Update on COVID-19 and influenza vaccine safety

Advisory Committee on Immunization Practices (ACIP) meeting

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Key points up front

- A statistical signal for ischemic stroke after Pfizer-BioNTech bivalent mRNA COVID-19 vaccine was detected in CDC's Vaccine Safety Datalink in persons aged ≥65 years during fall 2022; information was presented at prior ACIP meetings and efforts have been underway to evaluate the signal*
- Available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines, or when influenza vaccine is given alone
  - Variable and inconsistent results were obtained in some analyses of the risk of ischemic stroke following bivalent mRNA COVID-19 vaccination, simultaneous bivalent mRNA COVID-19 and influenza vaccination, and influenza vaccination alone†
  - Most study results have not shown an association between vaccination and ischemic stroke, and no clear pattern demonstrating increased risk has emerged
- Any real or theoretical risks of vaccine adverse events need to be placed in the context of the known benefits of COVID-19 and influenza vaccination in preventing COVID-19 and influenza disease and their potentially serious complications, including stroke
- Our vaccine safety monitoring systems are designed to be sensitive, and the detection and assessment of potential safety signals and communication of safety information to the public is an example of the vaccine safety monitoring process working

* https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-02-Shimabukuro-508.pdf; https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/03-COVID-Shimabukuro-508.pdf

† For the purpose of this presentation, "influenza vaccination alone" is defined as not with simultaneous COVID-19 vaccination but may include other types of non-COVID-19 vaccines

Topics

- Summary of analyses of ischemic stroke and bivalent mRNA COVID-19 and influenza vaccination
- Additional data on ischemic stroke
- Interpretation of data on ischemic stroke and bivalent mRNA COVID-19 and influenza vaccination and next steps

Selected analyses of ischemic stroke and bivalent COVID-19 and influenza vaccination

1. Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) of ischemic stroke after bivalent mRNA COVID-19 vaccination (Centers for Disease Control and Prevention)
2. Analysis of ischemic stroke after bivalent mRNA COVID-19 vaccination (Kaiser Permanente Southern California)
3. Analysis of stroke risk following bivalent mRNA COVID-19 vaccination among U.S. adults aged ≥65 years in CMS data (U.S. Food and Drug Administration)
4. Analysis of ischemic stroke after bivalent mRNA COVID-19 vaccination in patients aged ≥65 years using nation-wide patient electronic health records (Case Western Reserve University School of Medicine)
5. Analysis of stroke, myocardial infarction, and pulmonary embolism after bivalent Pfizer-BioNTech COVID-19 vaccination (EPI-PHARE Scientific Interest Group, France)
6. Analysis of bivalent mRNA COVID-19 vaccination and stroke in England (UK Health Security Agency and the London School of Hygiene and Tropical Medicine)
7. Analysis of the safety of monovalent and bivalent Pfizer-BioNTech COVID-19 vaccination in at-risk populations (Israel)

1.) VSD COVID-19 Rapid Cycle Analysis: Analyses of Ischemic Stroke after Pfizer-BioNTech Bivalent Booster Dose*

(April 2023 ACIP https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/03-COVID-Shimabukuro-508.pdf)

- Data source: VSD data contributing sites
- Methodology
  - *Primary*: Vaccinated concurrent comparator (i.e., bivalent vaccinated vs. bivalent vaccinated) using a 1–21-day risk interval and a 22–42-day comparison interval
  - *Supplemental*: Bivalent vaccinated vs. bivalent unvaccinated but eligible for bivalent vaccine in a 1–21-day risk interval
  - Age groups included 18–64 and ≥65 years
- Main findings
  - Statistical signal for ischemic stroke detected in primary analysis after Pfizer-BioNTech in the age group ≥65 years using a 1–21-day risk interval; signal attenuated over time
  - Post-signal assessment detected an elevated risk in the age group ≥65 years receiving same-day Pfizer-BioNTech and high-dose inactivated influenza (HD-IIV4) or adjuvanted inactivated influenza vaccine (aIIV4); finding attenuated over time
  - No elevated risk for ischemic stroke detected in supplemental analysis using secondary comparators
  - Additional supplemental analyses suggested that comparison interval (22–42 days) rates of ischemic stroke were lower than expected

* Conducted through the CDC Vaccine Safety Datalink Indefinite Delivery, Indefinite Quantity (IDIQ) contract

