From: "Edlin, Brian (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
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Subject: Draft Notes from January 26, 2023, VRBPAC meeting, Future Vaccination Regimens Addressing COVID-19
Date: Tue, 7 Feb 2023 06:00:34 +0000
Importance: Normal
Attachments: Draft_VRBPAC_meeting_notes.Future_Vaccination_Regimens_Addressing_COVID-19.vrbpac_meeting.1.26.2023.docx

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Hi Karen – Attached are our notes from the January 26, 2023, VRBPAC meeting, "Future Vaccination Regimens Addressing COVID-19."

Heartfelt thanks to all who helped with this project:
Getahun Aynalem
Laura Foliano
Anju Goel
Kendra Richardson
Anne Scheffey
Farhat Shireen
Erin Stroud
Lisa Thanjan
Kimberly Works
Lynne Wu

Thank you! – Brian

Brian R. Edlin, MD
CDC Clinical Immunization Safety Assessment (CISA) Project
Centers for Disease Control and Prevention
CISA COVIDvax

Predecisional Draft

FOOD AND DRUG ADMINISTRATION
178th VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE MEETING
JANUARY 26, 2023
Summary Notes

BOTTOM LINE(S) UP FRONT:

VRBPAC voting question

***Simplification* of current COVID-19 vaccine use:**

• *Vaccine composition*: Does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses in the U.S. to a single composition, e.g., the composition for all vaccines administered currently would be a bivalent vaccine (Original plus Omicron BA.4/BA.5)?

VOTE: YES – 21, NO – 0, ABSTAIN – 0

VRBPAC discussion topics for future periodic vaccination campaigns:

***Simplification* of COVID-19 vaccine use:**

• *Immunization schedule*: Please discuss and provide input on simplifying the immunization schedule to authorize or approve a two-dose series in certain young children, and in older adults and persons with compromised immunity, and only one dose in all other individuals.

Simplification garnered universal support. The details will require substantially more data.

***Periodic update* to COVID-19 vaccines:**

• *Vaccine composition:* Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccine composition, including to the currently authorized or approved vaccines, to be available for use in the U.S. in the fall of 2023.

Additional data will be needed to guide timing of strain selection and vaccination campaigns.

Sessions:

- **FDA presentation on Updating Boosters**
- **CDC presentations on COVID-19 Epidemiology and COVID-19 Vaccine Effectiveness and Safety**
- **FDA presentation on COVID-19 Vaccine Effectiveness and Safety**
- **NIH presentation on New Generation COVID-19 Vaccines**
- **Moderna presentation**
- **Pfizer presentation**
- **Novavax presentation**
- **Open Public Hearing**
- **FDA presentation on Considerations for Potential Changes to COVID-19 Vaccine Strain Composition**
- **Additional Q & A for CDC, FDA and Sponsor Presenters**
- **Committee Discussion and Voting**

FDA Briefing Document: https://www.fda.gov/media/164699/download

Considerations for Updating Boosters and Whether and How Primary COVID-19 Vaccine Strain Composition Should be Modified (David Kaslow, MD, FDA)

VRBPAC-01.26.23-M
eeting-Presentation-C

- Simplifying to one annual vaccine for most of general public would be advantageous.
- For example:
  - **One annual vaccine**: most adults, adolescents and older children, and young children who were previously immunized
  - **Additional dose(s)** for those with **risk-based** adjustments:
    - high-risk older adults
    - persons with compromised immunity
    - young children who have not been previously immunized). Similar approach to influenza vaccine.

CDC Update on Current Epidemiology of the COVID-19 Pandemic and SARS-CoV-2 Variants (Heather Scobie, PhD, MPH)

VRBPAC-01.26.23-M
eeting-Presentation-C

- Highest hospitalization spike was in infants < 6 mo during Omicron start (Jan-Feb 2021) before eligible for vaccine, currently 90% of this age group not completely vaccinated
- Nov. 2022- adults with bivalent booster had **16 x** lower risk for hospitalization than for unvaccinated and 3x lower risk of hospitalization than those without bivalent booster
- Nov. 2022- Children >5 with bivalent booster had **13 x** lower risk for dying compared to unvaccinated and 2x lower risk than those without bivalent booster.
- Increasing proportion of severe illness occurring in older adults 75+ and children <2.
- Increase in immunity (vaccine or infection derived) in all ages except children <2.

Discussion:

- **Dr. Perlman: We should be getting away from antibody neutralizing titers as a marker. (Dr. Gans agreed)**
- Q: (Dr. Gans)- What about geographic variation?
  A: variants sweep across country no matter where first detected.
- Q: (Dr. Hawkins) –How is home testing incorporated into variant composition data?
  A: it isn't. [It can't be.] Home testing, though, tends to involve less severe cases.
- Q: (Dr. Gellin) How long are people protected after vaccination?
  A: 3 mo for infection, longer for severe infection. (will be expanded upon later).

CDC Presentation: Update on Effectiveness and Safety of Original and Bivalent COVID-19 Vaccine

VRBPAC-01.26.23-M
eeting-Presentation-C

Ruth Link-Gelles, PhD, MPH

- VE of monovalent COVID-19 primary series against symptomatic infection among children 6 mo. Thru 4/5 years: [Moderna: 2 dose provides moderate protection (57%) 2 weeks after vaccination, but may wane. Pfizer 2 dose (39%) after dose 2 and 3, after dose 3 -not yet powered for estimate- not enough data
- Early VE of bivalent COVID-19 booster against symptomatic infection due to XBB/XBB1.5 in adults: bivalent booster provided added protection.

- Updates to VE of bivalent COVID-19 booster hospitalizations among adults (with additional month of data, confirmed bivalent is providing protection against hospitalization, and those who only received monovalent may have limited remaining protection-though at a much longer time since last dose).

VRBPAC-01.26.23-Meeting-Presentation-C

TOM SHIMABUKURO, MD, MPH, MBA, DIRECTOR ISO

- Bivalent booster since September 2022, 49.5 million doses given including 21.3 million in >65 y/o. CDC and partners monitor safety using multiple complementary systems. Safety data continue to support CDC recommendation that everyone eligible for booster get it.

NICOLA KLEIN, MD, PHD: SAFETY SIGNAL FOR STROKE WITH PFIZER IN AGE 65 AND OLDER

- VSD: established in 1990, collaboration of CDC with 9 health organizations, data from 12.5 million people across US (4% of US population). Describe RCA (rapid cycle analysis)
- VSD compares day 1 – 21 post bivalent vaccination with 22 – 42 days post vaccination.
- Excludes people with COVID-19 ≤ 30 days previously
- **Ischemic stroke signal in 65+ years, adjusted risk ratio is 1.47 (1.1- 1.9)**.
- VSD in over 20 years, has seen several signals. Once signal is seen, always need to check data quality analysis, different comparator, different analysis.
- As of Jan 8, has been signaling for few weeks, from Oct 16 - Jan 8
- 11/27/2022, first time seeing signals. Persistent but trending down.
- Signal cluster in days 11-22, not very strong signal (unlike myocarditis).
- Could be increased risk during days 1-21 interval or decreased risk in comparison interval (days 22-42).
- Median age 77, 14 (64%) had flu vaccine coadministration.
- 13/22 (60%) discharged home. 3/22 (14%) died.
- Risk was confined to those with high-dose or adjuvanted flu vaccine (not std dose or none)

Discussion

- Dr. Shimabukuro: Further evaluation underway: 1) Continue to monitor weekly and explore potential data-related explanations for the statistical signal in VSD. 2) Consider expanding chart review to all VSD sites. 3) Consult with other surveillance systems to better understand: possible role of concomitant high-dose or adjuvanted flu vaccination with COVID-19 vaccination and possible decreased rate of stroke in the 3-6 weeks following vaccination. (p. 26)
- **Dr. Perlman: It will be important to convey this information regarding ischemic stroke to the public in a way they can understand.**
- Q: (Dr Gans)- What other safety signals are being monitored routinely? A: (TS) -Showed slide 42 showing all prespecified outcomes being monitored and only signal was for ischemic stroke in VSD.
- Q: (Dr Gans) – How are you monitoring for long-COVID? A: (TS)-monitoring in VAERS, would be challenging to monitor in VSD.
- Q: (Dr Reingold): Compare rates to stroke and MI after influenza. Need to balance risk and benefit.

FDA Update on Original and Bivalent COVID-19 Vaccine Effectiveness and Safety (Richard Forshee, PhD)

Link to PDF: https://www.fda.gov/media/164815/download

Summary:

CBER Active Surveillance Program (BEST Initiative)

- Data sources are wide and varied for this surveillance program. It covers 100's of millions of patients across a wide time range.
- Rapid Cycle Analysis Data sources: CMS Medicare for 65+ and 3 data partners. Note: Not many peds patients compared to other groups.
- Immunization Information Systems: A concern is underreporting of vaccines in the health claims databases. To address this, have agreements with IISs to supplement the info on COVID-19 vaccination status.
- Phases of surveillance: Descriptive Monitoring provides descriptive statistics of vaccine doses and selected adverse events. Signal Detection performs sequential testing, while vaccine doses accumulate, to identify potential safety risks early; does not prove causal relationship. Signal Evaluation uses more robust study designs to evaluate potential safety signals.

Bivalent COVID-19 mRNA Vaccines Safety Surveillance

- Rapid cycle analysis- more than 7.3 million bivalent vax administered in 65+. Majority are Pfizer in this age group.
- Study design- RCA. Residents Aged ≥65 Years. No causal association established. Looking at the Pfizer and Moderna bivalent vaccines and various age groups. Comparing to historical rates.
- List of outcomes: Are similar to CDC outcomes. Closest analog to ischemic stroke is non-hemorrhagic stroke. How this is different from CDC – does not include TIA in this definition.
- Slide 11 shows signals. None identified in the 65+ group, including non-hemorrhagic stroke.
    - Adults- myocarditis and pericarditis in 18 to 35 population for Pfizer is signaling. This was observed with the monovalent versions as well.
- Of note, no signals where the surveillance period is over. For both bivalent vaccines, no AMI, DVT, Non-Hemorrhagic stroke. For Pfizer only: No Bell's Palsy, Common Site TTP, PE
- Comparing to 2019 rates for risk ratio, rates are below the historical comparison rates. Most recently the rate ratio is 0.76. No signal here.
- Concomitant influenza vaccination**:** 38% of Medicare recipients who received Pfizer bivalent, also received Flu vaccine on same day. No signal for non-hemorrhagic stroke identified. Further work to be done to segment out the different flu vaccine types administered with the COVID-19 vaccine.

COVID-19 Bivalent mRNA Vaccines RCA: Summary

- This is a large-scale signal detection study of two COVID-19 mRNA bivalent vaccines conducted in multiple claims databases.
- RCA surveillance detected a signal for myocarditis/pericarditis following BNT162b2 bivalent vaccine doses among 18-35 year olds.
- Among adults 65 years and older, several AEs have completed the surveillance period.
- Signal detection studies do not establish a causal relationship and further evaluation of signals is required in more robust studies.
- Surveillance is ongoing and expanded to < 5 year olds.

Data Suggesting Absence of Safety Risk for the Bivalent Boosters in Age 65y+

- No excess reports from VAERs; CMS database shows no increase in stroke; VA data show no increase in stroke; Various countries in Europe and Israel show no increase of stroke; Pfizer notes no increase in signal is global database or when compared to monovalent
- Because of the information seen from CDC and VSD, FDA is working on a formal epidemiologic study to prepare for potential vaccine coadministration in 2023-2024 (high dose or adjuvanted).

Real-World Effectiveness of mRNA COVID-19 Vaccines Among U.S. Nursing Home Residents Aged ≥65 Years

- Dec 13, 2020 to Nov 20, 2021. Looked at COVID-19 vaccination status (including monovalent boosters) and specified outcomes.
- Adjusted VE against death, pre-Delta, 2 doses was 70% effective. Delta period, 55.7% for 2 doses, 88.7% for boosted individuals. Adjusted VE against hospitalization, pre-Delta. 2 doses was 65.3% effective. Delta period, 40.4% for 2 doses, 76.8% for boosted individuals.
- Limitations: effects of increase of Delta share and potential waning of immunity over time coincided. Study period does not extend far into the booster dose administration phase.

Discussion:

- Dr. Chatterjee: Definition vs Ischemic (VSD) vs hemorrhagic stroke (FDA)
  - CDC included TIA, FDA did NOT include TIA
- Dr. Chatterjee: Study planned- with the signal from VSD, would it be prudent to separate doses of flu and COVID-19 vaccines for those over 65+? How is the FDA going to conduct the study?
  - Self-controlled analysis- using risk windows and control windows after COVID-19 vaccination. Look at individuals who got adjuvanted vs high dose flu on same day as bivalent booster. To assess- Is there an interaction between the two?
- Dr. Chatterjee: Is it a passive analysis, vs informed consent will be used?
  - Will be using health claim data in the Medicare system. Active surveillance, but there is no intervention.
- Dr. Reingold: Concern that people who have positive COVID-19 test may not have symptomatic COVID-19. May just happen to have a positive test on admission to hospital. May overestimate the burden of COVID-19 in your study. If we include individuals who don't have symptomatic COVID-19 disease, this would lead to underestimating the vaccine effectiveness, correct?
  - Yes, correct.
- Dr. McInnis: Comment: Coadministration can be pulling up two vaccines into same syringe vs concomitant administration is giving two different vaccines in 2 different syringes. Need to harmonize the language.
- Dr. Nelson: Myopericarditis signal noted for Pfizer in 18 to 35 group. How are these data consumed within the FDA?
  - We conduct follow-up studies. 1st obtain medical records. This association has been seen with the monovalent studies. Looked at the benefit-risk assessment, for myocarditis and pericarditis, for the authorizations and approvals, and that information has already been published.

NIH Presentation

Evaluation of Improved Generation COVID-19 Vaccines (20 min) John Beigel, MD

Link to PDF: https://www.fda.gov/media/164809/download

Summary:

Current strategy: Using antigenically diverse vaccine strains

- In March 2022- NIH started the CoVAIL trial. Looking at using current available vaccines. What are the different antigens we can use and how can we broaden the immune response? Includes adults only who had the primary series and booster and could have been previously infected or not. Study enrolled by stage and randomized to various variant vaccines or prototype.
- Antigenic map reflects relative distance between variants using relative titers of various antisera against them (rather than genetic sequences). Three-dimensional figures show increase in titers to different variants after vaccination with various antigens.

Variant antigens elicit modestly higher titers to variants of concern

- Any booster, including prototype, improves antibody titers across all strains
- Variant antigens elicit modestly higher titers compared to prototype for antigenically distant strains. Pfizer, Moderna, and Sanofi look similar, and all different from prototype.
- Vaccines containing omicron were similar to those not containing omicron (except for prototype)
- Bivalent vaccines perform similar to monovalent variant vaccines.

Current vaccines elicit lower neutralizing antibody titers to newly emerging variants

- Titers against variants that emerged within the past 9 months (e.g., BQ.1.1 and XBB.1) are relativity low.

Correlates of Protection Analysis: Efficacy Decreases with Lower Neutralizing Antibody Titer
Protection Against Transmission is Modest

- Some protection against transmission, but complete transmission protection is lacking

Current Vaccines Remain Effective Against COVID-19, but …

- Vaccine efficacy: Severe disease > Symptomatic infection >> Asymptomatic & Transmission
- High titers are not sustained over long periods of time
- The cross-reactive antibody titers to new variants emerging within a year are marginal
    - I.e., the antigenic landscape is not flattening enough to cover newly emerging strains with high titers

Next Generation SARS-CoV-2 Vaccines: Key Properties will be:

- Enhanced breadth of protection (variant proof)
- Improved durability
- Enhanced ability to block infection/transmission

Next Generation Vaccines - Potential approaches

- New antigens / constructs to generate broader response: Conserved element; Mosaic
- Induction of more durable immune response
- Targeting mucosal immunity: e.g. intranasal or oral administration, or parenteral administration with more mucosal immunity

How Do We Advance Next Generation Vaccines? Many questions to address. Neutralizing antibody does not explain all of VE. Neutralizing antibody likely does not contribute equally to VE for different outcomes. Mix and match study- 2022- There are differences in Pfizer and Moderna compared to Ad26. CD 4 and CD 8 responses differ.

- COVAIL trail is looking at T-cell analysis. COV2008 study with Janssen also looking at cell mediated immunity.
- Nasal IgA titers are related to protection. We don't know if vaccine changed the mucosal immune response or if these changes correlate with VE. Unclear what to measure for mucosal vaccines. IgA or IgG? CD4 or CD8? Mucosal or cellular responses or both? Systematic vs mucosal?

Evaluation of Next Generation COVID-19 Vaccines. Starts at the same place- non-inferiority**.**
Conclusions

- There is a public health need for next-generation vaccines
- Some next-generation vaccines can be advanced using data and assays similar to the pivotal trials…
    - Broader protection against emerging variants
    - Increased durability
- …but we also need to better understand the immune responses that protect against infection/transmission
    - Those are the outcomes that are increasingly important
- Together, this will allow identification of the most promising vaccine candidates to further decrease COVID-19 disease

Discussion:

- Dr. Gans: Committee agrees about need for correlates of immunity. Issue is time and making decisions without the data. Applaud the discussion. Question about the data you presented… did not include any of the BA.4 and BA.5 data, correct?
    - Started in March where we had BA.1. But, had a stage 4 that has BA.4 and BA.5, but the data are too speculative to present now.
- Dr. Levy: Need to learn how to do it better. Regarding the antibodies, these are all correlations, and we don't prove mechanism of VE. Could investigate serology to look at the types of antibodies. We don't look at innate immunity. mRNA vaccines could change immune parameters. How do these correlates play out in different populations- by age, medical status etc. Systems biology can be a tool but is costly. How do we nest that in clinical trials? Hope FDA will reflect and require more info on these different parameters.

