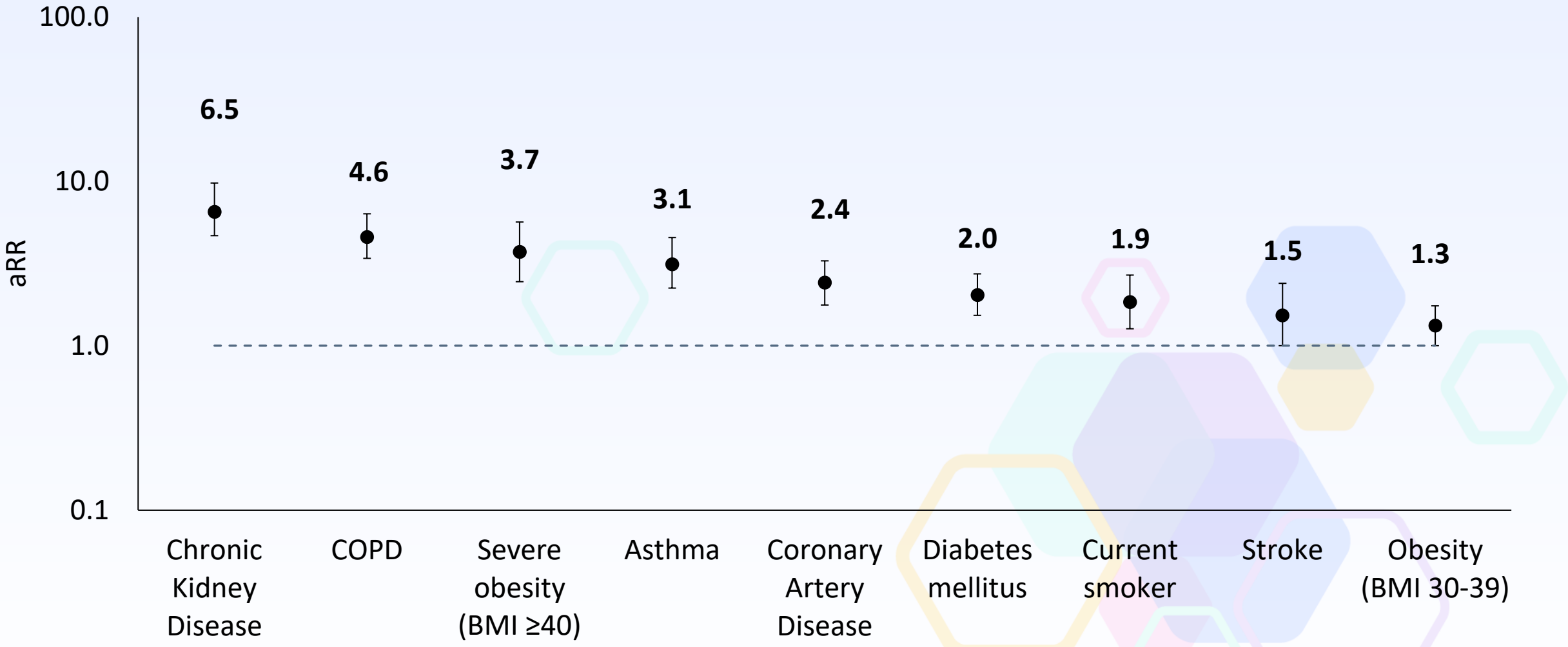


Unpublished data. Rates are adjusted using multipliers for the frequency of RSV testing during each season and the sensitivity of RSV diagnostic tests. Error bars represent 95% confidence intervals.

*Estimated rates exclude recorded hospitalizations among pregnant adults.

https://www.cdc.gov/rsv/research/rsv-net/index.html

Adjusted Rate Ratios for RSV-Associated Hospitalization by Chronic Condition among Community-Dwelling Adults Aged ≥50 Years



Unpublished data. Update on analysis from Woodruff et al. First presented to ACIP in February 2024: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf

BMI: Body Mass Index (kg/m^2), COPD: Chronic Obstructive Pulmonary Disease, aRR: adjusted rate ratio. Data are preliminary and unpublished. Adjusted rate ratios and 95% confidence intervals are derived from Poisson regression using Monte Carlo simulation methods and adjust for age, sex and race and ethnicity group. Error bars represent 95% confidence intervals.

Among community-dwelling adults aged ≥50 years, a history of **≥2 chronic conditions** and **age ≥75 years** were the strongest **independent** risk factors for RSV-associated hospitalization.

	aRR (95% CI)[1]
No. of chronic conditions[2]	
0	ref
1	2.1 (1.4, 3.2)
≥2	**7.3 (5.0, 10.6)**
Age group, years	
50–59	ref
60–74	1.9 (1.3, 2.7)
≥75	**6.0 (4.2, 8.6)**
Race or ethnicity group	
White, non-Hispanic	ref
Black, non-Hispanic	1.1 (0.8, 1.5)
Other race or Hispanic ethnicity	1.7 (1.3, 2.5)
Sex	
Male	Ref
Female	1.3 (1.0, 1.6)

[1] Adjusted rate ratios (aRR) and 95% confidence intervals (CI) were estimated using Poisson regression using Monte Carlo simulation.
[2] Includes history of asthma, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, current smoker, diabetes, stroke, obesity (BMI 30–39) or severe obesity (BMI ≥40)

Unpublished data. Update on analysis from Woodruff et al. First presented to ACIP in February 2024: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf

What do we know about conditions and risk factors not included in the RSV-NET analysis?

- Other medical conditions associated with increased risk of severe RSV disease
  - **Heart failure**
    - As many as 28% of adults hospitalized with RSV infection have chronic heart failure[1]
    - Among adults 65 years and older, hospitalization rates are 3.5x higher in those with versus without heart failure[1]
  - **Immune compromise**
    - Severe disease and high mortality (>20%), especially among lung transplant and hematopoietic cell transplant recipients[2,3]
- Persons living in **long-term care facilities** are also at increased risk of RSV hospitalization and severe outcomes[4,5]
  - Frequent cause of respiratory illness and outbreaks

1. Kujawski SA, et al. (2022) Rates of respiratory syncytial virus (RSV)-associated hospitalization among adults with congestive heart failure—United States, 2015–2017. PLOS ONE 17(3): e0264890. https://doi.org/10.1371/journal.pone.0264890
2. Ison MG, Hirsch HH. Community-Acquired Respiratory Viruses in Transplant Patients: Diversity, Impact, Unmet Clinical Needs. Clin Microbiol Rev. 2019 Sep 11;32(4):e00042-19. https://pubmed.ncbi.nlm.nih.gov/31511250/
3. Manuel O, Estabrook M; American Society of Transplantation Infectious Diseases Community of Practice. RNA respiratory viral infections in solid organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019 Sep;33(9):e13511 https://pubmed.ncbi.nlm.nih.gov/30817023/
4. Bosco E, et al. Estimated Cardiorespiratory Hospitalizations Attributable to Influenza and Respiratory Syncytial Virus Among Long-term Care Facility Residents. JAMA Netw Open. 2021 Jun 1;4(6):e2111806. https://pubmed.ncbi.nlm.nih.gov/34106266/
5. Childs A, et al. The burden of respiratory infections among older adults in long-term care: a systematic review. BMC Geriatr. 2019 Aug 5;19(1):210 https://pubmed.ncbi.nlm.nih.gov/31382895/

Other considerations: RSV disease severity and complications among adults not vaccinated against RSV

- Among unvaccinated adults, **disease severity of RSV-associated hospitalization is similar to severity of COVID-19- and influenza-associated hospitalization**.[1]
- **High incidence of acute cardiac events** among adults 50 and older hospitalized with RSV infection, including 1 in 12 adults (8.5%) with no documented underlying cardiovascular disease.[2]
- Patients hospitalized for RSV-associated disease often **require follow-up care and skilled nursing after discharge.**[3]

1. Surie D, Yuengling KA, DeCuir J, et al. Severity of Respiratory Syncytial Virus vs COVID-19 and Influenza Among Hospitalized US Adults. JAMA Netw Open. 2024 Apr 1;7(4):e244954. https://pubmed.ncbi.nlm.nih.gov/38573635/
2. Woodruff RC, Melgar M, Pham H, et al. Acute Cardiac Events in Hospitalized Older Adults With Respiratory Syncytial Virus Infection. *JAMA Intern Med.* 2024;184(6):602–611. doi:10.1001/jamainternmed.2024.0212
3. Walsh E, Lee N, Sander I, Stolper R, Zakar J, Wyffels V, Myers D, Fleischhackl R. RSV-associated hospitalization in adults in the USA: A retrospective chart review investigating burden, management strategies, and outcomes. Health Sci Rep. 2022 Apr 14;5(3):e556. doi: 10.1002/hsr2.556. PMID: 35509398; PMCID: PMC9059216.

Public health problem: summary of the available evidence Adults 60 years and older

- Annual rate of **RSV-associated hospitalization increases with increasing age**, with a steep rise at age 75 years.
- **Certain chronic medical conditions also increase risk** of RSV-associated disease. Age and chronic medical conditions are *independently* associated with increased risk.
- RSV is associated with **severe disease and has significant post-hospitalization sequelae among older adults.**

Public Health Problem: Work Group interpretation

- Is RSV of public health importance among adults **aged ≥75 years**?

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

- Is RSV of public health importance among adults **aged 60–74 years at increased risk of severe RSV disease**?

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?

Benefits and Harms overview

- Protein subunit RSV vaccines (Pfizer ABRYSVO, GSK AREXVY)
  - **Adults 75 years and older**
    - GRADE
    - Additional considerations
  - **Adults aged 60–74 years at increased risk of severe RSV disease**
    - GRADE
    - Additional considerations
- mRNA RSV vaccine (Moderna mRESVIA)
  - Repeat as above

GRADE Framework: PICO Question

Population	**Adults aged ≥75 years**
Intervention	Protein Subunit RSV Vaccine: Pfizer ABRYSVO (1 dose IM) **-or-** GSK AREXVY (1 dose IM)
Comparison	No RSV vaccine
Outcomes	▪ RSV lower respiratory tract disease (LRTD) ▪ Medically attended RSV LRTD ▪ Hospitalization for RSV respiratory illness ▪ Severe RSV respiratory illness requiring supplemental oxygen or other respiratory support ▪ Death due to RSV respiratory illness ▪ Serious Adverse Events (SAEs) ▪ Inflammatory neurologic events (e.g., Guillain-Barré syndrome) ▪ Reactogenicity (grade ≥3)

Summary of GRADE for protein subunit RSV vaccines in adults ≥75 years

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
RSV Lower Respiratory Tract Disease (LTRD)	Important	RCT (2)	Protein subunit RSV vaccination reduces RSV LRTD in adults aged ≥75 years.	**High**
Medically attended RSV LRTD	Critical	RCT (2)	Protein subunit RSV vaccination likely reduces medically attended RSV LRTD in adults aged ≥75 years.	**Moderate**
Hospitalization for RSV respiratory illness	Critical	RCT (2)	Protein subunit RSV vaccination may reduce hospitalization for RSV respiratory illness in adults aged ≥75 years.	**Low**
Severe RSV respiratory illness requiring O2/respiratory support	Important	RCT (2)	Protein subunit RSV vaccination may reduce severe RSV respiratory illness requiring supplemental oxygen or other respiratory support in adults aged ≥75 years, but the effect is very uncertain.	**Very low**
Death due to RSV respiratory illness	Important	RCT (2)	Zero events observed	Unable to evaluate
Harms				
Serious adverse events (SAEs)	Critical	RCT (4)	Protein subunit RSV vaccination likely results in little to no difference in SAEs in adults aged ≥75 years.	**Moderate**
Inflammatory neurologic events	Critical	RCT (4)	Protein subunit RSV vaccination may increase inflammatory neurologic events in adults aged ≥75 years, but the effect is very uncertain.	**Very low**
Reactogenicity (grade ≥3)	Important	RCT (4)	Protein subunit RSV vaccination may increase severe reactogenicity events in adults aged ≥75 years.	**Low**

Summary of GRADE for protein subunit RSV vaccines in adults ≥75 years

Outcome	Importance	Design (# of studies)	Findings	Evidence type
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Medically attended RSV LRTD	**Critical**	RCT (2)	Protein subunit RSV vaccination likely reduces medically attended RSV LRTD in adults aged ≥75 years.	**Moderate**
Hospitalization for RSV respiratory illness	**Critical**	RCT (2)	Protein subunit RSV vaccination may reduce hospitalization for RSV respiratory illness in adults aged ≥75 years.	**Low**
Severe RSV respiratory illness requiring O2/respiratory support	Important	RCT (2)	Protein subunit RSV vaccination may reduce severe RSV respiratory illness requiring supplemental oxygen or other respiratory support in adults aged ≥75 years, but the effect is very uncertain.	**Very low**
Death due to RSV respiratory illness	Important	RCT (2)	Zero events observed	Unable to evaluate
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Serious adverse events (SAEs)	**Critical**	RCT (4)	Protein subunit RSV vaccination likely results in little to no difference in SAEs in adults aged ≥75 years.	**Moderate**
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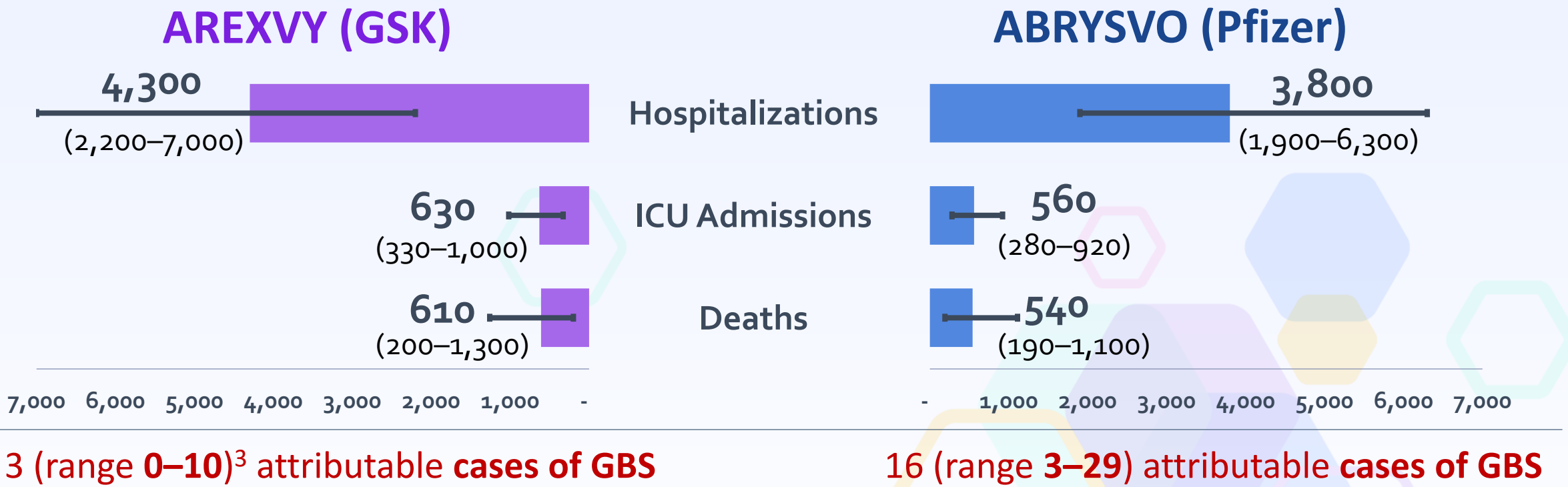
Reactogenicity (grade ≥3)	Important	RCT (4)	Protein subunit RSV vaccination may increase severe reactogenicity events in adults aged ≥75 years.	**Low**

Additional information on benefits/harms for protein subunit RSV vaccines in adults aged ≥75 years

Estimated RSV-Associated Outcomes[1] Preventable over 2 RSV Seasons vs. potential cases of GBS (*positive predictive value-adjusted* attributable risk of GBS in FDA-CMS partnership data among adults aged ≥65 years, 42-day risk interval[2])

Per 1 Million Vaccine Doses Administered to Adults Aged ≥75 Years:



3 (range **0–10**)[3] attributable **cases of GBS**

16 (range **3–29**) attributable **cases of GBS**

1. Range of outcomes avertable was calculated using published 95% confidence intervals (outpatient only) and adjusted 95% confidence interval of RSV-associated incidence of the outcome observed in RSV-NET
2. FDA self-controlled case series analysis, among CMS Medicare beneficiaries ≥65 years with Parts A, B, and D coverage who did not have a GBS claim in the 365 days before vaccination. Analysis based on diagnoses of GBS in inpatient claims data in risk interval (1–42 days after RSV vaccination) compared to control interval (43–90 days after RSV vaccination). GBS cases identified using ICD-10 diagnosis of GBS in primary position of inpatient claims coding. Estimates adjusted for outcome-dependent observation time, positive predictive value of diagnostic codes in identifying chart-confirmed GBS cases, and seasonality. Analysis includes patients with RSV vaccinations only through October 8, 2023 to allow for 90-day post-vaccination observation and 90% or greater claims data completeness. Claims data through April 6, 2024.
3. Self-controlled case series analysis estimated attributable risk of 3 (95% CI: -3, 10) GBS cases. However, the range was truncated at zero for Benefit/Risk analyses.

