Effectiveness of adult respiratory syncytial virus (RSV) vaccines, 2023–2024

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Goal of randomized vaccine trials is different from that of observational vaccine effectiveness (VE) studies

- Purpose of randomized vaccine trials is to answer the question:

> **"Can the vaccine reduce disease caused by the target infection, safely, under ideal conditions designed to detect a protective effect?"**

- To maximize chances of detecting a protective effect, vaccine trials often:
  - Enroll healthy individuals in the target population
  - Minimize or exclude enrollment of individuals with comorbidities that might reduce immunogenicity of vaccines

- Post-licensure observational VE studies are needed to assess vaccine performance in a **heterogeneous** population under **routine vaccine program conditions**

Clemens J, et. al. Evaluating New Vaccines for Developing Countries: Efficacy or Effectiveness? *JAMA*. 1996;275(5) 390–397. doi:10.1001/jama.1996.03530290060038

Limitations of RSV vaccine trials

	Randomized RSV vaccine trials[1,2]	Observational RSV VE studies
Immunocompromised patients	Excluded	Included
Adults aged ≥80 years	<8% of participants	≥25% of included adults
Any chronic condition	<52% of participants	≥94% of included adults
Endpoint or outcome	Symptomatic, RSV-associated ***lower respiratory tract disease***	RSV-associated ***emergency department (ED) visits***, ***hospitalization***, ***critical illness[3]***

[1]Papi A, et al; AReSVi-006 Study Group. Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med*. 2023;388(7):595-608
[2]Walsh EE, et al; RENOIR Clinical Trial Group. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *N Engl J Med*. 2023;388(16):1465-1477
[3]Critical illness is defined as intensive care unit admissions or death

Presentation outline for observational VE studies

Observational VE studies	Methods
IVY Network (CDC)	Test-negative design[1,2,3]
VISION (CDC)	
Veterans Health Administration (VHA)	Target trial emulation[4,5]
Medicare/end stage renal disease (ESRD) patients	Retrospective cohort

References for study design methods with relevant examples

[1] Chua H, et. al. The Use of Test-negative Controls to Monitor Vaccine Effectiveness: A Systematic Review of Methodology. *Epidemiology* 2020;31:43–64.

[2] Adams K, et. al. Vaccine effectiveness of primary series and booster doses against COVID-19-associated hospital admission in the United States. *BMJ* 2022;379:e072065.

[3] Thompson MG, et. al. Effectiveness of COVID-19 Vaccines in Ambulatory and Inpatient Care Settings. *N Engl J Med.* 2021;385:1355–1371.

[4] Hernan MA, et. al. Methods of Public Health Research – Strengthening Causal Inference from Observational Data. N Engl J Med. 2021;385(15):1345–48.

[5] Bajema KL, et. al. Effectiveness of COVID-19 Treatment with Nirmatrelvir-Ritonavir or Molnupiravir Among U.S. Veterans. Ann Intern Med. 2023;176(6):807–816.

Comparison of demographic characteristics among IVY, VISION, VHA, and Medicare/ESRD studies

Characteristic	IVY, no. (col %)	VISION, no. (col %)	VHA, no. (col %)	Medicare/ESRD, no. (col %)
	Total no. of patients	Total no. of patients	Total no. of patients	Total no. of patients
All patients	2,978	36,706	293,704[§]	69,279
Median age, years (IQR)	72 (66–80)	76 (69–84)	76 (72–80)	74 (70-80)
Age group, years				
60–74	1756 (59)	16,055 (44)	125,124 (43)	34,614 (50)[‡]
≥75	1222 (41)	20,651 (56)	168,580 (57)	34,665 (50)
Race and ethnicity				
White, non-Hispanic	1867 (63)	27,057 (74)	225,713 (77)	42,157 (61)
Black, non-Hispanic	582 (20)	3,160 (9)	30,359 (10)	14,767 (21)
Hispanic or Latino, any race	335 (11)	2,789 (8)	11,302 (4)	3,983 (6)
Other race, non-Hispanic*	101 (3)	3,395 (9)	5,971 (2)	3,604 (5)
Unknown†	93 (3)	305 (1)	20,358 (7)	-

* For VISION, “Other race, non-Hispanic” includes persons reporting non-Hispanic ethnicity and any of the following for race: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, other races not listed, and multiple races; because of small numbers, these categories were combined. For IVY, “Other race, non-Hispanic” includes Asian, American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander; because of small numbers, these categories were combined.

† For VISION, “Unknown” includes persons with missing race and ethnicity in their electronic health records. For IVY, “Unknown” includes patients who self-reported their race and ethnicity as “Other” and those for whom race and ethnicity were unknown. For VHA “Unknown” includes missing, unknown, or declined race or ethnicity.

§146,852 vaccinated persons were matched to 582,936 unvaccinated participants who were equally weighted to correspond to 146,852 matched unvaccinated participants.

‡Evaluation of Medicare fee-for-service claims data was restricted to adults aged 65 years and older.

Comparison of clinical characteristics among IVY, VISION, VHA, and Medicare/ESRD studies

Characteristic	IVY, no. (col %)	VISION, no. (col %)	VHA, no. (col %)	Medicare/ESRD, no. (col %)
	Total no. of patients	Total no. of patients	Total no. of patients	Total no. of patients
All patients	2,978	36,706	293,704	69,279
No. of chronic medical condition categories				
0	71 (2)	2,111 (6)	17,554 (6)	0 (0)
1	416 (14)	3,845 (10)	58,757 (20)	312 <1)
2	783 (26)	15,420 (42)	83,992 (29)	1,497 (2)
3	863 (29)	15,330 (42)	73,296 (25)	9,242 (13)
≥4	845 (28)	2,111 (6)	60,106 (21)	58,228 (84)
Immunocompromised*	720 (24)	8,435 (23)	32,996 (11)	17,499 (25)
Chronic lung disease†	1423 (48)	17,541 (48)	88,648 (30)	38,529 (56)
Cardiovascular disease§	2501 (84)	28,822 (79)	122,015 (42)	66,987 (97)
RSV vaccinated	265 (9)	3,275 (9)	146,852 (50)¶	6,734 (10)
Received GSK (Arexvy)	137 (61)**	2,409 (74)	43,875 (30)	4,562 68)
Received Pfizer (Abrysvo)	89 (39) **	865 (36)	101,623 (69)	2,172 (32)

* Slide 41 provides definitions of immunocompromise from each network
† Slide 42 provides definitions of chronic lung disease from each network
§ Slide 43 provides definitions of cardiovascular disease from each network
¶ Each RSV-vaccinated patient was matched to up to 4 unvaccinated, equally weighted patients, resulting in 50% of matched persons having an RSV vaccination. Among match-eligible patients, 4.5% received RSV vaccination.
** Of 265 RSV vaccinated patients in IVY, 226 (85%) had known product type, which is used as the denominator for these percentages.

VE against RSV-associated hospitalization among adults aged ≥60 years

IVY Network, October 1, 2023–March 31, 2024

IVY Network — 26 hospitals, 20 U.S. States

- **Design**: Test-negative, case-control design
- **Analysis period**: October 1, 2023 – March 31, 2024
- **Population**: Adults aged ≥60 years hospitalized with acute respiratory illness (ARI)* and RSV test results within 10 days of illness onset and 3 days of admission
  - **Cases:** ARI and test ***positive*** for RSV by NAAT or antigen test
    - Co-infections with SARS-CoV-2 or influenza were excluded
  - **Controls**: ARI and test ***negative*** for vaccine-preventable respiratory viruses, i.e., RSV, SARS-CoV-2 and influenza by RT-PCR†
- **Vaccination data:** Plausible self-report, electronic medical records (EMR), state and city vaccine registries
  - **Vaccinated:** Receipt of a single dose of either RSV vaccine (GSK or Pfizer) ≥14 days before illness onset
  - **Unvaccinated**: No RSV vaccination before illness onset
- **Specimens:** Nasal swabs obtained on all patients for central RT-PCR testing and whole genome sequencing

