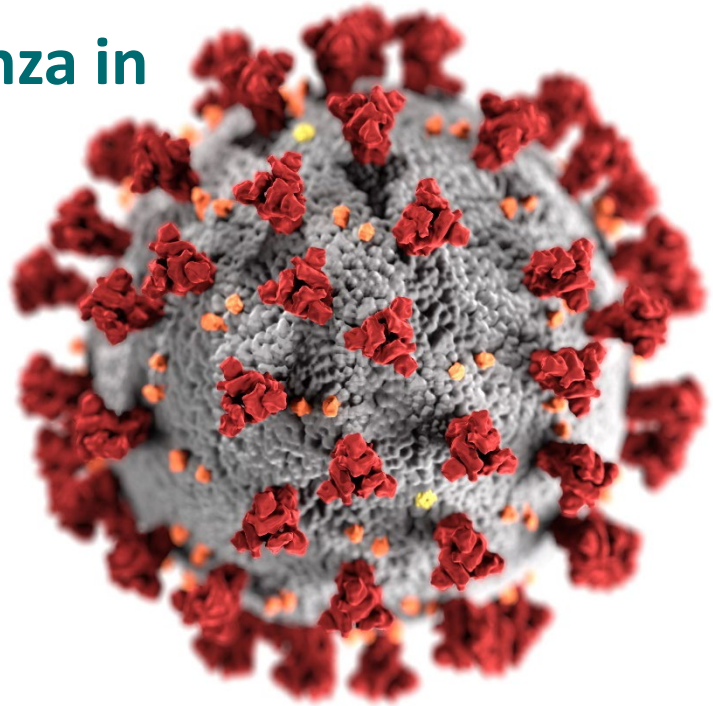
Ischemic Stroke, COVID-19 and Influenza in Adults Ages ≥65 Years: Interpretation & Next Steps



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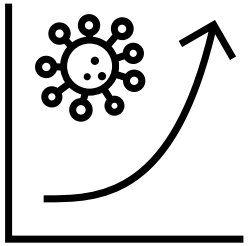
ACIP Meeting

February 24, 2023

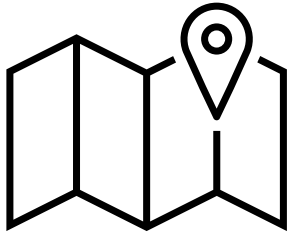
cdc.gov/coronavirus

Ischemic stroke, COVID-19, and influenza in review

Statistical signal for ischemic stroke identified in Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) monitoring



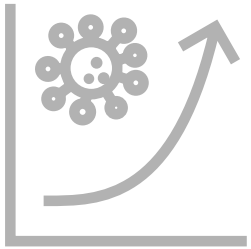
New and published data regarding relationships of ischemic stroke, COVID-19, and influenza



Work group interpretation and next steps

Ischemic stroke, COVID-19, and influenza in review

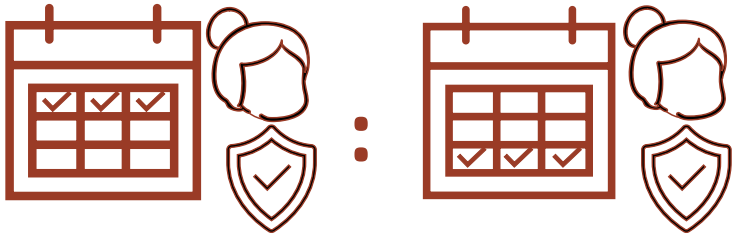
Statistical signal for ischemic stroke identified in VSD RCA monitoring



New and published data regarding relationships of ischemic stroke, COVID-19, and influenza

Work group interpretation and next steps

Review of statistical signal



Comparing rates in an early (“risk”) interval with rates in a later (“comparison”) interval

*Comparing rates in the early (“risk”) interval among boosted people vs booster eligible **un**-boosted people*

- Statistical signal identified for ischemic stroke after Pfizer-BioNTech COVID-19 mRNA bivalent booster dose vaccination in age group 65+ years in VSD RCA
  - Rate ratio has attenuated over time

- Supplemental analysis comparing boosted to un-boosted concurrent comparators did not show an elevated rate ratio

Review of statistical signal: coadministration


Coadministration*


Pfizer bivalent mRNA


High-dose/ adjuvanted flu vaccine

- Stratified analysis evaluating people with **coadministration** of high-dose or adjuvanted flu vaccination show a rate ratio of **1.65** (1.02—2.72; p=0.04)