- Dr. Rubin: If you induce immunity with a completely different mechanism, do we expect correlates of immunity to be the same?
    - No, we do not expect correlates of immunity to the be the same across different platforms.
- Dr. Hildreth: Convergent evolution happening. Are we looking at this with the vaccines?
    - Interesting question. Can't predict things too well. We can see genetic mutations and model the viral fitness, but don't know what the entire map is. We are not there.

MODERNA COVID-19 BIVALENT VACCINES PRIMARY SERIES AND BOOSTER (ANTONELLA LOZITO, PHARMD, MODERNA)

PDF: https://www.fda.gov/media/164810/download

- 278 million doses of the Moderna bivalent given worldwide; with no new signals
- Protected against infection and severe disease/hospitalization in real world studies
- Consistent safety and immunogenicity data observes in animal and human studies
- Primary series and boosters in children (6 months to 5 years)
- Booster in adults (greater than 18 years)
- The RNA technology allow us to rapidly respond to public health needs.

CLINICAL DATA WITH BIVALENT OMICRON VACCINES (RITUPARNA DAS, MD, PHD, MODERNA)

- 9700 individuals have been vaccinated with a Moderna variant containing vaccines
- We adapted vaccines to keep up with current circuiting strands.
- Summary of 2021; at the emergence of the first variants; we started making Beta containing bivalents.
- Presenting BA.4 data (included 511 patients. Follow up for 37 days, mediate age was 51, a SIGNIFICANT AMOUNT of person over 65 were enrolled.
- The results of BA4.5 Neutralizing antibodies After 4th dose was superior
- Those over 65 a similar antibody response to younger persons (18-55)
- Assessed BA.1 Bivalent vaccine as a primary series in 6 months – 5 years (Part 1): N : 179, 85 days after dose 1 (December 5, 2022). There was a mean age of 3 and 63% had prior SARS-Covid infection. There was no major difference to the primary vaccine. Systematically reports of fever were similar to both studies. NO grade 4 events.
- We believe bivalent as a primary dose will provide better protection.

REAL-WORLD EFFECTIVENESS DATA (RITUPARNA DAS, MD, PHD, MODERNA)

- BA.4/BA.5 Bivalent in immunocompetent individuals: provides additional protection against hospitalization to those who did not receive the Bivalent vaccine.
- Ongoing/planned: Primary series bivalent in those less than 6 months

PRECLINICAL RESULTS FROM AUTHORIZED AND INVESTIGATIONAL MULTIVALENT VACCINES (DARIN EDWARDS, PHD, MODERNA)

- Moderna continuous monitors for variants.
- RNA material and key manufacture steps are taken to be up to date for public response
- BA.4/B5 Bivalent started in Spring 2022 because requested from FDA.
- moderna ongoing monitoring has helped make 19 moderna covid-19 vaccines
- The novel composition are also included
- BA.4/BA5 Bivalent drives significant neuralization compared to monovalent vaccine across variants.

SUMMARY AND CONCLUSIONS (RITUPARNA DAS, MD, PHD, MODERNA)

- BA.4 met all immunogenic endpins; results were consistent for 18-65 and greater than 65
- Randomized US BA./4 bivalent confined the safety. Was not powered for different in COVID-19 rates; non significant trends to lower rates in BA.1 bivalent group compared to original Strand
- Cross neutralization has been observed for emerging omicron subvariants

Discussion:

- Safety data for BA1 Bivalent; reduced reactivity was noted on the slides.
    - We have seen this trend across our bivalent vaccines. We are not sure why but we have seen it consistently.

- Will Moderna conduct T-cell studies?
    - We have and will continue to study but our current work is on the serological correlations.

- There are differences between BA4 and BA5 clinical efficiently but they have the same S protein; how do you explain?
    - We do believe the BA5 dominated and has an infectious advantage over BA4; which was showed by the size of the waves of the world saw. The BA5 wave did come later in the study.

PFIZER/BIONTECH COVID-19 VARIANT VACCINES (KENA A SWANSON, PHD, PFIZER)

PDF: https://www.fda.gov/media/164813/download

Summary:

- The safety profile has been consistent on all vaccines
- Better matched COVID-19 vaccines restore waning immunity against the hospitalize observed in 3-6 months after vaccines Better neutralizing activity and increased protection against a range of COVID-19 outcome inducing less UC/ED visits and hospitalizations.
- Safety and clinical studies across age groups
- Clinical study evaluation of Bivalent at 30 ug at a 4th dose vaccine in those over 12years old→ GMR superiority was met (The baseline line tiers prior to 4th dose were normal.) OmicroBA.4/5 seroresponse also met non inferiority criterion.
- Response to Bivalent was better that Monovalent
- Higher neutralizing response with Bivalent BA 4/5 vaccine regardless of prior SARS-COV-2 infection.
- Additional studies will be for children under than 12 to evaluate Bivalent as a booster and primary series.
- Initial studies to assess safety and immunogenicity for a Bivalent booster those 6 months to under 5 years; response was higher in the 4th dose with GMC 1700.
- The Bivalent enhances protective immunity against the circulating omicron sub lineages. Benefits both SARS-COV2 native and those with prior infection.
- Real world effectiveness data is needed but may come late therefore on-going monitoring is needed to understand antigenic distance, immune escape and immune imprinting.
- Pfizer supports adapting the flu model and a pathway to ensure readiness to support COVID strands. The timeline produce a vaccine; if needed; is 100 days. To help protect the public response.
- Variant modified vaccine demonstrating safety across age groups.
- Better matched vaccines offer improved protection.
- An established model for vaccine strain selection and approval is critical to enable access to optimally matched vaccines.

Discussion:

- There was not a proper number of participants (20 children) under the age of 2. Plans?
    - The data that were presented was from a subset of children in our ongoing study. In the primary study 1 phase; there will have 90 children in the 6 months-2 years and 90 children in the 2 years to 5 years group.

- Comment: I don't think imprinting is real. Thoughts?
    - Response: We know looking at the entire data, if you have an omicron components within the vaccine you do see a see improved response to omicron and its sublineages. [So no evidence of imprinting.] But

we also know the history of influenza; where there may be imprinting so we will continue to monitor for SARS-COV-2

- In the new vaccines going forward will dosing considerations be reviewed again?
  - We understand and will explore the need to change the vaccine doses.

- It was stated it takes Pfzier 100 days to create a new vaccine. If we think about the flu model; if we need several strands withing a vaccine; what is the return time? Can Pfizer produce at a global demand?
  - Yes, we have the production capacity in a 100 day timeline; even with several strands components.
  - PFIZER IS ABLE TO BE FLEXIBLE WITH THE GLOBAL DEMAND.

- Comment: I DO NOT WANT THIS ENTIRE MEETING BE FOCUSED ON MRNA VACCINES.

NOVAVAX VACCINE REGIMENS ADDRESSING COVID-19 (DR. FILIP DUBOVSKY, MD, MPH, NOVAVAX)

PDF: https://www.fda.gov/media/164812/download

Summary:

- US/Mexico Adult Phase 3 Study: anti-rS IgG 12x higher against prototype strain compared with BA.5 initially; after booster, antibodies to BA.1, BA.2, and BA.5 were all close to levels associated with 90% efficacy
  - Infection-primed individuals increased their antibody levels 60-77x after primary series, achieving levels associated with 90% efficacy
- US Adolescent Phase 3 Study: 2 dose primary series initially had pseudovirus neutralization levels below the correlates of protection threshold for BA.1 and BA.4/5; after boosting, levels rose to those predicted to be protective
  - Antigenic cartography demonstrates decrease in fold-difference between Prototype and BA.4/5 from 28.8 with primary series to 1.74 after booster, indicating that the immune response is almost indistinguishable, regardless of strain
- Novavax booster after 3 mRNA doses: protective antibody levels and pseudovirus neutralization levels were comparable between prototype, BA.1, and bivalent types vaccine against the prototype strain, BA.1, and BA.5
- Novavax, Moderna, or Pfizer vaccination primary series followed by Novavax booster study: Novavax primary series participants had highest anti-rS titers for anti-prototype, anti-BA.1, and anti-BA.5
- Novavax or mRNA primary series followed by Novavax booster study: all regimens provide high levels of neutralizing response for prototype but suppressed with BQ.1.1 and even lower with XBB.1
- Epitope RBD mutations for BA.5, BQ.1.1, and XBB led to structural changes in binding regions that cause decreased binding and decreased neutralization of new strains
  - Indicates the changes in XBB lineage should be a target for new composition update to restore cross-reactivity for future forward drift variants.

Discussion:

- Dr. Berger: Has anything been done to look at vaccine performance with minority populations?
  - FD: We did not see race or ethnicity as important factor for immunogenicity with initial studies. Have not been able to do subanalyses but have some planned with bivalent work.
- Dr. Gans: You showed data showing that monovalent and bivalent vaccines are equally efficacious, but also suggested that new vaccines should include new strains.
  - FD: Our data suggests that vaccines are equally efficacious through BA.5, but XBB is different. VE is preserved even through early strains of current variants. We think that moving to a closer match would give better effectiveness in the future. We are indifferent to monovalent vs bivalent; we can manufacture both.

- Dr. Levy: Can you discuss what Novavax understands about the impact of Matrix M adjuvant on the breadth of the immune response against distinct coronavirus variants?
    - FD: Adjuvant is critical for functionality of driving neutralizing responses and breadth of responses. Matrix M also used for influenza vaccine that also demonstrated broad responses. If we can get a strain selection on the same antigenic tree, then the adjuvant will induce a broad response against future variants.
- Dr. Gellin: You are hoping for an end of Q1 decision on strains for a 6 month production?
    - FD: Yes, that is the time frame required. We would also want antigenically matched strain. Time frame could be shortened depending on how far we are in the process of creating antigenically matched strain.
- Dr. Chatterjee: Does Novavax have any candidates that are more conserved epitopes than spike protein?
    - FD: We are continuing to focus on spike protein since neutralizing responses against the spike protein are protective.

OPEN PUBLIC HEARING

[redacted] (No conflict) Kiwanis International

- Works with community-based organizations and is a vaccine ambassador
- Discussed the largest declines in childhood vaccination in the past 30 years (UNICEF)
- Suggested to increase the vaccine uptake by involving community-based organizations
- Collaborating and working with these organizations will increase vaccine trust and the motivation to receive vaccines in the community.
- Communities can help and make a difference in the vaccine efforts.

[redacted] (no conflict)

- In 2021, she was a healthy individual and traveling internationally. Now attributes her health decline including neurological symptoms to Moderna COVID-19 vaccine.
- [redacted] [MD PhD Baylor] blocked me. I was censored by media outlets.
- Twitter and other social media censored the discussion about the adverse events of the vaccines.
- Talk about the virus gained more circulation and vaccines antibodies are waning
- Many VAERS reports about adverse events and death after COVID-19 vaccines, throughout until January 2023. Why was no one alarmed?
- COVID- 19 shots should stop.
- FDA should have more transparency in data and rebuild the community trust by doing more research on these vaccines.

[redacted] (No conflict) ER nurse

- Claimed that after receiving the Pfizer vaccine, has not able to work due to AE
- Concerned about false information on COVID-19 safety monitoring.
- FDA did not have any concerns about the reported 770 AE and estimated 66% cases of myocarditis.
- Mention about the 73K reports of serious AE of mRNA vaccine as compared to 13K AE reports of all other vaccines since 2009
- Questioning VAERS safety signals related to Stroke, CVC, Afib, raised concern about the VAERS safety signal of children and lack of FDA and CDC response in following up on these signals.

[redacted] (No conflict)

- Concerned about excess deaths not explained by COVID-19, decreased birth rates, and unprecedented rates of sudden unexpected death among young people since COVID-19 vaccines were rolled out.
- VAERS and other countries' databases show thousands of deaths associated with COVID-19 vaccines.
- A Cleveland Clinic study found that a higher number of vaccine doses was associated with a greater risk of getting COVID-19. [This is true. https://www.medrxiv.org/content/10.1101/2022.12.17.22283625v1.full Cf. Fig. 2]
- Tolerance of spike protein and increased risk of severe chronic infection

- UK does not give booster doses to those under 50 years of age.
- Asked to show more safety data and evidence.

[redacted] (PhD) Financial conflict Involved in some tinnitus study, received 2K)

- He and his wife developed tinnitus after the vaccine, he emphasized its importance to be recognized.
- Mentioned T.S.'s email saying "cut him off."

[redacted], from organization called Interest of Justice

- Talked about Pfizer, death signals are increasing, concerned about the lack of enough data about the vaccines' safety. The ethical process of the informed consent is not being adhered to.
- Worried about the risky community's engagement, suggested looking at risk and benefit.

[redacted] (CSO, Ocugen)

- Ocugen (w. Wash. U.) has developed an inhalation COVID-19/flu mucosal vaccine that is safe and effective against infection and severe disease.
- Inhalation delivery device consists of a nebulizer and a disposable cup.
- No injections, no needles.
- Lower doses are protective when inhaled.
- Will develop an inhaled bivalent (Wuhan + latest VOC) COVID-19 vaccine by July 2023 and a quadrivalent seasonal flu vaccine for the 2024 flu season.

[redacted], RN

- The COVID-19 vaccine injured me. I loved my 17-year career. Fell ill within 12 hrs after receiving the vaccine. Agonizing arm pain. Didn't get any care. Because of the "safe and effective" narrative I was dismissed. Muscle spasms. Excrutiation humiliation of bowel and bladder incontinence. Dx transverse myelitis. Speaking is hard. Financial ruin. Lost a career that I loved. I filed a VAERS report and it disappeared from the system. Your complete disregard for vaccine-injured is shameful. Shame on you. CDC & FDA doesn't care.

[redacted] (no conflict)

- Blamed vaccine for stroke and cancer. "We all know people who suffered from the vaccine. Do you have hearts of stone?"

[redacted]

- Emphasis on informed consent without proper safety data raising the concern that vulnerable people are the first sample population to receive the vaccine.
- Courts coerce vaccines. Police power for travelling means people have to take the vaccine unwillingly if they want to travel.
- FDA abuses their power and denies people their human rights.

[redacted] (no conflict)

- Moderna shattered my life. Metallic taste. Chest pain. Tachycardia, bradycardia, myalgias, arthralgias, paresthesias, food allergies, and many more. Risks are censored and benefits are exaggerated. I'm an empty shell of my former self.
- There is no informed consent without mentioning the AEs

[redacted]

- 49-yo mom of 2 Wilmington NC. <tears>

[redacted]

- Discussed her personal experiences of tachycardia, dizziness, SOB, tingling, hands clamped, GI symptoms, low BP, dysautonomia, tinnitus

[redacted] (Former employee of pharmaceutical company)

- The process of drug approval includes meticulous and close monitored for adverse events
- These protocols were not followed in the process of COVID-19 vaccine authorization
- Concerned about deficient safety data for COVID-19 vaccines

[redacted]

- Personal experiences after receiving the Pfizer vaccine. Rt. calf tightness and pain, tingling hands and feet, nausea, headaches, racing heart, diarrhea, photosensitivity, numb and cold fingers and toes. Metallic taste. Anaphylactic-type. Multiple ministrokes. Small fiber neuropathy, Raynaud's, brain fog, tinnitus. But ivermectin worked!

[redacted], "The COVID Con," Calgary, CorrectPredictions.ca

- Pandemic is a scam. Claims that the vaccine is ineffective. No excess deaths in Canada due to COVID-19 infection. Make ivermectin available over the counter. Stop all COVID-19 injections immediately. Do no harm.

FDA Considerations for Potential Changes to COVID-19 Vaccine Strain Composition (Jerry Weir, PhD)

PDF: https://www.fda.gov/media/164807/download

Summary:

- SARS-CoV-2 Variants Continue to Evolve and Spread
- Updated COVID-19 Vaccines Elicit Improved Variant-Specific Neutralizing Antibody Titers
    - Results from all of the currently reported studies trend in the same direction, i.e., improved variant-specific neutralization following administration of the bivalent BA.4/5 vaccine compared to a monovalent vaccine booster without an Omicron component
- Updated COVID-19 Vaccines Provide Additional Protection Against Symptomatic Infection
    - Results from all currently available effectiveness studies strongly suggest additional benefit of the recommended bivalent booster vaccines

- The preponderance of the data from vaccine manufacturers and independent researchers indicate an improved antibody response to SARS-CoV-2 Omicron variants following mRNA booster vaccination with the recommended bivalent vaccine containing an Omicron BA.4/BA.5 component
    - Observational effectiveness data strongly suggest that bivalent booster immunization provides additional protection against symptomatic infection, emergency department/urgent care visits, and hospitalization
- Simplification of the COVID-19 vaccination regimen would contribute to easier vaccine deployment, better communication and may improve vaccine coverage
- Available immunogenicity and effectiveness data support the use of updated COVID-19 vaccines (bivalent ancestral and Omicron BA.4/BA.5) for booster vaccination
- An immunization schedule for future periodic COVID-19 vaccination campaigns would be simplified if a single dose of vaccine provided substantial additional protection for most individuals regardless of known vaccination status (e.g., no prior vaccination, primary series vaccination only, or primary series vaccination plus one or more booster vaccinations, etc.)
- Additional data needed to pursue a simplified periodic vaccination strategy may include a better understanding of age-based rates of virus exposure and vaccination and identification of risk groups that would benefit from an alternative immunization strategy
- Since broad spectrum, variant-proof vaccines do not yet exist, current Spike-based vaccines may need periodic updating to maintain effectiveness as SARS-CoV-2 continues to evolve

Discussion:

- Dr. Offit [argues SARS-CoV-2 variants reflect antigenic drift, not antigenic shift]: There are a couple things that were said I'd like clarity on. One that surprised me was when you likened the omicron strain to a shifted virus. I mean it's clearly an immunoevasive strain but it's evasive really for protection against mild disease. If you've been vaccinated, naturally protected or both you generally are protected against severe disease and that was true ever since omicron raised its head in southern Africa and then spread out. If we really ever do see a shifted virus, we're starting all over again and we certainly need to be prepared if that ever happens. But that's not this virus. This is really much more drift than shift.
    - Dr. Jerry Weir: I would only argue with you in the sense that up until omicron all of the drifting had been 1,2,3 amino acids and then all of a sudden it was 35 different amino acids it was it was quite a dramatic change.

