RSV Vaccination in Adults: Work Group Interpretations

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Overview

- **Summarize Work Group interpretations of:**
  - Current RSV vaccine safety surveillance data and the balance of estimated benefits and risks associated with protein subunit* RSV vaccination in adults ages 60 years and older
  - Coadministration of RSV vaccines with other adult vaccines
  - Clinical trial evidence on protein subunit RSV vaccination* in immunocompromised adults
- **Policy considerations for the adult RSV vaccine program**

*GSK's Arexvy and Pfizer's Abrysvo are protein subunit RSV vaccines. Moderna's mResvia is an mRNA RSV vaccine, not a protein subunit vaccine.

Work Group interpretation of updated RSV vaccine safety data and the balance of benefits and risks of protein subunit RSV vaccination in adults 60 years and older

RSV vaccine safety recap as of June 2024: Guillain-Barré syndrome (GBS)

- A small number of GBS cases were observed in clinical trials within 42 days after protein subunit RSV vaccination (GSK Arexvy, Pfizer Abrysvo). Due to the small number of cases, it was unclear whether they represented a genuine association between RSV vaccination and GBS.
- Post-licensure data from 2023–2024 from the Vaccine Adverse Event Reporting System (VAERS)[1], the Vaccine Safety Datalink (VSD)[2], and from the partnership between the Food and Drug Administration (FDA) and the Centers for Medicare and Medicaid Services (CMS)[3,4] suggested, but could not confirm, an elevated risk of GBS after protein subunit RSV vaccination.
- The current older adult RSV vaccine recommendation is intended to focus the vaccination program on older adults in whom the benefits of vaccination most clearly outweigh the potential risks (all adults aged ≥75 years, adults aged 60–74 years at increased risk of severe RSV disease).
- To date, there have been no cases of GBS within 42 days after Moderna mResvia vaccination in clinical trials; post-licensure safety surveillance for this vaccine began in June 2024 after licensure and data are not yet available.

1. https://www.cdc.gov/acip/downloads/slides-2024-02-28-29/05-RSV-Adults-Shimabukuro-508.pdf
2. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf
3. https://www.cdc.gov/acip/downloads/slides-2024-02-28-29/06-RSV-Adults-Lloyd--508.pdf
4. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/06-RSV-Adult-Lloyd-508.pdf

What have we learned about GBS risk from the FDA-CMS self-controlled case series analysis since June 2024?

As of June 2024:

- ~1.3 million protein subunit RSV vaccine doses, 28 GBS cases identified through diagnostic codes
- Elevated incidence rate ratio of GBS following both GSK Arexvy and Pfizer Abrysvo vaccination, but estimates were not statistically significant
- Data suggested difference in attributable risk by product[2]
  - GSK Arexvy: 3 excess cases per 1 million doses (95% CI: -3, 10)
  - Pfizer Abrysvo: 16 excess cases per 1 million doses (95% CI: 3, 29)
- No data available regarding concomitant vaccinations

Update October 2024:

- ~3.2 million protein subunit RSV vaccine doses, 95 GBS cases identified through diagnostic codes (24 excluded through medical record review[1])
- Elevated incidence rate ratio of GBS following both vaccines; results reached statistical significance for GSK Arexvy, but not for Pfizer Abrysvo, which had fewer doses administered
- Attributable GBS risk similar for both products[2]
  - GSK Arexvy: 7 excess cases per 1 million doses (95% CI: 2, 11)
  - Pfizer Abrysvo: 9 excess cases per 1 million doses (95% CI: 0, 18)
- 30–50% of doses were concomitantly administered with another vaccine; no evidence that concomitant vaccination explains the increase in GBS rate after protein subunit RSV vaccination

1. Brighton Collaboration (BC) case definition for GBS was applied, requiring Level 1–3 certainty: https://brightoncollaboration.org/guillain-barre-and-miller-fisher-syndromes-2/. Of the 95 initially identified cases, 51 were confirmed through medical record review, 24 were excluded (BC Level 4–5), and 20 did not have medical record available for review.
2. Residual confounding is possible, and the analysis was not designed to compare risk between the two vaccines. Baseline risk of GBS may impact estimated attributable risk.

