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

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ACIP Meeting
February 24, 2023
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

- 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

- 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

- COVID cohort estimated incidence of AIS is **2.10%** (1.97—2.23) within 6 months after COVID diagnosis, though stroke and COVID symptoms present **concomitantly** in >80% of cases

- 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

- 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)

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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

6. Rodriguez-Martin S et al, Neurology 2022; 00: e2199-e2160
7. Asghar Z et al, Vaccine 2015; 33: 5458-5463
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)
  - 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

*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

Incidence within -3 to 7 days of COVID-19 disease (93.5%)

Incidence within -3 to 7 days of influenza infection (90.9%)

*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

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

- 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)

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

  - 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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