Other benefit and harms considerations: Protein subunit RSV vaccines

- **Vaccine Safety Datalink (VSD) rapid cycle analysis signal for immune thrombocytopenic purpura (ITP)**[1]
  - VSD identified a statistical signal for ITP in adults ≥60 years who received GSK (AREXVY) RSV vaccination
    - Too early to determine if this represents a true association. After rapid medical record review, most were found not to be new cases of ITP occurring after RSV vaccination.

- **Co-administration with other vaccines**
  - Publicly available data on coadministration of GSK AREXVY or Pfizer ABRYSVO with other adult vaccines remain limited.[2,3]
  - Especially important consideration in older adults recommended to receive multiple vaccines (e.g., COVID-19, influenza, pneumococcal, recombinant zoster)

Abbreviations: VSD: Vaccine Safety Datalink

1. Donahue J. Presentation at June 2024 ACIP meeting.
2. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/03-RSV-Adults-Friedland-508.pdf
3. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/02-RSV-Adults-Gurtman-508.pdf

Benefits and Harms: Protein Subunit RSV vaccine in adults aged ≥75 years

- How substantial are the desirable anticipated effects among adults aged ≥75 years?

Minimal	Small	**Moderate**	**Large**	Varies	Don't know

- How substantial are the undesirable anticipated effects among adults aged ≥75 years?

Minimal	**Small**	**Moderate**	Large	Varies	Don't know

- Do the desirable effects outweigh the undesirable effects among adults aged ≥75 years?

Favors intervention (Protein subunit RSV vaccine)
Favors comparison (no vaccine)
Favors both
Favors neither
Unclear

GRADE Framework: PICO Question

Population	**Adults aged 60–74 years at increased risk of severe RSV disease**
Intervention	RSV Protein Subunit Vaccine: Pfizer ABRYSVO (1 dose IM) **-or-** GSK AREXVY (1 dose IM)
Comparison	No RSV vaccine
Outcomes	▪ RSV lower respiratory tract disease (LRTD) ▪ Medically attended RSV LRTD ▪ Hospitalization for RSV respiratory illness ▪ Severe RSV respiratory illness requiring supplemental oxygen or other respiratory support ▪ Death due to RSV respiratory illness ▪ Serious Adverse Events (SAEs) ▪ Inflammatory neurologic events (e.g., Guillain-Barré syndrome) ▪ Reactogenicity (grade ≥3)

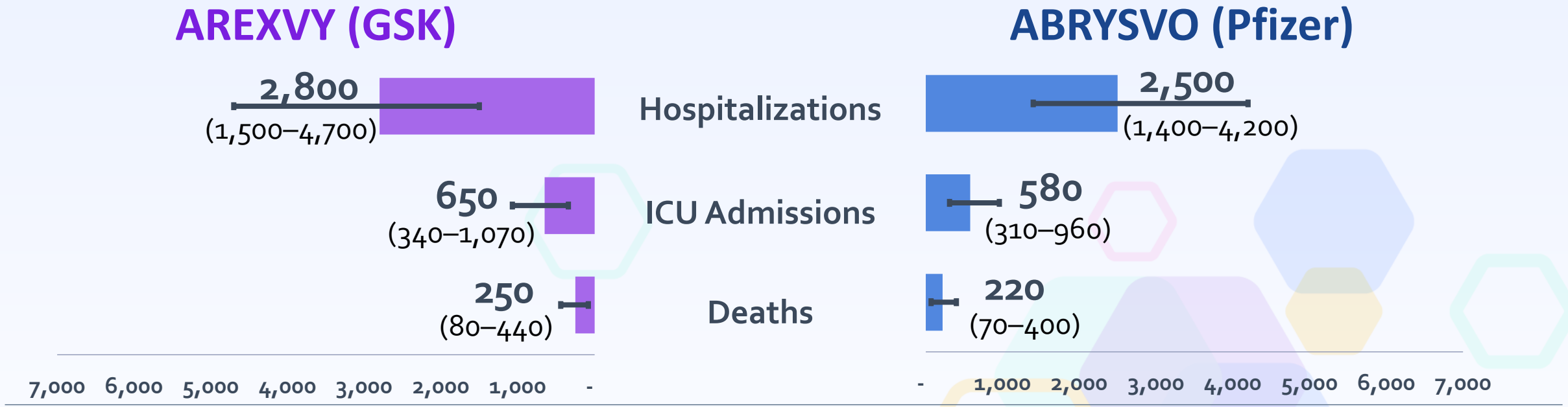
Summary of GRADE for protein subunit vaccines in adults aged 60–74 years at increased risk of severe RSV disease

Outcome	Importance	Design (# of studies)	Findings In adults aged 60-74 years at increased risk of severe RSV disease:	Evidence type
Benefits				
RSV Lower Respiratory Tract Disease (LTRD)	Important	RCT (2)	Protein subunit RSV vaccination reduces RSV LRTD.	**High**
Medically attended RSV LRTD	**Critical**	RCT (2)	Protein subunit RSV vaccination reduces medically attended RSV LRTD.	**High**
Hospitalization for RSV respiratory illness	**Critical**	RCT (2)	Protein subunit RSV vaccination may reduce hospitalization for RSV respiratory illness.	**Low**
Severe RSV respiratory illness requiring O2/respiratory support	Important	RCT (2)	Protein subunit RSV vaccination may reduce severe RSV respiratory illness requiring supplemental oxygen or other respiratory support, but the effect is very uncertain.	**Very low**
Death due to RSV respiratory illness	Important	RCT (2)	Zero events observed	Unable to evaluate
Harms				
Serious adverse events	**Critical**	RCT (4)	Protein subunit RSV vaccination likely results in little to no difference in SAEs.	**Moderate**
Inflammatory neurologic events	**Critical**	RCT (4)	Protein subunit RSV vaccination may increase inflammatory neurologic events, but the effect is very uncertain.	**Very low**
Reactogenicity (grade ≥3)	Important	RCT (4)	Protein subunit RSV vaccination may increase severe reactogenicity events.	**Low**

Additional information on benefits/harms for protein subunit vaccines in adults aged 60–74 years at increased risk of severe RSV disease

Estimated RSV-Associated Outcomes[1] Preventable over 2 RSV Seasons vs. potential cases of GBS (*positive predictive value-adjusted* attributable risk of GBS in FDA-CMS partnership data among adults aged ≥65 years, 42-day risk interval[2,3])

Per 1 Million Vaccine Doses Administered to Adults Aged 60–74 Years at Increased Risk of Severe RSV Disease:



3 (range **0–10**)[4] attributable **cases of GBS**

16 (range **3–29**) attributable **cases of GBS**

1. Range of outcomes avertable was calculated using published 95% confidence intervals (outpatient only) and adjusted 95% confidence interval of RSV-associated incidence of the outcome observed in RSV-NET
2. FDA self-controlled case series analysis, among CMS Medicare beneficiaries ≥65 years with Parts A, B, and D coverage who did not have a GBS claim in the 365 days before vaccination. Analysis based on diagnoses of GBS in inpatient claims data in risk interval (1-42 days after RSV vaccination) compared to control interval (43-90 days after RSV vaccination). GBS cases identified using ICD-10 diagnosis of GBS in primary position of inpatient claims coding. Estimates adjusted for outcome-dependent observation time, positive predictive value of diagnostic codes in identifying chart-confirmed GBS cases, and seasonality. Analysis includes patients with RSV vaccinations only through October 8, 2023 to allow for 90-day post-vaccination observation and 90% or greater claims data completeness. Claims data through April 6, 2024.
3. Although CMS data were limited to Medicare beneficiaries aged ≥65 years, results are extrapolated here to include adults aged 60-64 years.
4. Self-controlled case series analysis estimated attributable risk of 3 (95% CI: -3, 10) GBS cases. However, the range was truncated at zero for Benefit/Risk analyses.

Protein subunit RSV vaccine efficacy against primary clinical trial outcomes over time

Vaccine	Primary outcome	Efficacy (95% CI), months 0–12[a]	Efficacy (95% CI), months 13–24[a]
Pfizer ABRYSVO	RSV LRTI with ≥2 lower respiratory sx	**62%** (41, 76) Median **12** months follow-up per participant	**55%** (26, 73) Median **6** months follow-up per participant
	RSV LRTI with ≥3 lower respiratory sx	**86%** (63, 96) Median **12** months follow-up per participant	**74%** (27, 92) Median **6** months follow-up per participant

Abbreviations: CI: confidence interval, LRTI: lower respiratory tract illness, sx: signs or symptoms, LRTD: lower respiratory tract disease

a. Nominal efficacy during 12-month period. Not all trial participants contributing to estimate had full 12 months' follow up time during the period. Median per-participant follow-up time during each period is reported below each estimate.

Pfizer and GSK clinical trials used different primary endpoint definitions and had different follow-up time, so efficacy cannot be directly compared across trials.

Protein subunit RSV vaccine efficacy against primary clinical trial outcomes over time

Vaccine	Primary outcome	Efficacy (95% CI), months 0–12[a]	Efficacy (95% CI), months 13–24[a]
GSK AREXVY	RSV LRTD (≥2 or ≥3 lower respiratory sx)[b]	**79%** (58, 90) Median **12** months follow-up per participant	**59%** (34, 75) Median **12** months follow-up per participant

Abbreviations: CI: confidence interval, LRTI: lower respiratory tract illness, sx: signs or symptoms, LRTD: lower respiratory tract disease

a. Nominal efficacy during 12-month period. Not all trial participants contributing to estimate had full 12 months' follow up time during the period. Median per-participant follow-up time during each period is reported below each estimate.

b. GSK definition of LRTD required ≥2 lower respiratory symptoms or signs (including ≥1 sign), or ≥3 lower respiratory symptoms.

Pfizer and GSK clinical trials used different primary endpoint definitions and had different follow-up time, so efficacy cannot be directly compared across trials.

Revaccination with GSK AREXVY at 12 months does not increase efficacy, compared with a single dose

AReSVi-006

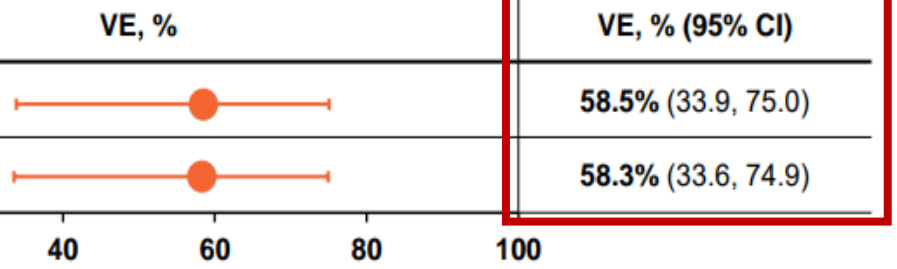
Vaccine efficacy against RSV-LRTD Season 2 only

mES Dose 2

18 month analysis	VE, % (95% CI)
Single dose	56.09 (28.17, 74.38)
Annual	55.94 (27.92, 74.29)

- Vaccine efficacy against first occurrence of RT-PCR-confirmed RSV-LRTD from 15 days post-Dose 2 up to end of season 2 in Southern Hemisphere, using Poisson method

	RSVPreF3 + AS01$_E$	Placebo	VE, %	VE, % (95% CI)
	Number of events (n/N)			
RSVPreF3 (Single dose)	**22** / 4,988	**106** / 10,031		**58.5%** (33.9, 75.0)
RSVPreF3 (Annual revaccination)	**22** / 4,968	**106** / 10,031		**58.3%** (33.6, 74.9)



Season 1 = From 1st October 2021 to 30 April 2022 for NH and from 1st March 2022 to 30 September 2022 for SH; Season 2 = From 1st October 2022 to 30 April 2023 for NH and from 1st March 2023 to 30 September 2023 for SH.

CI, confidence interval; LRTD, lower respiratory tract disease; mES, modified exposed set; NH, Northern Hemisphere; RT-PCR, reverse-transcriptase polymerase chain reaction; S2, Season 2; SH, Southern Hemisphere; VE, vaccine efficacy.

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Benefits and Harms Protein Subunit RSV vaccine in adults aged 60–74 years at increased risk of severe RSV disease

- How substantial are the desirable anticipated effects among adults aged 60–74 years at increased risk of severe RSV disease

Minimal	Small	**Moderate**	**Large**	Varies	Don't know

- How substantial are the undesirable anticipated effects among adults aged 60–74 years at increased risk of severe RSV disease?

Minimal	**Small**	**Moderate**	Large	Varies	Don't know

- Do the desirable effects outweigh the undesirable effects among adults aged 60–74 years at increased risk of severe RSV disease?