IVY

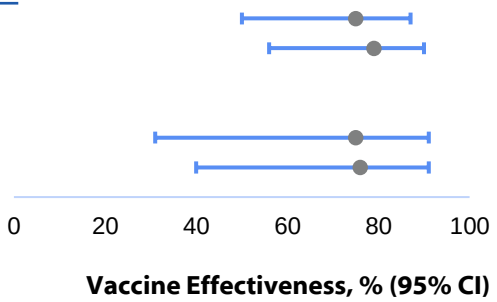
INVESTIGATING RESPIRATORY VIRUSES IN THE ACUTELY ILL

*ARI is defined as presence of any one of the following: fever, cough, shortness of breath, chest imaging consistent with pneumonia, or hypoxemia (SpO_2 <92% on room air or below baseline for chronic users)

† Doll MK, et. al. Effects of Confounding Bias in Coronavirus Disease 2019 (COVID-19) and Influenza Vaccine Effectiveness Test-Negative Designs Due to Correlated Influenza and COVID-19 Vaccination Behaviors. *Clin Infect Dis.* 2022;75(1):e564–71

VE against RSV-associated *hospitalization* among adults aged ≥60 years — IVY Network, 24 hospitals, 19 US states, *October 1, 2023–March 31, 2024*

Group	No. of vaccinated RSV case-patients/ total (%)	No. of vaccinated RSV control-patients/ total (%)	Days since RSV vaccination, Median (IQR)	Vaccine effectiveness, % (95% CI)
Adults ≥60 years, unweighted*	9/367 (2.5)	256/2611 (9.8)	84 (54–125)	**75 (50–87)**
Adults ≥60 years, IPVW†	9/367 (2.5)	256/2611 (9.8)	84 (54–125)	**79 (56–90)**
Age group, years, unweighted*				
60–74 years	4/214 (1.9)	118/1542 (7.7)	88 (57–128)	**75 (31–91)**
≥75 years	5/153 (3.3)	138/1069 (12.9)	81 (50–123)	**76 (40–91)**



VE was high against RSV-associated hospitalization and similar among adults aged 60–74 years and ≥75 years

Abbreviations: 95% CI = 95% confidence interval; IPVW = inverse probability of vaccination weighting; IQR = interquartile range

* Logistic regression models were adjusted for age, sex, race and ethnicity, U.S. Department of Health and Human Services region, and month of admission. VE was calculated as: (1 – adjusted odds ratio) x 100%.

† For the IPVW VE estimate, propensity for vaccination was modeled with *a priori* covariables, including age, sex, race and ethnicity, site, calendar month, Charlson Comorbidity Index (CCI), underlying medical conditions, long-term care facility residence, numbers of outpatient visits or hospitalizations in the previous year, and social vulnerability index (SVI) of community of residence. Weights were computed as the inverse of the probability of vaccination. Only SVI remained unbalanced between vaccinated and unvaccinated patients after weighting and was included as a covariate in the final logistic regression model.

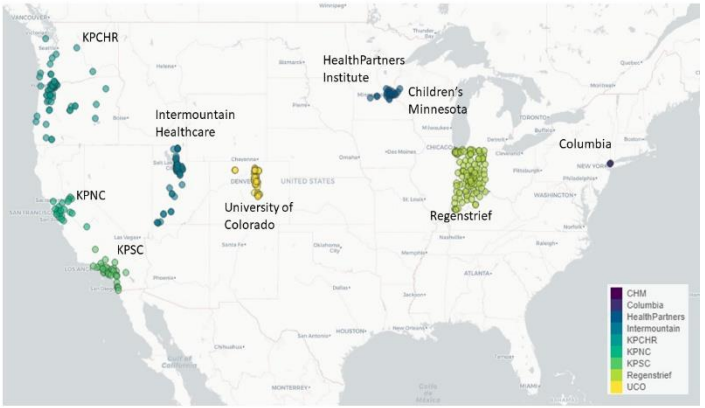
VE against RSV-associated ED visits, hospitalization, and critical illness among adults aged ≥60 years

VISION Network, October 1, 2023–March 31, 2024

VISION Multi-Site Network of Electronic Health Records

245 emergency rooms and 230 hospitals

- **Design:** Test-negative design analysis
- **Population:** Adults aged ≥60 years visiting a participating ED for or hospitalized with RSV-like illness (RLI)* with RSV test result within 10 days before or 72 hours after encounter
  - **Cases:** RLI with *positive* RSV antigen or NAAT
  - **Controls:** RLI with negative RSV NAAT
- **Vaccination data:** Documented by electronic health records, state and city registries, and claims data (subset of sites)
  - **Vaccinated:** Receipt of a single dose of either RSV vaccine (GSK or Pfizer) ≥14 days before illness onset
  - **Unvaccinated**: No RSV vaccination before illness onset
- **Covariate data:** Documented in electronic health records



VISION 2.0 partners included in this analysis –

ED: HealthPartners Institute, Intermountain Healthcare, KPNC, KPCHR, Regenstrief

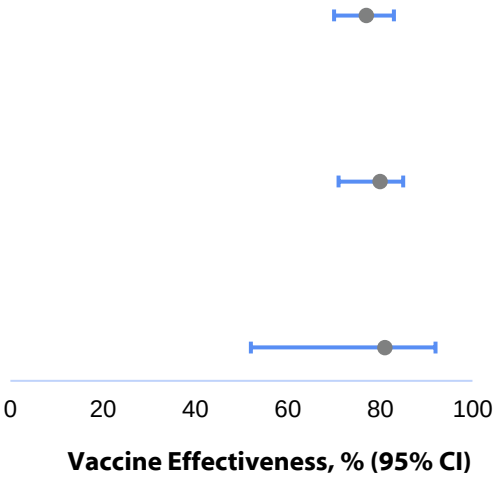
Inpatient: HealthPartners Institute, Intermountain, KPNC, KPCHR, Regenstrief, University of Colorado

- Note: KPSC does not participate in VISION adult RSV analyses.

*≥1 ICD-10 code indicating RSV-like illness (RLI), defined as COVID-19 pneumonia, influenza pneumonia, other viral pneumonia, influenza disease, bacterial pneumonia, ARDS, COPD exacerbation, asthma exacerbation, respiratory failure, other acute lower respiratory tract infection, sinusitis, acute upper respiratory tract infections, acute respiratory signs and symptoms, viral illness not otherwise specified, acute febrile illness signs and symptoms, sepsis, respiratory failure unspecified, and RSV disease.

VE against RSV-associated *ED visits*, *hospitalization*, and *critical illness* among immunocompetent adults aged ≥60 years, *October 1, 2023–March 31, 2024*

	Total	RSV-Positive, N (row %)	Median interval since last dose, days (IQR)	Vaccine Effectiveness*, % (95% CI)
RSV-associated *ED visits*				
≥60 years				
Unvaccinated (Ref)	33,491	2,645 (8)	NA	Ref
Vaccinated	3,030	57 (2)	67 (40–101)	**77 (70–83)**
RSV-associated *hospitalization*				
≥60 years				
Unvaccinated (Ref)	25,816	1567 (6)	NA	Ref
Vaccinated	2,455	35 (1)	74 (44–109)	**80 (71–85)**
RSV-associated *critical Illness*†				
≥60 years				
Unvaccinated (Ref)	24,506	257 (1)	NA	Ref
Vaccinated	2,425	5 (<1)	74 (44–109)	**81 (52–92)**



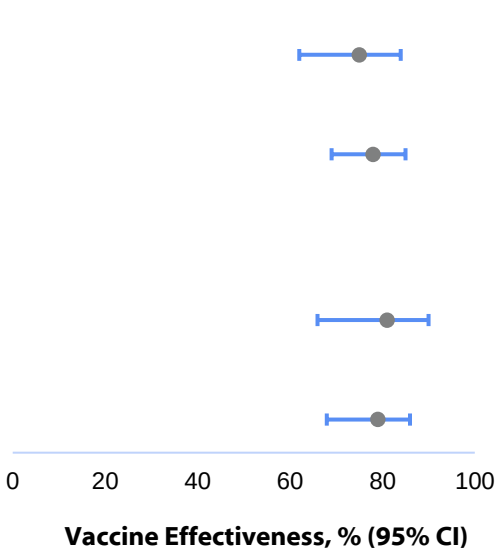
VE was high against RSV-associated ED visits, hospitalization, and critical illness

*Odds ratios used to calculate VE estimates were adjusted for age, race/ethnicity, sex, underlying medical conditions, social vulnerability index, site, calendar time, and geographic region. VE was calculated as (1-adjusted odds ratio)*100%.