- Dr. Offit: You had these conformationally similar epitopes recognized by this and I think that's why this is drift did not shift. I mean the good news is, from Wuhan to XBB.1.5 you still have conserved T cell epitopes in 80-85% which is why we're still protected against severe disease. In any case, the second point which I think is the more important point because it gets the strand composition. You alluded to the fact that that when you look at these bivalent vaccines you do see an increase in neutralizing antibodies which one could argue whether those are clinically significant increases and whether we've had studies that clearly show that this is clinically better than what we've had. But the thing I'm wondering about is this paper that was mentioned by Dr. Das, just published yesterday in the United Kingdom and now this paper by Whitaker that was just published in *Nature Medicine*. Both those studies we're looking at these monovalent vaccines against these omicron variants. We're giving 30 or 60 micrograms for Pfizer or 50 micrograms for Moderna. Do you think that's where we're heading? Is that what you mean when you talk about improving those vaccines where we wouldn't be then using the ancestral strain anymore and is there still a reason to use the ancestral strain?
    - Dr Weir: I can give you an opinion. But that's all. First of all, I think this is exactly the sort of thing that we would discuss at the next VRBPAC where we talk about strain composition. I think it would be a debate worth having, in fact it will probably be needed. We will need to have it on whether we should continue something like a bivalent vaccine containing a strain that hasn't existed in three years versus trying to tailor it more. I don't know the answer, my gut feeling is that a monovalent would have been a little better now than the bivalent, but I think there were reasons why we chose the bivalent which were pretty good at the time but the answer to the real question is where we are headed. I don't know. I think we evaluate the data, what we have at the time, and if we feel like we need to make a new recommendation, we make the best choice that we can. If that's a bivalent maybe that's what we do. If it's a monovalent, that's what we do. But I think we just follow the data we have.

- Dr. Levy: One of his slides (Dr.Weir) talked about maybe a single dose would suffice if it is given in the fall and I think we all need to think suffice for what? What are the goals of this program? Obviously, we're trying to prevent death and we're pretty good at preventing ICU admissions but are we also targeting mild to moderate disease /infection and of course this gets back to immunobridging the antibodies. What are the correlates of protection? Which may vary of course for each of these endpoints that we're trying to achieve and then we're talking about infants where the correlates pg protection may be distinct. So, does the FDA plan moving forward to analyze the correlates of protection for the different desirable endpoints in a population specific way?
    - Dr. Weir: First of all, I think you're right this is an extremely important topic. This is something that the not just the FDA is, but the government is interested in. We would like to have that information. I think everyone would love to have it. I will just counter by saying it is difficult to obtain and it's probably getting more difficult to obtain those correlates of protection data for COVID vaccines at this point. I definitely think everyone will keep trying and hopefully more information, more data will become available overtime.

- Dr. Levy: Certainly, with naive hosts. It may be easier.

- Dr. Chatterjee: Dr. Weir, you talked about the different manufacturers and the timelines and them updating the vaccines. What if a manufacturer decided not to update its vaccine? Would the FDA then withdraw the EUA or licensure of that particular product that they were using or is that not a topic that has been discussed so far?
  - Dr. Weir: It's probably not a topic that I can give you a definitive answer on today. It's not one that we haven't thought about. We would have to have a serious internal discussion about how to approach that.

- Comment: Dr. Chatterjee: I would encourage the FDA if they have not already thought about it to plan for a full licensure type approach rather than EUA's for these vaccines going forward.
  - Dr. Weir: We've definitely thought about it.

Additional Q & A for CDC, FDA, and Sponsor Presenters

Dr. Perlman: So, this part of the session we are going to have folks from the CDC, FDA and sponsors to answer questions that we couldn't get to before. 4

- Dr. Rubin: I really appreciate the fact that they presented data that's somewhat contradictory on the safety related to stroke and I appreciate it because we should be able to handle those sorts of data, they're real. I'd love to get their take on the public message. What should someone who is listening in from the public take away on the safety of vaccines relative to ischemic strokes?
  - Dr. Shimabukuro: I'll just reiterate that CDC continues to recommend that everyone eligible for a COVID-19 mRNA bivalent booster, or a flu vaccine get vaccinated. We detected a statistical signal, and we are in the process of assessing that signal and I think the evidence are not sufficient to conclude that there is a safety problem with respect to stroke. The CDC recommendations are that everyone who's eligible get a bivalent booster and we'll continue to do more work on this. Also, as Dr. Forshee mentioned additional more formal epidemiologic investigations and we will continue to make information available as it becomes known to us.
  - Dr. Forshee: Just add a little bit to what Tom had to say. I think the public should know that we have multiple systems in place to try to look for any potential safety signals with the vaccines and we really treated as a system where we have these early warning systems to try to know if there's some hint that we need to further evaluate. Then we move on to do more rigorous testing afterwards. So, with the multiple systems in place it is not at all surprising that we sometimes get signals in one system but not in another. We then need to do the hard work of evaluating it more rigorously.
  - Dr. Shimabukuro: If I could just follow up to Dr. Forshee's comment and just reinforce what Dr. Forshee mentioned. Our systems are designed to be sensitive to broadly capture potential safety concerns and to be able to rapidly assess those concerns and I think what you heard this morning with the CDC and VSD presentation and the FDA presentation and the thoroughness in which these findings are being assessed demonstrates that the safety system works, and you basically saw that process in action and working. I think the public and the medical community should be confident that the government has the systems in place to rapidly detect potential safety problems and assess them and we place a priority on communicating in a timely and transparent manner.

- Dr. Gans: My question for the safety group: How, overall, are we also handling some other potential ways in which these vaccines are impacting our population? So, obviously we heard some reports and there's some data out there. So how are we tracking, for instance, potential autoimmune and other of those entities that maybe aren't amenable to the rapid cycle?

- Dr Gans: My question for the Novavax group: Is there going to be Peds data that is going to be looked at and then when will that be available to us? I think what I heard mostly was non pediatric data. From all the groups I would love to know about a Moderna bank of preclinical data that maybe doesn't include the ancestral strain so we can start to answer that question about these other strains and if they're going to have more broadly immune studies as we've asked for. We know they're difficult to do but we really do need them which would include B,T and mucosal immunity.
    - Dr. Shimabukuro: You're correct. In our vaccine safety data link rapid cycle analysis our outcomes are prespecified. In our vaccine adverse event reporting system or VAERS we do not pre specify outcomes. That is a spontaneous reporting system and anyone can report: the patient, a parent, a healthcare provider and we accept all those reports without judging the clinical seriousness or how plausible the adverse event may be with respect to causation. So, we do have other systems to monitor outcomes beyond the rapid cycle analysis outcomes that were presented earlier today. At CDC, we also have a group called the Clinical Immunization Safety Assessment Project which does detailed clinical case-consultations at the request of healthcare provider. So, we take vaccine safety very seriously with respect to reports of people experiencing debilitating illnesses. We are aware of these reports of people experiencing long lasting health problems following COVID vaccination. In some cases, the clinical presentation of people suffering these health problems is variable and no specific medical cause for the symptoms have been found. We understand that illness is disruptive and stressful especially under those circumstances and we acknowledge these health problems have substantially impacted the quality of life for people and have also affected those around them. We hope for improvement and recovery, and we will continue to monitor the safety of these vaccines and work with partners to try to better understand these types of adverse events.
    - Dr. Dubovsky (Novavax): So, in the US we are authorized for ages 12 and above. We're currently in the midst of our pediatric development. We were vaccinating down to the youngest two years of age currently in the US with the plan to escalate down to six months of age after we hit the safety cohorts. There's a prepublication available on the archives with our partners and the Institute of India where they're publishing data for their pediatric study. In India, the vaccines are authorized above 7 years of age.
    - Dr. Das(Moderna): We showed our library of variant vaccines which we add to every month based on our ongoing viral surveillance and risk assessment and this allows us to be prepared for future strain selections. We also remain vigilant to be prepared to respond to an off-cycle strain selection for an immune evasive event. Last year we produced the BA.4 BA.5 bivalent vaccine in 90 days and that timeline is aligned with FDA's proposal and we welcome continued conversations with FDA, this committee and the CDC about future strain selection.

- Dr. Pergam: This is sort of a follow up on Dr. Gans's question. It feels like we're getting to a space where there is either people that are have received a series of vaccines, or have been infected by at least one strain of COVID at some point but the pediatric population still remains skeptical especially very young and I'm curious from the FDA's perspective if we are to switch to a new strain or a new vaccine bivalent as the primary vaccine series? Is there going to be an effort to do initial studies looking at these vaccine strains or these vaccines and their efficacy and in terms of primary infection seriousness?

- Dr. Pergam: As a second question: There's been a lot of discussion about the general population but I'm curious how the FDA is going to approach the immunosuppressed population particularly since the series and the number of vaccines given has been varied over the past few years and so I'm curious how they're going to address that particular population as you move forward with these vaccine recommendations.
    - Dr Marks: So, I think we recognize that for the immunocompromised we've had multiple vaccines and for the mRNA regimens right now it's been an extra vaccine as part of the primary series and whether that translates into two vaccines per year or what it would for an initial vaccination, I think that's

something that we'd like to have a discussion on and use the best available data that we have. The immunocompromised is a part of a real spectrum because the modest immunocompromised of a diabetic compared to the tremendous immunocompromise of somebody who's received CD20 depleting therapies, there's a real spectrum here that we're dealing with.

- Dr. Berger: This is actually a holdover from this morning when Dr. Scobie gave her a presentation on epidemiology. I didn't really appreciate the information on hospitalization rates and other impacts, and I was wondering if there were any granularity that that the CDC has been collecting, for instance, on length of stay or at least severity after hospitalization from this? I think one of the purposes here, is that we're hoping that vaccines can do, is keep the healthcare system from being overwhelmed and ensure that that capacity remains where it's needed so it's just that real question about what's what kind of granularity might the billable hospitalization rates at the moment.
    - Dr. Jones: So, for our hospitalization data we do have platforms such as COVID net that do include a length of stay and therapies given, ICU admission, oxygen etc, and we are able to have and will continue to publish on that data. For post hospitalization those would require different platforms. We have a number of platforms looking specifically at post COVID conditions which is perhaps a little bit different than what you're talking about. We haven't talked about a lot today but that would be the main one of the main focuses we're looking at.

- Dr. Gellin: Two questions, one for CDC and one for FDA. I think that since the CDC is about timing, …when in the calendar do we want to have on a population basis optimal protection? This is the seasonality question. And with that that then begs the question of when vaccines should be available, when vaccinations should commence and incorporating waning.
- Dr. Gellin: And then for the FDA, about composition, …the CDC data about the diversity of variance around the country is really quite revealing. We didn't see anything about the rest of the world, and I guess it begs the question of: we've seen in the background documents about coordination with WHO. This has been US northern hemisphere conversations. How is this going to happen with the rest of the world?
    - Dr. Jones: We have generally seen peaks during the winter months but there's certainly been interseasonal peaks as well and I think additional data will be needed, additional seasons will be needed. But, I agree with FDA's approach of fall campaigns to be an anticipation of maximum protection against both severe disease and infection during expected peak months during those winter months.

- Dr. Gellin: Had he wound back the clock and had you had this in place with a June selection in the past two years with the September availability, how would that have played out?
    - Dr. Jones: So, is the question of how many additional?

- Dr. Gellin: So, the question is if this policy was in place three years ago, June selection, September vaccine availability. If you look at what was available, they took a snapshot in June, and that vaccine showed up in September, how would that have worked for the fall and winter that followed?
    - Dr. Jones: It would be like to take a fairly complex model to really climb that out as far as say a largely alpha and some delta into a winter with delta and then omicron and how vaccines focused on those antigens may or may not have had improved protection over the initial vaccine and the same for and the following year. I think it's fairly interesting and complicated question that we had assumed there would be some improvement but it's hard to anticipate exactly how much that would be.
    - Dr. Marks: From the FDA perspective, we're starting to see some seasonality as was just now noted by Dr. Jones and I think we also see the potential advantages to the winter seasonality with a fall campaign. When do we have to worry about the worst overwhelming of the hospitals? It will be when we have influenza, RSV, and potentially COVID at the same time. The advantage of this also is that if we can see influenza vaccine and the COVID-19 vaccines occurring at the same visit it facilitates a vaccination

program that may lead to more people getting vaccinated and being protected and reducing the amount of disease we see. So, I think that overall, this seems like a reasonable way to go. I'll let Jerry Weir comment as well but we're very much of the mind that we would like to work with our global partners including WHO and other regulatory agencies to make sure we're well coordinated here. It's just a matter that not every Regulatory agency and WHO are not perhaps at the same place right now at this very moment but ultimately, we totally understand the need to have global surveillance cover, global coverage of these variants and ultimately good coordination with all of our partners.

- Dr. Weir: One thing I will add is that the WHO does have a group that monitors variants and at least occasionally makes recommendations. They don't have a set schedule for when they do this. About six months ago, they did invite us to join that and we enthusiastically accept it although it's still in the works for it to happen. But, we will clearly participate in that if it if we can work it out. You're right though that unlike flu the global distribution of variance is more variable and that's one reason I mentioned it in my slides. (I like that website called covariance because you can click on every country and you can actually see in real time how this differs) So going forward it is still challenging. Variants don't sweep across the world uniformly like they seem to do with influenza but, yes we'll continue to work with our partners throughout the world as best we can. Our primary responsibility is what's best for the US market and that's where our focus will be.

- Dr. Nelson: I've got two questions one is an extension of the last one regarding seasonality. I too had designed or hoped that we could design the release of the vaccine along with the influenza vaccine, but I noted from the data presented this morning and previously, that there is some seasonality. Yes, there is the predictable winter peak but there also seems to be late summer mini surge. My question to the CDC: Are these two peaks distinct or are they somehow connected? Perhaps targeting even, the earlier peak we may have some benefit in lowering the magnitude or severity of that second winter peak which might make timing of release along with the influenza vaccine a little more challenging.
  - Dr. Jones: I think it's a little bit too early to really predict with certainty if there will continue to be a big peak and a small peak. I mean compared to other pathogens it's been a relatively recent, just a couple to three years of data, that we have to observe. As far as specifically, is transmission from the smaller peak related to the greater peak? Well, recency of infection does affect your ability to be protected from infection and therefore transmission. We do have transmission modeling teams that are working on a various question and that's an interesting one for us to look at.

- Dr. Nelson: My second question is regarding safety. My question is regarding some of those rare adverse events. Can we also reassure the public and this committee that there are mechanisms in place that look at not only signals across the entire population but are identifying more rare adverse events and whether there are subpopulations within enhanced risk that we might be able to identify and perhaps better shape recommendations for vaccinations?
  - Dr. Shimabukuro: In our VAERS system, we do monitor again for all adverse events, and we do attempt to, at least for serious adverse events, to follow up and get additional medical records and information which may shed light on the condition of these of the individuals experiencing the adverse event. If there were particular concerns and subgroups ultimately, we would probably have to do Epi studies to look in those in those specific subgroups but in our monitoring for serious rare adverse events we do attempt to get as much clinical information as possible to assess comorbidities and existing conditions.
  - Dr. Forshee: I would just add that we do have a good bit of experience working with some very rare adverse events in our vaccine safety monitoring. In our flu safety surveillance, for example, we regularly monitor Guillain Barre Syndrome which is a very rare outcome and so we've been able to detect risks below one and 100,000 in terms of attributable our risk. So, because of the size of some of the systems that we use we are able to accurately estimate what the risks are for low risks or for subpopulations and

we have examples with previous vaccines where we've demonstrated that capability. And lot of this has been done in conjunction with the CDC.

- Dr. Shimabukuro: I mentioned previously our clinical immunization safety assessment network so that's a collaboration between CDC and academic medical centers and medical research centers with access to specialists and sub specialists. If we do get, at the individual level, a report of an adverse event and the patient has a comorbidity or an existing condition, we do have the ability to do in-depth clinical reviews of those cases and get feedback from our specialist.
    - Dr. Nelson: I'm very familiar with the great work of CISA and its origins in my former position at the Department of Defense and I think it highlights the communication problem that we've had and that we're great at identifying the absence of big signals and not really fortifying that with, yes we continue to look for those rare signals and yes, the individual events occur but not to the point where at which there needs to be a change in recommendation.

- Dr. Bernstein: There's been a lot of emphasis on neutralizing antibodies but personally I think more T cell data would be incredibly helpful and that being said is it known what the ideal amount of antigenic content and from which strains are needed for durable T cell memory by age? It's been mentioned about even having a bivalent vaccine for the primary series especially in young children and I would still want to maintain the T cell memory with whatever vaccine plan we put in place.

    - Dr. Weir: The short answer is no it's not known and one other thing everyone needs to keep in mind is a T cell response is a broad term. I don't even think we know whether the T-cell responses are CD4 T-cell response or CD8 response. I'm just saying there's a lot that's unknown but how much of that would contribute to protection and how it contributes to protection I think there's just so many unknowns still, unfortunately.
    - Dr.Bernstein: We think it's making a difference.
    - Dr. Weir: Nobody argues that I think we all agree that it's important. The real question is what is its relative role and how do you measure it if you really want to know how it contributes especially to something like severe disease versus symptomatic? It's just really hard to know at this point in time.

- Dr. Cohn: I have one question for the companies specifically I was wondering if you guys could talk a little bit more about immunization and very young children and if you guys are planning or thinking about doing anything like different schedules and different lengths between doses to align more in the long term with our routine immunization schedule. Or, if there would be an advantage of having some better spacing between the doses to allow for other T cell responses.