Favors intervention (Protein subunit RSV vaccine)
Favors comparison (no vaccine)
Favors both
Favors neither
Unclear

GRADE Framework: PICO Question

Population	**Adults aged ≥75 years**
Intervention	RSV Vaccine: Moderna mRESVIA (50 µg, single dose IM)
Comparison	No RSV vaccine
Outcomes	▪ RSV lower respiratory tract disease (LRTD) ▪ Medically attended RSV LRTD ▪ Hospitalization for RSV respiratory illness ▪ Severe RSV respiratory illness requiring supplemental oxygen or other respiratory support ▪ Death due to RSV respiratory illness ▪ Serious Adverse Events (SAEs) ▪ Inflammatory neurologic events (e.g., Guillain-Barré syndrome) ▪ Reactogenicity (grade ≥3)

Moderna mRESVIA in adults aged ≥75 years

Benefits: vaccine efficacy estimates

Outcome	Importance	Data Sources	Effect Estimate, Vaccine Efficacy (95% CI)[a]	Concerns in certainty assessment
RSV Lower Respiratory Tract Disease (LTRD)[b,c]	Important	One Phase 2/3 RCT in adults ≥60 years[1] • Mean efficacy follow up through 18 months post-vaccination per participant (median 19 months)[d]	44.0% (-34.6, 78.2%)	Imprecision (serious)[e]
Medically attended RSV LRTD[f,c]	Critical		39.0% (-58.8, 78.1%)	Indirectness (serious)[g] Imprecision (serious)[e]
Hospitalization for RSV respiratory illness[f]	Critical		80.1% (-363.7, 100%)[h]	Indirectness (serious)[f] Imprecision (very serious)[i]
Severe RSV respiratory illness requiring O2/respiratory support	Important		No data available	Unable to evaluate
Death due to RSV respiratory illness[d]	Important		Zero events observed	Unable to evaluate

a) Calculated as (1 – Incident Rate Ratio) x 100%. Events were included if they occurred >14 days post-vaccination.
b) Included data are from participants aged ≥75 years.
c) LRTD using co-primary endpoint of at LRTD with at least 3 signs or symptoms
d) Efficacy follow-up through maximum 24 months postvaccination per participants (median 19 months)
e) Serious concern for imprecision due to the confidence intervals containing absolute risk reduction estimates for which different policy decisions might be considered.
f) Included data are among all Moderna RCT participants (aged ≥60 years).
g) Serious concern for indirectness due to inclusion of adults aged 60–74 years.
h) Calculated using 0.5 correction factor to account for zero events in the placebo group. Data cut off April 2023.
i) Serious concern for imprecision due to the confidence intervals containing absolute risk reduction estimates for which different policy decisions might be considered and fragility of the estimate

1. Clinical trials.gov NTC:05127434. https://classic.clinicaltrials.gov/ct2/show/NCT05127434. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. N Engl J Med. 2023 Dec 14;389(24):2233-2244. doi: 10.1056/NEJMoa2307079. Plus additional data obtained directly from the manufacturer

Moderna mRESVIA in adults aged ≥75 years

Harms

Outcome	Importance	Data Sources	Effect Estimate, Risk ratio (95% CI)	Concerns in certainty assessment
Serious adverse events (SAEs)[a,b]	Critical	One phase 2/3 RCT[1], one phase 1 RCT[2]	1.00 (0.95, 1.05)	Inconsistency (serious)[c] Indirectness (serious)[d]
Inflammatory neurologic events[a,e]	Critical	One phase 2/3 RCT[1], one phase 1 RCT[2]	Zero events observed	Unable to evaluate
Reactogenicity (grade ≥3)[a,f]	Important	One phase 2/3 RCT[1], one phase 1 RCT[2]	1.54 (1.40, 1.68)	Indirectness (serious)[d]

a) Included data are among all Moderna RCT participants (aged ≥60 years).
b) Phase 2/3 RCT: Any time after vaccination. Phase 1 RCT: Within 12 months after vaccination.
c) Serious concern for inconsistency as the risk ratios observed in the phase 1 and phase 2/3 trials had different point estimates.
d) Serious concern for indirectness due to inclusion of adults aged 60–74 years.
e) Within 42 days after vaccination
f) Within 7 days after vaccination

1. Clinical trials.gov NTC:05127434. https://classic.clinicaltrials.gov/ct2/show/NCT05127434. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. N Engl J Med. 2023 Dec 14;389(24):2233-2244. doi: 10.1056/NEJMoa2307079. Plus additional data obtained directly from the manufacturer
2. Clinical trials.gov NTC:04528719. https://clinicaltrials.gov/study/NCT04528719?term=NCT04528719. Shaw CA, Essink B, Harper C, et al. Safety and Immunogenicity of an mRNA-Based RSV Vaccine Including a 12-Month Booster in a Phase I Clinical Trial in Healthy Older Adults. J Infect Dis. 2024 Feb 22:jiae081. doi: 10.1093/infdis/jiae081. Epub ahead of print. PMID: 38385566. Plus additional data obtained directly from the manufacturer, only included those who received the phase 2/3 vaccine formulation or placebo

Summary of GRADE for Moderna mRESVIA in adults aged ≥75 years

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
RSV Lower Respiratory Tract Disease (LTRD)	Important	RCT (1)	Vaccination with Moderna mRESVIA likely reduces RSV LRTD in adults aged ≥75 years.	**Moderate**
Medically attended RSV LRTD	Critical	RCT (1)	Vaccination with Moderna mRESVIA may reduce medically attended RSV LRTD in adults aged ≥75 years.	**Low**
Hospitalization for RSV respiratory illness	Critical	RCT (1)	Vaccination with Moderna mRESVIA may reduce hospitalization for RSV respiratory illness in adults aged ≥75 years, but the effect is very uncertain.	**Very low**
Severe RSV respiratory illness requiring O2/respiratory support	Important	RCT (1)	No data available to inform this outcome	Unable to evaluate
Death due to RSV respiratory illness	Important	RCT (1)	Zero events observed	Unable to evaluate
Harms				
Serious adverse events	Critical	RCT (2)	Vaccination with Moderna mRESVIA may result in little to no difference in SAEs in adults aged ≥75 years.	**Low**
Inflammatory neurologic events	Critical	RCT (2)	Zero events observed	Unable to evaluate
Reactogenicity (grade ≥3)	Important	RCT (2)	Vaccination with Moderna mRESVIA likely increases severe reactogenicity events in adults aged ≥75 years.	**Moderate**

Additional information on benefits/harms for Moderna mRESVIA in adults aged ≥75 years

Other benefit/harms considerations: co-administration

- Data on coadministration with mRESVIA and other adult vaccines are limited
- Coadministration of Moderna mRESVIA with seasonal quadrivalent influenza vaccine as well as mRESVIA with COVID-19 bivalent vaccine met non-inferiority criteria for immunogenicity.[1]

1. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/02-RSV-Adults-Das-508.pdf

Benefits and Harms Moderna mRESVIA in adults aged ≥75 years

- How substantial are the desirable anticipated effects among adults aged ≥75 years?

Minimal	Small	**Moderate**	**Large**	Varies	Don't know

- How substantial are the undesirable anticipated effects among adults aged ≥75 years?

Minimal	**Small**	Moderate	Large	Varies	Don't know

- Do the desirable effects outweigh the undesirable effects among adults aged ≥75 years?

Favors intervention (Moderna mRESVIA RSV vaccine)
Favors comparison (no vaccine)
Favors both
Favors neither
Unclear

GRADE Framework: PICO Question

Population	**Adults aged 60–74 years at increased risk of severe RSV disease**
Intervention	RSV Vaccine: Moderna mRESVIA (50 µg, single dose IM)
Comparison	No RSV vaccine
Outcomes	▪ RSV lower respiratory tract disease (LRTD) ▪ Medically attended RSV LRTD ▪ Hospitalization for RSV respiratory illness ▪ Severe RSV respiratory illness requiring supplemental oxygen or other respiratory support ▪ Death due to RSV respiratory illness ▪ Serious Adverse Events (SAEs) ▪ Inflammatory neurologic events (e.g., Guillain-Barré syndrome) ▪ Reactogenicity (grade ≥3)

Moderna mRESVIA vaccine in adults aged 60–74 years at increased risk of severe RSV disease

Benefits: vaccine efficacy estimates

Outcome	Importance	Data Sources	Effect Estimate, Vaccine efficacy (95% CI)[a]	Concerns in certainty assessment
RSV Lower Respiratory Tract Disease (LTRD)[b,c]	Important	One Phase 3 RCT in adults ≥60 years[1] • Mean efficacy follow up through 18 months post-vaccination per participant (median 19 months)[d]	66.8% (41.5, 82.1%)	None
Medically attended RSV LRTD[e,c]	Critical		39.0% (-58.8, 78.1%)	Indirectness (serious)[f] Imprecision (serious)[g]
Hospitalization for RSV respiratory illness[c]	Critical		80.1% (-363.7, 100%)[h]	Indirectness (serious)[f] Imprecision (very serious)[i]
Severe RSV respiratory illness requiring O2/respiratory support[c]	Important		Not data available	Unable to evaluate
Death due to RSV respiratory illness[c]	Important		Zero events observed	Unable to evaluate

a) Calculated as (1 – Incident Rate Ratio) x 100%. Events were included if they occurred >14 days post-vaccination.
b) Included data are from participants aged ≥60 years with ≥1 comorbidity (chronic obstructive pulmonary disease [COPD], asthma, chronic respiratory disease, heart failure, diabetes mellitus, advanced liver disease, advanced renal disease).
c) LRTD using co-primary endpoint of at LRTD with at least 3 signs or symptoms
d) Efficacy follow-up through maximum 24 months postvaccination per participants (median 19 months)
e) Included data are among all participants (aged ≥60 years).
f) Serious concern for indirectness due to inclusion of adults without comorbidities.
g) Serious concern for imprecision due to the confidence intervals containing absolute risk reduction estimates for which different policy decisions might be considered
h) VE calculated using 0.5 correction factor to account for zero events in the placebo group. Data cut off April 2023
i) Very serious concern for imprecision due to the confidence intervals containing absolute risk reduction estimates for which different policy decisions might be considered and fragility of the estimate

1. Clinical trials.gov NTC:05127434. https://classic.clinicaltrials.gov/ct2/show/NCT05127434. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. N Engl J Med. 2023 Dec 14;389(24):2233-2244. doi: 10.1056/NEJMoa2307079. Plus additional data obtained directly from the manufacturer

Moderna mRESVIA vaccine in adults aged 60–74 years at increased risk of severe RSV disease

Harms

Outcome	Importance	Data Sources	Effect Estimate, Risk ratio (95% CI)	Concerns in certainty assessment
Serious adverse events (SAEs)[a,b]	Critical	One phase 2/3 RCT[1], one phase 1 RCT[2]	1.00 (0.95, 1.05)	Inconsistency (serious)[c] Indirectness (serious)[d]
Inflammatory neurologic events[a,e]	Critical	One phase 2/3 RCT[1], one phase 1 RCT[2]	Zero events observed	Unable to evaluate
Reactogenicity (grade ≥3)[a,f]	Important	One phase 2/3 RCT[1], one phase 1 RCT[2]	1.54 (1.40, 1.68)	Indirectness (serious)[d]

a) Included data are among all participants (aged ≥60 years).
b) Phase 2/3 RCT: Any time after vaccination. Phase 1 RCT: Within 12 months after vaccination.
c) Serious concern for inconsistency as the risk ratios observed in the phase 1 and phase 2/3 trials had different point estimates.
d) Serious concern for indirectness due to inclusion of adults without comorbidities.
e) Within 42 days after vaccination
f) Within 7 days after vaccination

1. Clinical trials.gov NTC:05127434. https://classic.clinicaltrials.gov/ct2/show/NCT05127434. Wilson E, Goswami J, Baqui AH, et al. Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults. N Engl J Med. 2023 Dec 14;389(24):2233-2244. doi: 10.1056/NEJMoa2307079. Plus additional data obtained directly from the manufacturer
2. Clinical trials.gov NTC:04528719. https://clinicaltrials.gov/study/NCT04528719?term=NCT04528719. Shaw CA, Essink B, Harper C, et al. Safety and Immunogenicity of an mRNA-Based RSV Vaccine Including a 12-Month Booster in a Phase I Clinical Trial in Healthy Older Adults. J Infect Dis. 2024 Feb 22:jiae081. doi: 10.1093/infdis/jiae081. Epub ahead of print. PMID: 38385566. Plus additional data obtained directly from the manufacturer, only included those who received the phase 2/3 vaccine formulation or placebo

Summary of GRADE for Moderna mRESVIA vaccine in adults aged 60–74 years at increased risk of severe RSV disease

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
RSV Lower Respiratory Tract Disease (LTRD)	Important	RCT (1)	Vaccination with Moderna mRESVIA reduces RSV LRTD in adults aged 60–74 years at increased risk of severe RSV disease.	**High**
Medically attended RSV LRTD	Critical	RCT (1)	Vaccination with Moderna mRESVIA may reduce medically attended RSV LRTD in adults aged 60–74 years at increased risk of severe RSV disease.	**Low**
Hospitalization for RSV respiratory illness	Critical	RCT (1)	Vaccination with Moderna mRESVIA may reduce hospitalization for RSV respiratory illness in adults aged 60–74 years at increased risk of severe RSV disease, but the effect is very uncertain.	**Very low**
Severe RSV respiratory illness requiring O2/respiratory support	Important	RCT (1)	No data available to inform this outcome	Unable to evaluate
Death due to RSV respiratory illness	Important	RCT (1)	Zero events observed	Unable to evaluate
Harms				
Serious adverse events	Critical	RCT (2)	Vaccination with Moderna mRESVIA may result in little to no difference in SAEs in adults aged 60–74 years at increased risk of severe RSV disease.	**Low**
Inflammatory neurologic events	Critical	RCT (2)	Zero events observed	Unable to evaluate
Reactogenicity (grade ≥3)	Important	RCT (2)	Vaccination with Moderna mRESVIA likely increases severe reactogenicity events in adults aged 60–74 years at increased risk of severe RSV disease.	**Moderate**

Moderna mRESVIA vaccine efficacy against primary clinical trial outcomes over time

Primary outcome	Efficacy (95% CI), months 0–12[a]	Efficacy (95% CI), months 12–24[a]
RSV LRTD with ≥2 lower respiratory signs or symptoms	**56%** (42, 67) Mean **12** months follow-up per participant	**30%** (1, 51) Mean **7** months follow-up per participant
RSV LRTD with ≥3 lower respiratory signs or symptoms	**55%** (31, 71) Mean **12** months follow-up per participant	**36%** (-13, 64) Mean **7** months follow-up per participant

Abbreviations: CI: confidence interval, LRTD: lower respiratory tract disease

a. Nominal efficacy during 12-month period. Not all trial participants contributing to estimate had full 12 months' follow up time during the period. Mean per-participant follow-up during each period (reported below each estimate) was calculated by CDC using number of participants and total person-time provided by manufacturer.

Benefits and Harms Moderna mRESVIA in adults aged 60–74 years at increased risk of severe RSV disease

- How substantial are the desirable anticipated effects among adults aged 60–74 years at increased risk of severe RSV disease?

Minimal	Small	**Moderate**	**Large**	Varies	Don't know

- How substantial are the undesirable anticipated effects among adults aged 60–74 years at increased risk of severe RSV disease?

Minimal	**Small**	Moderate	Large	Varies	Don't know

- Do the desirable effects outweigh the undesirable effects among adults aged 60–74 years at increased risk of severe RSV disease?

Favors intervention (Moderna mRESVIA RSV vaccine)
Favors comparison (no vaccine)
Favors both
Favors neither
Unclear

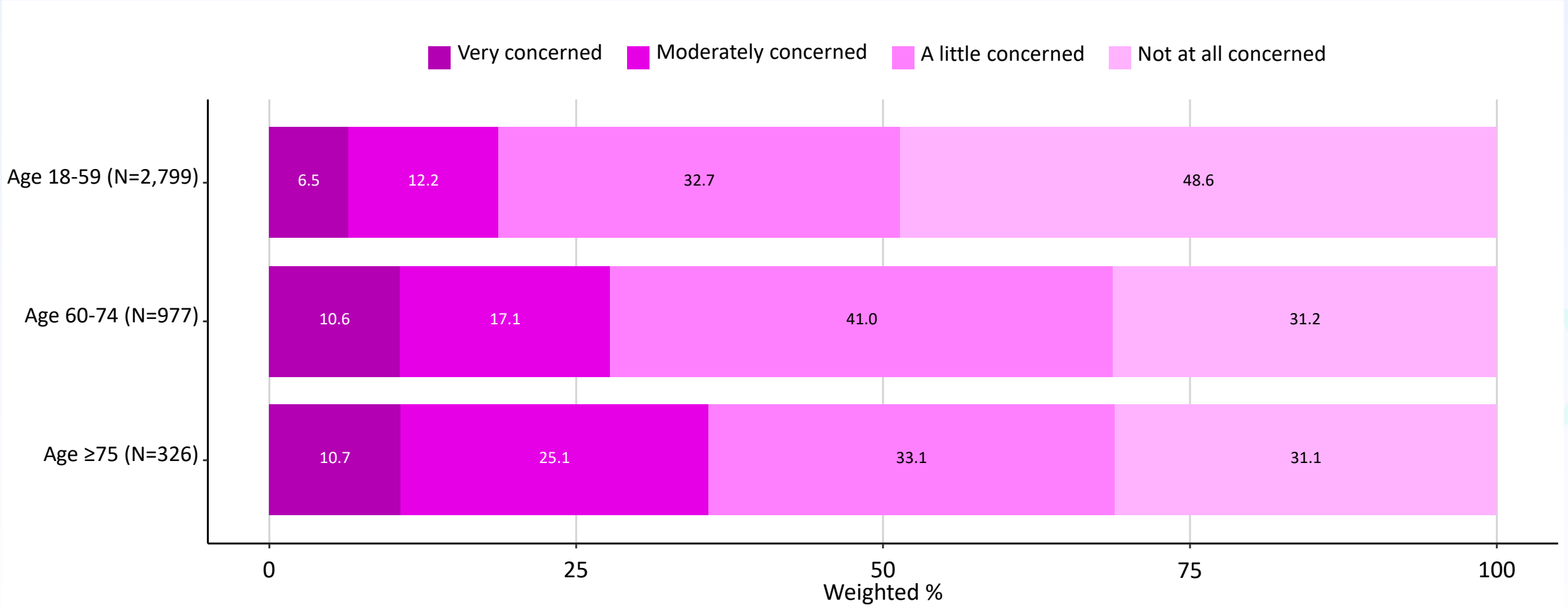
Values and preferences

- Do **adults 75 and older** feel the desirable effects of RSV vaccination are large relative to the undesirable effects?