- In the stratified analysis, rate ratio was **not elevated** in people who received **Pfizer-BioNTech bivalent mRNA** booster without simultaneous flu vaccine
- Separate analysis did **not** detect an elevated rate ratio for ischemic stroke after **flu vaccine** alone

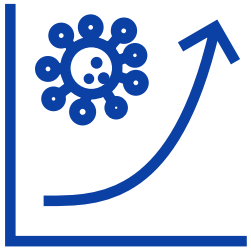
*Coadministration refers to administration of >1 vaccine in the same day.

Review of statistical signal: not identified in any other vaccine safety monitoring system

- No other VSD RCA pre-specified surveillance outcomes have signaled:
  - in **any** age groups,
  - for **either** of the mRNA COVID-19 bivalent booster vaccines, or
  - when data for the two mRNA vaccine types are **combined**.
- No evidence of a safety signal for ischemic stroke in other safety monitoring systems, though analyses in these systems generally did not have the ability to investigate coadministration with flu vaccine
  - Vaccine Adverse Events Reporting System (VAERS)
  - FDA Rapid Cycle Analysis (RCA) data in Centers for Medicare & Medicaid Services (CMS)
  - Veterans Administration (VA) RCA in the VA Electronic Health Record (VA EHR)
  - Pfizer global monitoring
  - Other global public health and regulatory systems
    - Canada
    - European Union
    - Israel

Ischemic stroke, COVID-19, and influenza in review

Statistical signal for ischemic stroke identified in VSD RCA



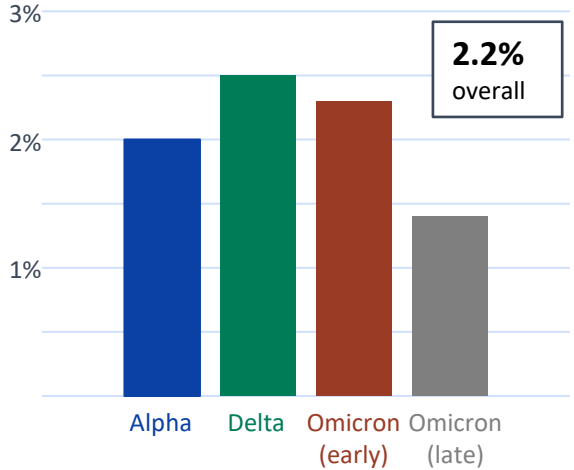
New and published data regarding relationships of ischemic stroke, COVID-19, and influenza

Work group interpretation and next steps

COVID-19 disease and acute ischemic stroke (AIS)

- Incidence of AIS hospitalizations was **10 times higher** during the 3 days post COVID diagnosis (IRR 10.3, [9.9–10.8]) compared with control periods, among Medicare beneficiaries ages ≥65 years[1]
- COVID cohort estimated incidence of AIS is **2.10%** (1.97—2.23) within 6 months after COVID diagnosis[2], though stroke and COVID symptoms present **concomitantly in >80%** of cases[3]
- COVID-19 patients who develop stroke are more likely to be of **older** age, have **more severe COVID-19 disease**, and more likely to have hypertension, diabetes, and coronary artery disease than those who do not[3]
- **COVID-19 vaccination is associated with reduced risk** of AIS after COVID-19 (aHR 0.40 [0.26-0.63]; aHR 0.41 [0.26-0.66] for ages ≥65)[4]

Percentage Hospitalized COVID Patients Aged 65+ with Stroke: COVID-NET, March 2020—October 2022



1) Yang Q et al. Neurology 2022; 98(8): e778-789. 2) Taquet M et al. Lancet Psychiatry 2021; 8(5): 416-427. 3) Nannoni S et al. International Journal of Stroke 2021; 16(2): 137-149. 4) Kim Y et al. JAMA 2022; 328(9): 887-889.