The Work Group has previously reviewed examples from other licensed and recommended vaccines of benefit-risk considerations in practice.

- **Seasonal influenza vaccine:** routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications. Adults aged ≥65 years should preferentially receive high-dose, recombinant, or adjuvanted influenza vaccines.[1]
  - *The data on the association between GBS and seasonal influenza vaccination are variable and inconsistent across influenza seasons. If there is an increased risk of GBS following influenza vaccination it is small, on the order of **1–2 additional cases per million doses** of influenza vaccine administered. Studies also suggest that it is more likely that a person will get GBS after getting influenza disease than after influenza vaccination.*[2]

1. Grohskopf LA, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72(No. RR-2):1–25. http://dx.doi.org/10.15585/mmwr.rr7202a1
2. Vellozzi C, Iqbal S, and Broder K. Guillain-Barré Syndrome, Influenza, and Influenza Vaccination: The Epidemiologic Evidence, *Clinical Infectious Diseases*, Volume 58, Issue 8, 15 April 2014, Pages 1149–1155, https://doi.org/10.1093/cid/ciu005.

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- **Recombinant zoster vaccine**: CDC recommends two doses of recombinant zoster vaccine (RZV, Shingrix) 2–6 months apart for adults aged ≥50 years and for adults aged ≥19 years who are or will be immunocompromised, for prevention of herpes zoster (shingles) and related complications.[3,4]
  - ***3–6 additional cases of GBS projected per million RZV vaccinated**.*[5]
  - *Risk-benefit analysis incorporated available data on risk of GBS following zoster disease and vaccination with RZV*

1. Grohskopf LA, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices— United States, 2023–24 Influenza Season. MMWR Recomm Rep 2023;72(No. RR-2):1–25. http://dx.doi.org/10.15585/mmwr.rr7202a1
2. Vellozzi C, Iqbal S, and Broder K. Guillain-Barré Syndrome, Influenza, and Influenza Vaccination: The Epidemiologic Evidence, *Clinical Infectious Diseases*, Volume 58, Issue 8, 15 April 2014, Pages 1149–1155, https://doi.org/10.1093/cid/ciu005.
3. Dooling KL, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103–108. http://dx.doi.org/10.15585/mmwr.mm6703a5
4. Anderson TC, et al. Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices— United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:80–84. http://dx.doi.org/10.15585/mmwr.mm7103a2
5. Janusz CB, et al. Projected risks and health benefits of vaccination against herpes zoster and related complications in US adults. Hum Vaccin Immunother. 2022 Nov 30;18(5):2060668. https://doi.org/10.1080/21645515.2022.2060668

The Work Group concluded that available data support existence of increased risk of GBS after protein subunit RSV vaccination[1]

- Available data suggest that risk is comparable to, and potentially greater than, that of other currently licensed and recommended adult vaccines.
- No evidence of a difference in risk between protein subunit vaccines[1] (GSK, Pfizer).
- The Work Group emphasized that risk of GBS associated with protein subunit RSV vaccines[1] should be considered in the context of the public health benefits of RSV vaccination.
- In June 2024, ACIP reviewed results of a mathematical modeling analysis comparing the numbers of RSV-associated hospitalizations, intensive care unit (ICU) admissions, and deaths avertable per 1 million persons vaccinated vs. the numbers of potential vaccine-attributable GBS cases.[2]
- This analysis has been updated to account for the most up to date information on protein subunit RSV vaccine effectiveness, duration of protection, and GBS risk[1].