† Critical illness was defined as intensive care unit admission and/or death

VE against RSV-associated *ED visits* and *hospitalization* by age group among immunocompetent adults aged ≥60 years, *October 1, 2023–March 31, 2024*

	Total	RSV-Positive, N (row %)	Median interval since last dose, days (IQR)	Vaccine effectiveness*, % (95% CI)
RSV-associated *ED visits*				
60–74 years				
Unvaccinated (Ref)	16,985	1303 (8)	NA	Ref
Vaccinated	1,139	23 (2)	66 (40–100)	**75 (62–84)**
≥75 years				
Unvaccinated (Ref)	16,506	1342 (8)	NA	Ref
Vaccinated	1,891	34 (2)	69 (40–101)	**78 (69–85)**
RSV-associated *hospitalization*				
60–74 years				
Unvaccinated (Ref)	11,048	670 (6)	NA	Ref
Vaccinated	836	11 (1)	75 (46–110)	**81 (66–90)**
≥75 years				
Unvaccinated (Ref)	14,768	897 (6)	NA	Ref
Vaccinated	1,619	24 (1)	74 (43–108)	**79 (68–86)**

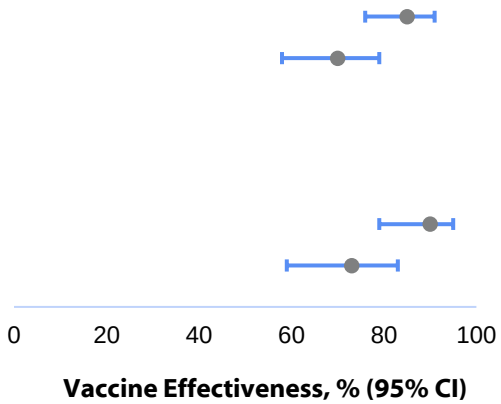


VE was similar among adults aged 60–74 years and ≥75 years for both outcomes

* Odds ratios used to calculate VE estimates were adjusted for age, race/ethnicity, sex, underlying medical conditions, social vulnerability index, site, calendar time, and geographic region. VE was calculated as (1-adjusted odds ratio)*100%.

VE against RSV-associated *ED visits* and *hospitalization* by time since RSV vaccination among immunocompetent adults aged ≥60 years, *October 1, 2023–March 31, 2024*

	Total	RSV-Positive, N (row %)	Median interval since last dose, days (IQR)	Vaccine effectiveness*, % (95% CI)
RSV-associated *ED visits*				
≥60 years				
Unvaccinated (Ref)	33,491	2,645 (8)	NA	Ref
Vaccinated 14–59 days earlier	1,300	19 (1)	36 (26–47)	**85 (77–91)**
Vaccinated 60–215 days earlier	1,728	37 (2)	95 (76–119)	**70 (58–78)**
RSV-associated *hospitalization*				
≥60 years				
Unvaccinated (Ref)	25,816	1567 (6)	NA	Ref
Vaccinated 14–59 days earlier	934	7 (1)	37 (26–48)	**90 (79–95)**
Vaccinated 60–215 days earlier	1,520	27 (2)	100 (79–125)	**73 (60–82)**

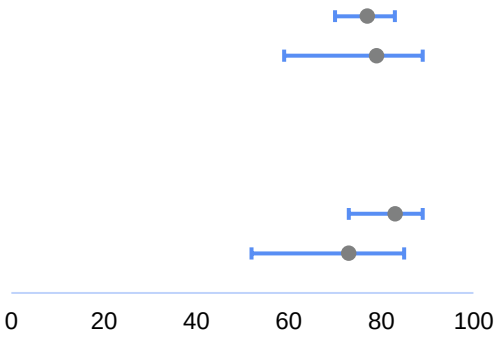


VE point estimates decreased with increased time since RSV vaccination with limited follow-up time within the season

* Odds ratios used to calculate VE estimates were adjusted for age, race/ethnicity, sex, underlying medical conditions, social vulnerability index, site, calendar time, and geographic region. VE was calculated as (1-adjusted odds ratio)*100%.

VE against RSV-associated *ED visits* and *hospitalization* by RSV vaccine manufacturer among immunocompetent adults aged ≥60 years, *October 1, 2023–March 31, 2024*

	Total	RSV-Positive, N (row %)	Median interval since last dose, days (IQR)	Vaccine effectiveness*, % (95% CI)
RSV-associated *ED visits*				
≥60 years				
Unvaccinated (Ref)	33,491	2,645 (8)	NA	Ref
GSK (Arexvy)	2,522	47 (2)	67 (40–99)	**77 (70–83)**
Pfizer (Abrysvo)	506	9 (2)	71 (40–108)	**79 (59–89)**
RSV-associated *hospitalization*				
≥60 years				
Unvaccinated (Ref)	25,816	1567 (6)	NA	Ref
GSK (Arexvy)	1,812	21 (1)	73 (43–105)	**83 (73–89)**
Pfizer (Abrysvo)	642	13 (2)	81 (48–116)	**73 (52–85)**

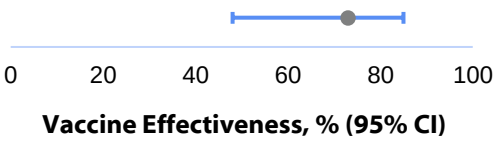


VE was similar between GSK and Pfizer RSV vaccines across outcomes

* Odds ratios used to calculate VE estimates were adjusted for age, race/ethnicity, sex, underlying medical conditions, social vulnerability index, site, calendar time, and geographic region. VE was calculated as (1-adjusted odds ratio)*100%.

VE against RSV-associated *hospitalization* among adults aged ≥60 years with immunocompromise† by age group, *October 1, 2023–March 31, 2024*

	Total	RSV-Positive, N (row %)	Median interval since last dose, days (IQR)	Vaccine effectiveness*, % (95% CI)
RSV-associated *hospitalization*				
≥60 years				
Unvaccinated (Ref)	7,615	314 (4)	NA	Ref
Vaccinated	820	10 (1)	72 (43–108)	**73 (48–85)**



RSV vaccines provided protection against RSV-associated hospitalization among people with immunocompromise

*Odds ratio was adjusted for age, race/ethnicity, sex, underlying medical conditions, social vulnerability index, site, calendar time, and geographic region. VE was calculated as (1-adjusted odds ratio)*100%.

†Defined based on presence of ICD-10 code corresponding to hematologic malignancy, solid malignancy, transplant, rheumatologic/inflammatory disorders, HIV, or other intrinsic immune condition or immunodeficiency in discharge diagnoses

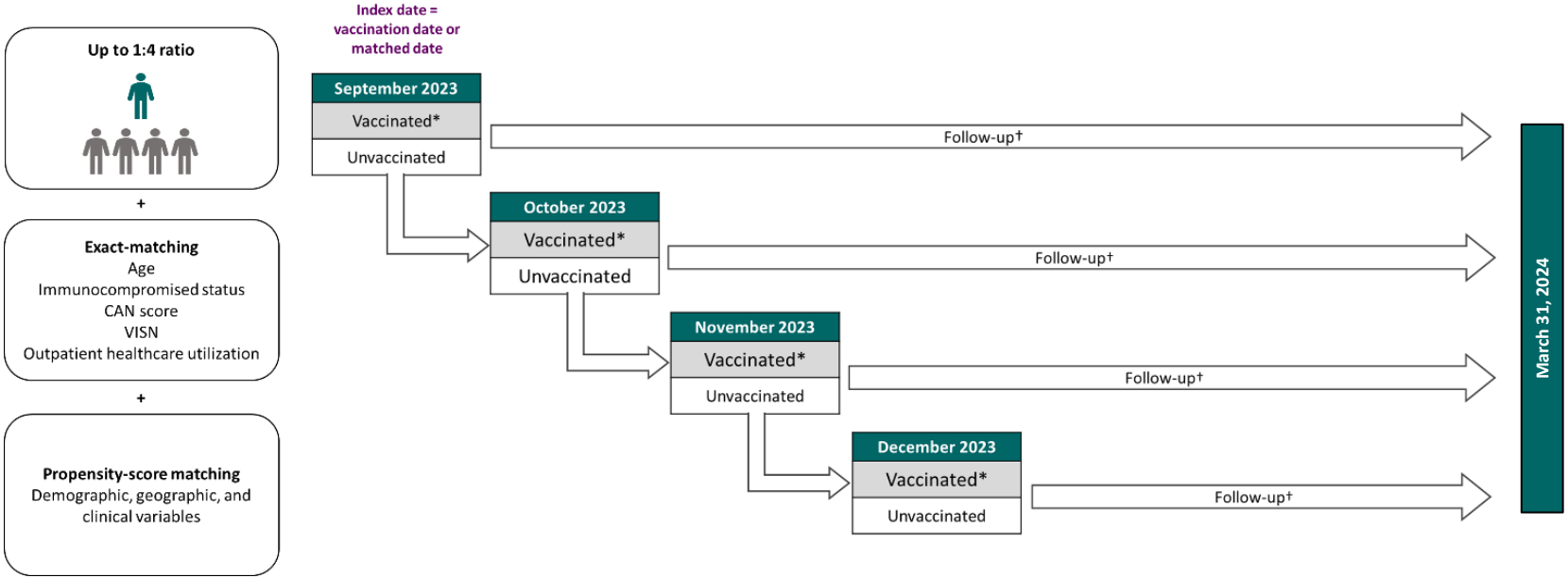
VE against documented RSV infection and RSV-associated ED/UC or hospitalization among adults aged ≥60 years