    - Dr. Das (Moderna): We do have a a study called baby Cove. It started enrolling and we're dose ranging right now. It's infants three to five months of age and we are using that eight-week interval to try to align with a routine pediatric vaccinations schedule and so we're going to select a dose and then we'll get into the placebo-controlled part of the study.
    - Dr. Swanson (Pfizer): We are also evaluating in children six months to less than five years of age. both the current dose regimen for the three-microgram bivalent vaccine but also extended intervals. We started in at the early days of the pandemic with that original schedule so we're further studying the longer intervals to see if there's any impact on the immunity as well.

- Dr. Reingold: A quick question in terms of what the package that companies will be required to submit. In the real-world telling people like me that need to come in on separate dates for the flu shot and their COVID shot is certainly not going to improve coverage and so are you going to require data about administration of the two vaccines on the same day?

- Dr. Weir: That is probably not something that I typically put in a package for an authorization or an approval of a strain change supplement. We certainly don't do it for influenza. On the other hand, those type of studies do get done at some point. I guess I would have to say we will we'll discuss it further about what type of studies like that would be needed from manufacturers if this becomes a major issue.
- Dr. Marks: We will be doing formal epidemiologic studies on coadministration of influenza vaccine with the COVID-19 vaccines and large databases. I think we'll have real-world evidence. We may also have some companies that are studying these together and I think point is very well taken that as we move into the next fall ideally, given that we were a little bit lackluster in our ability to get even the adult population vaccinated with boosters this fall, and (even the older adult population) that being able to have the data so that we can do concomitant flu and COVID vaccination may be very helpful so we'll take that back.

- Dr. Meissner: I'd like to respond to Dr. Beigel's presentation which was I thought very helpful and as well as his presentation at DINH symposium. Do we really want to stop asymptomatic infections by SARS CoV-2? First of all, I don't think that's a reasonable objective at least with the current generation of messenger RNA vaccines. You can certainly make the argument that an asymptomatic infection is desirable because it will stimulate both cellular and humoral immunity and it will kind of act like its own boost. We certainly want to stop the virus from circulating but that's probably not going to be possible because the vaccine as clever as it is, is always going to mutate and evolve and at least indefinitely find ways of avoiding the immunity that that humans build up. Do you really think that should be an objective of the vaccines?
  - Dr. Beigel: It's probably more than a discussion we can accomplished today. Certainly, decreasing the overall community load. If you decrease asymptomatic infection, you decrease transmission you can decrease that community load, I think that with the intent and there are some at least theoretical benefits as you articulated and I think how you balance those just requires a larger discussion.

- Dr. Lee: I wanted to follow up a little bit on this question of giving the flu vaccine and the COVID vaccine at the same time. While I recognize that we're probably increase on adherence or uptake. One of the things that struck me maybe something CDC can address. When I looked at the stroke data, I was sort of left with the question I know most of the people I think the COVID vaccine probably in close proximity temporally to the flu vaccine but is there any reason to believe that spreading those out temporarily might reduce the stroke risk?
  - Dr. Shimabukuro: The findings that were presented this morning on concomitant bivalence and flu vaccine we're actually a post hoc supplemental analysis that was part of the original signal detection there may be other reasons besides vaccination for observing those findings like unmeasured confounding or bias or other potential health systems issues. I don't think that the evidence are sufficient to conclude that there's an association there and given that talking about spacing out the vaccines may be a bit premature at this time and will just reinforce the CDC's recommendations for COVID vaccination and for flu vaccination have not changed.

  - Dr. Forshee: I would just quickly agree with Dr. Shimabukuro. We are going to be doing a more formal epidemiological study in Medicare to explore that question to just get a better understanding of whether there is any relation or any interaction there.

- Dr. Kim: Most of the discussions we've had today I have revolved around the messenger RNA vaccine what's the FDA's position and also its disposition on the Novavax protein subunit vaccine and for Novavax what is your current position on how your vaccine can be used in in the context of today's discussion?

  - Dr. Dubovsky: First, I mean we are approved in the US for primary a series as well as for boosting. Right now, there are no more individuals who need primary series unless you're talking about young children. So, we think we're very important tool for boosting in this upcoming season. And that's how we think

we should be used and the data I showed you today actually supports use of our vaccine in the booster just looks at the breadth of the immune response we induce, and we will be getting future variants from whatever string is selected. We can't chase the strains. So, in our opinion it's better to use a vaccine that can induce these broad responses against the variants that will eventually emerge.
    - Dr. Weir: I thought Dr. Kim just asked what our position was on Novavax? Did I miss part of the question?

- Dr. Kim: What are your costs considerations for the Novavax's protein subunit vaccine in the context of what we're talking about in terms of primary series and booster?
    - Dr. Weir: Well, we have already authorized Novavax for emergency use. So, I guess that's our position. You heard today they are able to, if a recommendation comes from this committee to update and change the vaccine, they said they are able and willing to do that, so I guess that's our position that they would do that if the committee makes a new recommendation. We've authorized them and that's where we are today.

- Dr. Sawyer: I have a question for the manufacturers that relates to the timing of strain selection and the distribution of a new product. If each of the manufacturer could let us know if they're headed towards single dose vial distribution or single dose distribution? This is going to be particularly important as we move from government funded vaccine to privately purchased vaccine. In my community, most pediatricians only offer the vaccine on a few specific days of the week or times of the day so that they don't waste product by opening a 10-dose vial and not having enough patients to use that and that's despite advice that that's OK to do. It certainly will not happen if the pediatricians have to purchase vaccine and then use up a vial on the same day that it's opened. At least one of the manufacturers has gotten 2 dose vials. I'm wondering what the future plans are and whether the 100-day timeline projected for mRNA from strain selection to product delivery would hold up if we needed single dose vials?
    - Dr. Perlman: So, could each of the manufacturers very briefly answer?
    - Dr Das (Moderna): We certainly hear you and we are moving towards single dose vials and prefilled syringes just to facilitate just that, and we do think we can achieve that in the timeline outlined.
    - Dr. Swanson (Pfizer): So, similarly we'll be transitioning from the multi dose vials to the single dose vial going forward and can support that with the future vaccine.
    - Dr. Dubovsky (Novavax): We're heading toward a uni-dose vial and we're aiming to get to a prefill syringe shortly after that.

- Dr. McGinnis: I have this comment that I'm going to restrict to this particular phase of things, so I guess this is directed for Jerry Weir. So, Jerry I think we kind of moved into this discussion that COVID is kind of like flu but actually COVID isn't like flu. In many ways, except its waves, we tend to try to treat it like flu and we think we can have a periodicity of the response but actually bringing into operationalize …how you might do that is actually the challenge. So, I see the suggestion that maybe by June is the good time to do and maybe it's a perfectly fine time but it seems to leave a very short time for manufacturers who manufacture both vaccines in order to get both of them on the dock. So, I'm very sympathetic that I don't have to operationalize this, but COVID is not flu as an infection or disease so I'm wondering how you see being able to build into an operationalized periodicity versus the need to have a decision and move and how much flexibility the manufacturers have?
    - Dr. Weir: Well to start off one of the reasons we asked manufacturers to come to this meeting was to tell us how much time they need. So, actually I heard something today that I hadn't heard before today and that was exactly how much time a protein-based manufacturer would need. We may have to go back and rethink this as far as the timing. As I said earlier, I put this out there as a placeholder, we would say we had an N of one this past year. We did it in June it seemed to work OK, but I think Dr. McGinnis we're all just going to have to maintain flexibility. You're right, there's not a good pattern. We will look

at this and we'll try to be flexible. We'll try to work with manufacturers to keep and get as many manufacturers on the market as we can because you and I have been through flu. Having options is important and you never know which one you're going to need so we'll continue to do this, and we'll be flexible, and we'll work with them as best we can.

- Dr. Chatterjee: My question is for the vaccine manufacturers so during the open public hearing we heard about a combination influenza COVID-19 vaccine product that's been evaluate by company and I was just curious to hear from you all whether you are developing this type of product as well and where you are in the development phase?
    - Dr. Swanson (Pfizer): So, we have initiated studies to evaluate the combination of flu COVID vaccines and are in early studies for that and as with all of our prior clinical studies you know robust safety assessments are part of that trial as well.
    - Dr. Das (Moderna): We have initiated a phase one trial for combination COVID and flu vaccines.
    - Dr. Dubovsky (Novavax): Earlier this year we announced data from our initial studies for a combination product as well and we just started a phase two study for combination influenza quadrivalent plus COVID and we're anticipating those data are going to be available sometime this year.

COMMITTEE DISCUSSION AND VOTE ON POLICY QUESTIONS

VOTING LANGUAGE UNDER DISCUSSION:

POLICY QUESTION:

Simplification of current COVID-19 vaccine use:

• VACCINE COMPOSITION: DOES THE COMMITTEE RECOMMEND HARMONIZING THE VACCINE STRAIN COMPOSITION OF PRIMARY SERIES AND BOOSTER DOSES IN THE U.S.TO A SINGLE COMPOSITION, E.G., THE COMPOSITION FOR ALL VACCINES ADMINISTERED CURRENTLY WOULD BE A BIVALENT VACCINE (ORIGINAL PLUS OMICRON BA.4/BA.5)?

Discussion:

- Dr. Meissner: I think this proposal is reasonable. I think that the vaccine strains should be harmonized among the different manufacturers. The issue of how frequently they should be administered is hard to say with precision at this particular point. We need to see what happens with disease burdens – we may or may not need annual vaccination. It's early in this process to answer that question. It's very hard to disentangle [different types of immune response]. We need to look at rates of disease [in addition to serology]. CDC needs to continue supplying data about deaths and hospitalizations truly caused by disease rather than just associated with it. Need to be careful about placing too much emphasis on serology.
- Dr. Bernstein: We still need to vaccinate unvaccinated so anything that results in better communication would be extremely valuable. How should outcome expectations be prioritized for COVID vaccine program in making these decisions? I don't think we can have it all - less infection, less transmission, less severe disease, and less long COVID and that seems to be a major challenge for public messaging. How do we prioritize?
    - Response: I think we should comment on vaccine composition.
    - Dr. Bernstein: I'm not sure that using a bivalent in the younger pediatric age group makes the most sense.
- Dr. Offit: I certainly support this. I think it's important to get closer to the strains that are circulating. The goal is to keep people out of the hospital and not overwhelm hospitals. For some medically frail, a mild infection could get them in the hospital. Some people in high risk groups (with comorbidity, elderly, immunocompromised) won't make a good immune response. We should always make the point of giving antivirals. The second issue is protecting against severe disease in the general population - we already have that vaccine in the Wuhan 1 strain. There's a role for T cells in that. That does not fit the flu model for me. Vaccinating everyone every year as for

flu, you really do need to be strain specific. If we miss with the [flu] vaccine strain, they have pretty much no protection, but that's not true for this virus. I support this voting question.

- Dr. Sawyer: I support this idea of harmonizing the composition. The voting question doesn't include time frame. I have some anxiety about amount of data in under 2 years old on bivalent doses. Question for FDA: How much data do we need to recommend a primary bivalent series for young children?
    - FDA Response: We will be looking at the totality of the data and some of the data from RNA vaccine is reinforcing. We agree that the numbers right now are small. As additional numbers come in, we will have a larger dataset in this age range. The reassuring thing is the safety profile we have seen with bivalent booster mirrors very well the original vaccine in this age range. Overall, one vaccine composition for all age groups will be helpful not to expose [recipients to] antigen that does not exist anymore. We care about the safety first and foremost.
- Dr. Berger: I agree with Dr. Offit. Our job is to simplify the experience and protect against severe disease. 16x more risk of hospitalization, 13x more risk of death [in unvaccinated] when compared with vaccinated. Need to have strain [in vaccine] that matches [circulating strain]. We are trying to provide the best protection and it makes sense to simplify this process. Some questions remain unanswered such as dosage amounts, especially in pediatric population. There are still questions about whether original strain will be included or we just switch to a different one. But overall moving toward a single composition makes sense to simplify this process.
- Dr. McInnes: Our challenge here is, have the bivalent boosters added any data to the monovalent? We don't have randomized comparisons to demonstrate protection against severe disease. It's a problematic message for the community. Gave example of patients who got sick after vaccine and she told them, imagine how sick you would have gotten if you had not gotten the vaccine. Not a great message to deliver. Should move to a more contemporary strain but could still get reinfected. Not sure message about getting more sick without vaccine resonates with recipients.
- Dr. Gans: Big challenge is vaccine composition and how we pick which particular strain will be in the upcoming vaccine. This question should be vaccine harmonization. There's a lot of agreement in that. I agree with that. What we are doing for the primary will be the same for the booster. We're seeing more and more children with co-infections and they are definitely more severe than if they had either/or. I think the protection is broader than what people are identifying as markers (severe disease and hospitalization), particularly in our youngest children. We have to get closest to what is circulating. I would support this. I think we're confusing people by saying composition and not harmonization.
- Dr. Wharton: I am supportive of this question. I do think there are some data gaps on optimization for children, questions about different dosages for primary series and booster for adults. There are some unanswered questions but this is absolutely the right thing to do. It will make things simpler. This is a good decision to make.
- Dr. Cohn: This is a very good decision to move forward from programmatic and implementation perspective. Most concerning data point was extremely low vaccination coverage in 6 months to 2 years of age. We have to do much better in simplification and optimization. We have to focus on getting those kids vaccinated.
- Dr. Hawkins: I support this approach. Vaccine effectiveness and safety are confirmed not withstanding discussion about pericarditis and myocarditis. Many consumers are accepting of annual influenza vaccination. Variation in vaccines might lead to more vaccine hesitancy and fatigue and [questioning of] FDA and CDC reliability. Reemphasize need for processes and protocol to fill knowledge gaps.
- Dr. Gellin: We can't keep doing what we're doing so we have to move on. Although the vaccines are good, we need better vaccines. I think this is a reasonable approach. This is not influenza and we need to keep paying attention to that so we don't follow that dogma. I don't think we're setting it in stone and we may need to adjust. Overall, this is a good path forward.

LANGUAGE PUT TO VOTE

VRBPAC Vote:

***Simplification* of current COVID-19 vaccine use:**

• *Vaccine composition*: Does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses in the U.S.to a single composition, e.g., the composition for all vaccines administered currently would be a bivalent vaccine (Original plus Omicron BA.4/BA.5)?

Vote Tally
Yes: unanimous 21/21
No: 0
Abstain: 0

POST VOTE DISCUSSION ON RATIONALE FOR VOTES:

Additional Discussion after the vote

- Dr. Bernstein: Anything that results in better public communication to get more vaccinated would be extremely valuable. I still have some questions but I think this is the right direction.
- Dr. Berger: We are looking to try to get a better vaccination rate and make this simplified. Lower hospitalizations and deaths [among vaccinated persons] - those numbers speak for themselves. I definitely support simplifying the process and harmonizing the composition between primary and boosters.
- Dr. Chatterjee: There's so much confusion in the community about these different formulations that I think anything we can do address the confusion and simplify things is going to be a good thing. There remains a need for these vaccines and for us to do our best to get them into arms. I think this is a step in the right direction.
- Dr. Cohn: I am in agreement but I don't want to forget that we saw data that monovalent primary series did well in younger children. There will be a period of time when bivalent primary series won't be available and we need to be clear that people should continue to get vaccinated and not wait for bivalent product.
- Dr. Gans: This isn't only convenience to increase the number of people vaccinated. Also moving toward the strains that are circulating is very important. The science supports this move.
- Dr. Kim: The updated vaccine data are encouraging. The vaccination rates for young age groups is very concerning. We should not repeat the path we've taken thus far. I enthusiastically support this.
- Dr. Offit: I agree with everything committee members said.
- Dr. Pergam *[garbled-difficult to hear]*: Making the process simpler for the community is going to be critical.
- Dr. Perlman: nothing to add
- Dr. Rubin: nothing to add
- Dr. Gellin: This is an opportunity as we make the move to evaluate every part of this and make sure that all the assumptions are the right ones. Other pivot point is how to get into the information age rather than carrying around paper vaccination cards.
- Dr. Hawkins: nothing to add
- Dr. Hildreth: I agree with the approach that's been taken here. There's confusion in the public about these vaccines and all the formulations and different manufacturers, and hopefully this will address some of that. I hope we can do better job vaccinating children. We have focused on mRNA vaccines but Novavax should be part of our conversation.
- Dr. Lee: nothing to add
- Dr. Levy: As we turn the corner from pandemic to endemic phase, today's vote marks a big practical win for the American people. This is going to simply things and benefit public health.
- Dr. McInnes: COVID is not flu. Any data to suggest bivalent is better than monovalent as booster? What's the public messaging when people get vaccinated and still get sick? This whole conversation is very mRNA focused. It may not be the best whether for priming or boosting so there is a need to make place for other platforms.

mRNA may not give us breadth of coverage. We know they induce neutralizing antibodies but they are short lived. Make sure we should not shut down other platforms in trying to achieve the best approach.

- Dr. Meissner: It's hard to predict the evolution of this virus. We can [can't?] say that new sequences will appear on a regular basis. Any assessment of vaccine efficacy is a snapshot in time based on circulating variants and background immunity that comes with vaccines or infections or both. Bivalent vaccine is reasonable and should be standardized. Agree that it's important to have more than 1 vaccine platform.
- Dr. Nelson: Fully support. Simpler is better. We saw great evidence today that closer is better. Hopefully simplification will spur vaccine acceptance in all age groups
- Dr. Reingold: I agree with Dr. Offit.
- Dr. Sawyer: Bivalent is better. Simple is better.
- Dr. Wharton: no additional comments.

TWO DISCUSSION TOPICS: FUTURE PERIODIC VACCINATION CAMPAIGNS:

DISCUSSION QUESTION #1:

Simplification of COVID-19 vaccine use:

• Immunization schedule: Please discuss and provide input on simplifying the immunization schedule to authorize or approve a two-dose series in certain young children, and in older adults and persons with compromised immunity, and only one dose in all other individuals.