1. GSK's Arexvy and Pfizer's Abrysvo are protein subunit RSV vaccines. Moderna's mResvia is an mRNA RSV vaccine, NOT a protein subunit vaccine. To date, Moderna's mResvia vaccine has NOT been associated with increased risk of Guillain-Barré syndrome. Post-licensure safety surveillance for mResvia began recently in June 2024.
2. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/09-RSV-Adult-Hutton-508.pdf

Benefits and risks of protein subunit RSV vaccination (GSK Arexvy, Pfizer Abrysvo): methods updates

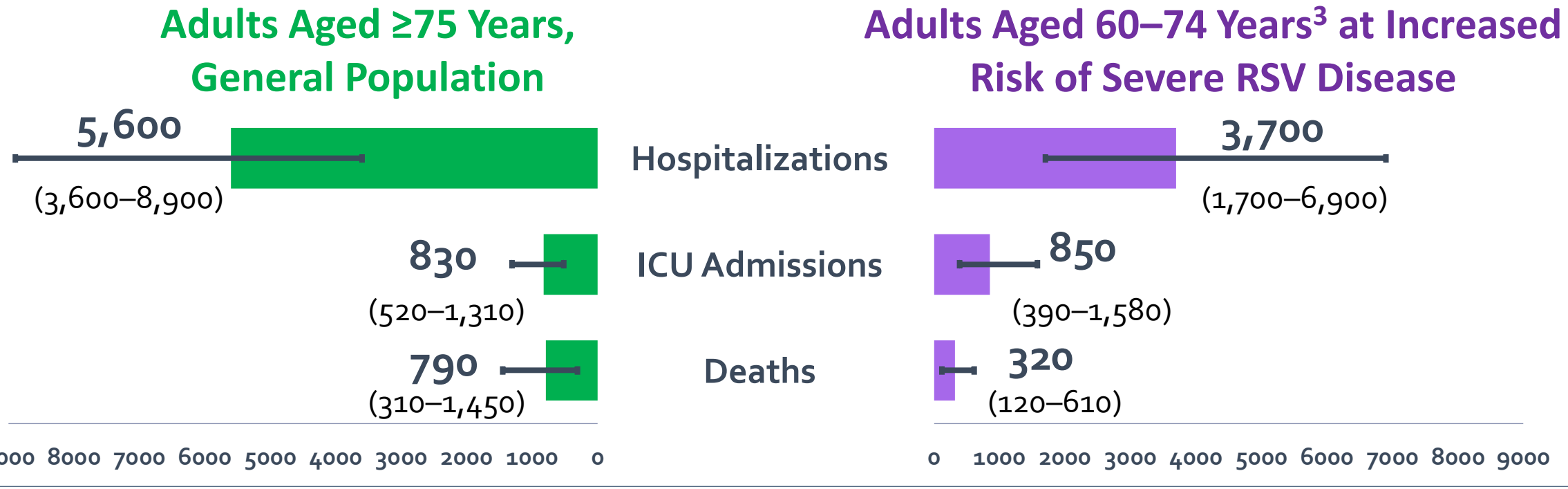
Same model presented in June 2024, with the following changes:

- Updated attributable risk estimates for GBS as presented earlier this morning
- Updated vaccine effectiveness (VE) assumptions
  - Protein subunit RSV vaccination assumed to confer 36 months of protection (increased from 24 months)
  - Inclusion of preliminary first-season VE estimates against RSV-associated hospitalization from a retrospective cohort study in Medicare beneficiaries aged ≥65 years[1] in the meta-analyses of first-season VE against hospitalization[1–4]
- Base case evaluates protein subunit RSV vaccination generally, rather than the GSK and Pfizer vaccines individually

1. Unpublished results from analysis conducted by the Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), Office of Biostatistics and Pharmacovigilance (OBPV) in partnership with the Centers for Medicare and Medicaid Services (CMS). Personal communication with CDC.
2. Surie D, Self WH, Zhu Y, et al. Investigating Respiratory Viruses in the Acutely Ill (IVY) Network. RSV Vaccine Effectiveness Against Hospitalization Among US Adults 60 Years and Older. JAMA. 2024 Oct 1;332(13):1105-1107. https://pubmed.ncbi.nlm.nih.gov/39230920/
3. Payne AB, Watts JA, Mitchell PK, et al. Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis. The Lancet. 2024;404(10462):1547-1559. https://doi.org/10.1016/S0140-6736(24)01738-0
4. Unpublished results from the Veterans Health Administration presented in June 2024: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf

Estimated RSV-Associated Outcomes[1] Preventable over 3 RSV Seasons vs. attributable risk of GBS estimated from self-controlled case series analysis through FDA-CMS partnership, 42-day risk interval[2]

Per 1 Million Persons Vaccinated with Protein Subunit RSV Vaccine:



0–18[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 with chart verification requiring Brighton Collaboration Level 1–3 certainty. Estimates adjusted for outcome-dependent observation time, seasonality, and (when chart review could not be performed) the positive predictive value of diagnostic codes in identifying chart-confirmed GBS cases. Analysis includes patients with RSV vaccinations only through January 28, 2024 to allow for 90-day post-vaccination observation and 90% or greater claims data completeness. Claims data through July 13, 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. Credible range spans the lowest lower bound and highest upper bound of attributable risk estimates for the GSK and Pfizer RSV vaccines.

Credit: Dr. David Hutton, U. Michigan

The Work Group also reviewed updated safety data from the Vaccine Safety Datalink (VSD) on protein subunit RSV vaccines[1].

- No statistical signal for GBS in rapid cycle analysis to date.
- As was seen in June 2024[2], there is a numerical imbalance in the number of GBS cases after GSK Arexvy vaccination in adults aged ≥60 years, but the number of cases is small. The system is currently underpowered to determine whether there is an association with GBS.
- Similarly[2], after medical record review, there is a numerical imbalance in the small number of cases of immune thrombocytopenia (ITP) after GSK Arexvy vaccination without another simultaneous vaccine in adults aged ≥60 years, but due to the small number of cases, the system is currently underpowered to determine whether there is an association with ITP.
- Fewer doses of Pfizer Abrysvo were administered in VSD, and no conclusions can be drawn from this system regarding the safety of this vaccine at this time.

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2. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf

Work Group interpretations on co-administration of RSV vaccines with other adult vaccines

Work Group interpretations of new co-administration data

- Co-administration of RSV vaccines and other recommended adult vaccines, in particular seasonal influenza and COVID-19 vaccines, is common
- The Work Group was reassured to see these first-ever data from Pfizer demonstrating that co-administration of protein subunit RSV vaccine, mRNA COVID-19 vaccine, and high-dose influenza vaccine was safe and generated a non-inferior humoral immune response
- The Work Group acknowledged the findings of an inferior RSV neutralizing antibody response with co-administration of Moderna RSV vaccine and high-dose influenza vaccine, but feels clinical significance of this finding is currently unknown
- These data should also be put in context of a lack of a consistent pattern in combinations of RSV vaccine and other concomitant vaccinations that resulted in inferior immune responses

Summary of RSV coadministration data with influenza and/or COVID-19 mRNA vaccines in which non-inferiority of humoral immune response was assessed in older adults

	GSK RSV vaccine	Pfizer RSV vaccine	Moderna RSV vaccine
Standard dose influenza vaccine	Coadministration non-inferior	*No data available*	Coadministration non-inferior
Adjuvanted influenza vaccine	Coadministration non-inferiority criteria not met • RSV titers: non-inferior • Influenza titers: H3N2 HAI[1] titers inferior w/ coadministration	Coadministration non-inferior	*No data available*
High-dose influenza vaccine	Coadministration non-inferior	Coadministration non-inferior[2]	Coadministration non-inferiority criteria not met • RSV titers: RSV-A and B neutralizing antibody titers inferior w/ coadministration • Influenza titers: non-inferior
mRNA COVID-19 vaccine	*No data available*	Coadministration non-inferior	Coadministration non-inferior

1. HAI: hemagglutination inhibition. Humoral immune response against influenza A/Darwin H3N2 was also assessed post-hoc via microneutralization, which resulted in a geometric mean titer (GMT) ratio similar to the HAI GMT ratio, with a slightly narrower confidence interval: 1.23 (95% CI: 1.06–1.42). Non-inferiority criteria were not specified for post-hoc analyses. Prespecified non-inferiority criteria for the HAI GMT ratio required that the 95% CI upper bound was <1.50.
2. When given as 3-way coadministration (high-dose influenza vaccine + COVID-19 vaccine + Pfizer RSV vaccine)

Work Group interpretations of new co-administration data (continued)

- The Work Group notes our limited understanding of clinical significance of decreased antibody titers with RSV vaccine co-administration.
- Given the considerable benefits of co-administration and the evidence of safety of co-administration, the Work Group continues to feel co-administration is **acceptable**.[1]
- In addition, the Work Group looks forward to learning more about Moderna's analysis on immunologic correlates of protection for RSV as peer-reviewed methods become available.