Veterans Health Administration (VHA), September 1, 2023 – March 31, 2024

Overall study design

- Emulated a target randomized controlled trial of RSV vaccination (GSK [Arexvy] or Pfizer [Abrysvo]) compared with no RSV vaccination for the prevention of documented RSV infection and RSV-associated ED/urgent care (UC) visits or hospitalization among Veterans ≥60 years
- Enrollment: September 1 – December 31, 2023
- Follow-up extended through March 31, 2024
- Executed 4 monthly, nested sequential trials during the enrollment period

Nested sequential trial study design with matching



Abbreviations: CAN, Care Assessment Need; VISN, Veteran Integrated Service Network

* Cohort members who receive an RSV vaccine during a given trial month are no longer eligible for a subsequent trial month. Cohort members who remain unvaccinated, alive, and who do not test positive for RSV through the end of a given trial month are eligible for a subsequent trial month.

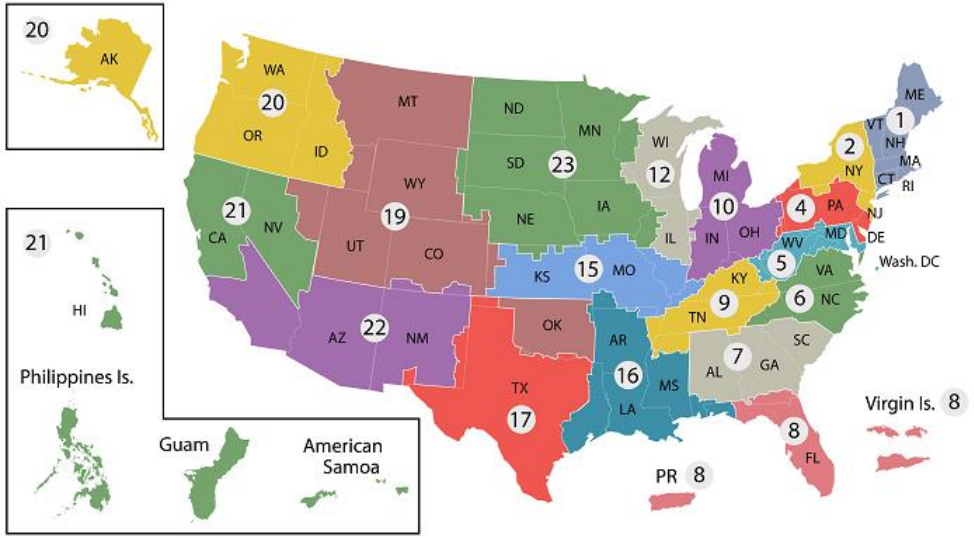
† Follow-up begins on the day following the index date (date of RSV vaccination occurring anytime during a given trial month or same date for the matched unvaccinated comparator) and extends until occurrence of the outcome, death, or end of the study period on March 31, 2024.

Data sources

- The Department of Veterans Affairs Corporate Data Warehouse (CDW) integrates real-time, electronic health record (EHR) data across all VHA facilities
- RSV tests were performed on respiratory specimens within VHA using nucleic acid amplification or antigen testing
- RSV vaccinations were administered at VHA facilities or outside facilities and recorded in the VHA EHR

https://www.va.gov/HEALTH/visns.asp

VHA Network



18 regional systems of care
172 medical centers
1,138 outpatient sites of care

Eligibility

- VHA enrollees ≥60 years during September 1 – December 31, 2023

- Engaged in VHA care: ≥1 primary care encounter within 18 months prior to the first day of each trial month

- Excluded:
  - Missing ZIP codes
  - Any RSV vaccination prior to the first day of each trial month
  - Any positive RSV test results in the 90 days preceding the start of each trial month

Outcomes, Follow-up, and Analysis

- **Outcomes**
  - Primary outcome: Any positive RSV test result occurring from day 14 following the index date through the end of the study period on March 31, 2024*
  - RSV-associated emergency department (ED) or urgent care encounters (UC)†
  - RSV-associated acute hospitalizations†

- **Negative outcome control:** incidence of laboratory-confirmed RSV infections 0–13 days following the index date

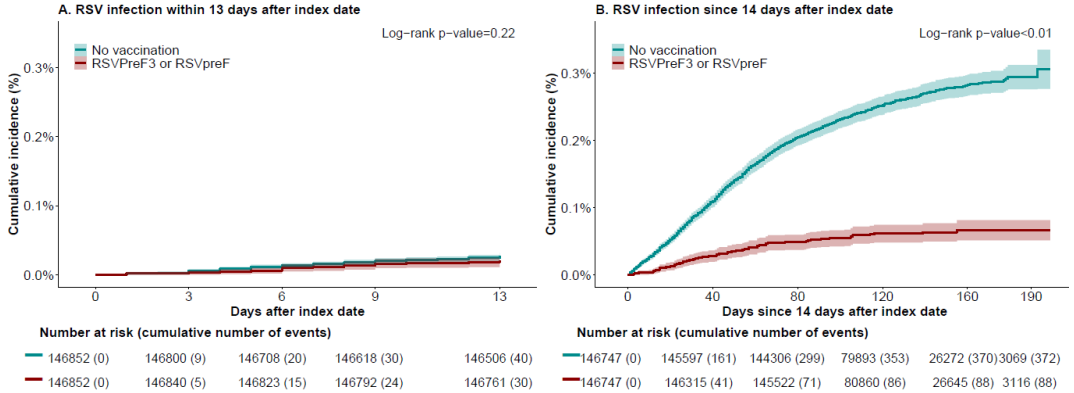
- **Vaccine effectiveness = (1 – hazard ratio) x 100**

*Primary analysis is limited to matched groups in which patients did not have a positive RSV test result during days 0–13 following the index date.
†Occurring ±1 day of the eligible positive RSV test result.