- Dr. Rubin: For those never infected or vaccinated, we would not give a priming dose, we will give a single dose? Data suggest that a 2 dose series is better. Seems everyone who is not vaccinated or does not have a good record should get 2 doses. We know nothing about dosing intervals and how it affects the protection that we get. We really want to do those studies. It is important to collect more data. Important to know in advance what kind of data should be collected.
    - Dr. Marks: The concept is if you are vaccinated or were infected, you might have one dose vs multiple doses. We don't want to limit you to thinking about a 2 dose series. Multiple dose series could be 2 doses.
- Dr. Gans: This is in previously immune individuals, so do we need to continue to need boosters? What will be the timing of that? Will be different discussion for different groups. Need age-specific and underlying condition-specific information. We are in a different place now. I'm not sure 2 doses [are sufficient]. We need persistence studies to answer some of the questions. We need broad immunogenicity studies combined with efficacy and persistence data, naïve vs immune.
- Dr. Chatterjee: Echo Hayley's [Dr. Gans] comments. Add that I would want to see a lot more data on young children. The numbers are too few for us to make scientifically sound decisions. We have entered an endemic phase - this allows us to go back and look at the science.
- Dr. Wharton: Given where we are with the vast majority of US population having been vaccinated or many individuals having had COVID or vaccine and COVID, it does feel we need to reset our vaccine recommendation. A single dose regardless of what they got before really does make sense. Uncertainty about the exceptions. Need to look carefully at protection and dosage for young children and other at risk groups. Good decision to make now, maybe not forever. This feels like the right thing to do now.
- Dr. Sawyer: I support this approach. Simpler is better. Pediatricians are used to changing dose based on age and high risk groups. This is definitely the way to go.
- Dr. Offit: Underline what Dr. Gans said. This virus will be with us for years if not decades. There will always be vulnerable groups. We need 2 pieces of information: 1) Need CDC to tell us exactly who is getting hospitalized and dying (ages, immunocompromised). 2) Immunological data about what exactly are predictors for who is at risk. Then we can make decision about who gets vaccinated with what and when.

- Dr. Pergam *[garbled]*: Confusion because 2 different formulations for peds. Need to be considering 2 different platforms.
- Dr. Reingold: Back to point about whether vaccines are able to prevent infection. Even though most people with polio don't get very sick, we think it's important to prevent even rare serious outcomes by protecting everyone. Public health messaging needs to be much better. Prevent serious illness, hospitalization, and death.
- Dr. Gans: Need immunogenicity, efficacy, and safety data (look at signals) to answer question about how often [to vaccinate]. There's rich global data, opportunity to collaborate.
    - Dr. Marks: We have been working with network through international conference of medicine regulators, 60 countries exchanging pharmacovigilance info. When safety signal comes up we can query others, ex. stroke safety signal not seen overseas. Agree this is fantastic opportunity to collaborate.
- Dr. Meissner: Question of interchangeability once they're standardized. Issue for both peds and adults will be mixing vaccines. We have some information about heterogeneous immunization. FDA may want to consider.
- Moderator Dr. Perlman: **Summary**:
    - Everyone thought good idea to simplify schedule.
    - We need more data on younger children and older adults and immunocompromised.
    - Maybe 2 doses won't be adequate - need more data to figure out who should get 2 vs 1 dose.
    - Committee supportive of general principle.
    - Dr. McInnes (?): mRNA platform may not be the best. Should leave space for more discussion [about other vaccine types].
    - Dr. Berger: We also need data on dosage, not just number of doses and who gets them.

DISCUSSION QUESTION #2:

Periodic update to COVID-19 vaccines:

• Vaccine composition: Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccine composition, including to the currently authorized or approved vaccines to be available for use in the U.S. in the fall of 2023.

- Dr. Chatterjee: Critically important that we pay attention to immunology (epidemiology?) - variants and how vaccines are holding up against them. Must be mindful that continue to be effective. Discussion on the timing of any proposed changes is interesting. The late spring versus early summer timeframe is something to be part of our discussion to provide the formulation to the manufacturers. Manufacturers indicated that they can manufacture in time for the fall.
- Dr. Lubin(?): I am also supportive. We don't know what is going to happen. Evidence that there is slight advantage for omicron strains. We're not going to know how often to do it. Reasonable to think about another one for the fall – that would be ok for step 1. Hard to say it will be annual at this point.
- Dr. Gans: As we come out of the pandemic, we have a moment to step back and think of composition more broadly. We have to understand how the drift/shift of variants will impact our immunity in preventing severe outcomes. Suggest go back and look at dosing, particularly at pediatric populations. Maybe the idea is not more dosing but a higher dosage like with flu for elderly. Look at different strategies for different people, not one size fits all.
- Dr. Pergam *[garbled]*: Hesitation with flu once a year approach. Can't chase strains but may be value in meeting and discussing this at different time points. I'm not sure we have the data to make this decision. Do we include the primary strain in future vaccines?
- Dr. McInnes: Left with approach of mRNA that works well for short period of time. We've leapfrogged over data that we normally have. Convinced we need broader protection. In the long run we could be chasing this virus. Plea for ongoing research on broader protection - may be different platform or different approach.
- Dr. Gellin: asked question to clarify discussion topic

  - Response Dr. Marks: May meet again around May. Proposing at least 1 meeting per year on strain selection. We agree with everyone – this isn't flu, but flu has served as the model for strain selection.
  - Name? In order to answer some of the questions, we have to keep surveillance systems going from multiple federal agencies to get the data we need for the future.
- Dr. Nelson: Interested in getting granular data about dose response curve, important for composition, will help in deciding which and how many strains to put in vaccine. Fear of shorter window of opportunity to get this vaccine and unpredictability of strains. Need to communicate value in getting vaccine outside typical flu window. Appeal for leaving the window open for availability of these vaccines for entire year with unpredictable seasonality at this point.
- Dr. Gans: Asked for longer period of time before next meeting to get additional data.
- Dr. Bernstein: Emphasized Dr. Nelson's comments. This pattern is not necessarily the flu and may need to meet more than once a year, may need to get vaccine more frequently or over the summer.
- Moderator Dr. Perlman: Need to continue doing extensive sequencing of virus genome. Precedent with previous human coronavirus 229E – sera from 30 years ago doesn't neutralize virus now because it has changed. May help decide whether to include original strain in vaccine.

Summary:

  - Agreement that updating vaccine composition is good
  - Need info about how it's working, epidemiology, efficacy, more info about T cell and B cells and non-neutralizing antibody responses
  - Need combination of different strategies (for example, mRNA and protein vaccines)
- Dr. Marks: Thanked all. Heard that need to use data-driven approach to get to simplest scheme for vaccination but not oversimplified. Today is 200th anniversary of death of Edward Jenner, who pioneered variolation for prevention of smallpox. Will continue to monitor safety and effectiveness of these vaccines and continue working with scientists

[Historical Addendum: According to the Massachusetts Historical Society, variolation was used in Africa, the Ottoman Empire, India, and China long before its use in the Western Hemisphere. Variolation involved inoculating a small amount of pus from a smallpox lesion into healthy people. The Western world discovered the practice when Onesimus, an African man enslaved by Cotton Mather, told Mather about it. Mather described it to John Adams's great uncle, Zabdiel Boylston, who began variolating people during the Boston smallpox outbreak in 1721. Edward Jenner pioneered a smallpox vaccine 75 years later, in 1796, which differed from variolation, by using material from a cowpox sore.]

From: "Edlin, Brian (CDC/DDID/NCEZID/DHQP)" [redacted]

To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted] "Lale, Allison (CDC/DDID/NCEZID/DHQP)" [redacted]

Cc: "Foliano, Laura (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted] "Works, Kimberly (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted] "Thanjan, Lisa (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted] "Richardson, Kendra (CDC/DDID/NCIRD/OD) (CTR)" [redacted] "Scheffey, Anne (CDC/DDID/NCEZID/DHQP)" [redacted]

Subject: Draft notes from April 19, 2023 ACIP meeting on revisions to COVID-19 vaccine schedules

Date: Fri, 21 Apr 2023 12:38:08 +0000

Importance: Normal

Attachments: draft_notes.COVID-19_vaccine_policy.ACIP.4.19.2023.docx

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Hi Karen – Please find draft notes from the April 19, 2023 ACIP meeting on revisions to COVID-19 vaccine schedules attached. Thanks to Kim, Kendra, Lisa, Laura, and Annie for their work on them. Thank you – Brian

Brian R. Edlin, MD
CDC Clinical Immunization Safety Assessment (CISA) Project
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention Atlanta, Georgia 30329
COVID-19 Vaccines
April 19, 2023

Welcome & Introductions
Dr. Grace Lee (ACIP Chair)
Dr. Melinda Wharton (ACIP Executive Secretary, CDC)

Summary

- Dr. Wharton: More than 670 million doses of COVID-19 vaccines have been administered to 270 million people in the United States. At ACIP's February meeting, there was discussion of a proposal to move towards a single dose of an updated vaccine for most people, with additional doses needed only for young children with no exposure to infection or vaccine and for others such as immunocompromised people. With yesterday's regulatory action by the Food and Drug Administration, a large step was taken in this direction. Today we'll be discussing this with ACIP. But first I'd like to ask our FDA colleagues to provide an update on yesterday's action.

New FDA COVID-19 Vaccine Guidance

- Peter Marks: FDA's action yesterday was an initial effort based on the totality of evidence available to simplify the vaccination regimen for most individuals and authorize the current bivalent vaccines to be used for all doses administered to individuals six months of age and older, including an additional dose or doses for certain populations.
- Most people previously vaccinated with an original or monovalent COVID-19 vaccine, who has not yet received the dose of a bivalent vaccine may receive **a single dose of a bivalent vaccine**, and most unvaccinated individuals may receive **a single dose of a bivalent vaccine** rather than multiple doses of the original monovalent mRNA vaccines.
- Most individuals who have **already received** the single dose of the bivalent vaccine are **not currently eligible** for another dose, with exceptions.
- The FDA intends to make decisions about future vaccination for all of the various populations after receiving recommendations on the fall strain composition at an FDA Advisory Committee meeting to be held in **June**. The strain selection will be discussed for the next coming year season.
- Individuals **≥ 65 years** who have received a single dose of a bivalent vaccine may receive **one additional dose of vaccine at least four months after their bivalent dose**. Most individuals with certain kinds of **immunocompromising** conditions who have received the bivalent COVID-19 vaccine may receive **a single additional dose of bivalent COVID-19 vaccine at least two months after that bivalent dose**.
- **Additional doses may be administered at the discretion of and at intervals determined by their health care provider.**
- The one exception is for **immunocompromised individuals six months through four years of age**. The eligibility for additional doses will depend on the vaccine previously given to the individual.
    - **Children 6 mos – 5 yrs who are unvaccinated** may receive a **two-dose series of the Moderna bivalent vaccine**.
    - **Children 6 mos – 4 yrs** may receive a **three-dose series of the Pfizer BioNTech bivalent vaccine**
    - **Children 5 yrs** may receive either **two doses of a Moderna bivalent vaccine** or a **single dose of the Pfizer BioNTech bivalent vaccine**.
    - **Children 6 mos – 5 yrs who have received 1-3 doses of a monovalent COVID-19 vaccine** may receive **a bivalent vaccine** to complete the initial vaccination series.
- This updated regimen is still complicated but is an interim step until the next cycle of strain selection is determined in late spring early summer. Ultimately, the goal is to have a simple regimen for both patients to easily understand and providers to easily administer. The key message is that, at this time, for older children

and adults up to age 65, a single bivalent vaccine is appropriate for prevention of COVID 19 in our current emergency use authorizations.

Discussion

- Dr. Wharton: I know there's a lot of interest in non mRNA vaccines. Could you briefly address the implications of yesterday's actions for recipients who have previously received non-RNA vaccines?
    - Dr. Marks: For those who have received non mRNA vaccines. Those vaccines we will be discussing with those vaccine manufacturers how to further update those vaccines so that there will be options available as we move forward. Yesterday's actions do not affect those other vaccines at this time.
- Dr. Lee: Just recognize that this is an evolution of recommendations, or authorizations over time and that appreciate we your attempt to try and get us to a more simplified future state. We look forward to discussing this interim step.

Introduction
Dr. Matthew Daley (ACIP, WG Chair)
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/01-COVID-Daley-508.pdf

COVID-19 vaccine program updates
Dr. Georgina Peacock (CDC/NCIRD)
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/02-COVID-Peacock-508.pdf

Summary

- The Public Health Emergency and the COVID-19 Vaccination Program will end on May 11, 2023
  Possible reduced submission of vaccine administration data from some jurisdictions which may limit completeness of administration data on a national level
- HHS recently announced intent to amend the declaration under the PREP Act to extend immunity liability to pharmacists, pharmacy interns, and pharmacy technicians to administer COVID-19 and seasonal influenza vaccines through December 2024.

Discussion:

- Dr. Duchin: Can you say more about the cessation of reporting of vaccine administration data, which are critical to ensuring equity, access, and distribution. What will be provided to state and local health departments who administer these vaccines and carry out many of the relationships with our community providers?
    - Dr. Peacock: There is not a complete cessation of reporting of administration data. There will be some decrease in reporting after this public health emergency has ended. Most of that is related to state laws that prohibit sharing these data with the federal government. We are working with our state partners to see if there are ways to continue to receive both vaccine administration data related to COVID but also to routine vaccinations. We are putting both an extension of the data use agreement into place for COVID and then also routine vaccination data use agreements are also being negotiated right now and being put into place. There is still a provision within that provider agreement that they need to report administration data of COVID vaccine. We won't have the full picture of what is going on nationally. State health departments will still have these data within their Immunization Information Systems. We still will have different ways to look at ensuring equity as we move forward. It does add some challenges. We've supported a lot of partners, who have been working with community-based organizations to look at both the access issue and the confidence issues. That work is continuing to be funded and continues to move forward. As we implement a domestic vaccine program that serves people across the lifespan, the infrastructure that has

been built to serve children over the last 30 years through the Vaccines for Children program provides a basis for how we look at providing vaccines for adults through the VFA program. Built into that is that need to increase the infrastructure which is essentially the jurisdictions of the awardees is that we fund and that is an important part of the VFA proposal.

- Dr. Sanchez: Could you clarify the amendment to the PREP Act in terms of how it applies to vaccines provided to children and also to pregnant women?

    - Dr. Peacock: The PREP Act allowed for a number of vaccinators to vaccinate children and adults all the way down to the age of three. There are state laws that are different in different states that that designate who can be vaccinators and the PREP Act extended the ability to pharmacists, pharmacy techs and pharmacy interns to be able to vaccinate. This was applicable to the COVID-19 vaccine, influenza vaccine, and also for routine childhood vaccinations. In this amendment to the PREP Act provisions for vaccination for flu and for COVID-19 were continued down to the age of three. **The provision was not extended for routine childhood immunizations. So, it reverts back in states to whatever their state law is. I have no details about pregnant women.**

COVID-19 vaccine safety updates
Dr. Tom Shimabukuro (CDC/NCEZID)
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/03-COVID-Shimabukuro-508.pdf

Update: v-safe after vaccination health checker
Dr. Tom Shimabukuro
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/04-COVID-Shimabukuro-508.pdf

Summary:

- Ischemic stroke following bivalent Pfizer-BioNTech mRNA COVID-19 booster vaccination in people ages 65+ years: The rate ratio in VSD Rapid Cycle Analysis has slowly attenuated from 1.92 to 1.26 and has not met signaling criteria during the past 10 weekly analyses.

- VAERS monitoring: COVID-19 mRNA bivalent booster vaccination and ischemic stroke
    - No unusual or unexpected reporting patterns observed
    - No evidence of a safety concern detected for ischemic stroke with either mRNA COVID-19 bivalent boosters in VAERS monitoring

- 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

Discussion:

- Dr. Kane: African Americans have a greater incidence of stroke than Whites and are 50% more likely to have a stroke compared to the White adults. African Americans between 45 and 64 years of age have a threefold higher incidence of stroke. Did you stratify the stroke incidence side effect data by race and ethnic populations? There may be a more critical side effect for this population that has higher prevalences of hypertension, obesity, diabetes, and high cholesterol. Would there be a higher risk for African Americans over the age of 65?
    - Dr. Shimabukuro: We do collect data on race and ethnicity in VAERS. But because VAERS is passive and we're dependent on reporters filling in that information. We don't analyze the data by race ethnicity, but we collect the data. We also do have that information in VSD. We are limited in our in our ability to analyze data at that level in VSD, because of small numbers, but that is important, and we can explore ways of getting better visibility on race and ethnicity. At least for the for the VSD RCA, race and ethnicity are not a primary variable in in the RCA because the finer you slice the data you run into a small numbers problem.

COVID-19 vaccine effectiveness updates
Dr. Ruth Link-Gelles -CDC/NCIRD

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/05-COVID-Link-Gelles-508.pdf

Summary:

1. Updates on vaccine effectiveness (VE) of monovalent vaccines against **symptomatic infection in children aged 6 months-4 years (Pfizer-BioNTech) and 6 months-5 years (Moderna).**

   - Children have much lower vaccination coverage, but a high prevalence of prior infection
   - Complete monovalent primary series helped provide protection against symptomatic SARS-CoV-2 infection for at least the 3 months after vaccination.
   - Waning of monovalent Moderna primary series VE against symptomatic infection occurs by 4-6 months after 2nd dose. Waning of Pfizer-BioNTech could not be assessed.
   - Children should stay up to date with COVID-19 vaccines.
   - CDC will continue to monitor VE in this age group, including against severe disease and for bivalent doses.

2. Update on VE of monovalent and bivalent vaccines against **severe disease in adults with and without immunocompromising conditions.**

   - Bivalent boosters provide additional protection against ED/UC visits and hospitalization, though there is evidence of waning after 60 and especially 120 days.
   - Protection against hospitalization in adults ≥ 65 yrs wanes less than against ED/UC visits.
   - For most people who received monovalent doses and are eligible for a bivalent booster, more than a year has elapsed since last monovalent dose. Because of waning, they may have limited remaining protection.
   - Vaccines provide durable protection against the most critical illness (mechanical ventilation and death).
   - CDC will continue ongoing monitoring of VE, including for all outcomes and all authorized vaccines in the U.S. with a focus on assessing new policy recommendations and VE in populations at higher risk of severe disease.