- Do **adults 60–74 at increased risk of severe RSV disease** feel the desirable effects of RSV vaccination are large relative to the undesirable effects?

- Is there important variability in how these adults value the main outcomes?

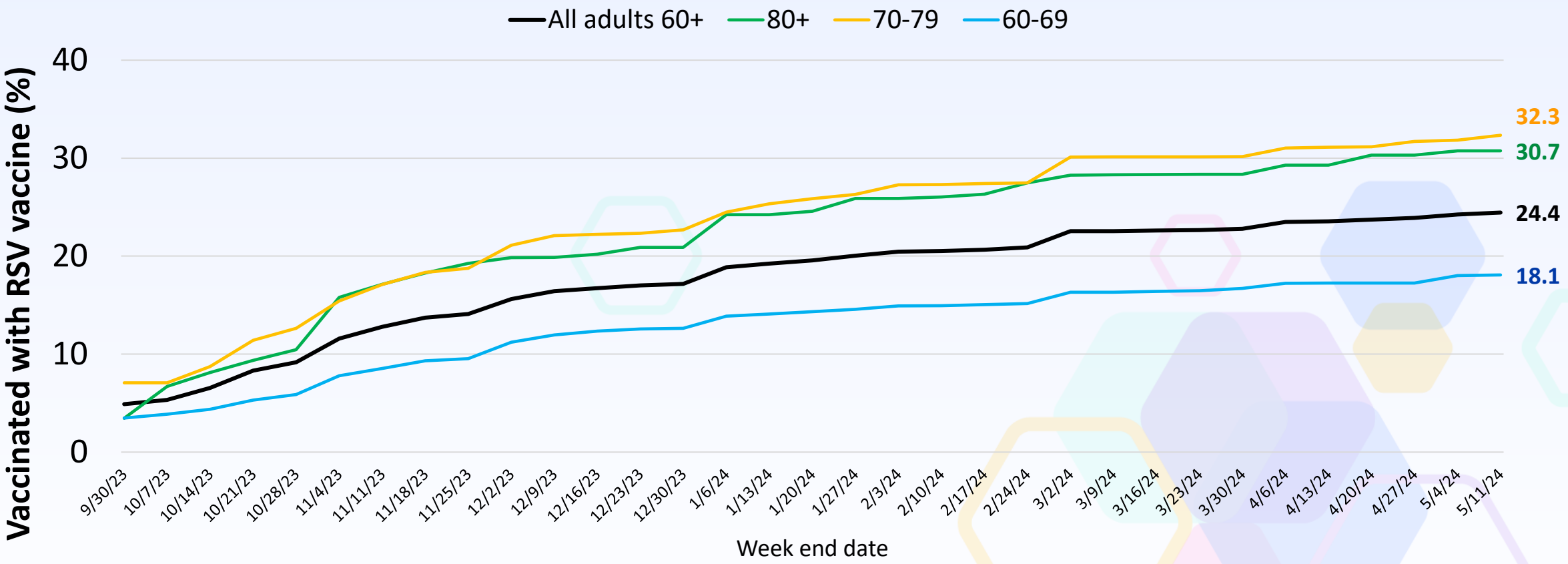
Concern about Getting RSV Disease Among Adults ≥60 Years of Age, by Age Group, Omnibus Surveys, April 4–26, 2024 (N=4,102)



Omnibus Surveys: data for this analysis were collected through the Ipsos KnowledgePanel and NORC AmeriSpeak Omnibus Surveys, which use probability-based panels to survey a nationally representative sample of U.S. adults aged 18 years and older. CDC fields questions about vaccination status, intent, knowledge, attitudes, beliefs, and behaviors on each survey for 2 waves each month, for a combined sample size of ~4,000 respondents. These slides present results from April 2024. Data were weighted to represent the non-institutionalized U.S. population and mitigate possible non-response bias. All responses are self-reported.

RSV Vaccination Among Adults ≥60 Years of Age, by Age Group September 2023–May 2024 (n=156,281)

National Immunization Survey-Adult COVID Module (NIS-ACM)



National Immunization Survey-Adult COVID Module (NIS-ACM). The NIS-ACM is a random-digit-dial cellular telephone survey of adults age ≥18 years in the U.S. Respondents are sampled within all 50 states, District of Columbia, five local jurisdictions (Bexar County TX, Chicago IL, Houston TX, New York City NY, and Philadelphia County PA), Guam, Puerto Rico, and the U.S. Virgin Islands (sampled in 2023 only). Data are weighted to represent the non-institutionalized U.S. population. All responses are self-reported.
https://www.cdc.gov/vaccines/imz-managers/coverage/rsvvaxview/adults-60-coverage-intent.html

Risk of Guillain-Barre Syndrome (GBS)

- While we do not have any data specifically looking at how adults value estimated protection against RSV in relation to potential risk of GBS, a few considerations:

1. Adults are willing to accept some rate of vaccine-associated adverse events for the benefit of preventing disease[1]
2. Individual baseline and vaccine-associated risk of GBS may differ by age group and presence of chronic conditions
3. Willingness to accept risk of GBS after vaccination may differ by age and health status and perceived risk of RSV-associated disease[2]

1. Scherer LD, Shaffer VA, Patel N, Zikmund-Fisher BJ. Can the vaccine adverse event reporting system be used to increase vaccine acceptance and trust? Vaccine. 2016 May 5;34(21):2424-2429. https://pubmed.ncbi.nlm.nih.gov/27049120/
2. Prosser LA, Payne K, Rusinak D, et al. Valuing health across the lifespan: health state preferences for seasonal influenza illnesses in patients of different ages. Value Health. 2011;14(1):135-143. https://pubmed.ncbi.nlm.nih.gov/21211495/

Values: summary of the available evidence
Adults 60 years and older

- In the first RSV season after ACIP made a shared clinical decision-making recommendation for adults 60 years and older, **an estimated 20–30% of U.S. adults in this age group received RSV vaccination.**
- Vaccination uptake was **higher among adults ≥70 years** than among adults 60–69 years.
- We **do not have data on how adults value risk of protection against RSV versus potential risk of GBS**, but this may vary by age or other factors.

Values

- Do **adults aged ≥75** years feel that the desirable effects of RSV vaccination are large relative to the undesirable effects?

No	Probably no	Probably Yes	Yes	Varies	Don't know

- Is there important uncertainty about, or variability in, how much **adults aged ≥75 years** 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

Values

- Do **adults aged 60–74 years at increased risk of severe RSV disease** feel that the desirable effects of RSV vaccination are large relative to the undesirable effects?

No	Probably no	Probably Yes	Yes	Varies	Don't know

- Is there important uncertainty about, or variability in, how much **adults aged 60–74 years at increased risk of severe RSV disease** 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

Acceptability

Would recommending RSV vaccination for **adults 75 and older** be acceptable to key stakeholders?

Would recommending RSV vaccination for **adults 60–74 at increased risk of severe RSV disease** be acceptable to key stakeholders?

Feasibility

Is it feasible to implement RSV vaccination for **adults 75 and older**?

Is it feasible to implement RSV vaccination for **adults 60–74 at increased risk of severe RSV disease**?

Based on survey data, physicians think shared clinical decision-making increases time and confusion[1]

68% strongly agreed SCDM will require more time with patients

44% either strongly or somewhat agreed they find it hard to explain what a SCDM recommendation means to patients

76% either strongly or somewhat agreed SCDM creates confusion

42% either strongly or somewhat agreed they did not know how to implement SCDM as intended by the ACIP

Kempe A, Lindley MC, O'Leary ST, et al. Shared Clinical Decision-Making Recommendations for Adult Immunization: What Do Physicians Think? *J Gen Intern Med*. 2021;36(8):2283-2291. https://pubmed.ncbi.nlm.nih.gov/33528783/ . Numbers cited based on General Internal Medicine physician responses, N=281).

CDC and ACIP have heard feedback that the RSV SCDM recommendation has been difficult to implement

- SCDM **conversations are challenging and time-consuming.**
- Compared to universal recommendations, SCDM **does not have a clear call to action.**
- **Standing orders** - often used by medical assistants, nurses, and pharmacists – are **difficult under SCDM**.
- **Approximately 80%** of all older adult RSV vaccinations have been given in pharmacies. Not all providers who give vaccines are comfortable with the SCDM conversation or feel it is within their scope of practice.
- In the specific instance of RSV vaccines, there are also concerns about the ability to complete the type of risk-benefit discussion intended by ACIP with the RSV SCDM recommendation.

Dr. Carla Black, ACIP Meeting February 2024: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/04-RSV-Adults-Black-508.pdf

Financial and insurance barriers

- Vaccine acquisition cost relatively high
  - Costly upfront investment to carry RSV vaccines
- RSV vaccine billed under Medicare Part D
  - Millions of Medicare beneficiaries are not enrolled in Part D
  - Part D generally described as more challenging to access and implement than Part B so providers may be less likely to carry vaccine in their practices and instead refer to pharmacies

Schedule complexity

- Multiple adult RSV vaccine products
- Different storage and handling requirements
  - Moderna mRESVIA requires frozen storage or if refrigerated use within 30 days
- Adult vaccine schedule is increasingly complex including multiple products with different schedules

Acceptability and Feasibility: Summary of the available evidence

All adults aged 75 years and older

- Makes vaccination the "default"
- Easier to incorporate into standing orders, clinical decision support, and messaging
- Covers those at highest risk without asking providers to do extensive individualized risk assessment

- "Universal" RSV recommendation only for some ages
- Ongoing challenge in complexity of adult schedule
- Repeated recommendation changes may cause confusion

Acceptability and Feasibility: Summary of the available evidence

Risk-based recommendation adults aged 60–74 years

- Compared with a shared clinical decision-making recommendation, a **risk-based recommendation** will provide more clarity to providers and public about who **should** get an RSV vaccine
- Easier to incorporate into standing orders, clinical decision support, and messaging

- Risk-based recommendations are still more challenging to implement than universal recommendations
- Eligible risk factors for RSV vaccination will not align with other adult vaccines
- Repeated recommendation changes may cause confusion

Acceptability

- Would recommending RSV vaccines for **adults aged ≥75 years** be acceptable to key stakeholders?

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

- Would recommending RSV vaccines for **adults aged 60–74 years at increased risk of severe RSV disease** be acceptable to key stakeholders?

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

Feasibility

- Is it feasible to implement **protein subunit** RSV vaccination among **adults aged ≥75 years?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

- Is it feasible to implement **Moderna mRESVIA** vaccination among **adults aged ≥75 years?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

Feasibility

- Is it feasible to implement **protein subunit** RSV vaccination among **adults aged 60–74 years at increased risk of severe RSV disease?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

- Is it feasible to implement **Moderna mRESVIA** vaccination among **adults aged 60–74 years at increased risk of severe RSV disease?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

Resource Use

Is an RSV vaccine program for adults a reasonable and efficient allocation of resources for:

- **Adults 75 and older?**
- **Adults 60–74 at increased risk of severe RSV disease?**

Work Group considerations regarding societal resource use toward RSV vaccination in older adults at current list prices

- RSV vaccination **is likely cost-effective for:**
  - Adults aged 75 years and older
  - Adults aged 60–74-year with risk factors for severe RSV disease
- RSV vaccination **is likely NOT cost-effective in adults aged 60–74 years *without* risk** factors.
  - Therefore, a *universal* RSV vaccination in adults aged 60–74 years is likely NOT a reasonable and efficient allocation of societal resources
- There remains **substantial uncertainty** in key parameters that impact cost effectiveness:
  - Uncertainty in incidence of medically attended RSV illness, particularly hospitalizations
  - Uncertainty in RSV-attributable mortality
  - Uncertainty in duration of protection from a single dose of RSV vaccination
  - Real-world vaccine effectiveness of Moderna mRESVIA; analyses currently rely on clinical trial efficacy estimates
- **For all 3 manufacturers, Work Group felt that if RSV vaccine list prices were substantially reduced, then RSV vaccination may be a cost-effective intervention for a broader adult population.**

Resource use

- Is **protein subunit** RSV vaccination a reasonable and efficient allocation of resources in adults **aged ≥75 years**?

No	Probably No	Probably Yes	Yes	Varies	Don't know

- Is **Moderna mRESVIA** vaccination in **adults aged ≥75 years** a reasonable and efficient allocation of resources?

No	Probably No	Probably Yes	Yes	Varies	Don't know

Resource use

- Is **protein subunit** RSV vaccination a reasonable and efficient allocation of resources in adults **aged 60–74 years at increased risk of severe RSV disease**?

No	Probably No	Probably Yes	Yes	Varies	Don't know

- Is **Moderna mRESVIA** vaccination in **adults aged 60–74 years at increased risk of severe RSV disease** a reasonable and efficient allocation of resources?

No	Probably No	Probably Yes	Yes	Varies	Don't know

Equity

What would be the impact on health equity of recommending RSV vaccination for:

- **Adults 75 and older?**
- **Adults 60–74 at increased risk of severe RSV disease?**

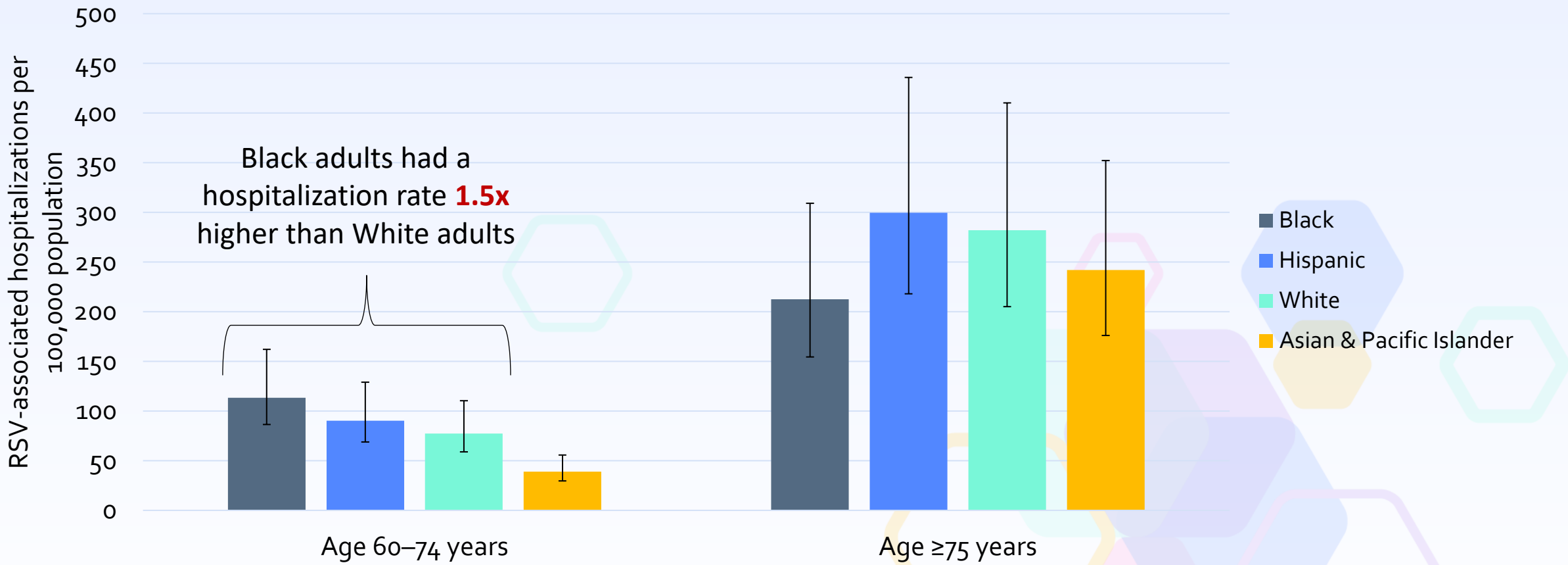
Median age of non-pregnant adults aged ≥18 years with RSV-associated hospitalizations by race and ethnicity* — RSV-NET, 2014–2015 to 2022–2023

	Unweighted	Weighted %	Median Age	Interquartile range (IQR)
Overall	17,847	-	69	(58–81)
White	10,755	62.2	73	(63-82)
Black	3,529	20.4	**62**	**(50-71)**
Hispanic	1,434	8.3	**62**	**(48-76)**
Asian or Pacific Islander	1,020	5.9	73	(59-83)
American Indian or Alaska Native	90	0.5	**64**	**(54-73)**
Multiple races	89	0.5	75	(58-84)
Unknown	367	2.1	68	(57-78)

Median **age of hospitalization is lower among Black, Hispanic, and American Indian/Alaska Native** persons than White and Asian/Pacific Islander persons.