2.) Ischemic Stroke after Bivalent COVID-19 Vaccination: A Self-Controlled Case Series Study*

(Xu et al., 2023 https://www.medrxiv.org/content/10.1101/2023.10.12.23296968v1)

- Data source: Kaiser Permanente Southern California electronic health record data
- Methodology
  - Modified self-controlled case series using age groups ≥12, 12–64 and ≥65 years
- Main findings
  - No elevated risks detected for either Pfizer-BioNTech or Moderna in any age groups in automated data with a 21-day risk interval
  - No elevated risks detected for either Pfizer-BioNTech or Moderna in the age group ≥65 years in automated data with a 42-day risk interval
  - There were several analyses with statistically significant elevated risks in the age group 12–64 years in automated data with a 42-day risk interval
    - Pfizer-BioNTech and simultaneous influenza vaccination, overall and in those with a history of SARS-CoV-2 infection
    - Moderna in those with a history of SARS-CoV-2 infection
  - After limiting signaling analyses to chart-verified cases, the findings were no longer statistically significant

* Funding provided through NIAID/NIH Award Number R01 AI168209

3.) Evaluation of Stroke Risk Following COVID-19 mRNA Bivalent Vaccines Among U.S. Adults Aged ≥65 Years*

(Lu et al., 2023 https://www.medrxiv.org/content/10.1101/2023.10.10.23296624v1)

- Data source: Medicare claims data
- Populations: Community-dwelling Medicare beneficiaries aged ≥65 years
  - Primary population: Recipients of bivalent mRNA COVID-19 vaccine
  - Secondary population: Recipients of high-dose (HD-IIV4) or adjuvanted (aIIV4) influenza vaccine
- Methodology: Modified self-controlled case series with Farrington adjustment
- Main findings
  - Primary population analyses showed no consistent stroke risk after mRNA COVID-19 vaccination
  - An increased risk was observed with concomitant (same day administration) influenza vaccination
    - Non-hemorrhagic stroke after Pfizer-BioNTech + HD-IIV4/aIIV4 with a 22–42-day risk interval
    - Transient ischemic attack after Moderna + HD-IIV4/aIIV4 with a 1–21-day risk interval
  - Secondary population analyses showed a small increased risk of non-hemorrhagic stroke after HD-IIV4 or aIIV4 with a 22–42-day risk interval, and the risk remained for people without concomitant bivalent mRNA COVID-19 vaccination

* Funding provided by the FDA as part of the SafeRx Project, a joint initiative of the CMS and FDA

4.) Ischemic stroke after COVID-19 bivalent vaccine administration in patients aged 65 years and older: analysis of nation-wide patient electronic health records in the United States*

(Gorenflo et al., 2023 https://www.medrxiv.org/content/10.1101/2023.02.11.23285801v1)

- Data source: TriNetX, a cloud-based analytics platform that includes electronic health record data from >90 million unique patients in the United States
- Methodology
  - Retrospective cohort study among people aged ≥65 years
- Main findings
  - Patients who received bivalent Pfizer-BioNTech COVID-19 vaccination had a similar hazard for ischemic stroke encounters compared to those who received bivalent Moderna COVID-19 vaccination, but had a lower hazard than those who received the monovalent Pfizer-BioNTech or Moderna COVID-19 booster vaccines in the 1–21 or 22–42 days post-vaccination

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5.) Stroke, Myocardial Infarction, and Pulmonary Embolism after Bivalent Booster

(Jabagi et al., 2023 https://www.nejm.org/doi/full/10.1056/NEJMc2302134)

- Data source: French National Health Data System linked to the national coronavirus disease 2019 (Covid-19) vaccination database
- Methodology
  - Matched cohort study (1:5) in people aged ≥50 years
  - Recipient of monovalent vaccine matched to recipients of bivalent mRNA COVID-19 vaccine*; followed for 21 days after vaccination
- Main findings
  - Compared to monovalent Pfizer-BioNTech COVID-19 vaccination, bivalent Pfizer-BioNTech COVID-19 vaccination was not associated with an increased risk of ischemic stroke, hemorrhagic stroke, myocardial infarction, or pulmonary embolism in people aged ≥50 years
  - The authors previously found no increase in the incidence of stroke, acute myocardial infarction, or pulmonary embolism after administration of the monovalent Pfizer-BioNTech COVID-19 vaccine