Discussion:

- Dr. Chen: Evidence that more recent doses are more effective, why are we even including original Wuhan strains in the vaccines?
  - Response: Will defer comments to a later session.

- Dr. Subata: After 3rd dose of Pfizer, VE dropped, any theories?
  - Response: Point estimate dropped but confidence intervals are wide. Follow-up time was also longer after 3rd dose than after 2nd dose. Data are not powered to break down to time from dose.

- Dr. Long: Aim of vaccination program? Symptomatic disease/herd protection, I don't think we have much evidence of that. Effect of boosters are modest/short lived. They protect against death/mechanical ventilation. Curve of epidemic is very important.
  - Response – Yes, goal is prevention of severe disease. Don't have statistical power to look at this.
- Vaccine effectiveness data are limited. What can be done post-marketing to get better VE data?
  - Rita Das/Moderna: Yes, we're working with Kaiser to get better VE data.
  - Pfizer: We're working with Kaiser to get better VE data too.

Updates to COVID-19 Vaccine policy: Data and Workgroup considerations

Dr. Sara Oliver, CDC/NCIRD

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/06-COVID-Oliver-508.pdf

Summary:

- Adults ≥ 65 yrs continue to have highest hospitalization rates; rates in younger groups are now lower than ever.
- Our goal is simple recommendations.
  1. Single formulation for mRNA vaccines. Bivalent vaccines induce immune response when given as primary series or booster, tho data to directly compare outcomes after monovalent and bivalent are limited.
  2. Single doses (possibly annual) for ≥6 yrs for most individuals. Some young children likely still need a prime and boost to optimize immunity. Children 6 mo-5yrs need 2 doses including 1 bivalent.
  3. Flexibility for vulnerable populations because of the complexity.
- See slides for explanation and recommendations by age and immunocompetence status.
- FDA – Bivalent mRNA COVID-19 vaccines are now authorized for all indications.
- FDA – Removed authorizations for monovalent mRNA COVID-19 vaccines. BLAs are still in place for monovalent products but existing doses are expiring.
- No changes to current language in other COVID-19 vaccine authorizations (Novavax, Janssen)
- Work group will continue to review data and evaluate the COVID-19 vaccine program.

Discussion:

- (Bahta): Question 1- about race and ethnicity concerns. Question 2- Why aren't we updating recommendations for Novavax and J&J?
  - Response by Dr. Oliver: Working to provide updates for fall/winter.

Clinical considerations updates

Dr. Evelyn Twentyman, CDC/NCIRD

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/07-COVID-Twentyman-508.pdf

Summary: New recommendations are simple and singular for most, flexible for people at higher risk, and customized recommendations for young children.

1. Most people ≥6 years without immunocompromise who have not yet received a bivalent mRNA dose: 1 bivalent mRNA dose. Vaccination is complete at this time for those who already received a bivalent mRNA dose.
2. Flexible for people at higher risk of severe disease/age ≥ 65 yrs: optional additional bivalent mRNA dose at least 4 months after first bivalent mRNA dose.
3. Flexible for people ≥6 years with immunocompromise: Optional additional bivalent mRNA dose at least 2 months after first bivalent mRNA dose. Then additional bivalent mRNA doses can be given as needed 2 months after last bivalent mRNA dose for certain people (stem cell transplant, CAR-T therapy, B-cell depletion, others).
4. Customized recommendations for young children 6 mo.-5 yrs.: See slides for recommendations customized based on prior COVID-19 vaccination history, brand, and immune status.

For providers: Revision of guidance materials/ICC is underway and a COCA call is scheduled for 5/11/2023.

- Bivalent COVID-19 coverage generally decreases with decreasing age.
- Bivalent COVID-19 coverage is lower among certain races/ethnicities
- Bivalent COVID-10 coverage is lower among those with lower income and those without health insurance.

Discussion:

- Dr. Cotton: Question for FDA regarding immunocompromised children. Will there be guidance on flexibility? The new guidance leaves immunocompromised children who received Pfizer without ability to get another bivalent dose. They remain unprotected.
    - Kaslow: They can get an additional bivalent dose, then possible additional doses per discretion of provider. Same also for adults.
    - Dr. Marks: Will update about Pfizer when more data. We take your point and will consider it.

- Several doctors including Dr. Lee, Dr. Sanchez, Dr. Reese, Dr. Heckel are concerned about the dose of the Moderna bivalent in children (10 micrograms vs monovalent which was 25 micrograms), the need for clarification for immunocompromised children, and that recommendations are quite complex because they differ by age (4 yrs/5 yrs/6 yrs/4 turning 5 yrs/5 turning 6 yrs), brand, and immune status. They are advocating for more protection for the immunocompromised: should they get 2nd optional booster now or wait until fall?
    - Response by Dr. Twentyman: CDC/we are creating a table for every age.
    - Response by Dr. Kaslow/Marks: For Moderna, immunocompromised children 6 mo-4yr can get 3rd dose of either 10 or 25 micrograms.
    - Response by Dr. Twentyman: I don't think getting a dose now would preclude them from getting one in fall.

- Dr. Kane: Bridge program for uninsured adults – any recommendation for outreach? Coverage will do little without outreach to let them know about it. Vaccine uptake is quite low in this population.
    - Response by Dr. Peacock: Throughout pandemic have provided funds for outreach (PAVE program). Covid supplemental funding due to go thru 2024.

Public Comment

- PC#1: Childcare center owner. Children need early approval to next round of vaccines. Please simplify the process for children getting vaccinated. Would be beneficial for pregnant, high BMI individuals, and others to get another bivalent. It is too early to move to just an annual vaccination.
- PC#2: Should grant pregnant individuals access to getting an additional booster dose. WHO says that pregnant individuals should get one if it has been at least 6 months since the last dose. Woman in third trimester that have gotten bivalent booster a year or more ago can't protect their unborn child as effectively as possible.
- PC#3: Project Scientist. Moderna reaction- fever, malaise, heart palpitations. Novavax for booster- no side effects noted. Novavax offers lasting protection and should be considered for more people. Guidelines make it impossible for Novavax as a second booster. Under 12 should also have access to Novavax.
- PC#4: Attorney. Travelers need vaccination before entering the US. Should not differentiate by vaccination status. Vaccines do not prevent disease. Policy does not apply to Americans- unfair. Can have an active infection and still fly, as long as still vaccinated. US is losing money on tourism.

Discussion:

- Dr. Loehr: Wanted to note the public comment on pregnant women getting the vaccine under shared decision making. Has the CDC or FDA considered this?
    - Dr. Sara Oliver: There is an upcoming workgroup call to discuss this issue and review the data. At this time, no additional doses authorized during pregnancy.

- Ms. Veronica McNally: 1. What is the timing of communication material for general public. 2. Is the CICP still be the place for vaccine injury claims?
    - Dr. Sarah Oliver: Will work on updating as soon as possible. ICC and other clinical education material needs updates. This may not all be ready at the same time as when the CDC director signs off.

  - Dr. Reed Grimes: CICP covers vaccines deployed in response to public health emergency and pandemics. COVID-19 vaccines are still covered.

- Dr. Helen Keipp Talbot: What about healthcare workers who work with high-risk patients? We know that all transmission is not stopped, but it helps, especially if more recently vaccinated. Consider adding healthcare workers who work with vulnerable populations to be allowed to get another updated bivalent booster.
  - Dr. Grace Lee: FYI: CMS still requires for primary series and booster dose for HCW.
  - Dr. Sara Oliver: We continue to encourage HCP to get a bivalent booster. Will review additional data about this with ACIP.
  - Dr. Mary Beth Hance: CMS is looking into these changes in recommendation. As of right now, no change.

- Dr. Pablo Sanchez: "Up to date" = having received a bivalent booster. Caution with this because may be other technical issues with this, like with travel and healthcare settings. The term "up to date" carries a lot of weight.
  - Dr. Sara Oliver: No change in up to date. The second booster is not required for up to date. CDC recommends getting the most recent booster available to you.

- Dr. Sybil Cineas: Recommendations are easier for 6+, but still confusing for under 6. What material will CDC provide to make this easier? Any considerations for an app, like the pneumococcal vaccine app?
  - Dr. Evelyn Twentyman: Creating a breath of information- flowcharts, tables. Also have tools on the website- CDC booster tool- which help determine next dose.

- Dr. Marci Drees: Re: Healthcare workers- Difficult time getting new healthcare workers with previous recommendations. This change simplifies things and will make hiring easier. Flexibility is nice for second booster; uptake may be low.

- Dr. Mathew Daley: What can we do to fill the gaps where we don't have sufficient data? E.g.:
  1. Immunocompromised children < 5 yrs who received Pfizer primary series
  2. People with chronic comorbidities without immune compromise
  3. 5-year-olds – can we do without a whole separate set of recommendations for 5-year-olds?
  4. Adults ≥ 65 yrs getting high-dose influenza coadministered with COVID-19 vaccine.

  Gaps cause confusion and consternation. They have a certain circumstance and can't find a solution that fits. FDA can only do something if there are data to support it. For manufacturers, can you do studies to provide the data needed to close these gaps? Can sponsors fill the gaps?
  - Pfizer Rep: We would like to work with the FDA to correct these gaps.
  - Moderna Rep: We are committed with working with the FDA. We do have the data for bivalent vaccine for children and we are open to simplification.
  - Novavax Rep: We are submitting data to the FDA around adolescent booster and have more data involving the immunosuppressed.

- Dr. Sarah Long: Immunologically, there is no difference between 4, 5, and 6 year-olds. There is no reason to have so much unnecessary drama around these ages. FDA can avoid this. This is really defeating for pediatricians who must stock these doses.

- Dr. John Beigel: The AAP is concerned about the commercialization of these vaccines. The fear is when these vaccines become commercialized uptake will be much worse. It has been rumored the cost will be $100-$130 each and a minimal order of 100 doses needed. Very few pediatric practices are going to be able invest in purchasing these vaccines; especially since reimbursement is unknown. Therefore, fewer practices would be involved and fewer people will get vaccinated. I would suggest when commercialization does occur that

providers who choose to participate receive incentives to make it feasible for them, that reimbursement be ensured, and that unused vaccines can be refund for credit.

- Dr. Sanchez: If we really want to simplify for children; I don't see the need to break down the 4 and 5 age groups. Could it be allowed to change current brand guidelines; for example, merge the two age groups?
    - Dr. Oliver: We know that with respect to simplifying pediatric regimens, we're not done. CDC and FDA both acknowledge the issues around the 4-5 age groups and dose variation number between brands. From my understanding, we cannot change the age cut offs at this time. We hope in the next several months, as fall approaches, to change the cut offs with new data.

- Dr. Sanchez: I would encourage the agencies to recommend that pregnant women get another booster without waiting for the fall. I would urge a first and second bivalent booster; especially if it has been more than six months.

Notes taken and assembled by CISA medical and nursing officers
Laura Foliano
Kimberly Works
Lisa Thanjan
Kendra Richardson
Brian Edlin
Anne Scheffey

From: Anne Boyd [redacted]
To: "Museru, Oidda I. (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Emmanuel Walter, M.D." [redacted] Lynn Harrington [redacted] Michelle McCart [redacted]
Subject: RE: CISA Flu-COVID study update - human subjects
Date: Mon, 30 Jan 2023 19:37:55 +0000
Importance: Normal
Attachments: Outcome_Letter.pdf
Inline-Images: image003.jpg

Hi Oidda,

Please find the outcome letter from Duke's IRB acknowledging the UPIRTSO for the COVID Flu study.

Thank you,
Anne

Anne M Boyd
Scientific Program Leader
Duke Human Vaccine Institute
[redacted]
Duke Human Vaccine Institute
Duke University School of Medicine

Upcoming OOO: 2/13/2023 – 2/17/2023

From: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, January 18, 2023 4:33 PM
To: Emmanuel Walter, M.D. <chip.walter [redacted]; Schmader, Kenneth DURVAMC [redacted] Kawsar Talaat [redacted] Elizabeth Schlaudecker [redacted] Cortese, Margaret (CDC/DDID/NCEZID/DHQP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Anne Boyd [redacted] Museru, Oidda I. (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Youngblood, Laura (CDC/DDID/NCEZID/OD) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Duffy, Jonathan M. (CDC/DDID/NCEZID/DHQP) [redacted] Sharma, Shashi (CDC/DDID/NCEZID/DHQP) [redacted] Aynalem, Getahun (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Subject: CISA Flu-COVID study update - human subjects
Importance: High

Dear Dr. Walter, Dr. Schmader, Dr. Talaat, and Dr. Schlaudecker:

As you are aware, CDC and FDA are evaluating a vaccine safety signal for ischemic stroke in people ages 65 years and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. More information is available here: CDC & FDA Identify

Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older | CDC and summarized below. Today (January 18, 2023) CDC study staff met with CISA Principal investigators to discuss human subjects considerations regarding the CISA Simultaneous mRNA COVID-19 and IIV4 Vaccination Study - Full Text View - ClinicalTrials.gov. We agreed that each of the 3 CISA sites will notify their IRB about this signal and follow local policies as they pertain to this study. In addition, out of an abundance of caution, the PIs agreed to pause enrollment of persons age 65 years and older in this CISA study, until after the FDA VRBPAC meeting on 1/26/23; the situation will be reassessed after that meeting.

Additional information about the signal is below.

- "Following the availability and use of the updated (bivalent) COVID-19 vaccines, CDC's Vaccine Safety Datalink (VSD), a near real-time surveillance system, met the statistical criteria to prompt additional investigation into whether there was a safety concern for ischemic stroke in people ages 65 and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Rapid-response investigation of the signal in the VSD raised a question of whether people 65 and older who have received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22-42 following vaccination"
- "Although the totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk, we believe it is important to share this information with the public"
- "No change in vaccination practice is recommended. CDC continues to recommend that everyone ages 6 months of age and older stay up-to-date with COVID-19 vaccination; this includes individuals who are currently eligible to receive an updated (bivalent) vaccine."
- "CDC and FDA will continue to evaluate additional data from these and other vaccine safety systems. These data and additional analyses will be discussed at the upcoming January 26 meeting of the FDA's Vaccines and Related Biological Products Advisory Committee." Vaccines and Related Biological Products Advisory Committee January 26, 2023 Meeting Announcement - 01/26/2023 | FDA
- The EUA factsheets and package inserts for COVID-19 vaccines have not changes for mRNA COVID-19 vaccines. COVID-19 Vaccines | FDA

Sincerely,

Karen R. Broder, MD
Captain, United States Public Health Service
Chief Medical Officer
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
[redacted]

DukeHealth
Institutional Review Board

NOTICE OF DECLARATION OF UNANTICIPATED PROBLEM INVOLVING RISK TO SUBJECTS OR OTHERS

The purpose of this e-mail is to notify you that IRB review of the following safety event is complete and the IRB has declared that the problem/event does represent an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO). The assessment and corrective actions are adequate. No further action is required.

Event ID: Pro00109102-SE-8.0

Event Name: Vaccine safety signal for ischemic stroke in people ages 65 years and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent

Date Reviewed: January 23, 2023

Protocol ID: Pro00109102

Protocol Name: Safety of Simultaneous versus Sequential Administration of mRNA COVID-19 Vaccines and Quadrivalent Inactivated Influenza (IIV4) in Adults and Adolescents: A Randomized Observer Blinded Study

Principal Investigator: Emmanuel Walter

Safety Signal Notification from Sponsor - CDC_18JAN2023

DUHS Institutional Review
[redacted]

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted] "Cortese, Margaret (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Museru, Oidda I. (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: CISA Flu-COVID study update - human subjects
Date: Tue, 31 Jan 2023 16:13:26 +0000
Importance: Normal
Inline-Images: image001.jpg

Is "Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO)" a formal term used in their research? It's really more of an unanticipated preliminary finding involving a potential risk, but it looks like UPIRTSO might be an official or formal study term, which is fine.

