CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older

TOUGH QUESTIONS AND ANSWERS

How often do you see these sorts of preliminary signals for the COVID-19 vaccine?

- Not often. Preliminary signals often emerge as we have more experience with a product and accumulate data. All signals are assessed for further evaluation.
- To date, this particular system, VSD, has identified 1 "true" signal associated with the COVID-19 vaccine (for myocarditis) - meaning a signal that is an actual health risk, albeit a relatively rare one.
    - Preliminary signals from VSD are run through an assessment, including comparing findings to other vaccine safety monitoring systems.
- VSD uses a type of analysis that allows us to conduct near real-time safety monitoring. VSD rates are then assessed weekly. If the rate of adverse events among vaccinated people in the risk period is higher than among during the comparison window, it results in a signal and prompts further investigation into whether the vaccine may be associated with an adverse event. All potential signals are further analyzed to verify the signal and quantify if a true health risk exists.

Do you typically notify the public when a signal hasn't been confirmed? If not, why are you doing so now?

- We routinely communicate early about preliminary vaccine safety data. We strive to be timely and transparent in our communications.
- CDC and FDA are currently working together to assess if there is a causal association between stroke and vaccination. At this point there is insufficient information to conclude if a true health risk exists.
- Given the importance of transparency in the confidence people feel about the safety of COVID-19 vaccines, we are sharing this signal with the public now as we continue to evaluate additional data to determine if this is a true association.

The statistical signal has been described as "preliminary." Would you characterize it as a strong preliminary signal or a weak one?

- We need to distinguish the signal observed here from the determination of any associated safety risk. Though a preliminary signal has been identified, multiple other lines of evidence suggest that this signal may not be confirmed on further evaluation, and thus, the totality of the evidence does not suggest a true safety risk exists at this time that should change clinical practice.
- Currently, the signal is slightly elevated but stable/persistent. The rate ratios seen so far are significantly lower than statistical signals seen for issues like myocarditis.
- This statistical signal has a slightly elevated rate ratio (a measure of relative risk) that has just exceeded our pre-specified threshold for statistical significance. Similar findings have not been observed in other vaccine safety monitoring systems in the United States and have not been observed in other global monitoring programs. Additional analyses are underway to evaluate if this finding represents a true clinical risk. At this point there is insufficient information to conclude a true health risk exists.

How long will it take you to confirm whether this signal is more than preliminary? When will you communicate an update about this again?

- Scientists are working to determine if this is a true association.
- Our analyses become more stable with more data. We're hopeful to have a clearer picture from the assessment and more data in the coming weeks.

- In January, CDC and FDA will share updates to the assessment in planned upcoming vaccine safety meetings, including with ACIP's COVID-19 Vaccine Working Group and FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). CDC and FDA have already briefed the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST).

When did CDC first notice this signal?

- In mid-December, CDC had sufficient information to conclude that the statistical signal was persisting and began a series of supplementary analyses to further evaluate the potential reasons for the persistent statistical finding. This assessment is still underway.

What percentage of signals do not turn out to be clinically significant?

- Many signals that are detected in our monitoring systems do not end up indicating true increased risk.

What data points need to be met to confirm the certainty of this signal?

- CDC is continuing to monitor VSD data weekly and explore potential data-related explanations for the statistical signal.
- When CDC identified a potential signal in mid-December, CDC:
    - assessed data quality, including diagnostic codes and comparison groups
    - began comparing data to other monitoring systems, including FDA (CMS data) and VA
    - conducted a temporal scan analysis to assess clustering of cases following vaccination
    - examined if the rates between the two groups were caused by decreased risk in the comparison window or increased risk in risk window, or combination of both
- By mid-February, CDC will:
    - review cases to confirm diagnoses and better characterize the cases (i.e., if ischemic strokes reported were actually transient ischemic attacks, also known as TIAs),
    - continue to conduct weekly temporal scan analysis,
    - conduct sub-analyses of different segments (strata) of the population,
    - develop statistical models that stratify by confounding factors (e.g., comorbidities or other conditions, risk factors, vaccine uptake patterns, coadministration of other vaccines),
    - review more data as it continues to accumulate weekly and exploring potential data-related explanations for the signal,
    - evaluate the signal further in other data systems (i.e., in CMS, VA), and
    - communicate findings on CDC's website and other communication channels.
- In the next several months, there is consideration for expanding chart reviews and conducting additional medical record reviews confirming the case diagnosis, onset date, and if the cases had any documented history of COVID-19 disease.
- FDA may conduct a definitive study using appropriate epidemiologic study designs such as self-controlled or other designs.

What is the timing estimate on the confirmation of this preliminary data?

- Please see the above answer.
- CDC hopes to assess all factors listed above by mid-February 2023.
- Signal assessment analyses and supplementary analyses in the data system where the signal was detected are underway. The timeline for these assessments will take weeks. The timeline for formal epidemiologic studies in other data systems will take months.

- Additional expected data will make the assessment stronger. CDC will continue to update on its assessment of whether a causal association between bivalent booster vaccine and ischemic stroke exists.

Is this finding going to result in any revisions in the vaccine schedule for adults 65 and older?

- No, CDC is not changing the current routine vaccination recommendations based on this signal, which to date, has not shown up in other safety monitoring systems. There continues to be overwhelming evidence of the benefits of COVID-19 vaccination. CDC will continue to share information in a timely and transparent manner as it becomes available.

Has stroke and COVID-19 vaccinations been studied previously?