1. This language is different from CDC's General Best Practices Guidelines for Immunization, which states that with limited exception, routine administration of all age-appropriate doses of vaccines simultaneously is recommended for persons for whom no specific contraindications exist at the time of the visit.

Kroger A, Bahta L, Long S, Sanchez P. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Updated July 22, 2024; accessed October 22, 2024

Work Group interpretations on use of RSV vaccines in adults with immune compromise

First RSV vaccine trials in immunocompromised persons

- During today's meeting, GSK and Pfizer presented clinical trial data on use of their RSV vaccines in adults aged ≥18 years with immune compromise.
- These are the first clinical trial results in these populations at high risk of severe RSV disease.
- Notably, these trials studied the safety of and the immune response to RSV vaccination, but did not estimate efficacy against clinical endpoints.

What did we learn from these clinical trials?

GSK Arexvy

- Trial included adults aged ≥18 years with renal or lung transplant
- One month after a single dose of Arexvy, these participants had lower RSV neutralizing antibody titers, compared with immunocompetent adults aged ≥50 years
- After a second dose of Arexvy one month after the first, RSV neutralizing antibody titers increased and were similar to those in immunocompetent adults aged ≥50 years at 2 months post-vaccination
- Measures of cellular immunity after Arexvy vaccination were similar between immunocompromised participants and immunocompetent participants

- **No specific safety concerns were identified in either clinical trial, though one participant in each trial experienced renal transplant rejection after RSV vaccination (judged by investigator to be unrelated to vaccination)**

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Pfizer Abrysvo

- Trial included adults aged ≥18 years with autoimmune disorders on immunomodulator therapy, solid organ transplant, end-stage renal disease on dialysis, or non-small cell lung cancer on therapy
- One month after a single dose of Abrysvo, these participants had similar RSV neutralizing antibody titers, compared with immunocompetent adults aged ≥60 years from Pfizer's main phase 3 trial
- The neutralizing antibody response in participants with autoimmune disorders on immunomodulator therapy and solid organ transplant appeared lower than in adults with end-stage renal disease
- A second dose of Abrysvo one month after the first did not appreciably increase neutralizing antibody titers

- **No specific safety concerns were identified in either clinical trial, though one participant in each trial experienced renal transplant rejection after RSV vaccination (judged by investigator to be unrelated to vaccination)**

Work Group interpretations

- The Work Group was encouraged to see clinical trial data in this population but would have preferred to see data among adults with the most severe forms of immune compromise, who are at highest risk of severe RSV disease (e.g., hematopoietic stem cell transplant, recent lung transplant).
- The Work Group also felt that Pfizer's inclusion of adults with end-stage renal disease on dialysis used too broad a definition of immune compromise.
- The Work Group expressed uncertainty in whether neutralizing antibody titers will correspond to similar clinical efficacy observed in immunocompetent older adults.
- Absent clinical efficacy data, the Work Group expressed uncertainty in whether 2 doses of GSK's Arexvy would be required to result in adequate protection against severe RSV disease in solid organ transplant recipients.

Policy considerations

The Work Group affirms that the current older adult RSV vaccine recommendations are appropriate.

- **Adults aged ≥75 years should receive a single dose of RSV vaccine**
- **Adults aged 60–74 years who are at increased risk of severe RSV disease should receive a single dose of RSV vaccine**

- While uncertainty remains regarding the magnitude of GBS risk associated with protein subunit RSV vaccination*, the Work Group believes that the benefits of RSV vaccination outweigh risks among the populations for whom RSV vaccination is currently recommended.