Influenza, Influenza Vaccination, and Stroke

- Association between recent respiratory infection and increased stroke risk noted in some observational studies [1,2]
- Two randomized studies assessing stroke as a specific outcome did not note a significant effect of influenza vaccination on stroke risk [3, 4]
- Stroke has been evaluated as an outcome in several observational studies, some of which have reported decreased risk with vaccination [5-8]
- Benefit of influenza vaccination has been noted in some studies examining major cardiovascular outcomes (some including stroke within a composite outcome) [4,8]
- Limitations:
  - Potential reduction in stroke risk varies and is not seen in all studies
  - Populations, study designs, outcome definitions, and analytic methods vary across studies
  - Observational data are more subject to bias
  - Overall limited data concerning specific influenza vaccines and stroke-specific risk

1. Smeeth L et al, N Engl J Med 2004; 351: 2611-8
2. Zurrú MC et al, Stroke 2009; 40: 1986-90
3. Loeb M et al, Lancet Global Health 12 2022; 10: e1835-e1844
4. Phrommintikul A et al, Eur Heart J 2011; 32: 1730–1735
5. Holodinsky JK et al, Lancet Resp Health 2022; 7: e914-e922
6. Rodriguez-Martin S et al, Neurology 2022; 00: e2199-e2160
7. Asghar Z et al, Vaccine 2015; 33: 5458-5463
8. Chiang MH et al, Am Heart J 2017; 193: 1-7

Healthcare data sources used to describe current incidence of stroke

PCORnet© The National Patient-Centered Clinical Research Network

- Data includes **electronic health records** associated with ambulatory, ED, and inpatient settings
- Covers **all** patients in participating health systems, or ~10% of the US population ages ≥65 years
- Used to rapidly assess incidence of stroke across diverse US population over the late Omicron period within 2022, **with recent COVID-19 or influenza** and incidence overall

HealthVerity

- Data includes **medical claims** from closed payor systems related to ambulatory, ED, and inpatient settings
- Data is **linked to vaccination data** from the Federal Retail Pharmacy Program
- Covers patients **insured** through Medicare Advantage, or ~25% of the US population ages ≥65 years
- Used to rapidly assess incidence of stroke across insured US population, **with recent COVID-19 or influenza vaccination** and incidence overall

Methods used to describe current incidence of stroke

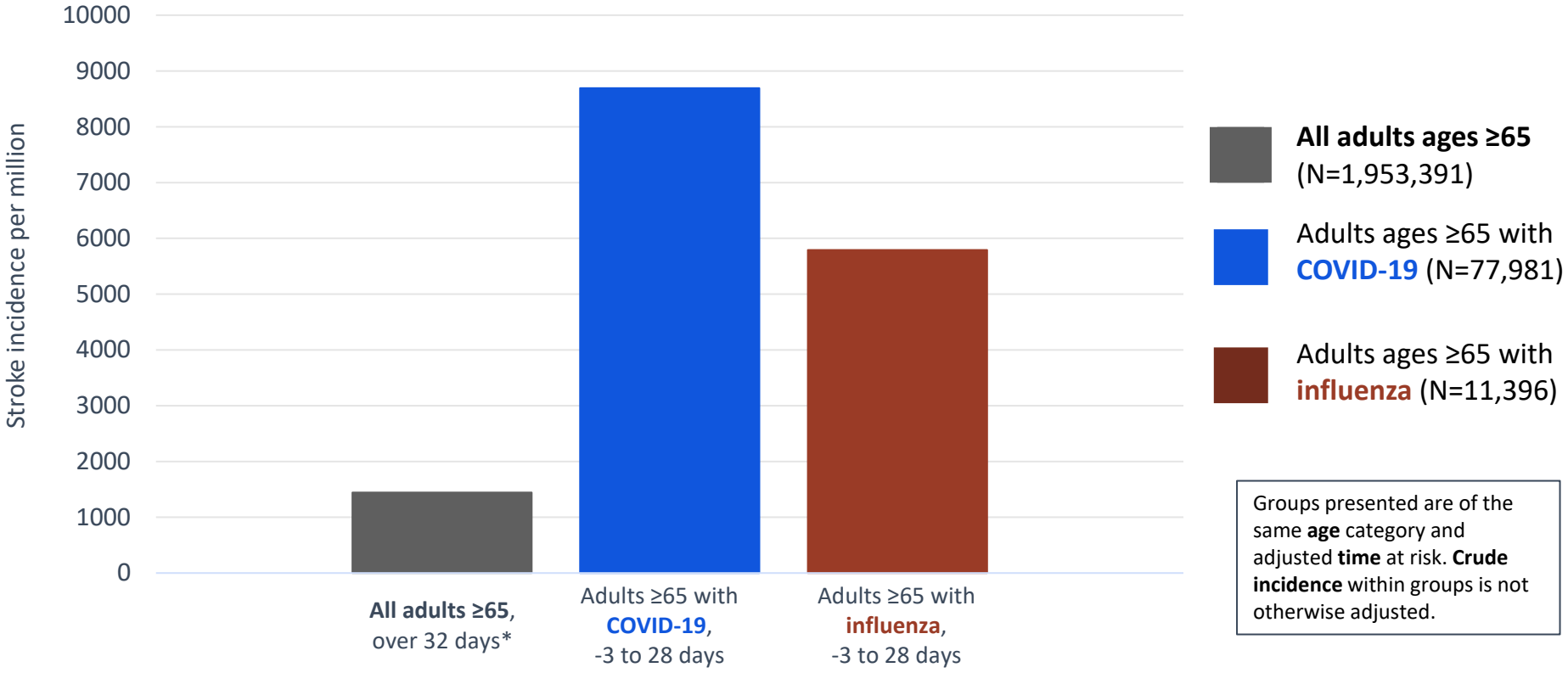
PCORnet© The National Patient-Centered Clinical Research Network