*contains omicron BA.4–BA.5 strains; used in the United States

6.) BA.1 Bivalent COVID-19 Vaccine Use and Stroke in England*

(Andrews et al., 2023 https://jamanetwork.com/journals/jama/fullarticle/2806456)

- Data source: National Health Service hospital admissions in England linked to the National Immunisation Management System
- Methodology
  - Self-controlled case-series design in people aged ≥50 and ≥65 years (1–21-day risk window) with further analysis in people aged ≥65 years given simultaneous bivalent mRNA COVID-19† and influenza vaccination‡
- Main findings
  - No increased risk of stroke in the 21 days after vaccination with either the Pfizer-BioNTech or the Moderna bivalent mRNA COVID-19 vaccines
  - Similar results obtained for ischemic and hemorrhagic stroke for the subset of people aged ≥65 years given influenza vaccine on the same day as the bivalent mRNA COVID-19 vaccine

* Funded by the UK Health Security Agency; † Contains omicron BA.1 strain; not used in United States; ‡ persons aged ≥ 65 years 95% received quadrivalent or trivalent adjuvanted influenza vaccine (no high-dose influenza vaccine used)

7.) Safety of monovalent and bivalent BNT162b2 mRNA COVID-19 vaccine boosters in at-risk populations in Israel: a large-scale, retrospective, self-controlled case series study*

(Yamin et al., 2023 https://www.sciencedirect.com/science/article/pii/S1473309923002074?via%3Dihub)

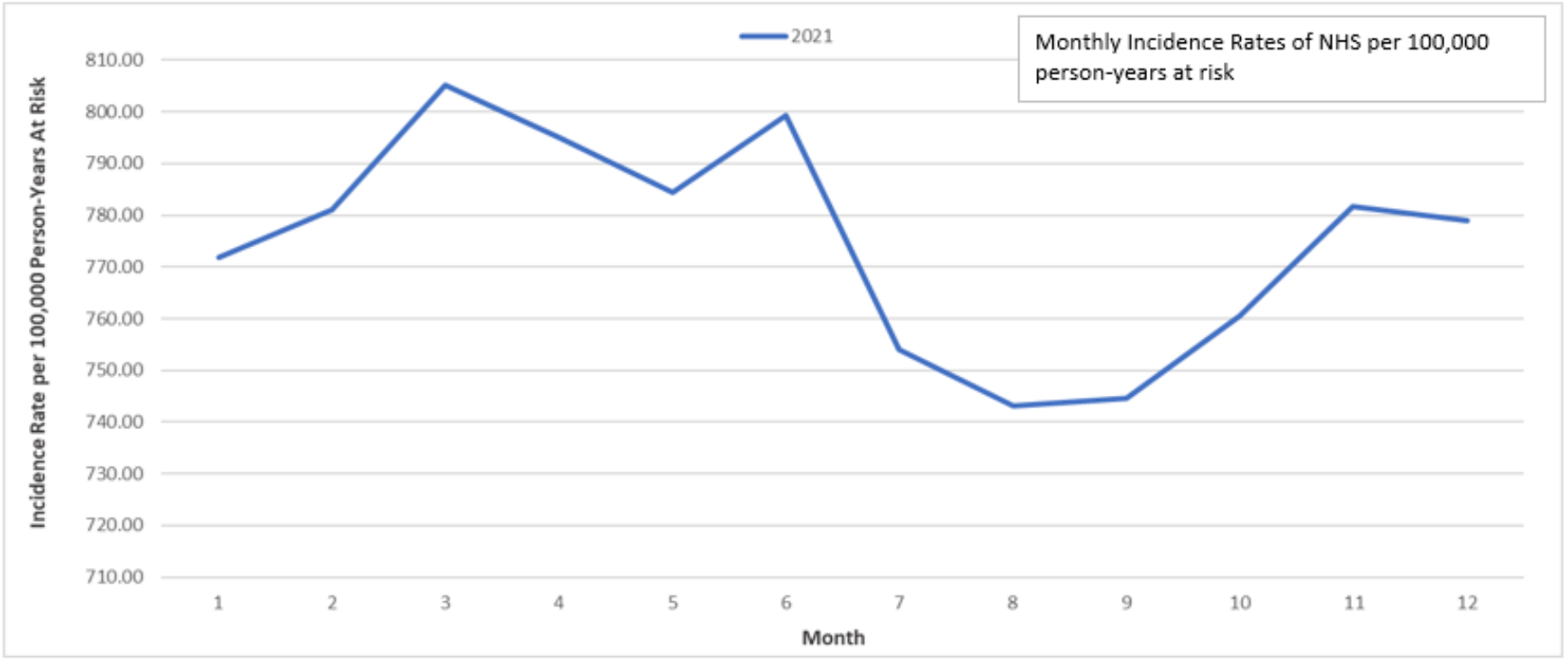
- Data source: Clalit Health Services medical records (largest healthcare organization in Israel with over 3.5 million enrollees, 1.2 million aged ≥60 years)
- Methodology
  - Self-controlled case-series
- Main findings
  - No safety signals detected for ischemic stroke after either monovalent or bivalent Pfizer-BioNTech COVID-19 vaccines used in Israel in the overall analysis or in people aged ≥65 years