Cumulative incidence of documented RSV infections and associated healthcare events following the matched index date, September 1, 2023–March 31, 2024

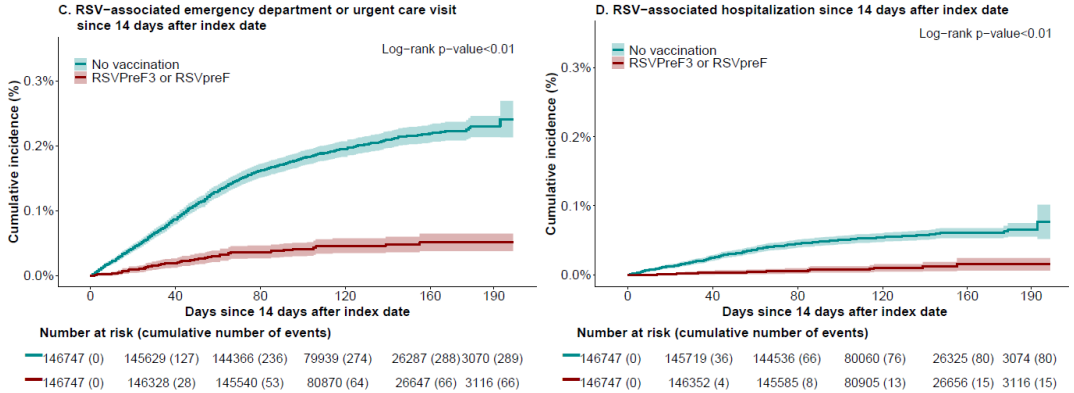
Negative Outcome Control

Documented RSV Infection



RSV-associated ED or UC Encounter

RSV-associated Acute Hospitalization



VE against documented RSV infection and RSV-associated ED/UC visit or hospitalization, intention to treat*

	RSV vaccination (GSK or Pfizer) (N = 146,747)			No Vaccination (N = 146,747)			
	No. of Events	Follow-up (person-years)	Incidence Rate (events / 1000 person-years)	No. of Events	Follow-up (person-years)	Incidence Rate (events / 1000 person-years)	Vaccine Effectiveness, % (95% CI)
Documented RSV infection from 14 days after index date	88	51,281	1.7 (1.4–2.1)	372.0	50,911	7.3 (6.6–8.1)	**77 (71–81)**
RSV-associated ED or UC visit	66	51,286	1.3 (1.0–1.6)	289·3	50,929	5.7 (5.1–6.4)	**77 (71–82)**
RSV-associated hospitalization	15	51,298	0.3 (0.2–0.5)	80·3	50,975	1.6 (1.3–2.0)	**82 (69–89)**

*Median follow-up 124 days [IQR 102 to 150 days]

VE against documented RSV infection by age and immunocompromised* subgroups

		RSV Vaccination (GSK or Pfizer)			No Vaccination			
	N	No. of Events	Follow-up, person-years	Incidence Rate (events/ 1000 person-years)	No. of Events	Follow-up, person-years	Incidence Rate (events/ 1000 person-years)	Vaccine Effectiveness, % (95% CI)
Age group								
60–69 years	28,247	17	7,494	2.3 (1.3–3.6)	74.9	7,474	10.0 (7.9–12.4)	**78 (63–86)**
70–79 years	82,734	47	22,251	2.1 (1.6–2.8)	204.8	22,168	9.2 (8.0–10.6)	**77 (69–83)**
≥80 years	35,691	26	9,601	2.7 (1.8–4.0)	93.5	9,500	9.8 (8.0–12.0)	**72 (59–81)**
Immunocompromised*								
No	135,936	71	36554	1.9 (1.5–2.5)	325.5	36,354	9.0 (8.0–10.0)	**78 (72–83)**
Yes	10,639	16	2753	5.8 (3.3–9.4)	54.2	2,730	19.9 (15.2–25.8)	**71 (52–83)**

*Immunocompromised was defined as receipt of immunosuppressive (excluding steroids) or cancer medications within 90 days or 1 year of the index date (depending on the medication), HIV with most recent CD4 ≤2 years prior to index date ≤200 cells/mm3, or hematologic malignancy documented ≤2 years prior to index date.

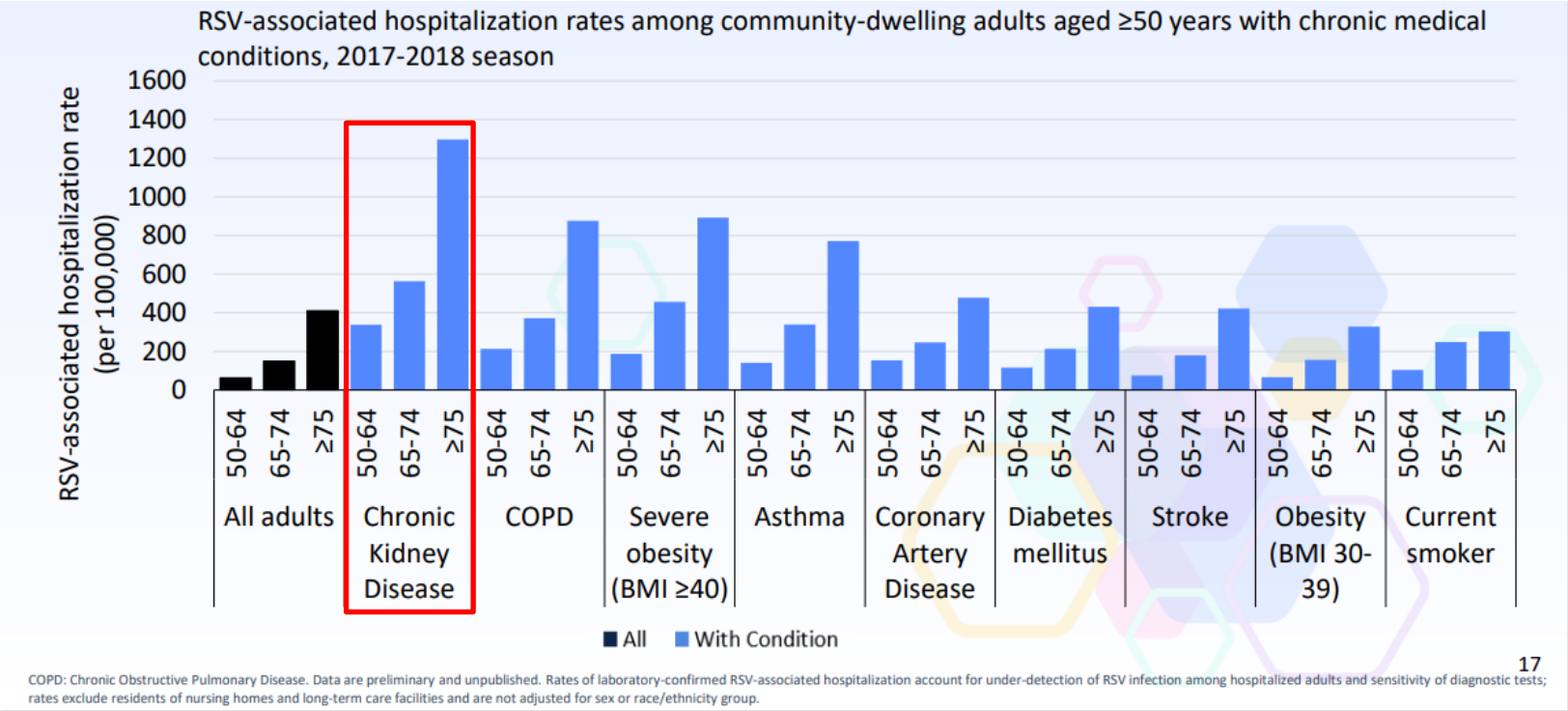
VE against documented RSV infection by RSV vaccine manufacturer

	RSV vaccination				No Vaccination			
	N	No. of Events	Follow-up, person-years	Incidence Rate (events/ 1000 person-years)	No. of Events	Follow-up, person-years	Incidence Rate (events/ 1000 person-years)	Vaccine Effectiveness, % (95% CI)
Vaccine product								
GSK (Arexvy)	43,853	22	13,411	1.6 (1.0–2.5)	94	13,326	7.1 (5.7–8.6)	**77 (64–85)**
Pfizer (Abrysvo)	101,542	66	25,505	2.6 (2.0–3.3)	281·2	25,376	11.1 (9.9–12.4)	**77 (70–82)**

VE against RSV-associated hospitalization among adults aged ≥65 years with end stage renal disease (ESRD)

CMS Medicare Claims data, October 1, 2023–February 24, 2024

Adults with chronic kidney disease had a higher rate of RSV-associated hospitalizations compared with all adults