From: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Monday, January 30, 2023 9:11 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Cortese, Margaret (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Museru, Oidda I. (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: CISA Flu-COVID study update - human subjects

Sharing as FYI.
Study team will meet tomorrow.
Thanks,

Karen

From: Anne Boyd [redacted]
Sent: Monday, January 30, 2023 2:38 PM
To: Museru, Oidda I. (CDC/DDID/NCEZID/DHQP) [redacted] Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Emmanuel Walter, M.D. [redacted] Lynn Harrington [redacted] Michelle McCart [redacted]
Subject: RE: CISA Flu-COVID study update - human subjects

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Anne M Boyd
Scientific Program Leader
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[redacted]
Duke Human Vaccine Institute
Duke University School of Medicine

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Sent: Wednesday, January 18, 2023 4:33 PM
To: Emmanuel Walter, M.D. [redacted]; Schmader, Kenneth DURVAMC [redacted]; Kawsar Talaat [redacted]; Elizabeth Schlaudecker [redacted]; Cortese, Margaret (CDC/DDID/NCEZID/DHQP) [redacted]; McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Anne Boyd [redacted] Museru, Oidda I. (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Youngblood, Laura (CDC/DDID/NCEZID/OD) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Duffy, Jonathan M. (CDC/DDID/NCEZID/DHQP) [redacted] Sharma, Shashi (CDC/DDID/NCEZID/DHQP) [redacted]; Aynalem, Getahun (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Subject: CISA Flu-COVID study update - human subjects
Importance: High

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Karen R. Broder, MD
Captain, United States Public Health Service
Chief Medical Officer
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
[redacted]

From: "Museru, Oidda I. (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: ISO ALL HANDS UPDATES
Date: Thu, 26 Jan 2023 00:18:02 +0000
Importance: Normal
Attachments: CISA_Project_Team_Update__ISO_All_Hands_Meeting_2023.1.26.docx

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Hi Mike,

Attached, please find the SICA project updates for the ISO All Hands meeting tomorrow.
Thanks,
Oidda

ISO - All Hands Meeting 01/23/2023

CISA project Team updates

- **Staffing update:**
  - Welcome CISA new staff
  - Shannon Xydis – CISA PHA
  - CISA Clinicians (Contractors)

- **CISA Project COVIDvax update:**

  - **CISA COVID-19 On-Call Clinical Consultation Service for Vaccine Safety**
    - Operating COVID-19 vaccine safety inquiries (24/7 on-call).
    - CISA COVID-19 Inquiry Tracker -weekly report ending on 1/21/2023

CISA COVID Inquiry Tracker Weekly Repor

    - CISA mpox Inquiry Tracker -weekly report ending on 1/21/2023

CISA mpox Inquiry Tracker Weekly Repor

- **CISA enhanced public health surveillance activities:**
  - CISA is providing technical support on the following COVID-19 enhanced surveillance activities:
    - Multisystem Inflammatory Syndrome in Children (MIS-C)- reviewing pediatric cases 5 -11 years old.
    - Myocarditis Outcomes after mRNA COVID-19 Vaccination Investigation (MOVING) project
    - Thrombosis with Thrombocytopenia Syndrome (TTS)
    - Case investigation of anaphylaxis after mRNA COVID-19 vaccine
    - Allergy – Guidance

CISA subject matter expert (SME)

- CISA is providing technical support on the following activities:
  - Interim Clinical Considerations (iCC) issues related to COVID-19 Vaccines (working on allergy and MIS-C guidance section)

  - Neuro WG

- **CISA Clinical Consult WG call:**
  - Feb 7, 2023, 5-6 pm CISA WG1: Gross hematuria after dose 2 of Pfizer COVID-19 vaccination.
  - Feb 8, 2023, 12-1pmCISA WG1: pediatric patient with neurologic symptoms after routine 4-month immunizations

- **CISA Research Portfolio call:** No update**s**

- **CISA clinical research update (Active studies)**:
  - Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children (Pediatric COVID-19 Vaccination in Young Children RCT)
    - New study, will be conducted at Duke (Lead) and 3 contributing sites - Cincinnati, Columbia, and Kaiser
    - 1/27/2023, 3-5pm Study WG call for protocol development. Duke is leading, CCHMC, Columbia, Kaiser, and CDC will participate.

  - CISA COVID-19 Maternal Vaccination –Duke, Boston, and Cincinnati (ClinicalTrials.gov NCT04826640)
    - Protocol was posted on ClinicalTrials.gov
    - Enrollment: 142 subjects (Target **350** subjects)

  - COVID-19 and IIV4 Vaccination- Duke, Cincinnati, and Johns Hopkins (ClinicalTrials.gov NCT05028361)
    - Protocol was posted on ClinicalTrials.gov
    - Enrollment: 304 subjects (Target **450** subjects)
    - Due to a vaccine safety signal for ischemic stroke in people ages 65 years and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent- the PIs agreed to pause enrollment of persons aged ≥65 – until after the FDA VRBPAC meeting on 1/26/23.

  - COVID-19 Pediatric Vaccination -Duke, Cincinnati, Columbia, and Kaiser (ClinicalTrials.gov NCT05157191)
    - Protocol was posted on ClinicalTrials.gov
    - Enrollment: 231 subjects (Target **320** subjects)

  - Simultaneous RZV and aIIV4 Vaccination – Duke and JHU (Clinicaltrials.gov ID: NCT05007041)
    - Enrollment: 112 subjects (Target **400** subjects)

  - Syncope study – Duke (Clinicaltrials.gov ID: NCT04772755)

- Enrollment completed on 6/15/22. Enrolled 340 (100%) subjects

- Flublok maternal study – Duke, Boston, and CCHMC (ClinicalTrials.gov ID: NCT03969641)
  - The results from have been posted to clinicaltrials.gov at https://clinicaltrials.gov/ct2/show/NCT03969641?term=NCT03969641&draw=2&rank=1.
- Apnea study - Duke/UNC and CCHMC (ClinicalTrials.gov ID: NCT03530124)
  - Enrollment ended in October 2021
  - Total enrollment: **223** subjects (target **300** subjects)
  - Apnea abstract was submitted to PAS

- **COVID-19 surveillance projects publications updates:**

- **CISA Publication Manuscripts updates**:
  - Cortese M M, et al Surveillance for multisystem inflammatory syndrome in U.S. children aged 5-11 years who received Pfizer-BioNTech COVID-19 vaccine, November 2021−March 2022 manuscript was submitted to the Journal.

  - Schmader KE, Liu,CK, Flannery B, Rountree W, Auerbach H, Barnett ED, Schlaudecker EP, Todd CA, Poniewierski M, Staat MA, Harrington T, Li R, Broder KR, Walter EB. Immunogenicity of Adjuvanted versus High-Dose Inactivated Influenza Vaccines in Older Adults: A Randomized Clinical Trial. The Manuscript is under review-Journal of *Immunity and Ageing.*

- **CISA Contracts updates**: (if time permits)
  - CISA is working with OAS on the New CISA IDIQ

From: "Sharma, Shashi (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Museru, Oidda I. (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: Additional Item to Discuss during Teams Meeting regarding FOIA 23-00947 - Lukos Clinical Contract 15135
Date: Mon, 17 Apr 2023 18:03:20 +0000
Importance: Normal

Thanks.

From: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Monday, April 17, 2023 12:54 PM
To: Sharma, Shashi (CDC/DDID/NCEZID/DHQP) [redacted]; Museru, Oidda I. (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: Additional Item to Discuss during Teams Meeting regarding FOIA 23-00947 - Lukos Clinical Contract 15135
Importance: High

From: Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Monday, April 17, 2023 11:14 AM
To: Olson, Christine (CDC/DDID/NCEZID/DHQP) [redacted] Kim, Sehwa (Susan) (CDC/DDID/NCEZID/DHQP) [redacted] Moro, Pedro (CDC/DDID/NCEZID/DHQP) [redacted] Gallego, Ruth (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Shay, David (CDC/DDID/NCEZID/DHQP) [redacted]; McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]; Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Starrett, Tracie (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Kroop, Seth (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: Additional Item to Discuss during Teams Meeting regarding FOIA 23-00947 - Lukos Clinical Contract 15135
Importance: High

Good morning,

Please see the attached FOIA Request. I would like to close this out by recommending that the FOIA Office work with the requester to narrow the scope. Along with our request to narrow the scope, I want to provide them with a volume cost estimate since the requester is only willing to pay $25.00. At this time, we only need one person from each team that will have a complete set up documents to respond to the volume cost estimate. Please identify that one person in your group, review the attached request, and provide me with the following:

- The amount of time it will take to conduct the search and review the documents
- The number of pages (best guess)
- Sample of your responsive documents… 3 - 5 pages from each SME

I look forward to receiving your estimate by Wednesday, 19th close of business. If you have any questions, please call me.

Thank you so much,
-p

From: Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, April 12, 2023 3:30 PM
To: Mitchell, Elnetta (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Alldredge, Berta (CDC/DDID/NCEZID/DHQP) [redacted]; Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: Additional Item to Discuss during Teams Meeting regarding FOIA 23-00947 - Lukos Clinical Contract 15135

Hi Elnetta and PerStephanie,

Thank you for today's discussion regarding FOIA for the Lukos Clinical contract. This contract provides vaccine safety clinical services for the Pregnancy Registry, VAERS and CISA teams.

If you need more detailed info other than hiring updates and monthly reports, please get with the following SMEs/Technical Monitors:

1. Pregnancy Registry: Christine Olson [redacted] Andrea Sharma [redacted]
2. CISA: Sehwa Kim [redacted] Mike McNeil [redacted] Karen Broder [redacted]
3. VAERS: Pedro Moro [redacted], Ruth Gallego [redacted]

Thanks,

Bonita Johnson
Principal Management Official
Immunization Safety Office/DHQP/NCEZID
[redacted]

From: Mitchell, Elnetta (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Sent: Wednesday, April 12, 2023 3:00 PM
To: Alldredge, Berta (CDC/DDID/NCEZID/DHQP) [redacted] Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: Additional Item to Discuss during Teams Meeting regarding FOIA 23-00947 - Lukos Clinical Contract 15135

Attached is an additional item to discussion during Teams Meeting regarding FOIA 23-00947

Elnetta Mitchell, MBA
Goldbelt C6, LLC
DHQP/NCEZID/CDC
Centers for Disease Control and Prevention
[redacted]

From: "Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" [redacted] "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" [redacted], "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted], "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted] "Kim, Sehwa (Susan) (CDC/DDID/NCEZID/DHQP)" [redacted] "Olson, Christine (CDC/DDID/NCEZID/DHQP)" [redacted], "Sharma, Andrea J. (CDC/DDID/NCEZID/DHQP)" [redacted], "Shay, David (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted] "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted] "Hood, Terrell (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: Lukos Clinical Contract - Monthly Status Report (May 2023)
Date: Tue, 6 Jun 2023 17:41:11 +0000
Importance: Normal
Attachments: May_23_Lukos_Monthly_Report.docx
Inline-Images: image001.png

Hi VAERS, CISA, Pregnancy Registry: Lukos monthly report is attached for May 2023.

Thanks,

Bonita
[redacted]

From: Brian McKibben <brian.mckibben[redacted]
Sent: Tuesday, June 6, 2023 12:45 PM
To: Alldredge, Berta (CDC/DDID/NCEZID/DHQP) [redacted] Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: laura.hedrick[redacted]
Subject: MSR

Berta/Bonita,

See attached monthly report for May. Of note, the VAERS clinician task is missing the last few days (after May 27th) of data since our project coordinator (Carol Ennulat) is on vacation and Ruth Gallego was unavailable before she left. Other than that, everything is correct.

Please let me know if you have any questions.

Thanks
Brian

Brian McKibben
Director of Operations, Lukos
[redacted]

Monthly Status Report **Lukos, LLC**

Supporting Vaccine Adverse Event Reporting, Clinical Immunization Safety Assessments, and the V-Safe Pregnancy Registry (VAERS, CISA)

Date:	June 6, 2023
Contract ID:	15135
Reporting Period:	May 1 – May 31, 2023

I. Task 2 VAERS Clinicians, Task 4 VAERS project coordinator

a. Accomplishments: Through May 27, 2023

Task	Outcome/Accomplishment
Total Assigned cases (all abstractors)	• 31,071 Cumulative
Total Incomplete/No Abstraction Status (awaiting medical records)	• Unable to obtain number as Ruth Gallego could not get download to run
May Assigned abstraction cases	• 4,802
May Completed abstraction/adjudication cases	• 2,763
Onboarding/Training new hires	• 3 new abstractors receiving live cases (had been in practice) • 1 abstractor still in training • 1 new hire projected for 6/22/2023

b. Status of on-going projects

Project	Monthly Status
AESI < 18	• Ongoing project • 1 abstractor assigned • 7 new cases assigned; 19 completed
Myocarditis all ages	• Ongoing project • 4 abstractors assigned • 28 new cases assigned; 44 completed
Thrombotic Thrombocytopenia Syndrome (TTS)	• Ongoing project • 5 abstractors assigned • 54 new cases assigned; 87 cases completed
Guillain Barre' Syndrome (GBS)	• Ongoing project • 1 abstractor assigned • 14 new cases assigned; 14 completed
Guillain Barre' Syndrome adjudication	• Ongoing project • 1 abstractor assigned • 13 new cases assigned; 13 adjudications completed

Shoulder Injury after Vaccine Administration (SIRVA) Need Liza	• Completed project • 3 abstractors assigned who transitioned back to original AESI • 615 total cases assigned; 615 completed
Death Project	• Ongoing project • 12 abstractors assigned and trained • 3259 new cases assigned; 1142 completed
Coagulopathy Project	• Ongoing project • 14 abstractors assigned • 1416 new cases assigned; 198 completed
Pregnancy	• Ongoing project • 2 abstractors assigned • 37 total new cases for mother and infant AESI's; 52 cases completed
Bivalent COVID/ Influenza Co-Administration project	• Ongoing project/no new cases added • 3 abstractors assigned • 475 total assigned cases; all completed; some still pending medical records
Stroke Project	• Completed project • 6 abstractors who transitioned back to original AESI • No new cases assigned; 1 completed
GBS following PCV20 vaccine	• Ongoing project • 2 abstractors assigned • 11 total assigned cases; 8 cases completed
Medical Records team	• Ongoing project • 3 abstractors assigned • Enhanced performing enhanced surveillance/obtaining records for seizure <6, myo <18, coagulopathy, monkeypox, and death medical records
Quality Control	• De-duplication of cases continues • Four abstractors completed quiz re-take; 100% achieved passing score • Dual abstraction analysis underway; expect completion in June 2023

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
None identified	•

II. Task 3 CISA Physicians: March 2023

a. Accomplishments

Task	Outcome/Accomplishment

Case/Work Assignments
(Cases include - Triage only, Clinician Assist, Enhanced inquiry, mini consult, or Full consult)
 	
• Clinical on calls assignments: M – F (9:00 am – 5:00 pm)
• CISA's research coordination
  ○ Submit CIS's scientific products for clearance and get cleared
  ○ Submit CIS's manuscripts and abstracts to **CDC Forecasting Portal** and Forecast Reporting
  ○ Review CISA's research protocols and SAPs
  ○ Follow-up on the regulatory requirement and sever adverse events (SAE) reporting of CIAS' research projects
  ○ Attend and follow-up on action items from standing and ad hoc research calls with Duke and Vanderbilt Universities
• Support the Shoulder Injury Related to Vaccine Administration (SIRVA) working group by reviewing reported cases to VAERS
Update ISO-VaxSafety manuscripts list
 	
• Lit review for pediatric ADEM after Pediarix, MMRV
• Lit review for Vomiting and nausea after Bexero vaccination
Review of SOAP note and written responses relating to V/N after Bexero vaccination
 	
• Night coverage as scheduled
	• Available for consultations and other task assigned
	
	• CISA's scientific products (manuscripts, abstracts, concept proposals, presentation etc.) are cleared
	
	• Severity and their relationship to CISA research study product of reported SAEs is assessed.
	
	• Identify action items for follow up from standing and ad hoc research calls with Duke and Vanderbilt Universities
	
	• Reviewed SIRVA cases reported to VAERS
	
	• Support the in the literature review of Flu/COVID-19 vaccination co-administration immunogenicity and safety studies
	
	• Completed trainings and projects during night coverage when not actively receiving EOC calls.
	• Provided written response and communication with provider

List cases involved in the reporting month: *(List # of total cases- specify Completed vs. In Progress) (Specify type of case: Full consult/Mini consult/Enhanced inquiry/Clinician assist inquiry/Triage only clinician assist inquiry)- Description below)*	• ADEM following catch-up vaccination with Pediarix an MMRV • Vomiting after receiving Bexero vaccination • 1 case possibly going to consult or "enhanced inquiry live" which involves significant time in scheduling, meetings, and independent work on VAERS search and literature presentation • 1 completed (Enhanced inquiry) end of April, but had follow up with clinician about a couple of questions in May • Completed follow up response as an updated final response with additional resources on 5/4 • Inadvertent live virus MMR vaccine given to 57 year old man on lefluomide (immunosuppressive medication) for rheumatoid arthritis -read about lefluomide and rheumatoid arthritis

	-call provider to obtain history, vaccination records, and follow up issues -draft SOAP for CISA presentation -assist in coordinating meeting of provider and CISA experts -provide comments for the response -send out response -complete redcap • Steven-Johnsons syndrome (SJS) after exposure to flu vaccine, tyelnol and a possible infection in a 7 year old girl. Vaccination guidance now she is 20. -call provider's office to try to reach him -attend meeting with leadership to decide on final action -work on draft email to provider • Transverse myelitis and HIB, Prevnar, and Dtap. Obtained history, review of multiple medical records, wrote up SOAP for internal review, literature review, review of multiple FDA package inserts, 2012 IOM reports, and VSD, VAERS, CISA publications, ACIP recommendations • Severe nausea and vomiting after MenB vaccine. Wrote SOAP, reviewed FBA package insert, ACIP guidance and MMWR, Lit review, VAERS search • 1 case, part enhanced inquiry with possible second part full consult • CISA inquiry: GBS following COVID-19 vaccine
Special Meetings	
Standard calls - CISA AM/PM calls and CISA site calls	• Discuss daily cases/inquiries on the CISA tracker
Special meetings attended Special meetings attended • CISA AM management huddle ▪ CISA weekday AM meeting ▪ Standing CISA (Vanderbilt) Check-In Calls ▪ CISA Research Coordination Standing Meeting ▪ CISA COVID Babies/CISA COVID Peds Standing Study Call ▪ CISA Adult COVID ▪ CISA Maternal COVID Standing Call ▪ CISA RZV and allV4 Standing Call • CISA Research admin calls with Duke • SIRVA review meeting • Meeting of the Advisory Committee on Immunization Practices (ACIP) ▪ ACIP influenza WG call--egg allergy discussion ▪ CISA WG 1 Case Consultation: Meningoencephalitis following vaccinations CISA WG1 Case Consultation: Myocarditis following recent vaccines	• Attend review of key leadership/management updates • Discussed cases (inquiries) and exchange experiences. • Discussed CISA's research portfolio issues Identify research action items for follow-up