* Supported by Israel Science Foundation (grant 3409/19), within the Israel Precision Medicine Partnership

Additional data on ischemic stroke

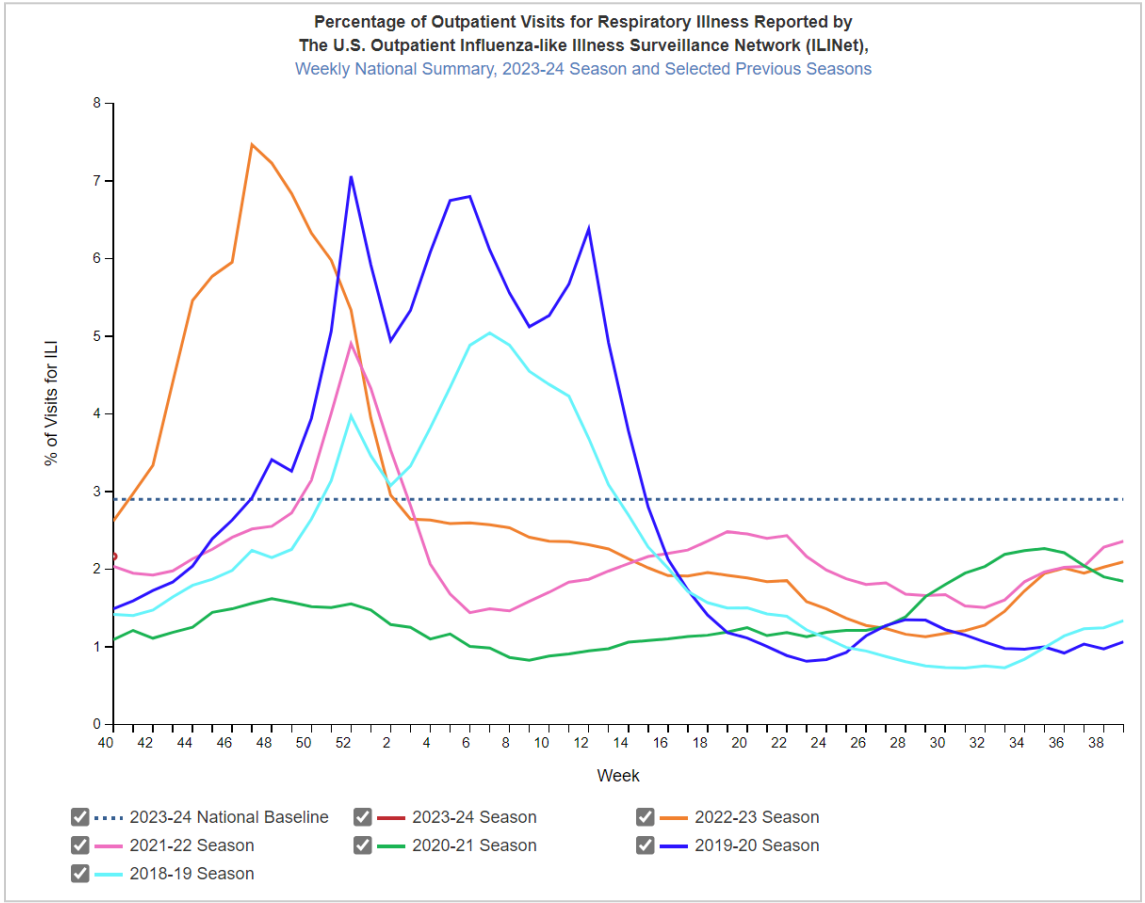
- No unusual or unexpected reporting patterns observed, and no evidence of a safety concern detected for ischemic stroke with either of the bivalent mRNA COVID-19 vaccines in Vaccine Adverse Event Reporting System (VAERS) monitoring
- FDA monitoring in the CMS data and Department of Veterans Affairs monitoring in the VA system did not detect any safety signals for ischemic stroke following bivalent mRNA COVID-19 vaccination using historical comparator designs
- A separate ad hoc CDC analysis during the bivalent Pfizer-BioNTech ischemic stroke signal assessment did not detect an elevated risk for ischemic stroke after influenza vaccination alone
- Surveillance conducted by international regulatory and public health partners did not detect a safety concern for ischemic stroke following bivalent mRNA COVID-19 vaccination
- No evidence of a safety signal for ischemic stroke detected in the manufacturers' global monitoring of bivalent mRNA COVID-19 vaccination
- No safety signals were detected for ischemic stroke for primary series or monovalent boosters for Pfizer-BioNTech or Moderna COVID-19 vaccines in U.S. and global monitoring)
- Data suggest COVID-19 and influenza disease are associated with an increased risk of stroke
  ACIP Ischemic Stroke, COVID-19 and Influenza in Adults Ages greater than or Equal to 65 years-Feb. 24, 2023 (cdc.gov)