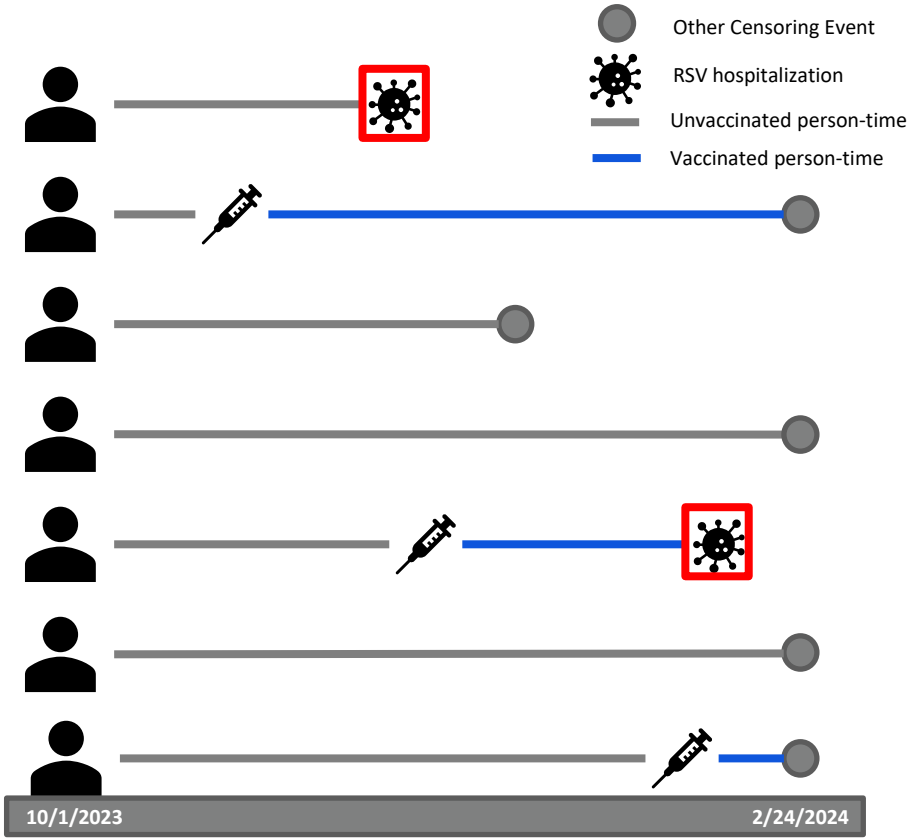


Data source: Rebecca C. Woodruff, PhD. Chronic Conditions as Risk Factors for RSV-Associated Hospitalization. ACIP Meeting. February 29, 2024. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/03-RSV-Adults-Woodruff-508.pdf

Medicare/ESRD: Overview

- **Design:** Retrospective cohort
- **Data source:** Medicare fee-for-service claims data*
- **Population:** Persons aged ≥65 with ESRD†
- **Exposure:** RSV vaccination‡
- **Index date:** October 1, 2023
- **Censoring events:**
  - *RSV hospitalization*§
  - Other censoring event¶
  - End of study period (February 24, 2024)
- **VE = (1 - adjusted hazard ratio**) x 100%**

where adjusted hazard ratio = $\frac{rate\ of\ RSV\ hospitalization_{vaccinated}}{rate\ of\ RSV\ hospitalization_{unvaccinated}}$



*Data sources included Medicare Enrollment Database (EDB) and Common Medicare Environment (CME), Common Working File (CWF) and Shared System Data (SSD) Medicare Parts A/B/D claims data, Minimum Data Set (MDS), and CDC/ATSDR Social Vulnerability Index (SVI)

†At least 1 dialysis encounter (excluding acute kidney injury) in the 90 days before the index date (persons with end stage renal disease receiving dialysis are eligible for Medicare benefits, regardless of age). Investigation was underpowered to estimate VE among persons aged 60-64 years with ESRD.

‡Record of receipt of RSV vaccine dose versus no recorded receipt of RSV vaccine dose using administration codes listed on claims data. Beneficiaries were considered "vaccinated" ≥14 days after the date of vaccine dose administration.

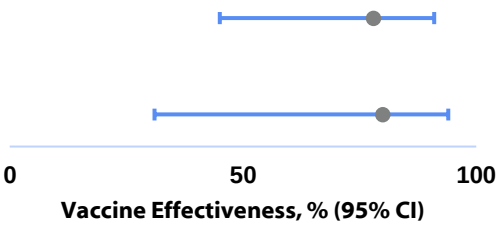
§ RSV hospitalizations identified from Medicare claims data using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) diagnosis code specific to RSV (J20.5, J21.0, or B97.4) listed on at least one inpatient facility claim in the primary position OR a code specific to RSV pneumonia (J12.1,) in any position OR a code specific to RSV in any position paired with pneumonia or acute respiratory failure outcome code

¶Death, disenrollment in Medicare parts A/B/D, enrollment in Medicare Part C, nursing home stay lasting ≥100 days, admission to hospice facility, kidney transplant, receipt of a second RSV vaccine dose

**Hazard ratios adjusted for sex, age group, race, social vulnerability index (SVI), 2022-2023 influenza vaccination status, and Updated (2023-2024 Formula) COVID-19 vaccination status.

Medicare/ESRD: VE against RSV-associated hospitalization* among adults aged ≥65 years with ESRD†, by immunocompromise status§, *October 2023–February 2024*

Immunocompromise status | vaccination status	# of Beneficiaries	# of Outcomes	Median Follow-up Time (Days) ¶	Vaccine Effectiveness, % (95% CI)**
Without Additional Immunocompromise				
Unvaccinated (Ref)	47,176	275	146	Ref
Vaccinated††	4,604	<11§§	91	**78 (45–91)**
With Additional Immunocompromise				
Unvaccinated (Ref)	15,369	136	146	Ref
Vaccinated	2,130	<11§§	90	**80 (31–94)** ¶¶



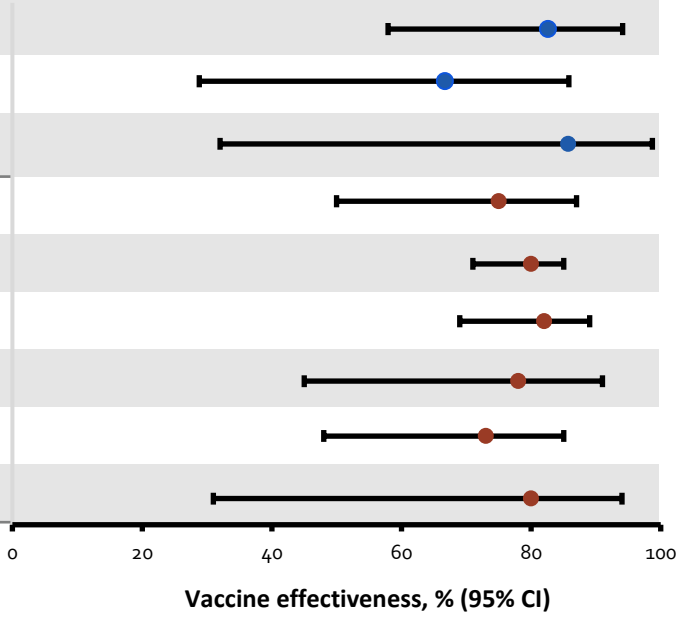
RSV vaccination provided protection against RSV-associated hospitalization among adults with ESRD on dialysis

*RSV-associated hospitalizations identified from Medicare claims data using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) diagnosis code specific to RSV (J20.5, J21.0, or B97.4) listed on at least one inpatient facility claim in the primary position OR a code specific to RSV pneumonia (J12.1,) in any position OR a code specific to RSV in any position paired with pneumonia or acute respiratory failure outcome code.
†Defined as having at least one dialysis encounter (excluding acute kidney injury) in the 90 days preceding the index date. Persons with end stage renal disease receiving dialysis are eligible for Medicare benefits, regardless of age.
§At least 2 encounters with a discharge diagnosis for an immunocompromising condition (hematologic malignancy, solid tumor malignancy, transplant, rheumatologic/inflammatory disorders, other intrinsic immune conditions or immunodeficiency) within 183 days before the index date.
¶A single beneficiary can contribute follow-up time in multiple categories.
**Adjusted for sex, age group, race, social vulnerability index (SVI), 2022-2023 influenza vaccination status, and Updated (2023-2024 Formula) COVID-19 vaccination status. VE was calculated as (1 − adjusted hazard ratio) x 100%.
††Record of receipt of RSV vaccine dose versus no recorded receipt of RSV vaccine dose using administration codes listed on claims data. Beneficiaries were considered "vaccinated" ≥14 days after the date of vaccine dose administration.
§§ Centers for Medicare & Medicaid Services (CMS) cell suppression policy limits the minimum cell size.
¶¶Some estimates are imprecise, which might be due to a relatively small number of persons in each level of vaccination or case status. This imprecision indicates that the actual VE could be substantially different from the point estimate shown, and estimates should therefore be interpreted with caution.