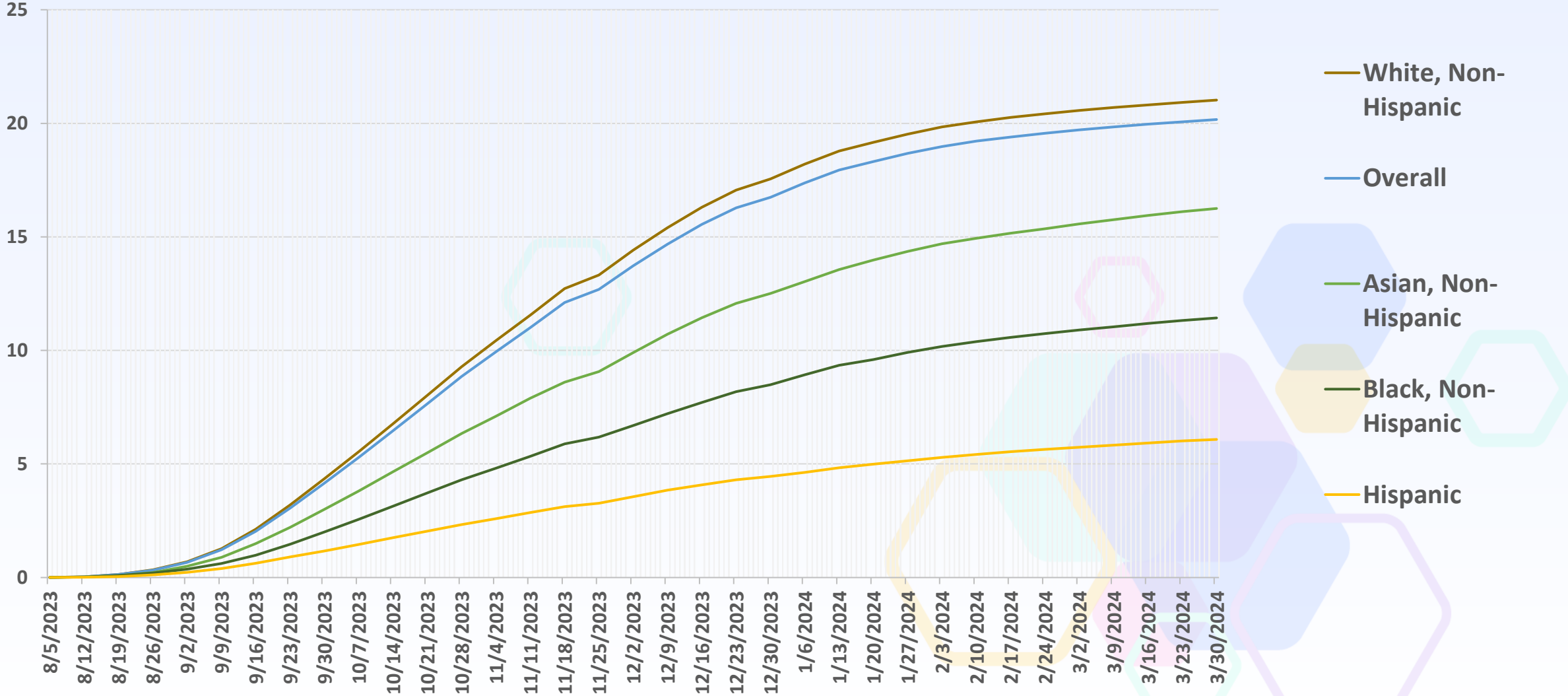
*Black, White, American Indian/Alaska Native and Asian/Pacific Islander people were categorized as non-Hispanic; Hispanic people could be of any race.

RSV-associated hospitalization rates by age group and race and ethnicity*, RSV-NET, 2018–2019



https://www.cdc.gov/rsv/research/rsv-net/index.html Unpublished data. Rates are adjusted using multipliers for the frequency of RSV testing during each season and the sensitivity of RSV diagnostic tests. Error bars represent 95% confidence intervals. Estimated rates exclude recorded hospitalizations among pregnant adults. Black, White, and Asian/Pacific Islander people were categorized as non-Hispanic; Hispanic people could be of any race. Hospitalization rates among American Indian and Alaska Native persons are not shown due to small numbers. There may be unmeasured confounding, especially in the oldest age group. Although incidence appears lower in Black adults 75 and older than in White adults, if Black adults are less likely to survive to age 80 or 90 years, then differences in underlying age distribution may be driving this finding.

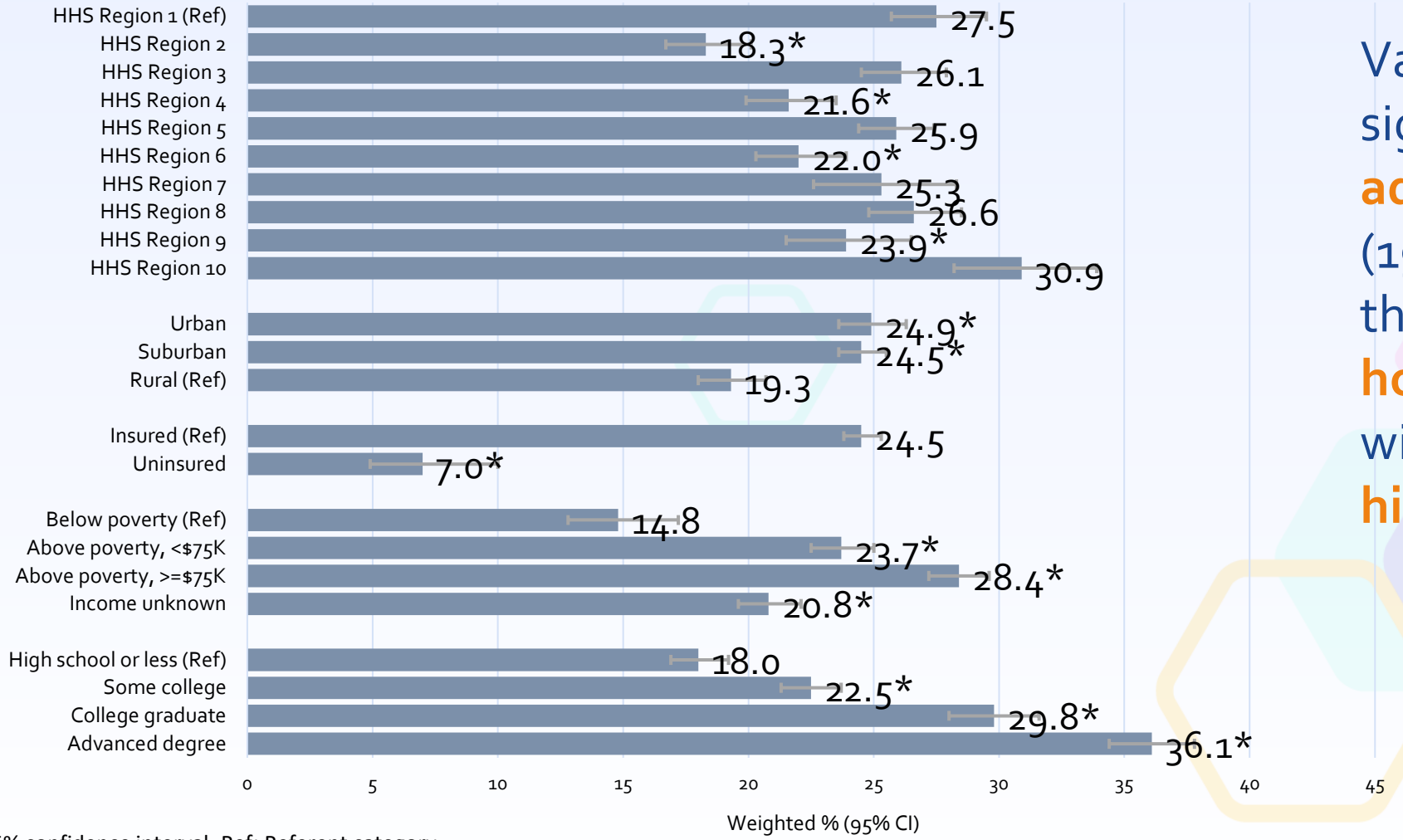
Weekly cumulative RSV vaccination coverage, by race and ethnicity, Medicare fee-for-service beneficiaries aged ≥65 years and enrolled in a Part D plan, United States



Data source: Centers for Medicare & Medicaid Services Chronic Conditions Warehouse. Estimates are based on data released by CMS through March 30, 2024. Overall includes persons categorized as 'Unknown' for race and ethnicity category. Data can be accessed at: https://www.cdc.gov/vaccines/imz-managers/coverage/rsvvaxview/adults-65yrs-older-coverage.html

RSV Vaccination Coverage Among Adults ≥60 Years of Age, by end of March 2024 (n=156,281)

National Immunization Survey-Adult COVID Module (NIS-ACM)



Vaccination coverage was significantly **lower** among **adults in rural areas** (19.3%), **uninsured** (7.0%), those with **lower household income**, and with educational level of **high school or less** (18.0%).

HHS Regions
1: CT,ME,MA,NH,RI,VT
2: NJ,NY,PR,VI
3: DE,DC,MD,PA,VA,WV
4: AL,FL,GA,KY,MS,NC,SC,TN
5: IL,IN,MI,MN,OH,WI
6: AR,LA,NM,OK,TX
7: IA,KS,MO,NE
8: CO,MT,ND,SD,UT,WY
9: AZ,CA,HI,NV,GU
10: AK,ID,OR,WA

CI: 95% confidence interval; Ref: Referent category.
*Statistically significant at p<0.05 compared to the referent category.
Kaplan-Meier estimates are based on cumulative data through April 27, 2024.

Equity: Summary of the available evidence

All adults aged 75 years and older

- Practicality and value of issuing a simple and clear message **may remove barriers** to vaccination
- Adults with **undiagnosed** chronic medical conditions would be included in the recommendation

- Universal recommendations do not guarantee equity; even if coverage increases across all groups, **disparities between groups** may remain

Equity: Summary of the available evidence
Adults aged 60–74 years at increased risk of severe RSV disease

- Clarifying who is at risk **may remove barriers** to vaccination
- May increase coverage among racial/ethnic minority groups in whom prevalence of chronic conditions is higher in 60–74 age group

- Adults with **undiagnosed** chronic medical conditions may be deemed ineligible for vaccination under a risk-based recommendation; under shared clinical decision-making, some of these adults may have obtained RSV vaccination

Equity

- What would be the impact on health equity of recommending RSV vaccination in **adults aged ≥75 years?**

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

- What would be the impact on health equity of recommending RSV vaccination in **adults aged 60–74 years at increased risk of severe RSV disease?**

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

Summary

Domain	Question	Work Group Judgements	
	Adults aged 75 years and older	Protein Subunit RSV Vaccines (Pfizer and GSK)	Moderna
Public Health Problem	Is RSV of public health importance?	Yes	
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate/Large	Moderate/Large
	How substantial are the undesirable anticipated effects?	Small/Moderate	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention	Favors intervention
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Yes/Probably yes	
	Is there important variability in how patients value the outcomes?	Probably not important variability	
Acceptability	Is the intervention acceptable to key stakeholders?	Yes	
Feasibility	Is the intervention feasible to implement?	Yes/Probably yes	Yes/Probably yes
Resource Use	Is the intervention a reasonable and efficient allocation of resources?	Yes/Probably yes	Yes/Probably yes
Equity	What would be the impact on health equity?	Increased/Probably increased	

Domain	Question	Work Group Judgements	
	Adults aged 60–74 years at increased risk of severe RSV disease	Protein Subunit RSV Vaccines (GSK and Pfizer)	Moderna
Public Health Problem	Is RSV of public health importance?	Yes	
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate/Large	Moderate/Large
	How substantial are the undesirable anticipated effects?	Small/Moderate	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention	Favors intervention
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 outcomes?	Probably not important variability	
Acceptability	Is the intervention acceptable to key stakeholders?	Yes/Probably yes	
Feasibility	Is the intervention feasible to implement?	Yes/Probably yes	Yes/Probably yes
Resource Use	Is the intervention a reasonable and efficient allocation of resources?	Yes/Probably yes	Yes/Probably yes
Equity	What would be the impact on health equity?	Probably increased	

Work Group Considerations

- The shared clinical decision-making (SCDM) recommendation was made in the setting of uncertainty about both the estimated benefits and potential risks of RSV vaccination.
- Now there is real-world evidence of robust protection against RSV-associated hospitalization during the first season after vaccination among adults 60 and older, including among adults 75 and older and adults with chronic medical conditions.
- On the other hand, uncertainty remains regarding the magnitude of potential risk of Guillain-Barre syndrome (GBS).
- The Work Group believes the GBS signal continues to warrant close attention and additional follow-up.
- **A transition from SCDM to a universal recommendation among adults 75 years and older and a risk-based recommendation among adults aged 60–74 years and is intended to:**
  - **Maximize vaccination among persons most likely to benefit** among whom we now have real-world evidence of protection
  - **Minimize vaccination among persons least likely to benefit** while additional safety data accrue

Additional Work Group discussions

- **The Work Group discussed the role of potential preferential recommendations between products, but felt that the strength of the available evidence did not meet the standard for a preferential recommendation at this time.**
- Reasons cited included:
  - Current safety analyses are interim and based on a small numbers of GBS cases.
  - Unknown relative duration of protection across products
  - Need for revaccination and potential risk of GBS associated with additional doses unknown
  - Changes based on limited evidence may have unintended programmatic consequences

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Among all adults aged ≥75 years:

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

Among adults aged 60–74 years at increased risk of severe RSV disease:

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

Evidence to Recommendations Framework

Summary: Work Group Interpretations– Is there sufficient information to move forward with a recommendation?