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The Work Group continues to evaluate recommendations for the use of RSV vaccines in adults aged <60 years, acknowledging there are now two FDA-approved products for RSV prevention in this age group

- **The Work Group recognizes several important factors:**
  - While risk of severe RSV disease increases with age, adults aged <60 years with certain chronic medical conditions have an elevated risk of severe RSV disease: some may have risk comparable to that in older adults
  - Adults from certain racial and ethnic groups may be at increased risk of these conditions at younger ages, compared with White adults
  - Conditions that elevate the risk of severe RSV disease may differ by age group; conditions that place adults aged 60–74 years at increased risk of severe RSV may not confer the same degree of absolute risk in adults aged 18–59 years
  - Developing RSV vaccine policy in adults <60 years will require careful consideration of the balance of public health benefits and risks in this population

The Work Group continues to evaluate recommendations for the use of RSV vaccines in adults aged <60 years, acknowledging there are now two FDA-approved products for RSV prevention in this age group

- As was discussed at the June 2024 ACIP meeting, the Work Group felt additional data on the potential risk of GBS associated with RSV vaccination were essential prior to considering RSV vaccine recommendations in adults aged <60 years
- Today we have seen updated results increasing certainty that protein subunit RSV vaccination* is associated with GBS risk, though uncertainty remains regarding the magnitude of risk
- The Work Group will use these data to continue evaluating risks and benefits, including in which groups among adults younger than 60 years the estimated benefits outweigh the risks

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The Work Group continues to evaluate recommendations for the use of RSV vaccines in adults aged <60 years, acknowledging there are now two FDA-approved products for RSV prevention in this age group

- Regarding immunocompromised adults, the Work Group recognizes this is a heterogeneous group who are not all at the same risk of severe RSV disease
- While the data presented today covered a subset of those with immune compromise, the Work Group does not feel they substantially increase certainty that those with the most severe forms of immune compromise will benefit from vaccination (e.g., hematopoietic stem cell transplant recipients)
- Therefore, the Work Group did not feel that the data presented today motivated an immediate policy expansion for this group in younger adults, particularly while the FDA-CMS analysis on GBS risk is still ongoing

At the June 2024 ACIP meeting the Adult RSV Work Group indicated they would like to see the following data before moving to vote on an RSV vaccine recommendation for adults aged <60 years:

- **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.**
- **Data on duration of protection and immune response after re-vaccination.**
  - The Work Group 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.[1]
  - 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.[2] Pfizer immunogenicity data at a 12-month re-vaccination interval has also shown a weaker humoral immune response, compared with the response after dose 1.[3]

1.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. Clinical Infectious Diseases. Vol 78(6):1732-1744. Jan 2024.
2. Gerber, S. Arexvy (Adjuvanted RSVPreF3) 2-Year Update. Presented at the Advisory Committee on Immunization Practices meeting, Atlanta, GA; June 26, 2024. https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/03-RSV-Adult-Gerber-508.pdf.
3. Walsh EE et al. Respiratory Syncytial Virus Prefusion F Vaccination: Antibody Persistence and Revaccination, The Journal of Infectious Diseases, *The Journal of Infectious Diseases*, Vol. 230(4) Pages e905–e916. Oct. 2024. https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiae185/7644684.

Today the Work Group continues to feel additional data are necessary before moving to vote on an RSV vaccine recommendation for adults aged <60 years:

- **Final results from the FDA-CMS analysis from the first season of RSV vaccination in Medicare beneficiaries**
  - The Work Group continues to feel that depending on certainty of findings, additional data may be needed, and will continue to evaluate other sources of safety data
- **Pending certainty in safety findings, data demonstrating vaccine efficacy or effectiveness against clinical endpoints in the most severely immunocompromised adults**
  - While the Work Group appreciates new immunogenicity data, they do not feel these data are sufficient to support age expansion without final FDA-CMS results on GBS risk
- **Immunogenicity data after revaccination with longer time intervals following initial vaccination**
  - Additional data on longer re-vaccination intervals is expected from ongoing manufacturer clinical trials

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