Summary

Observational VE studies show RSV vaccines protect against severe RSV disease, similar to results from trials, although endpoints differ

Outcome	Analysis	Vaccine efficacy/effectiveness, % (95% CI)
Symptomatic, RSV-associated lower respiratory tract disease (LRTD)	GSK trial (≥2 or 3 sx LRTD, primary endpoint)†	83 (58–94)
	Pfizer trial (≥2 sx LRTI, co-primary endpoint)*	67 (29–86)
	Pfizer trial (≥3 sx LRTI, co-primary endpoint)*	86 (32–99)
RSV-associated hospitalization	IVY Network, adults ≥60 years§	75 (50–87)
	VISION, adults ≥60 years, immunocompetent	80 (71–85)
	VHA, adults ≥60 years§	82 (69–89)
	Medicare ESRD, otherwise immunocompetent, ≥65y	78 (45–91)
	VISION, immunocompromised	73 (48–85)
	Medicare ESRD, additional immunocompromise, ≥65y	80 (31–94)



Abbreviations: LRTI = lower respiratory tract infection; LRTD = lower respiratory tract disease; sx = symptoms or signs; y = years

† Papi A, et. al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. *N Engl J Med*. 2023;388:595–608. See slide 44 for detailed definitions.
* Walsh E, et. al. Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults. *N Engl J Med*. 2023;388:1465–77. See slide 44 for detailed definitions.
§ Includes patients with immunocompromising conditions in the displayed VE estimate.

Limitations of observational VE studies

- RSV vaccine uptake in these study populations was 5–10%
  - Early adopters of new vaccines may have different healthcare-seeking behaviors than the general population, which could bias VE estimates upward*
- Multivariable adjustment and inverse-probability-of-vaccination-weighting were used to minimize bias, but residual bias from unmeasured confounding may remain
- Definitions of immunocompromise varied across studies and studies were not powered to assess VE for specific types of immunosuppression
- Median duration since RSV vaccination in these studies was 3–4 months, which is insufficient follow-up time to determine duration of RSV vaccine effectiveness beyond a season

* Sullivan SG, et. al. *Am J Epidemiol.* 2016;184(5):345–353.

Conclusions

- Under real-world conditions, RSV vaccination (GSK or Pfizer) provided protection against severe RSV disease among US adults aged ≥60 years in this first season of use

- These results build on those from RSV vaccine trials in two ways:
  - Provide evidence of VE against RSV-associated ED visits, hospitalizations, and critical illness
  - Demonstrate protection in a population that more closely represents those at high-risk of severe RSV disease, including
    - Adults aged 75 years or older
    - Adults with a composite of various immunocompromising conditions
    - Adults with underlying conditions, especially cardiopulmonary disease

- Ongoing monitoring of RSV VE is needed to confirm findings from this season and assess durability of RSV vaccine protection

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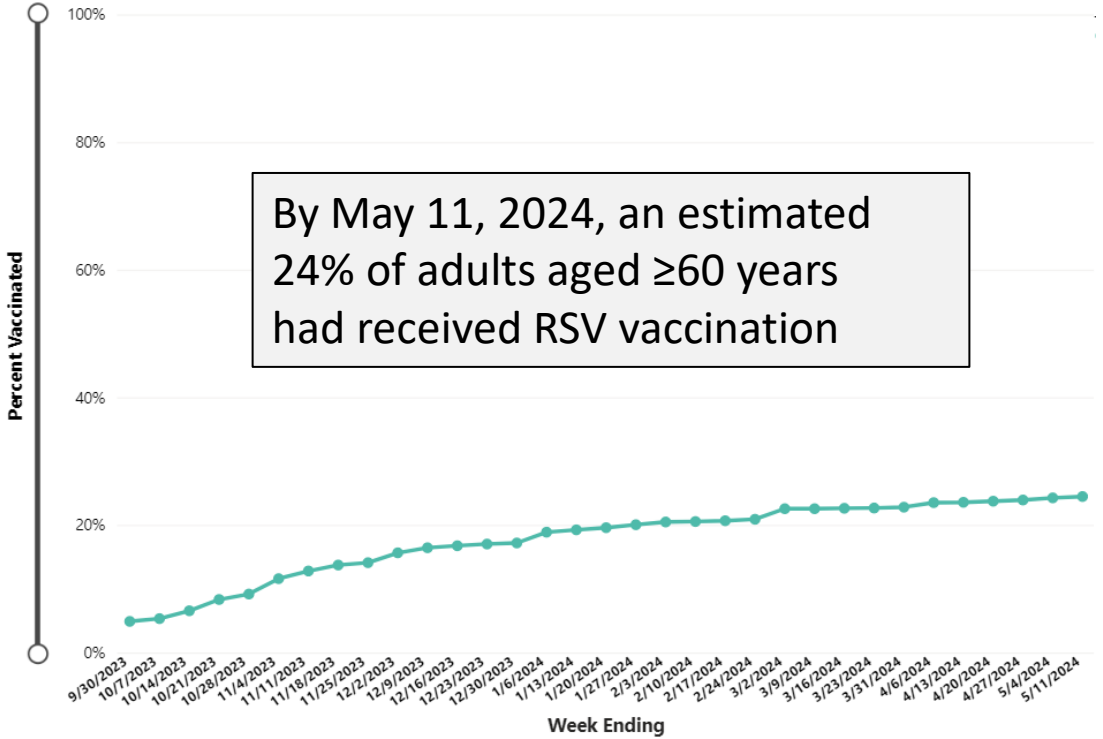
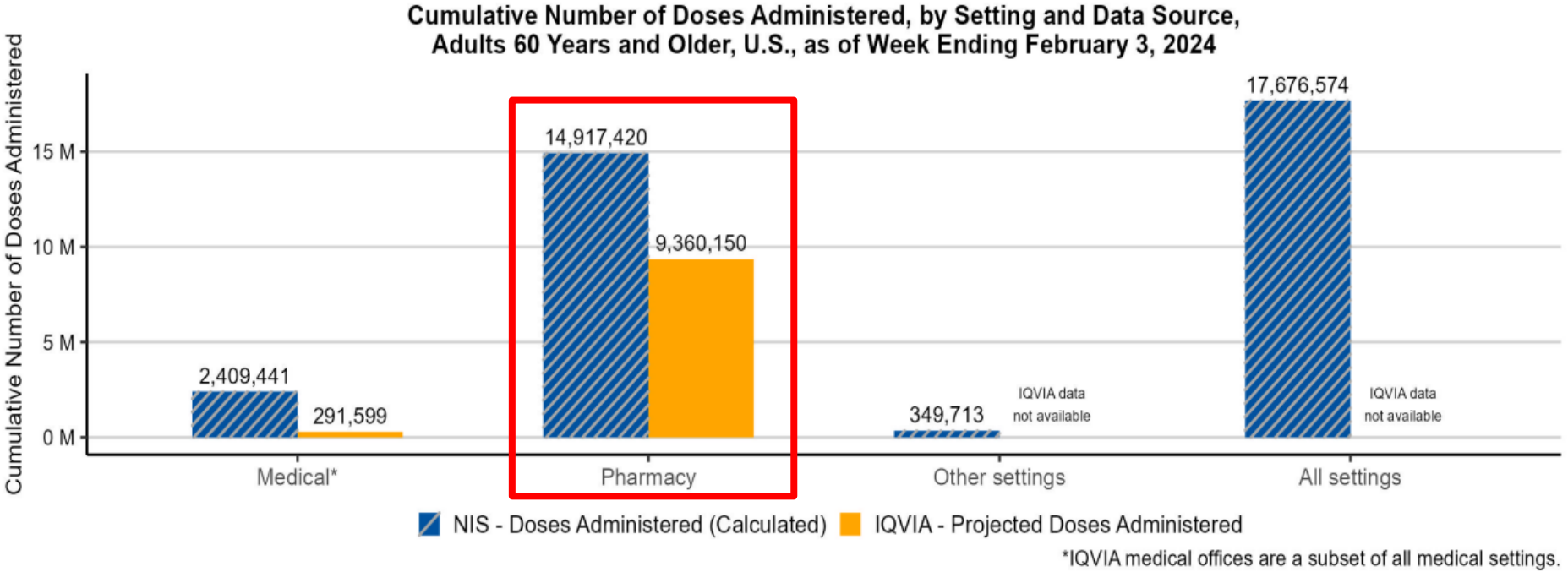
Additional slides