Among all adults aged ≥75 years:

Yes	**No**

Among adults aged 60–74 years at increased risk of severe RSV disease:

Yes	**No**

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Type of recommendation, all adults aged ≥75 years

- We recommend the intervention

Type of recommendation, adults aged 60–74 years at increased risk of severe RSV disease

- We recommend the intervention

Proposed ACIP vote language

1. ACIP recommends adults 75 years of age and older receive a single dose of RSV vaccine.[a,b]
2. ACIP recommends adults 60–74 years of age who are at increased risk of severe RSV disease[c] receive a single dose of RSV vaccine.[a,b]

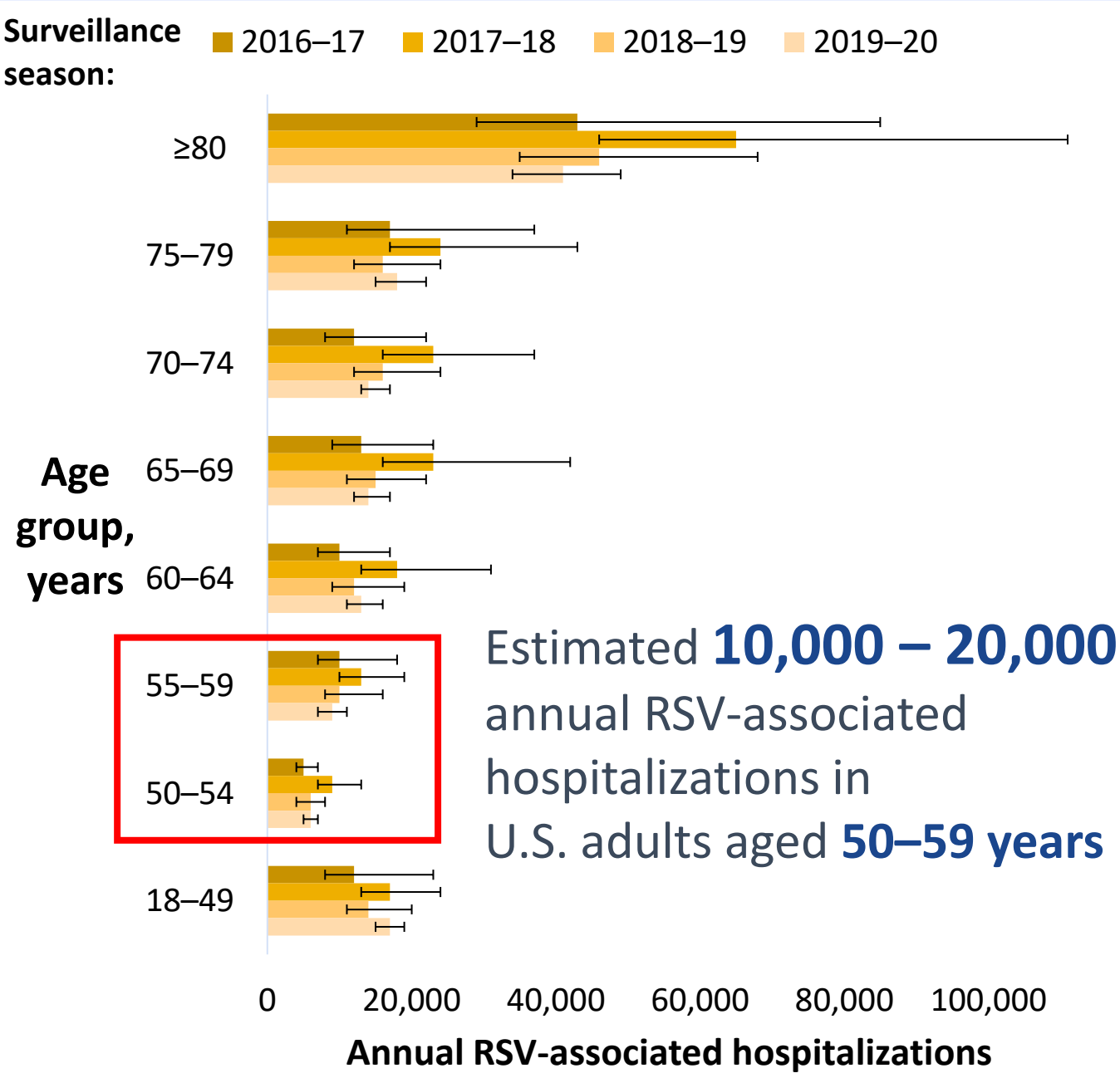
a. RSV vaccination is recommended as a single lifetime dose only. Persons who have already received RSV vaccination are NOT recommended to receive another dose.
b. These recommendations would supplant the current recommendation that adults 60 years of age and older may receive RSV vaccination, using shared clinical decision-making. Adults 60–74 years of age who are **not** at increased risk of severe RSV disease would NOT be recommended to receive RSV vaccination.
c. CDC will publish Clinical Considerations that describe chronic medical conditions and other risk factors for severe RSV disease for use in this risk-based recommendation.

Should adults aged 50–59 years at increased risk of severe RSV disease be recommended to receive a single dose of RSV vaccination?

EtR Domain: Public Health Problem

Is the problem of public health importance **among adults aged 50–59 years at increased risk of severe RSV disease?**

Estimated annual number of RSV-associated hospitalizations* among adults aged ≥18 years by age group and year, RSV-NET, 2016–17 to 2019–20



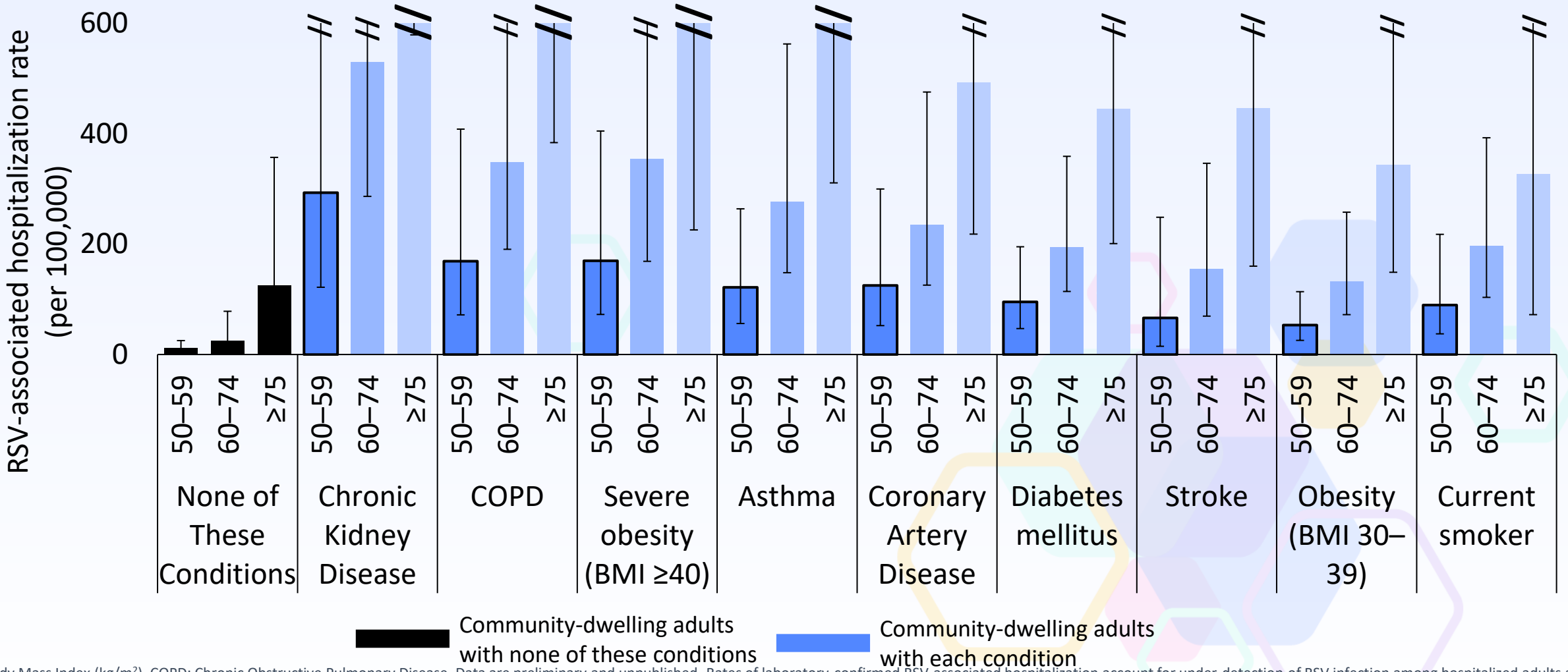
Estimated **10,000 – 20,000** annual RSV-associated hospitalizations in U.S. adults aged **50–59 years**

Preliminary unpublished data. Hospitalization counts are adjusted using multipliers for the frequency of RSV testing during each season and the sensitivity of RSV diagnostic tests. Error bars represent 95% confidence intervals.

*Estimated hospitalizations exclude recorded hospitalizations among pregnant adults.

https://www.cdc.gov/rsv/research/rsv-net/index.html

RSV-associated hospitalization rates among community-dwelling adults aged ≥50 years with chronic medical conditions, 2017–2018 season



BMI: Body Mass Index (kg/m^2), COPD: Chronic Obstructive Pulmonary Disease. Data are preliminary and unpublished. Rates of laboratory-confirmed RSV-associated hospitalization account for under-detection of RSV infection among hospitalized adults and sensitivity of diagnostic tests. Poisson regression using Monte Carlo simulation estimated rates and 95% confidence intervals (represented by error bars). Rates for community-dwelling adults exclude residents of nursing homes and long-term care facilities and are not adjusted for sex or race/ethnicity group.

Public Health Problem: Work Group interpretation

- Is RSV of public health importance among adults aged **50–59 years at increased risk of severe RSV disease?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

EtR Domain: Benefits and Harms 50–59

- How substantial are the desirable anticipated effects?

- How substantial are the undesirable anticipated effects?

- Do the desirable effects outweigh the undesirable effects?

GRADE Framework: PICO Question

Population	**Adults aged 50–59 at increased risk of severe RSV disease**
Intervention	RSV Vaccine: GSK AREXVY (1 dose IM)
Comparison	No RSV vaccine
Outcomes	▪ RSV lower respiratory tract disease (LRTD) ▪ Medically attended RSV LRTD ▪ Hospitalization for RSV respiratory illness ▪ Severe RSV respiratory illness requiring supplemental oxygen or other respiratory support ▪ Death due to RSV respiratory illness ▪ Serious Adverse Events (SAEs) ▪ Inflammatory neurologic events (e.g., Guillain-Barré syndrome) ▪ Reactogenicity (grade ≥3)

GSK AREXVY vaccine in adults aged 50–59 years at increased risk of severe RSV disease Benefits: Geometric Mean Ratio (GMR) of neutralizing antibody titers[1]

	n	GMT (95% CI), 30 days post-vaccination	n	GMT (95% CI), 30 days post-vaccination	GMR (95% CI)[a], Cohort 1a vs. Cohort 2	Met Noninferiority Objective[b]
	Cohort 1a: Adults aged 50–59 years at increased risk of severe RSV disease		Cohort 2: Adults aged ≥60 years			
RSV-A[c]	343	8922.7 (8118.2, 9806.9)	342	7440.1 (6768.4, 8178.5)	1.20 (1.05, 1.37)	Yes
RSV-B[d]	343	10054.7 (9225.4, 10958.7)	341	8062.8 (7395.9, 8789.9)	1.25 (1.10, 1.41)	Yes

Abbreviations: CI = confidence interval; GMT = geometric mean titer; GMR = geometric mean ratio

a) The manufacturer calculated GMR as Cohort 2 / Cohort 1a. However, here, the reciprocal is shown: Cohort 1a / Cohort 2. GMR values >1 indicate higher GMTs in Cohort 1a (adults 50–59 at increased risk), compared with Cohort 2 (adults ≥60).

b) Noninferiority objective was lower bound of the confidence interval ≥0.67, when evaluating the GMR Cohort 1a / Cohort 2.

c) Serological assays for the determination of antibodies against RSV-A are performed by neutralization assay. The corresponding antibody titers were expressed in ED60 (serum estimated dilution inducing 60% inhibition in plaque-forming units). Assessed at Day 31 , where Day 1 was day of vaccination

d) Serological assays for the determination of antibodies against RSV-B are performed by neutralization assay. The corresponding antibody titers were expressed in ED60. Assessed at Day 31 , where Day 1 was day of vaccination.

1. https://clinicaltrials.gov/study/NCT05590403, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/02-gerber-adult-RSV-508.pdf, unpublished data obtained from manufacturer

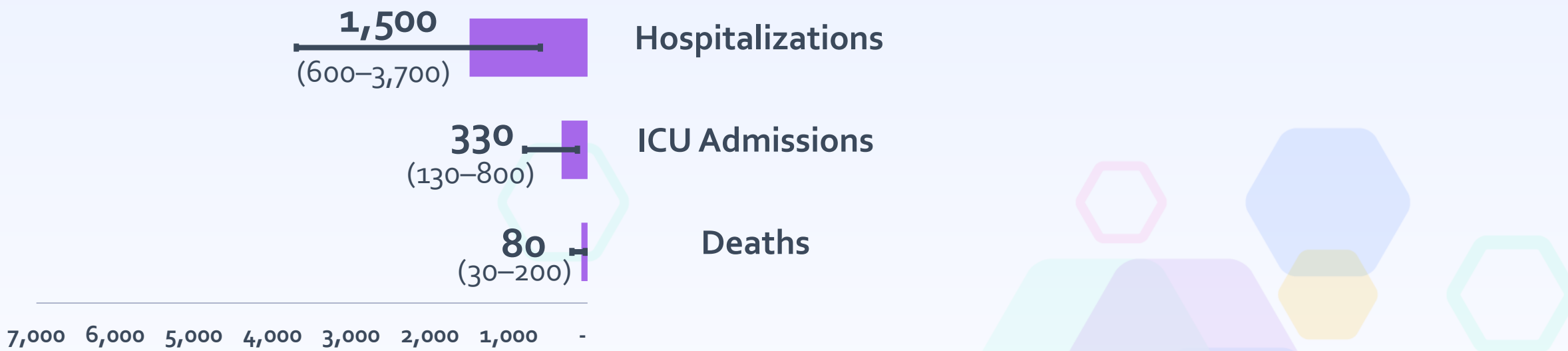
Summary of GRADE for GSK AREXVY in adults aged 50–59 years at increased risk of severe RSV disease

Outcome	Importance	Design (# of studies)	Findings In adults aged 50-59 years at increased risk of severe RSV disease:	Evidence type
Benefits				
RSV Lower Respiratory Tract Disease (LTRD)	Important	RCT (1)	Vaccination with GSK AREXVY likely reduces RSV LRTD	**Moderate**
Medically attended RSV LRTD	Critical	RCT (1)	Vaccination with GSK AREXVY likely reduces medically attended RSV LRTD	**Moderate**
Hospitalization for RSV respiratory illness	Critical	RCT (1)	Vaccination with GSK AREXVY may reduce hospitalization for RSV respiratory illness	**Very Low**
Severe RSV respiratory illness requiring O2/respiratory support	Important	RCT (1)	Vaccination with GSK AREXVY may reduce severe RSV respiratory illness requiring supplemental O2 or other respiratory support	**Very Low**
Death due to RSV respiratory illness	Important	RCT (1)	Zero events observed	Unable to evaluate
Harms				
Serious adverse events	Critical	RCT (1)	Vaccination with GSK AREXVY may result in little to no difference in serious adverse events	**Low**
Inflammatory neurologic events	Critical	RCT (1)	Zero events observed	Unable to evaluate
Reactogenicity (grade ≥3)	Important	RCT (1)	Vaccination with GSK AREXVY increases severe reactogenicity events	**Moderate**

Additional information on benefits/harms for adults aged 50–59 years at increased risk of severe RSV disease

Estimated RSV-Associated Outcomes[1] Preventable over 2 RSV Seasons vs. potential cases of GBS (*positive predictive value-adjusted* attributable risk of GBS in FDA-CMS partnership data among adults aged ≥65 years, 42-day risk interval[2,3])

Per 1 Million Doses of GSK AREXVY Administered to Adults Aged 50–59 Years at Increased Risk of Severe RSV Disease:



3 (range **0–10**)[4] attributable **cases of GBS**

1. Range of outcomes avertable was calculated using published 95% confidence intervals (outpatient only) and adjusted 95% confidence interval of RSV-associated incidence of the outcome observed in RSV-NET
2. FDA self-controlled case series analysis, among CMS Medicare beneficiaries ≥65 years with Parts A, B, and D coverage who did not have a GBS claim in the 365 days before vaccination. Analysis based on diagnoses of GBS in inpatient claims data in risk interval (1-42 days after RSV vaccination) compared to control interval (43-90 days after RSV vaccination). GBS cases identified using ICD-10 diagnosis of GBS in primary position of inpatient claims coding. Estimates adjusted for outcome-dependent observation time, positive predictive value of diagnostic codes in identifying chart-confirmed GBS cases, and seasonality. Analysis includes patients with RSV vaccinations only through October 8, 2023 to allow for 90-day post-vaccination observation and 90% or greater claims data completeness. Claims data through April 6, 2024.
3. Although CMS data were limited to Medicare beneficiaries aged ≥65 years, results are extrapolated here to adults aged 50-59 years.
4. Self-controlled case series analysis estimated attributable risk of 3 (95% CI: -3, 10) GBS cases. However, the range was truncated at zero for Benefit/Risk analyses.