- Cohort definitions designed to capture **incident** stroke
  - ICD10 diagnosis (I63.X)
  - **Exclusion** of patients with history of stroke
- Cohort definitions designed to capture patients with recent COVID-19 and influenza
  - Positive laboratory tests (COVID-19 and influenza)
  - ICD10 diagnoses (B97.29, U07.1, J10.1, J10.2, J11.1, J11.2, J09.X, J10.8X, J11.8X)
  - COVID-19 medications
  - No COVID-19 in the 30 days prior
- Description of incidence of stroke across:
  - Entire cohort, using average incidence over 32 days
  - Recent COVID or flu diagnosis: 3 days prior to 28 days post

HealthVerity

- Cohort definitions designed to capture **incident** stroke
  - ICD10 diagnosis (I63.X)
  - Inpatient place of service
  - **Exclusion** of patients with history of stroke
- Cohort definitions designed to capture recent bivalent mRNA and influenza vaccination
  - All applicable CVX, CPT/HCPCS, and NDC codes
  - No evidence of prior stroke/TIA during observation period or COVID-19 in the 30 days prior
- Description of incidence of stroke across:
  - Entire cohort, using average incidence over 29 days
  - Recent vaccination: within 28 days following bivalent mRNA vaccination, flu vaccination, or coadministration of both vaccines

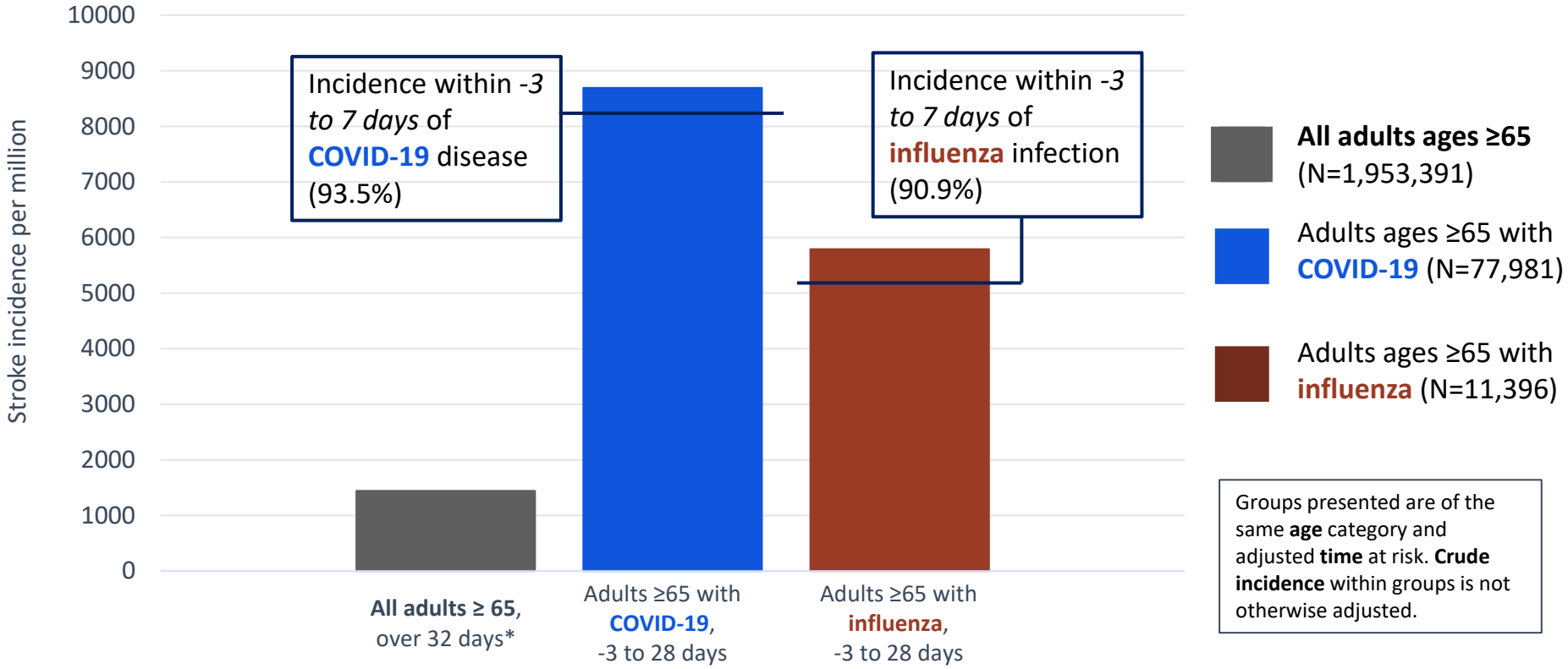
Stroke incidence among all adults ages ≥65 years, with COVID-19, and with influenza during late Omicron: PCORnet, Sep-Dec 2022