Monthly incidence rates of non-hemorrhagic stroke (NHS) in Medicare claims data suggesting seasonality*



* From eFigure 1. Monthly Incidence Rates of NHS, TIA, NHS/TIA, and HS per 100,000 Person-Years at Risk, in Lu et al., 2023 https://www.medrxiv.org/content/10.1101/2023.10.10.23296624v1

Outpatient visits for respiratory illness in the United States from ILINet



Interpretation of analyses of ischemic stroke and bivalent COVID-19 and influenza vaccination

- Variable and inconsistent results were obtained in some analyses of risk of ischemic stroke following bivalent COVID-19 vaccination, simultaneous bivalent COVID-19 and influenza vaccination, and influenza vaccination alone
  - There is a lack of consistency in findings from different data systems, when using different methods, across age groups, and across sub-group analyses
  - The most common findings across studies are findings of no association
  - Multiple comparisons were conducted in studies without adjusting for multiplicity; few reached statistical significance
  - The studies were not designed to account for a potential protective effect of vaccination on stroke in later post-vaccination periods
  - Adjusting for seasonality and restricting analyses to chart-verified cases frequently resulted in attenuated findings or findings that were no longer statistically significant
  - Remaining statistically significant findings tended to be relatively small in magnitude (i.e., RRs<2)
  - Ischemic stroke cases in the analyses are predominantly occurring in older people and in people in the upper ranges of the age groups studied (e.g., upper range of a 12–64-year-old age group); relatively few cases are in younger people

Interpretation of analyses of ischemic stroke and bivalent COVID-19 and influenza vaccination (cont.)

- Available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines, or when influenza vaccine is given alone
- Most study results have not shown an association between vaccination and ischemic stroke, and no clear pattern demonstrating increased risk has emerged
- Seasonality of stroke risk and an unusual respiratory illness pattern in 2022-2023 could be impacting the results of some of these analyses; unrecognized SARS-CoV-2 infection could also play a role in occurrence of stroke after vaccination
- Any real or theoretical risk needs to be placed in the context of the known benefits of COVID-19 and influenza vaccination in preventing COVID-19 and influenza disease and their potentially serious complications, including stroke
- Simultaneous vaccination provides substantial benefits in keeping patients up-to-date with recommended vaccines and protected from vaccine preventable diseases
- Our vaccine safety monitoring systems are designed to be sensitive, and the detection and assessment of the ischemic stroke signal and communication to the public is an example of the vaccine safety monitoring process working

Next steps

- Conduct additional analyses on the possible relationship between ischemic stroke and bivalent mRNA COVID-19 vaccination, simultaneous administration of bivalent mRNA COVID-19 and influenza vaccines, and influenza vaccine alone
- Continue vigilant safety monitoring of 2023–2024 COVID-19 and influenza vaccines, including for ischemic stroke

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