As reviewed for adults 60 and older, there are a number of additional considerations

- Revaccination at 12 months does not appreciably increase efficacy, compared with a single dose.
- Optimal timing of re-vaccination is unknown.
- No available clinical trial immunogenicity, efficacy, or safety data in severely immune compromised persons (e.g., hematopoietic cell or solid organ transplant recipients).

Benefits and Harms GSK AREXVY vaccine in adults aged 50–59 at increased risk of severe RSV disease

- How substantial are the **desirable anticipated effects** among adults aged 50–59 years at increased risk of severe RSV disease

Minimal	Small	Moderate	Large	Varies	Don't know

- How substantial are the **undesirable anticipated effects** among adults aged 50–59 years at increased risk of severe RSV disease?

Minimal	Small	Moderate	Large	Varies	Don't know

- Do the **desirable effects outweigh the undesirable effects** among adults aged 50–59 years at increased risk of severe RSV disease?

Favors intervention (GSK AREXVY)
Favors comparison (no vaccine)
Favors both
Favors neither
Unclear

Majority opinion Minority opinion

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Among adults aged 50–59 years at increased risk of severe RSV disease:

Is there sufficient information to move forward with a recommendation?

Yes	No

As of the June 26, 2024 ACIP meeting, the Work Group majority has concluded there is currently insufficient evidence to make a recommendation regarding RSV vaccination in adults 50–59 years at today's meeting.

Work Group Considerations on the use of GSK AREXVY in adults 50–59 years at increased risk of severe RSV disease

This represents an opinion that additional information is needed to determine the best policy for RSV vaccination in adults aged 50–59 years.

- As demonstrated during the public health problem domain, the majority of the Work Group felt that RSV-associated disease is or probably is a public health problem among adults aged 50-59 years at increased risk of severe RSV disease.
- This opinion is NOT a recommendation *against* the use of RSV vaccine in adults aged 50–59 years.
- **Rather, the Work Group believes more information is needed to make a population-level policy recommendation.**

The decision to postpone making a recommendation is primarily driven by uncertainty in the balance of estimated benefits of RSV vaccine and potential risk of GBS, specifically among adults aged 50–59 years

- Among adults aged 50–59 years, in whom the absolute rates of RSV-associated disease are lower, the **balance of risk and benefits is more uncertain** than among older age groups.
- The Work Group recognizes that postponing a policy recommendation may mean some adults aged 50–59 years who might benefit from RSV vaccination will not receive a dose this fall.

The Work Group will continue active deliberation on the best policy recommendation in this age group as more data become available and will bring a recommendation for ACIP's consideration as soon as the Work Group believes there is sufficient evidence.

Before making a recommendation for adults aged 50–59 years the Work Group would like to review additional data

- **At least one complete season of safety surveillance data.**
  - **Depending on certainty of findings, additional data may be needed.**
- Immunobridging data in adults with immune compromise.
  - Clinical trials including adults with immune compromise are underway.
- Data on duration of protection and immune response after re-vaccination
  - Work Group has expressed concern that to date there are no data showing re-vaccination will restore protection if efficacy wanes over time.
  - While restoration of protection with re-vaccination is likely, efficacy in GSK's pivotal phase III trial did not improve after re-vaccination at a 12-month interval.
  - GSK immunogenicity data at 12- and 24-month re-vaccination intervals have shown a weaker humoral immune response, compared with the response after dose 1.

The Work Group recognizes equity is an important concern in the use of RSV vaccines in adults aged 50–59 years and they considered equity in their deliberations.

The Work Group is committed to ongoing assessment of RSV vaccination in adults

- This includes adults aged 50–59 years and pending licensure, use of RSV vaccine in adults aged <50 years.
- The Work Group will continue to review data available from clinical trials, real-world vaccine effectiveness, and safety monitoring.
- While the timeline of availability of sufficient safety and other data is unknown for a recommendation in adults **50–59 the Work Group will present to ACIP the status of their deliberations as soon as there are updated considerations.**

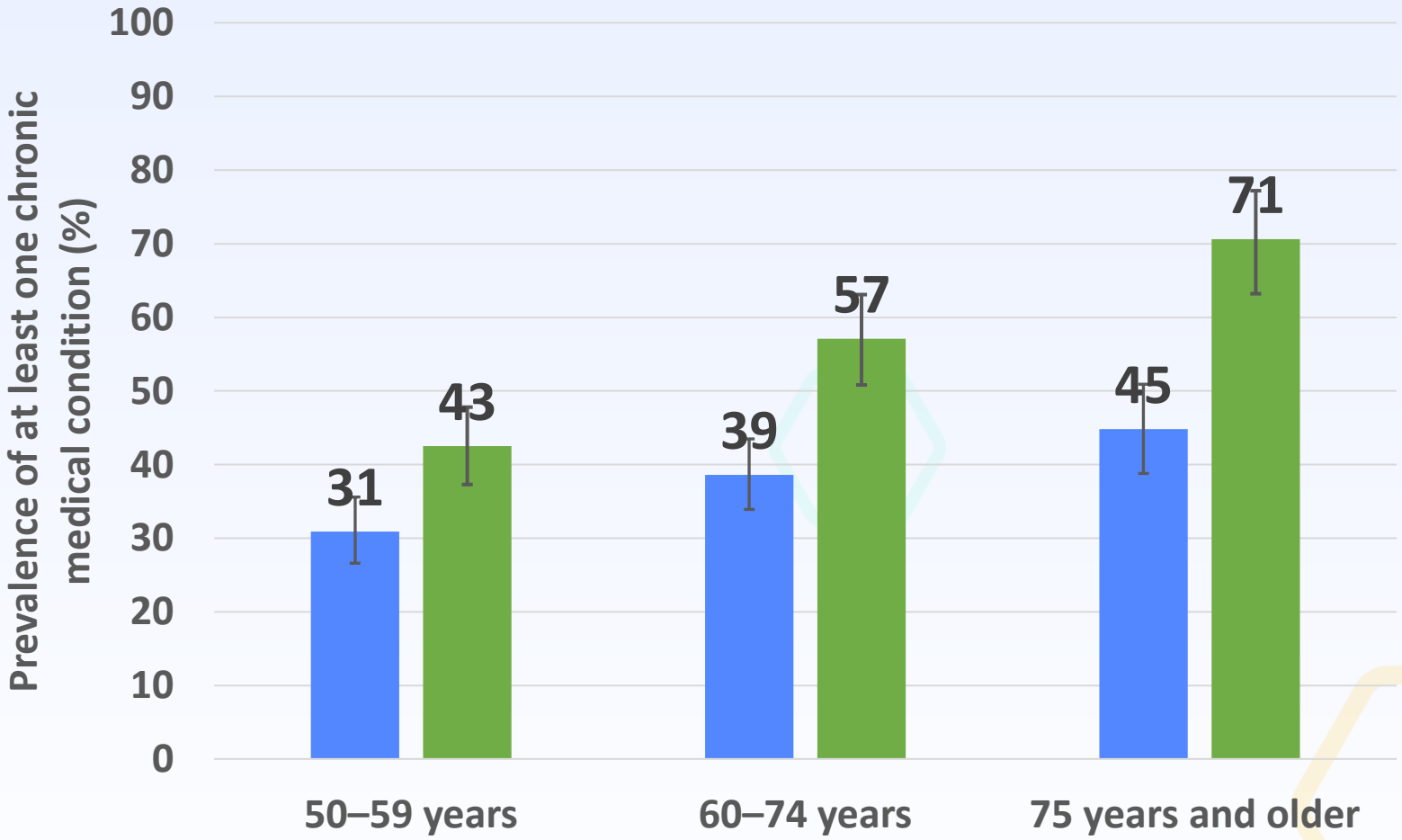
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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

Back-Up Slides

Prevalence of ≥1 chronic medical condition among adults 75 and older is at least 45% using a narrow definition of chronic medical conditions* and may be as high as 71% when using a broad definition**

National Health and Nutrition Examination Survey (NHANES), 2015–2018.



***Narrow definition,** at least one of:

- Serious heart disease
- Diabetes **with complication**
- Chronic obstructive pulmonary disease
- Asthma
- Severe obesity (BMI ≥40 kg/m^2)
- Liver condition
- Chronic kidney disease, **stage 4 or 5**

****Broad definition,** as above, OR:

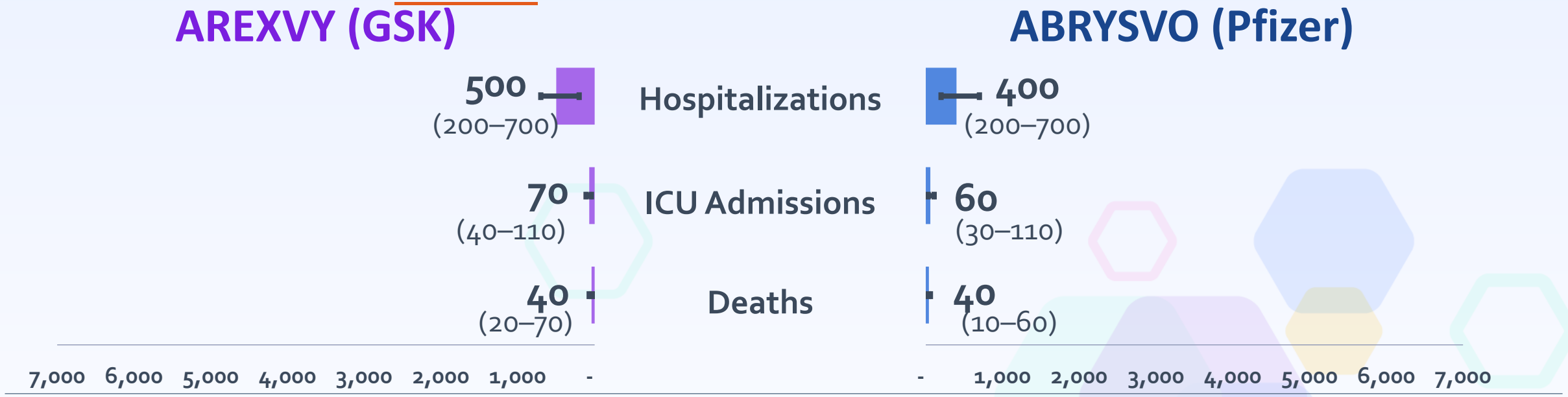
- Diabetes **with or without** complication
- Chronic kidney disease, **stage 3, 4, or 5**
- Cancer or malignancy in past 2 years

BMI: body mass index

SOURCE: National Center for Health Statistics (NCHS), National Health and Nutrition Examination Survey (NHANES), 2015–2018. All estimates are crude estimates with no age adjustment and age is age at interview. Error bars represent Korn and Graubard 95% confidence intervals. NHANES is representative of the civilian, non-institutionalized U.S. population. For "narrow" definition: Severe obesity was defined as BMI ≥40 kg/m^2. Diabetes with complication was defined as 1) having diabetes: self-reported diabetes, fasting plasma glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5%, AND 2) having one of the following complications of diabetes assessed within the survey: serious heart disease as defined below, chronic kidney disease (stage 3, 4, or 5) defined as estimated glomerular filtration rate (eGFR) <60 (stages 3–5) further defined below, or having self-reported diabetes and having a doctor previously told them that diabetes affected their eyes or that they have retinopathy. Other complications of diabetes are not included in this definition. Serious heart disease was defined based on self-report as diagnosed congestive heart failure, coronary heart disease, angina, or heart attack, or angina grades 1 or 2 determined by the Rose Angina Questionnaire. Asthma was defined as self-reporting ever being diagnosed with asthma and still having asthma. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <30 (stages 4–5), and using a forward equation for adjustment of creatinine because of methods changes. eGFR calculated using the 2021 CKD-EPI creatinine equation (https://www.nejm.org/doi/10.1056/NEJMoa2102953). Urine albumin is not included in this definition. Chronic obstructive pulmonary disease (COPD) was defined as self-reported diagnosed COPD, emphysema, or current chronic bronchitis. Liver condition was defined as self-reporting ever being diagnosed with any kind of liver condition and still having any kind of liver condition. Having at least one of the above conditions for the narrow definition was defined based on the seven (7) conditions listed. For "broad" definition: conditions were defined identically except diabetes was defined as self-reported diabetes, fasting plasma glucose ≥126 mg/dL, or hemoglobin A1c ≥6.5% without complication; chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) <60 (stages 3,4, or 5); and cancer or malignancy in past 2 years was added. This was defined as self-reporting having "ever been told by a doctor or other health profession that you had cancer or a malignancy of any kind" and reporting age at diagnosis in years as being within 2 years of current age in years. As participant age and age at diagnosis for cancer or malignancy are top-coded for ages 80 years and above, those who are aged 80 years and above and report having diagnosis at age 78 years or above are coded as having cancer or malignancy in the past 2 years; this results in an inflated estimate. Of those with any history of cancer or malignancy ages 50–79 years, 18.6% had a diagnosis within the past 2 years. Of those with any history of cancer or malignancy ages 80 years and above, 36.0% had a diagnosis at ≥ age 78 years. Having at least one of the above conditions for the broad definition was defined based on the eight (8) conditions listed. Among the fasting sample, ~94% had complete data for all reported medical conditions, ~6% were missing data for one (1) medical condition, <1% were missing data for two (2) medical conditions, and none were missing data for three (3) or more medical conditions. Estimates of having ≥1 condition are weighted using fasting sample weight.

Estimated RSV-Associated Outcomes[1] Preventable over 2 RSV Seasons vs. potential cases of GBS (*positive predictive value-adjusted* attributable risk of GBS in FDA-CMS partnership data among adults aged ≥65 years, 42-day risk interval[2,3])

Per 1 Million Vaccine Doses Administered to Adults Aged 60–74 Years Without Select Chronic Medical Conditions[4]:



3 (range **0–10**)[5] attributable **cases of GBS**

16 (range **3–29**) attributable **cases of GBS**

1. Range of outcomes avertable was calculated using published 95% confidence interval (outpatient only) and adjusted 95% confidence interval of RSV-associated incidence of the outcome in RSV-NET
2. FDA self-controlled case series analysis, among CMS Medicare beneficiaries ≥65 with Parts A, B, and D coverage who did not have a GBS claim in the 365 days before vaccination. Analysis based on diagnoses of GBS in inpatient claims data in risk interval (1-42 days after RSV vaccination) compared to control interval (43-90 days after RSV vaccination). GBS cases identified using ICD-10 diagnosis of GBS in primary position of inpatient claims coding. Estimates adjusted for outcome-dependent observation time, positive predictive value of diagnostic codes in identifying chart-confirmed GBS cases, and seasonality. Analysis includes patients with RSV vaccinations only through October 8, 2023 to allow for 90-day post-vaccination observation and 90% or greater claims data completeness. Claims data through April 6, 2024.
3. Although CMS data were limited to Medicare beneficiaries aged ≥65 years, results are extrapolated here to include adults aged 60-64 years.
4. Without chronic obstructive pulmonary disease, asthma, coronary artery disease, diabetes mellitus, chronic kidney disease, and severe obesity (body mass index ≥40 kg/m^2)
5. Self-controlled case series analysis estimated attributable risk of 3 (95% CI: -3, 10) GBS cases. However, the range was truncated at zero for Benefit/Risk analyses.

Storage & handling requirements

GSK AREXVY	Pfizer ABRYSVO	Moderna mRESVIA
10-pack of single-dose kits	Supplied as single dose, or as a 5-pack of single-dose kits	Supplied as single dose pre-filled syringe or 10-pack
Reconstitution required: single dose vial of lyophilized powder (antigen component) + single dose vial of liquid (adjuvant component)	**Reconstitution required:** single dose vial of lyophilized powder (antigen component) + single dose vial OR prefilled syringe with sterile water diluent	No reconstitution required
Both components should be refrigerated (2 to 8°C) in original container, protected from light	Product should be refrigerated (2 to 8°C) in original container, protected from light	Store frozen (-40 to -15°C), may be stored refrigerated (2 to 8°C) for up to 30 days prior to use, protected from light
After reconstitution, the product should be administered within **4 hours**, otherwise discarded	After reconstitution, the product should be administered within **4 hours**, otherwise discarded	The pre-filled syringes may be stored at room temperature (8 to 25°C) for a total of **24 hours** after removal from refrigerated conditions, otherwise discard

Moderna thawing conditions and times

2.2 Preparation for Administration

MRESVIA is supplied as a pre-filled syringe that contains a frozen suspension that must be thawed prior to administration.