Groups presented are of the same **age** category and adjusted **time** at risk. **Crude incidence** within groups is not otherwise adjusted.

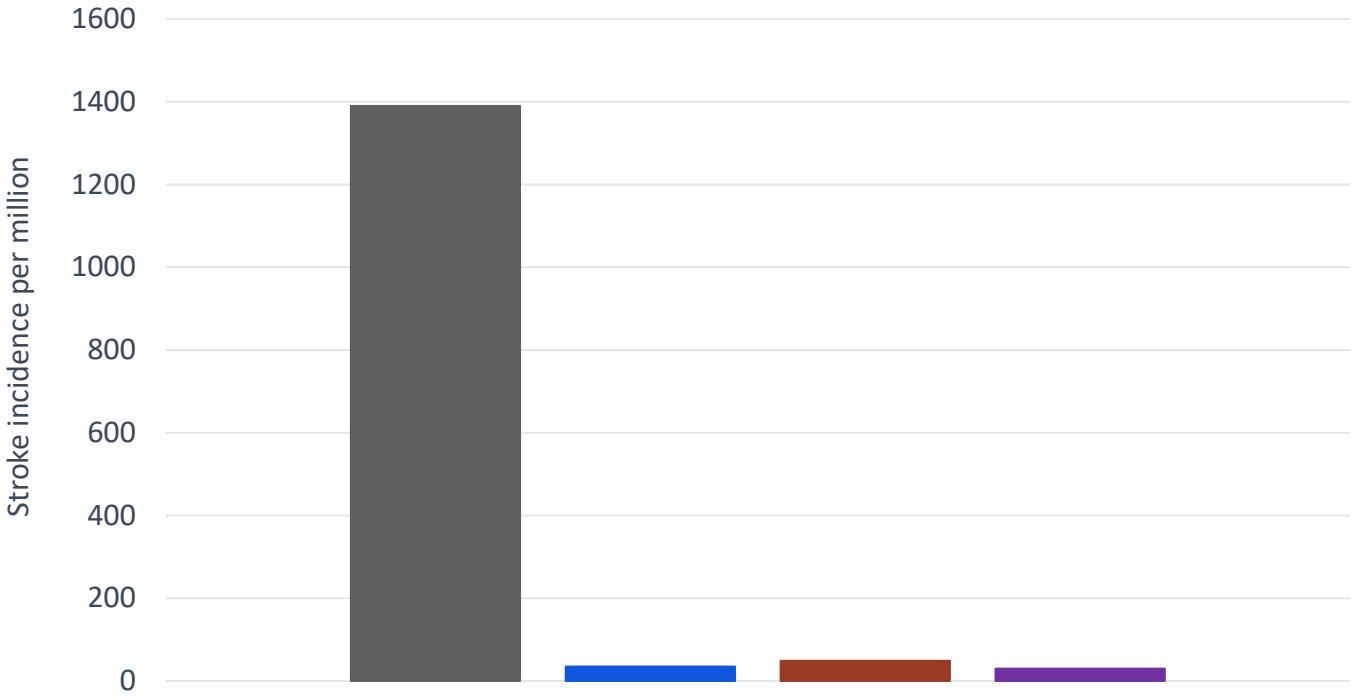
*Average stroke incidence among adults aged 65+ in Sep-Dec 2022 in the full PCORnet cohort per million over 32 days.