- Yes. CDC performs safety monitoring of vaccines to assess and identify serious outcomes. Clinical trials for the bivalent booster did not show serious safety concerns. An interim analysis of 6.2 million people (all ages) who received the primary series of the vaccine found no significant associations between vaccination with mRNA COVID-19 vaccines and selected serious health outcomes, including stroke, 1 to 21 days after vaccination. CDC typically conducts retrospective analyses for specific adverse outcomes if signals are detected through surveillance systems.
- FDA has routinely evaluated 'Hemorrhagic' and 'Non-hemorrhagic' stroke 1-28 days following vaccination as part of its COVID-19 Vaccine Safety Surveillance efforts. This monitoring evaluates 16 or more outcomes for adult patients who received the primary series, monovalent boosters and bivalent boosters. FDA has found no signals for stroke in any of their analyses.

Should people with a family history of stroke be concerned?

- As with any condition, people with increased risk of stroke can consult their healthcare providers. It is important to note that at this time it is unclear if a true risk of stroke exists.

What is CDC doing about this?

- CDC is currently conducting additional analyses. Signal assessments typically take weeks to months. CDC hopes to have a clearer picture of the signal by mid-February.
- For the issue of stroke, relative risk is particularly difficult to parse out as ischemic stroke was already common in the U.S population prior to the introduction of COVID-19 vaccines.
- CDC has notified the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST) and will brief the COVID-19 Vaccines Work Group and Vaccines and Related Biological Products Advisory Committee (VRBPAC) later in January, as scheduled. These groups advise on the safety, development, and administration of vaccines and are critical to the risk assessment process.

What is FDA doing about this?

- FDA continues to evaluate and monitor Hemorrhagic and Non-hemorrhagic stroke outcomes in the CMS dataset for persons 65 years of age and older.
- FDA continues to evaluate and monitor Hemorrhagic and Non-hemorrhagic stroke outcomes in three large commercial health plan databases for persons 65 years of age and older.
- FDA may conduct a definitive study using appropriate epidemiologic study designs such as self-controlled or other designs.

Could the difference actually represent the opposite, that is a protective effect for stroke? How can we know?

- Additional analysis would be needed to better characterize the background rate of stroke in this population.

Tell me more about the single monitoring system that identified this signal and how this was evaluated? What is the Vaccine Safety Datalink (VSD)?

- The Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office, integrated health care organizations, and networks across the U.S. The VSD started in 1990 and continues today to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization. As of September 28, 2022, there are 13 VSD sites that provide clinical, methodological, and data expertise; 11 are data providing sites.
- The VSD uses electronic health data from participating sites to monitor and assess the safety of vaccines. This includes information on vaccines: the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day. The VSD also uses information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays.
- The VSD conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). When there are new vaccines that have been recommended for use in the United States or if there are changes in how a vaccine is recommended, the VSD will monitor the safety of these vaccines.
- The VSD has a long history of monitoring and evaluating the safety of vaccines. Since 1990, investigators from the VSD have published many studies to address vaccine safety concerns.
- VSD does ongoing analyses of electronic health record (EHR) data from several integrated healthcare organizations to detect associations for pre-specified clinical outcomes.
- VSD uses validated methods to conduct near real-time sequential safety monitoring called Rapid Cycle Analysis (RCA). Findings of associations in RCA are considered statistical signals; further refinement of the analysis needs to occur once a statistical signal is identified to verify the signal and quantify the risk if a true signal exists.
- The following steps are taken to assess a signal identified in RCA:
    - Check data quality, especially of diagnostic codes
    - Review charts to confirm or exclude cases as true incident cases; 'quick' chart reviews (i.e., incident physician diagnosed case with symptom onset in risk window) can generally be performed within several days
    - Check inputs, 'background incidences' (i.e., temporal trends)
    - Check whether comparison groups are defined appropriately
    - Check other analyses that use a different control group (e.g., concurrent vs. historical) or compare with a different vaccine
    - Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window
    - Evaluate the signal further in other data systems (i.e., in CMS, VA). Other signal detection and assessment systems exist, such as CDC's v-safe (signal detection only), the FDA's CMS collaboration and BEST, VA near real-time sequential monitoring, and DoD's DMSS.
    - Conduct a definitive study using appropriate epidemiologic study designs (e.g., logistic regression analysis)

How does CDC determine the risk vs. benefit for COVID-19 vaccines?

- CDC evaluates the benefits of COVID-19 vaccines through multiple methodologies, employing various methods and using information collected through different surveillance platforms or electronic health records, among other avenues. In addition, COVID-19 vaccines continue to undergo the most comprehensive and intense safety monitoring in U.S. history. These data are presented and discussed through ongoing benefit-risk analyses to both the ACIP COVID-19 vaccines Work Group and the public ACIP meetings. These analyses have

continued to demonstrate that COVID-19 vaccination is the single best way to protect people from serious COVID-19 illness and the benefits continue to outweigh the risks. As with all emerging data for the vaccines, CDC and ACIP will continue to evaluate the balance of benefits and risks for COVID-19 vaccines.

What is an ischemic stroke?

- Most strokes are ischemic strokes. An ischemic stroke occurs when blood clots or other particles block the blood vessels to the brain. Fatty deposits called plaque can also cause blockages by building up in the blood vessels. During a stroke, parts of the brain become damaged or die. A stroke can cause lasting brain damage, long-term disability, or even death. Some health conditions and lifestyle habits can increase your risk for stroke.