Cumulative RSV vaccine coverage among adults aged ≥60 years, September 30, 2023 – May 11, 2024



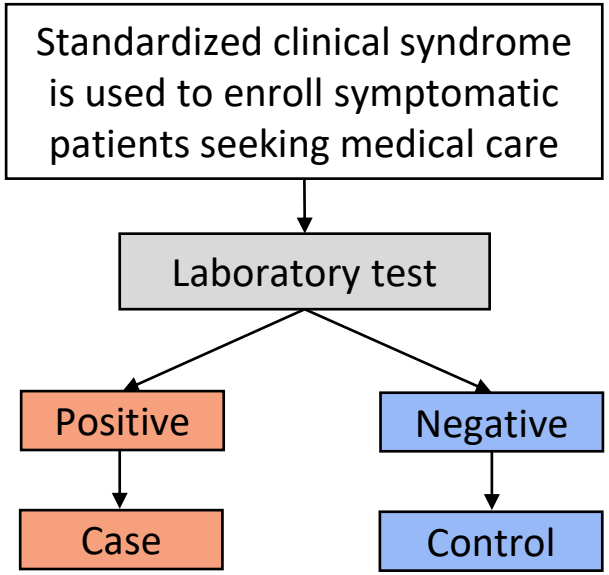
Data source: National Immunization Survey – Adult COVID Module. Available at: Respiratory Syncytial Virus (RSV) Vaccination Coverage and Intent for Vaccination, Adults 60 Years and Older, United States | CDC. Accessed on June 13, 2024.

Most RSV vaccinations were administered in pharmacy settings



Data source: Dr. Carla Black. Implementation update: older adult RSV vaccination. ACIP Meeting, February 29, 2024. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2024-02-28-29/04-RSV-Adults-Black-508.pdf

Test-negative Design (TND)



- **Advantage of TND compared with traditional case-control or cohort analyses**
  - Efficiency in enrolling cases and controls from the same location with the same clinical syndrome
  - Reduces selection bias due to healthcare-seeking behavior

Chua H, et. al., The Use of Test-negative Controls to Monitor Vaccine Effectiveness: A Systematic Review of Methodology. *Epidemiology*. 2020;31(1): 43–64.

Definitions of immunocompromise for each observational VE analysis

Analysis	Immunocompromising conditions
IVY Network	Active solid tumor or hematologic malignancy (i.e., newly diagnosed malignancy or treatment for a malignancy within the previous 6 months), solid organ transplant; bone marrow/hematopoietic stem cell transplant, HIV infection, congenital immunodeficiency syndrome; use of an immunosuppressive medication within the previous 30 days.
VISION	Defined based on presence of ICD-10 code corresponding to hematologic malignancy, solid malignancy, transplant, rheumatologic/inflammatory disorders, other intrinsic immune condition or immunodeficiency, or HIV in discharge diagnoses.
Veterans Health Administration	Receipt of immunosuppressive or cancer medications within 90 days or 1 year of index date, depending on the medication OR HIV with most recent CD4 lymphocyte count ≤2 years prior to index date ≤200 cells/mm3 OR Hematologic malignancy documented ≤2 years prior to index date.
Medicare/ESRD	At least 2 encounters with a discharge diagnosis for an immunocompromising condition (Hematologic malignancy, other intrinsic immune conditions or immunodeficiency, solid malignancy, transplant, or rheumatologic/inflammatory disorders) within 183 days before the index date.

Definitions of chronic lung disease for each observational VE analysis

Analysis	Chronic lung disease definition
IVY Network	Asthma, chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, pulmonary hypertension, home oxygen use (except at night for sleep disorder), tracheostomy, home non-invasive ventilation (except at night for sleep disorder), home invasive ventilation.
VISION	Documentation of ICD-10 code corresponding to one or more of the following conditions among discharge diagnosis codes for encounter: asthma, chronic obstructive pulmonary disease, cystic fibrosis, other chronic lung disease.
Veterans Health Administration	Any documentation of the following ICD-10 codes within 2 years prior to the index date: B44.81, I27.x, I28.x, J40.x, J41.x, J42.x, J43.x, J44.0, J44.1, J44.9, J45.x, J47.x, J63.1, J68.4, J70.1, J81.1, J82.8x, J84.03, J84.10, J84.112, J84.17x, J84.89, J98.2-.3, M05.10x-.19, M30.1, P25.0, P25.8, Q32.2-.2, Q33.x, T79.7XXx, T81.82Xx
Medicare/ESRD	Claim listing ICD-10 code corresponding to one or more of the following conditions within 365 days from the index date: asthma, chronic obstructive pulmonary disease, other chronic lung disease.

Definitions of cardiovascular disease for each observational VE analysis

Analysis	Cardiovascular disease definition
IVY Network	Heart failure, peripheral vascular disease that limits mobility, prior myocardial infarction, cardiac arrhythmias (including atrial fibrillation, and ventricular arrhythmias), valvular heart disease, hypertension, untreated thoracic or abdominal aneurysm.
VISION	Documentation of ICD-10 code corresponding to one or more of the following conditions among discharge diagnosis codes for encounter: heart failure, ischemic heart disease, hypertension, other heart disease, pulmonary embolism, heart valve disorders, atrial fibrillation and flutter, congenital heart disease.
Veterans Health Administration	Any documentation of the following ICD-10 codes within 2 years prior to the index date: ICD10 codes: E08.52, E09.52, E10.5x, E11.5x, E13.5x, G45.9, I20.0-.1, I20.8-.9, I20.0x, I21.0x-.9x, I21.Ax, I22.x, I24.x, I25.x, I50.x, I63.x, I65.x, I70.x, I73.9, I74.0x, I74.10, I74.19, I74.3-.8, I75.02x, I77.1, I96.x, L97.101-.104, L97.109, L97.111-.114, L97.119, L97.121-.124, L97.129, L97.201-.204, L97.209, L97.211-.214, L97.219, L97.221-.224, L97.229, L97.301-.304, L97.309, L97.311-.314, L97.319, L97.321-.324, L97.329, L97.401-.404, L97.409, L97.411-.414, L97.419, L97.421-.424, L97.429, L97.501-.504, L97.509, L97.511-.514, L97.519, L97.521-.524, L97.529, L97.801-.804, L97.809, L97.811-.814, L97.819, L97.821-.824, L97.829, L97.901-.904, L97.909, L97.911-.914, L97.919, L97.921-.924, L97.929, Z95.1, Z95.5, Z98.61
Medicare/ESRD	Claim listing ICD-10 code corresponding to one or more of the following conditions within 365 days from the index date: heart failure, ischemic heart disease, hypertension, other cardiovascular disease.

Case definitions of lower respiratory tract illness or disease in RSV vaccine trials[1,2]

GSK (Arexvy)[1]

- RSV LRTD (primary outcome)
  - ≥2 lower respiratory **symptoms** or **signs**, including ≥1 **sign**, OR
  - ≥3 lower respiratory **symptoms**

- Lower respiratory **symptoms**:
  - Sputum, cough, dyspnea
- Lower respiratory **signs**:
  - Wheezing, crackles/rhonchi, tachypnea, hypoxemia, oxygen supplementation

Pfizer (Abrysvo)[2]

- RSV LRTI with ≥2 lower respiratory signs/symptoms (co-primary outcome)
- RSV LRTI with ≥3 lower respiratory signs/symptoms (co-primary outcome)

- Lower respiratory signs/symptoms:
  - Sputum, cough, shortness of breath, wheezing, tachypnea

[1]Papi A, et al; AReSVi-006 Study Group. Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med*. 2023;388(7):595-608
[2]Walsh EE, et al; RENOIR Clinical Trial Group. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *N Engl J Med*. 2023;388(16):1465-1477