Early stroke incidence among adults ages 65+ years with COVID-19, and with influenza during late Omicron: PCORnet, Sep-Dec 2022



*Average stroke incidence among adults aged 65+ in Sep-Dec 2022 in the full PCORnet cohort per million over 32 days.

Stroke incidence among all adults ages ≥65 years and recently vaccinated adults ages 65+ years during late Omicron: HealthVerity, Sep-Oct 2022



Groups presented are of the same **age** category and adjusted **time** at risk. **Crude incidence** within groups is not otherwise adjusted.

All adults ages ≥65 (N=3,651,579)

Adults ages ≥65 with recent **bivalent mRNA vaccination** (N=593,766)

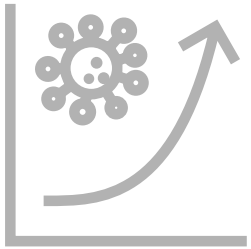
Adults ages ≥65 with recent **influenza vaccination** (N=875,170)

Adults ages ≥65 with recent **coadministration** of bivalent mRNA + influenza vaccines (N=164,836)

*Average stroke incidence among adults aged 65+ in Sep-Oct 2022 in the full HealthVerity cohort per million over 29 days.

Ischemic stroke, COVID-19, and influenza in review

Statistical signal for ischemic stroke identified in VSD RCA monitoring



New and published data regarding relationships of ischemic stroke, COVID-19 disease, and influenza

Work group interpretation and next steps

Work group interpretation and next steps

- Review of safety data is reassuring, and must continue. Priorities include:
  - Continuing to closely follow the intermittently statistically significant signal in VSD, with continued review by VaST and colleagues
  - Continuing supplementary analyses to clarify the relationship between this signal and:
    - any specific vaccine
    - coadministration of vaccines
    - confounding
  - Continuing the most intensive vaccine safety surveillance in US history
- Review of healthcare data demonstrates high incidence of stroke at time of diagnosis with COVID-19 or influenza. Priorities include:
  - Increasing awareness of the risk of stroke with COVID-19 disease and influenza
  - Continuing to encourage uptake of the bivalent COVID-19 boosters

Work group interpretation and next steps

- The COVID-19 ACIP Work Group remains confident in **current** COVID-19 vaccine recommendations.
  - **No changes to current recommendations** regarding coadministration of vaccines
- CDC and partners anticipate the opportunity to review and consider upcoming analyses prior to the 2023-2024 flu season.

Acknowledgements

- Tegan Boehmer
- Matt Ritchey
- Julia Raykin
- Sharon Saydah
- Stacey Adjei
- Jennifer Wiltz
- Jason Block
- PCORnet Sites
- Sara Baca
- Lisa Groskopf
- Jill Ferdinands
- Janet Wright
- Fátima Coronado
- Sandra Jackson
- VaST Working Group
- Lauri Markowitz
- Robert Merritt
- Xin (Cindy) Tong
- Hilda Razzaghi
- Catherin Bozio
- Morgan Najdowski
- Shikha Garg
- Carrie Reed
- Aaron Kite-Powell
- Kathleen Hartnett
- Fiona Havers
- Chris Taylor
- COVIDNet
- Adi Gundlappali
- Aaron Harris
- Emily Koumans
- Pragna Patel
- Jennifer Giovanni
- Mark Swancutt
- Karl Soetebier
- Tom Shimabukuro
- Eric Weintraub
- Karen Broder
- Immunization Safety Office
- Erika Edding
- Aron Hall
- Sara Oliver
- Katherine Fleming-Dutra
- Ruth Link-Gelles
- Danielle Moulia
- Megan Wallace
- Monica Godfrey
- Julianne Gee
- Kelcie Landon
- Ben Silk
- Sarah Meyer
- Elisha Hall
- Melinda Wharton
- Barbara Mahon

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