Thaw each syringe before use, either in the refrigerator or at room temperature, following the instructions in Table 1.

Table 1: Thawing Conditions and Times

Configuration	Thaw in Refrigerator	Thaw at Room Temperature
Carton of one pre-filled syringe in single blister pack	Thaw between 2°C to 8°C (36°F to 46°F) for 60 minutes. Let each pre-filled syringe stand at room temperature for between 10 and 20 minutes before administering the vaccine.	Thaw between 15°C to 25°C (59°F to 77°F) for 45 minutes. If MRESVIA is thawed at room temperature, the vaccine is ready to be administered.
Carton of 10 pre-filled syringes in blister packs	Thaw between 2°C to 8°C (36°F to 46°F) for 155 minutes. Let each pre-filled syringe stand at room temperature for between 10 and 20 minutes before administering the vaccine.	Thaw between 15°C to 25°C (59°F to 77°F) for 140 minutes. If MRESVIA is thawed at room temperature, the vaccine is ready to be administered.

mRESVIA Prescribing Information: https://www.fda.gov/media/179005/download

Back-Up Slides: GRADE

Protein subunit RSV vaccines in adults aged ≥75 years

Benefits: vaccine efficacy estimates

Outcome	Importance	Data Sources	Effect Estimate, Vaccine Efficacy[a] (95% CI)	Concerns in certainty assessment
RSV Lower Respiratory Tract Disease (LRTD)[b,c]	Important	Two Phase 3 randomized controlled trials (RCT) in adults ≥60 years[1,2] • Pfizer RCT: Mean efficacy follow up through **16 months** post-vaccination per participant (median 17) • GSK RCT: Mean efficacy follow up through **19 months** post-vaccination per participant (median 23)	69.4% (36.6, 85.3)	None
Medically attended RSV LRTD[b,d]	Critical		76.6% (58.5, 86.8)	Indirectness (serious)[e]
Hospitalization for RSV respiratory illness[f]	Critical		75.7% (-12.5, 94.8)	Indirectness (serious)[e] Imprecision (serious)[g]
Severe RSV respiratory illness requiring O2/respiratory support[f]	Important		62.7% (-88.7, 92.6)	Inconsistency (serious)[h] Indirectness (serious)[e] Imprecision (serious)[g]
Death due to RSV respiratory illness[f]	Important		Zero events observed	Unable to evaluate

a) Calculated as (1 – Incidence Rate Ratio) in meta-analyses using data provided by manufacturers. Events were included if they occurred >14 days post-vaccination.

b) **Case definitions differed across RCTs.** Pfizer RCT included co-primary outcomes of lower respiratory tract illness (LRTI) with ≥2 or ≥3 lower respiratory signs/symptoms. Data included are for 3-symptom LRTI. GSK RCT included a single primary outcome of LRTD.

c) Included data are from participants aged ≥75 years.

d) Included data are from Pfizer RCT participants aged ≥75 years, and among all GSK RCT participants (aged ≥60 years).

e) Serious concern for indirectness due to inclusion of adults aged 60–74 years.

f) Included data are from all participants (aged ≥60 years) from both RCTs. Data from GSK include only a mean follow up time of 15 months per participant (median 18 months).

g) Serious concern for imprecision due to the confidence intervals containing absolute risk reduction estimates for which different policy decisions might be considered.

h) Serious concern for inconsistency because the point estimates between the studies differed substantially, although the confidence intervals overlapped

1. Papi A, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. NEJM 2023; 388:595–608 https://doi.org/10.1056/NEJMoa2209604 and Ison MG, Papi A, Athan E, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. CID. 2024; online ahead of print https://doi.org/10.1093/cid/ciae010 plus additional data obtained directly from the manufacturer
2. Walsh EE, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. NEJM 2023. 388(16): 1465-1477. https://doi.org/10.1056/NEJMoa2213836 plus additional data obtained directly from the manufacturer

Protein subunit RSV vaccines in adults aged ≥75 years

Harms

Outcome	Importance	Data Sources	Effect Estimate, Relative risk[a] (95% CI)	Concerns in certainty assessment
Serious adverse events (SAEs)[b,c]	Critical	Two phase 3 RCTs[1,2] Two phase 1/2 RCTs[3,4]	1.01 (0.93, 1.10)	Indirectness (serious)[d]
Inflammatory neurologic events[b,e]	Critical		1.76 (0.29, 10.77)	Indirectness (serious)[d] Imprecision (very serious)[f]
Reactogenicity (grade ≥3)[b,g]	Important		1.92 (0.78, 4.70)	Indirectness (serious)[d] Inconsistency (not serious)[h] Imprecision (serious)[i]

a) Pooled relative risk estimates were calculated in meta-analyses using data provided by manufacturers.
b) Included data are from all participants from all trials (aged ≥60 years).
c) Within 6 months after vaccination
d) Serious concern for indirectness due to inclusion of adults aged 60–74 years.
e) Within 42 days after vaccination
f) Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and fragility in the estimate.
g) Pfizer RCTs: within 7 days after vaccination. GSK phase 3 RCT: within 4 days after vaccination. GSK phase 1/2 RCT: within 7 days after vaccination.
h) Inconsistency noted due to I^2 value of observed trial outcomes 58%, but this was expected due to differing reactogenicity results for each vaccine observed in post-licensure data.
i) Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered

1. Papi A, Ison MG, Langley JM, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. NEJM. 2023; 388:595–608 https://doi.org/10.1056/NEJMoa2209604 plus additional data obtained directly from the manufacturer
2. Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. 2023. 388(16): 1465-1477. https://doi.org/10.1056/NEJMoa2213836 plus additional data obtained directly from the manufacturer
3. Leroux-Roels I, David MG, Steenackers K, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomized Clinical Trial, The Journal of Infectious Diseases, Volume 227, Issue 6, 15 March 2023, Pages 761–772, https://doi.org/10.1093/infdis/jiac327 plus additional data obtained directly from the manufacturer
4. Falsey AR, Walsh EE, Scott DA, et al. Phase 1/2 Randomized Study of the Immunogenicity, Safety, and Tolerability of a Respiratory Syncytial Virus Prefusion F Vaccine in Adults with Concomitant Inactivated Influenza Vaccine. The Journal of Infectious Diseases. 225(12): 2056-2066. https://doi.org/10.1093/infdis/jiab611 plus additional data obtained directly from the manufacturer

RSV protein subunit vaccines in adults aged 60–74 years at increased risk of severe RSV disease

Benefits: vaccine efficacy estimates

Outcome	Importance	Data Sources	Effect Estimate, Vaccine Efficacy[a] (95% CI)	Concerns in certainty assessment
RSV Lower Respiratory Tract Disease (LTRD)[b,c]	Important	Two phase 3 randomized controlled trials (RCT) in adults ≥60 years[1,2] • Pfizer RCT: Mean efficacy follow up through **16 months** post-vaccination per participant (median 17) • GSK RCT: Mean efficacy follow up through **19 months** post-vaccination per participant (median 23)	73.1% (58.7, 82.4)	None
Medically attended RSV LRTD[b,c]	Critical		72.7% (52.9, 84.2)	None
Hospitalization for RSV respiratory illness[d]	Critical		75.7% (-12.5, 94.8)	Indirectness (serious)[e] Imprecision (serious)[f]
Severe RSV respiratory illness requiring O2/respiratory support[d]	Important		62.7% (-88.7, 92.6)	Indirectness (serious)[e] Imprecision (serious)[f] Inconsistency (serious)[g]
Death due to RSV respiratory illness[d]	Important		Zero events observed	Unable to evaluate

a) Calculated as (1 – Incidence Rate Ratio) in meta-analyses using data provided by manufacturers. Events were included if they occurred >14 days post-vaccination.

b) **Case definitions differed across RCTs.** Pfizer RCT included co-primary outcomes of lower respiratory tract illness (LRTI) with ≥2 or ≥3 lower respiratory signs/symptoms. Data included are for 3-symptom LRTI. GSK RCT included a single primary outcome of LRTD.

c) Included data are from participants aged 60–74 years with ≥1 comorbidity (GSK: Pre-existing comorbidities of interest includes COPD, Asthma, Any chronic respiratory/pulmonary disease, Chronic heart failure, Diabetes mellitus Type 1 or Type 2, Advanced liver or renal disease) (Pfizer: Current tobacco use, diabetes, lung disease [including COPD], heart disease [including congestive heart failure], liver disease, renal disease)

d) Included data are from all participants (aged ≥60 years) from both RCTs. Data from GSK include only a mean follow up time of 15 months per participant (median 18 months).

e) Serious concern for indirectness due to inclusion of adults without chronic medical conditions.

f) Serious concern for imprecision due to the confidence intervals containing absolute risk reduction estimates for which different policy decisions might be considered.

g) Serious concern for inconsistency because the point estimates between the studies differed substantially, although the confidence intervals overlapped

1. Papi A, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. NEJM 2023; 388:595–608 https://doi.org/10.1056/NEJMoa2209604 and Ison MG, Papi A, Athan E, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. CID. 2024; online ahead of print https://doi.org/10.1093/cid/ciae010 plus additional data obtained directly from the manufacturer
2. Walsh EE, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. NEJM 2023. 388(16): 1465-1477. https://doi.org/10.1056/NEJMoa2213836 plus additional data obtained directly from the manufacturer

RSV protein subunit vaccines in adults aged 60–74 years at increased risk of severe RSV disease

Harms

Outcome	Importance	Data Sources	Effect Estimate, Relative Risk (95% CI)[a]	Concerns in certainty assessment
Serious adverse events (SAEs)[b,c]	Critical	Two phase 3 RCT[1,2] two phase 1/2 RCT[3,4]	1.01 (0.93, 1.10)	Indirectness (serious)[d]
Inflammatory neurologic events[b,e]	Critical	Two phase 3 RCT[1,2] two phase 1/2 RCT[3,4]	1.76 (0.29, 10.77)	Indirectness (serious)[d] Imprecision (very serious)[f]
Reactogenicity (grade ≥3)[b,g]	Important	Two phase 3 RCT[1,2] two phase 1/2 RCT[3,4]	1.92 (0.78, 4.70)	Indirectness (serious)[d] Imprecision (serious)[h] Inconsistency (not serious)[i]

a) Pooled relative risk estimates were calculated in meta-analyses using data provided by manufacturers.
b) Included data are from all participants (aged ≥60 years).
c) Within 6 months after vaccination
d) Serious concern for indirectness due to inclusion of adults aged 60–74 years.
e) Within 42 days after vaccination
f) Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered and fragility in the estimate.
g) Pfizer RCTs: within 7 days after vaccination. GSK phase 3 RCT: within 4 days after vaccination. GSK phase 1/2 RCT: within 7 days after vaccination.
h) Serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered.
i) Inconsistency noted due to I^2 value of observed trial outcomes 58%, but this was expected due to differing reactogenicity results for each vaccine observed in post-licensure data.

1. Papi A, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. NEJM 2023; 388:595–608 https://doi.org/10.1056/NEJMoa2209604 and Ison MG, Papi A, Athan E, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. CID. 2024; online ahead of print https://doi.org/10.1093/cid/ciae010 plus additional data obtained directly from the manufacturer
2. Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. 2023. 388(16): 1465-1477. https://doi.org/10.1056/NEJMoa2213836 plus additional data obtained directly from the manufacturer
3. Leroux-Roels I, David MG, Steenackers K, et al. Safety and Immunogenicity of a Respiratory Syncytial Virus Prefusion F (RSVPreF3) Candidate Vaccine in Older Adults: Phase 1/2 Randomized Clinical Trial, The Journal of Infectious Diseases, Volume 227, Issue 6, 15 March 2023, Pages 761–772, https://doi.org/10.1093/infdis/jiac327 plus additional data obtained directly from the manufacturer
4. Falsey AR, Walsh EE, Scott DA, et al. Phase 1/2 Randomized Study of the Immunogenicity, Safety, and Tolerability of a Respiratory Syncytial Virus Prefusion F Vaccine in Adults with Concomitant Inactivated Influenza Vaccine. The Journal of Infectious Diseases. 225(12): 2056-2066. https://doi.org/10.1093/infdis/jiab611 plus additional data obtained directly from the manufacturer

GSK AREXVY vaccine in adults aged 50–59 years at increased risk of severe RSV disease
Benefits: immunobridging

Outcome	Importance	Data Sources	Effect Estimate, Geometric mean titer ratio	Effect estimate, efficacy[a] (95% CI) in adults aged ≥60 years	Concerns in certainty assessment
RSV Lower Respiratory Tract Disease (LTRD)	Important	One phase 3 RCT in adults aged 50–59 and ≥60 years[1] One phase 3 RCT in adults aged ≥60 years[2]	Adults 50–59 at increased risk vs. adults ≥60: RSV-A: 1.20 (95% CI: 1.05, 1.37)[b] RSV-B: 1.25 (95% CI: 1.10, 1.41)[b]	73.3% (60.7, 82.3) Assessed using mean 19 mo. follow up	Indirectness (serious)[c]
Medically attended RSV LRTD	Critical			77.6% (58.3, 88.9) Assessed using mean 19 mo. follow up	Indirectness (serious)[c]
Hospitalization for RSV respiratory illness	Critical			76.4% (-102.3, 97.2) Assessed using mean 15 mo. follow up	Indirectness (serious)[c] Imprecision (very serious)[d]
Severe RSV respiratory illness requiring O2/respiratory support	Important			76.4% (-102.3, 97.2) Assessed using mean 15 mo. follow up	Indirectness (serious)[c] Imprecision (very serious)[d]
Death due to RSV respiratory illness	Important			Zero events observed	Unable to evaluate

a) Calculated as (1 – Incidence Rate Ratio) using data provided by manufacturer. Events were included if they occurred >14 days post-vaccination.
b) Titers assessed through neutralization assay on Day 31, where Day 1 was day of vaccination.
c) Serious concern for indirectness as the outcome was evaluated using immunobridging data as a surrogate for vaccine efficacy and there is no established correlate of protection
d) Very serious concern for imprecision due to the vaccine efficacy estimate confidence interval in adults 60 and older containing estimates for which different policy decisions might be considered, and for fragility of the estimate.

1. https://clinicaltrials.gov/study/NCT05590403, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/02-gerber-adult-RSV-508.pdf, unpublished data provided by manufacturer
2. Papi A, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. NEJM 2023; 388:595–608 https://doi.org/10.1056/NEJMoa2209604, Ison MG, Papi A, Athan E, et al. Efficacy and Safety of Respiratory Syncytial Virus (RSV) Prefusion F Protein Vaccine (RSVPreF3 OA) in Older Adults Over 2 RSV Seasons. CID. 2024; online ahead of print https://doi.org/10.1093/cid/ciae010, additional data obtained directly from the manufacturer

GSK AREXVY vaccine in adults aged 50–59 years at increased risk of severe RSV disease Harms

Outcome	Importance	Data Sources	Effect Estimate, relative risk (95% CI)	Concerns in certainty assessment
Serious adverse events (SAEs)[a]	Critical	One phase 3 RCT[1]	1.12 (0.43, 2.55)	Imprecision (serious)[b] Indirectness (serious)[c]
Inflammatory neurologic events[d]	Critical		Zero events observed	Unable to evaluate
Reactogenicity (grade ≥3)[e]	Important		2.81 (1.45, 5.45)	Indirectness (serious)[c]

a) Within 6 months after vaccination
b) Serious concern for impression due to the width of the confidence interval containing estimates for which different policy decisions might be considered
c) Serious concern for indirectness due to inclusion of adults without chronic conditions that increase the risk of severe RSV disease.
d) Within 42 days after vaccination
e) Within 4 days after vaccination

1. https://clinicaltrials.gov/study/NCT05590403, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/02-gerber-adult-RSV-508.pdf, unpublished data provided by manufacturer