• IDSA (Infectious Disease Society) meeting 5/4 Thur • CDC COCA (clinician outreach and communication activity) call 5/11 Thur • FDA VRBAC maternal RSV vaccines 5/18 Thur • Daily management huddle meeting at 8:30 am • Attendance of office hour meetings as scheduled (1-3x/week) • Weekly meet up with Jyothi Gunta to discuss contractor roles on the team • Executive management meeting x 2 to discuss ongoing cases with leadership • 1-2 meetings/week for MOVING project • Immunocompromised patient project – meeting and presentation • Multiple attempts to reach providers for MOVING project • Note taking for VRPBAC meeting Leadership meeting with Karen related to the clinical service	• Update on covid vaccine • Information about Avian Influenza (H5N1) • Update about covid vaccine use • Review and vote on maternal RSV vaccine

b. Status of on-going projects

Project	Status
• Manuscript: Review of Immunogenicity of Adjuvanted versus High-Dose Inactivated Influenza Vaccines in Older Adults: A Randomized Clinical Trial Talking points • Literature review: Flu/COVID-19 vaccination co-administration immunogenicity and safety studies • Manuscript: Reporting patterns of vaccine adverse events by reporter type in the Vaccine Adverse Event Reporting System (VAERS) • Manuscript: Reports of Shoulder Inquiry Related to Vaccine Administration in the Vaccine Adverse Event Reporting System, 2018-2022 • Deep dive allergy project for covid vaccine -Read literature on the topic -continue to work on excel data -continue to work on summary of data • MOVING study, 1 year follow up interviews	• Ongoing

• MIS-C Literature Review on postvaccination of COVID-19 after a history of MIS-C	• Attended multiple meetings (5/9,5/10,5/11,5/17, 5/19, 5/23,5/30) to work on construction of survey, survey strategies for MOVING study on 5- 11 yo patients • Reviewed medical records, phoned/emailed cardiologists or pediatricians to complete the 18 mo clinical follow up survey for 5-11 yo patients For MIS-C work, spent many hours reading and sorting through literature on PubMed database for papers discussing postvaccination in MIS-C patients; Created an Excel spreadsheet with lit review information to be later shared/presented with CDC leadership
• V safe Extended Follow Up Project • Work on presentation for flu/COVID coadministration studies • Participate in COVID adult study meeting • Participate in CISA research coordination meeting • Participate in CISA study administration meeting • Meet with Dr. Broder and Geta 2x to discuss follow up for flu/COVID coadministration study project • Meet with Dr. Broder 3 times to listen to and provide feedback on IDSA presentation • Review and assess 2 Maternal COVID study SAE's	• Phone received for follow-up calls • In contact with team, plans for project to begin in June

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
none	

III. Task 5 Pregnancy medical officer/epidemiologist, Task 6 Pregnancy clinician

a. Accomplishments

Task	Outcome/Accomplishment
Medical record abstractions	• 238 initial abstractions completed (counted at the dyad level)
Medical record re-abstractions	• 60 re-abstractions
Medical record "backfills"	• 99 Backfilled records
HTN review	• 116 records were reviewed for hypertensive disorders during pregnancy

Abstraction-re-abstraction Comparison	• Completed comparison tool for 41 records for the April comparison tool
Medical record reconciliation	• Completed reconciliation for 30 records for the April comparison tool
Quality control checks	• Reviewed data for all records requiring QC. Specific QC variables addressed: Date of birth and pregnancy outcome; Diagnosis dates for BD; BI summary answers; Induction due to HTN; All IMC variables. Total of 58 records

b. Status of on-going projects

Project	Status
V-safe pregnancy registry extended follow-up	• Started interviews in mid-November-ongoing • Interviews have begun by Abt and are ongoing • 99% call completed
Clinical adjudication of birth defects with medical record data (medical record abstraction [MRA] Vpoint)	• Meet weekly to discuss cases for clinical adjudication of birth defects using medical record data with three birth defect subject matter experts; specific topics addressed regarding coding: PFO vs ASD; PDA; hydronephrosis; hemangioma • Inclusion criteria for certain birth defects discussed within the adjudicators and SOP updated-ongoing
Pregnancy outcomes among people with COVID-19 after COVID-19 vaccination	• Waiting on code review by data analysts and then need data to be replicated
Review of medical records for birth defect adjudication	• Ongoing
Clinical Review of Birth defects	• Ongoing
Medical record abstraction and reabstraction	• Ongoing

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
None at this time	

From: "Moran, Kerri (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Hamburger, Tanya (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older
Date: Thu, 23 Feb 2023 14:18:13 +0000
Importance: Normal
Attachments: COVID_Booster_Call_List_(1).xlsx

The partners we invited to the safety signal call on Jan 13 is in the attached under the tab, Option 1.

Just for context, OADC opted to keep the call on the smaller side, but we created alternative lists that had additional partners we would have liked to have added if the call could be expanded.

Kerri T. Moran
Associate Director for Partnerships
Division of Healthcare Quality Promotion (DHQP)
Centers for Disease Control and Prevention (CDC)
[redacted]

From: Moran, Kerri (CDC/DDID/NCEZID/DHQP)
Sent: Thursday, February 23, 2023 8:58 AM
To: Hamburger, Tanya (CDC/DDID/NCEZID/DHQP) [redacted] Sharan, Martha (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older

Kerri T. Moran
Associate Director for Partnerships
Division of Healthcare Quality Promotion (DHQP)
Centers for Disease Control and Prevention (CDC)
[redacted]

From: DHQP Partners (CDC)
Sent: Friday, January 13, 2023 2:01 PM
To: NCIRD Partnerships (CDC) [redacted]
Subject: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older

Good afternoon,

For years, U.S. government agencies have used multiple, complimentary safety monitoring systems to help detect possible vaccine statistical signals as early as possible and to facilitate further investigations, as appropriate.

As part of routine surveillance, CDC detected a preliminary signal for stroke in people ages 65 and older who received the Pfizer-BioNTech COVID-19 bivalent mRNA vaccine. As a response to the signal, CDC and FDA examined several large databases including, Medicare's database of 5 million doses, VA's database of millions of veterans, in addition to Israel and European countries' databases.

Today's announcement mirrors FDA's July 2021 signal announcement that wasn't picked up in CDC system and that FDA did not think was likely to be of clinical significance. For the sake of transparency, the agencies issued a statement about the signal and the results of our investigation so far.

To date, they have not seen an association or increased risk in stroke from vaccines in these databases. **The totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk.**

CDC, FDA, and (Partners, you can add your organization here if you choose) continue to believe that the updated bivalent vaccines are safe and effective and provide the best protection against COVID-19, and we continue to encourage Americans of all ages to get their updated COVID-19 shot right away.

Attached you will find a Tough Q&A document that may be helpful to you and your members. If you have questions, please direct them to [redacted]

Thank you for your continued partnership.

CDC's Division of Healthcare Quality Promotion Strategic Partnership Team

From: "Marks, Peter" <[redacted]
To: "McNeill, Lorrie" [redacted], "Witten, Celia (CBER)" [redacted] "Anderson, Steven" [redacted], "Forshee, Richard" [redacted]
Cc: "Frantz-Bohn, Susan" [redacted]
Subject: RE: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax
Date: Tue, 17 Jan 2023 14:28:36 +0000
Importance: Normal
Inline-Images: image001.png; image002.jpg

Dear Lorrie,

I think that we have to acknowledge that this did not go well and work with our colleagues to see how to do it better next time.

First of all, we need to agree on when such announcements should be made in the first place, and then we need to figure out how to do them appropriately. My understanding is that Dr. Califf will be driving a discussion of this further.

Best Regards,
Peter

From: McNeill, Lorrie [redacted]
Sent: Tuesday, January 17, 2023 8:34 AM
To: Marks, Peter [redacted]; Witten, Celia (CBER) [redacted] Anderson, Steven [redacted]; Forshee, Richard [redacted]
Cc: Frantz-Bohn, Susan [redacted]
Subject: FW: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Good morning, all – under the heading of "damned if you do and damned if you don't," sharing the Pink Sheet article below.

Lorrie

From: Patel, Bharti [redacted]
Sent: Tuesday, January 17, 2023 6:26 AM
To: OC OCOD Contacts [redacted]
Subject: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

- 16 Jan 2023
- **ANALYSIS**
- 
- [redacted]

Executive Summary

US vaccine surveillance systems were triggered, but so far further investigation clears the bivalent COVID vaccine of any new safety concern. CDC and FDA's attempt to control the narrative appears to have backfired, however, making what looks to be a non-issue

more controversial than it needed to be due to limited public communication.

Source: Shutterstock

Pfizer Inc./BioNTech SE's bivalent COVID-19 vaccine is under continued investigation over a preliminary safety signal related to strokes in people ages 65, though thus far the signal identified in the Vaccine Safety Datalink has not been confirmed in other monitoring systems, leading regulators to conclude that it is very unlikely the signal represents a true clinical risk.

That news, made public on 13 January, should largely have represented a win for US public health agencies – demonstrating that systems put in place to rapidly warn of potential harms worked by quickly identifying a possible safety concern and leading to the necessary follow up evaluations.

However, the rollout of the information was haphazard and piecemeal leading to confusing headlines (some played up the possible stroke link while others were more cautious) and criticism from public health experts about the lack of transparency, which among other negatives allows anti-vaccine messaging to thrive unchecked.

The potential safety signal was first publicly revealed in a *Washington Post story* that then linked to an update that the US Centers for Disease Control and Prevention and Food and Drug Administration posted quietly on their websites.

The agencies did not more widely notify the press or health care professionals. FDA did not include the update it its daily news roundup on 13 January.

Sparse Details For The Public

Furthermore, the CDC and FDA announcement was fairly sparse in detail, lacking key pieces of information that were present in the Washington Post story, such as the number of strokes identified in the Vaccine Safety Datalink (VSD). The Post story says the VSD picked up the safety signal in late November, another detail not mentioned on the CDC and FDA announcement.

The agencies confirmed to the *Pink Sheet* that VSD identified 130 ischemic strokes out of about 550,000 Pfizer bivalent vaccines administered to people 65 and older. Those strokes took place within the first three weeks of getting the updated vaccine and raised a question of whether people getting the vaccine were more likely to have a stroke in the 21 days following vaccination compared with days 22-44 following vaccination.

VSD conducts near real-time safety monitoring, assessing rates weekly. If the rate of adverse events among vaccinated people in the risk period is higher than among the comparison window, it results in a signal and prompts further investigation into whether the vaccine may be associated with an adverse event, CDC explained.

The signal was not identified with the Moderna, Inc. bivalent COVID-19 vaccine or in other safety studies, including the Vaccines Adverse Event Report System. Studies using the Centers for Medicare and Medicaid Services database and the Veterans Affairs database did not reveal an increased risk of ischemic stroke, nor did a review of Pfizer-BioNTech's global safety database or other countries' data, CDC and FDA said.

Ongoing Evaluations

FDA and CDC are continuing to evaluate data on the signal and plan to discuss their latest findings at the 26 January FDA Vaccines and Related Biological Products Advisory Committee, but they emphasized that "the totality of the data current suggests that it is

very unlikely that the signal in VSD represents a true clinical risk."

The agencies argued their notice, despite the lack of confirmation of a safety concern thus far, was done in the name of public trust and transparency.

"Transparency and vaccine safety are top priorities for the FDA and CDC. Posting about this signal, and describing our assessment that this does not pose a health risk is exemplary of this. Both agencies want to underscore our continued confidence in the safety and effectiveness of the vaccines, and our hope is that trough our transparency – the public will as well."

However, the way the information was conveyed, led to questions about the agencies' true commitment to transparency.

'A Rorschach Test'

"I think the mistake they make is not having some kind of public discussion of it today or yesterday or whatever. Preferably not five o'clock on Friday before a long weekend," said Diana Zuckerman, blaming in part confusing language in the FDA and CDC webpage update, along with a lack of more proactive and formal public communication, for news headlines that more strongly pointed to a stroke link than the totality of the agency communication suggests.

"When I look at the CDC thing and knowing how this works, I'm like wow, there's a lot of ambivalence in this article. You know, it's not clear. It kind of is a Rorschach test in the eyes of the beholder," said Zuckerman, who is the President of the National Center for Health Research.

"This is the problem. They don't want to be asked questions. They want to control the narrative, so to speak, and they can't control the narrative. And by trying to control it, they're getting the very mistrust that they say they don't want," Zuckerman added.

The lack of a stronger media presence from top agency officials on the issue and the missing pieces of data also led to criticism from Rick Bright, who previously served as the Deputy Assistant Secretary for Preparedness and Response and the Director of the Biomedical Advanced Research and Development Authority.

"Completely irresponsible, yet it's what we've come to expect from the current CDC Director. Another missed opportunity to educate and do the right thing," Bright tweeted.

Preferential Media Access May Have Backfired

Giving preferential access to one media outlet with limited follow up likely backfired and made people more skeptical of safety work the agencies seem to have handled well, said Peter Lurie, president of the Center for Science in the Public Interest, and former associate commissioner for public health strategy and analysis at FDA.

"The problem is that in the current environment if people can detect attempts to control the story, then people overlay their own interpretations of the reason for that," Lurie said.

"I guess the best way to approach it, if you're in the agency's point of view, is to try to stick with … what you would do, irrespective of the situation to begin with," he said.

"That's your best defense: follow the science, follow your processes, do what you always do," Lurie said.

"I don't see any reason why the release of this information couldn't have been done in the conventional fashion, which is by whatever press release they wanted to put out available to all to all outlets. That would have been the better way, because now people will wonder, justifiably or otherwise."

"It would be concerning if they only quietly let one news outlet know and updated their website. They seem to indicate that they investigated this safety signal further before making it known to the public so they could and should have been more transparent about this," said Reshma Ramachandran an assistant professor at Yale who has previously studied identification of safety signals, regulatory action and any publicity.

"I understand the need to not stoke anti-vax sentiment unnecessarily, but given that FDA has repeatedly stated that they view addressing misinformation a priority, to me, a lesson learned from everything that happened last year for the agency would be to be as transparent as possible to earn the public's trust to do so," Ramachandran said.

"I'm glad they plan to discuss this at their upcoming vaccines advisory committee though."

History of Quiet Moves

This is not the first time the US government has made COVID-19 vaccine safety related updates quietly.

FDA took a low-key approach when it updated vaccine emergency use authorizations to specifically state that sponsors report all incidences of myocarditis and pericarditis, no matter their severity. (Also see "All Myocarditis, Pericarditis Cases With COVID-19 Vaccines Now Must Be Reported To VAERS" - Pink Sheet, 13 Sep, 2022.)

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From: "McNeill, Lorrie" [redacted]
To: "Marks, Peter" [redacted] "Witten, Celia (CBER)" [redacted]
"Anderson, Steven" [redacted] "Forshee, Richard"
<Richard.Forshee [redacted]
Cc: "Frantz-Bohn, Susan" [redacted]
Subject: RE: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax
Date: Tue, 17 Jan 2023 14:33:22 +0000
Importance: Normal
Inline-Images: image001.png; image002.jpg

Thanks Peter, agree this needs to be sorted through so the process works better going forward. Please let us know how we can assist with those discussions.

Lorrie

From: Marks, Peter [redacted]
Sent: Tuesday, January 17, 2023 9:29 AM
To: McNeill, Lorrie [redacted] Witten, Celia (CBER) [redacted] Anderson, Steven [redacted] Forshee, Richard [redacted]
Cc: Frantz-Bohn, Susan [redacted]
Subject: RE: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Dear Lorrie,

I think that we have to acknowledge that this did not go well and work with our colleagues to see how to do it better next time.

First of all, we need to agree on when such announcements should be made in the first place, and then we need to figure out how to do them appropriately. My understanding is that Dr. Califf will be driving a discussion of this further.

Best Regards,
Peter

From: McNeill, Lorrie [redacted]
Sent: Tuesday, January 17, 2023 8:34 AM
To: Marks, Peter [redacted] Witten, Celia (CBER) [redacted] Anderson, Steven [redacted] Forshee, Richard [redacted]
Cc: Frantz-Bohn, Susan [redacted]
Subject: FW: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Good morning, all – under the heading of "damned if you do and damned if you don't," sharing the Pink Sheet article below.

Lorrie

From: Patel, Bharti [redacted]
Sent: Tuesday, January 17, 2023 6:26 AM
To: OC OCOD Contacts [redacted]
Subject: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

- 16 Jan 2023
- **ANALYSIS**

[redacted]

Executive Summary

US vaccine surveillance systems were triggered, but so far further investigation clears the bivalent COVID vaccine of any new safety concern. CDC and FDA's attempt to control the narrative appears to have backfired, however, making what looks to be a non-issue more controversial than it needed to be due to limited public communication.

Source: Shutterstock

Pfizer Inc./BioNTech SE's bivalent COVID-19 vaccine is under continued investigation over a preliminary safety signal related to strokes in people ages 65, though thus far the signal identified in the Vaccine Safety Datalink has not been confirmed in other monitoring systems, leading regulators to conclude that it is very unlikely the signal represents a true clinical risk.

That news, made public on 13 January, should largely have represented a win for US public health agencies – demonstrating that systems put in place to rapidly warn of potential harms worked by quickly identifying a possible safety concern and leading to the necessary follow up evaluations.

However, the rollout of the information was haphazard and piecemeal leading to confusing headlines (some played up the possible stroke link while others were more cautious) and criticism from public health experts about the lack of transparency, which among other negatives allows anti-vaccine messaging to thrive unchecked.

The potential safety signal was first publicly revealed in a *Washington Post story* that then linked to an update that the US Centers for Disease Control and Prevention and Food and Drug Administration posted quietly on their websites.

The agencies did not more widely notify the press or health care professionals. FDA did not include the update it its daily news roundup on 13 January.

Sparse Details For The Public

Furthermore, the CDC and FDA announcement was fairly sparse in detail, lacking key pieces of information that were present in the Washington Post story, such as the number of strokes identified in the Vaccine Safety Datalink (VSD). The Post story says the VSD picked up the safety signal in late November, another detail not mentioned on the CDC and FDA announcement.

The agencies confirmed to the *Pink Sheet* that VSD identified 130 ischemic strokes out of about 550,000 Pfizer bivalent vaccines administered to people 65 and older. Those strokes took place within the first three weeks of getting the updated vaccine and raised a question of whether people getting the vaccine were more likely to have a stroke in the 21 days following vaccination compared with days 22-44 following vaccination.

VSD conducts near real-time safety monitoring, assessing rates weekly. If the rate of adverse events among vaccinated people in the risk period is higher than among the comparison window, it results in a signal and prompts further investigation into whether the vaccine may be associated with an adverse event, CDC explained.

The signal was not identified with the Moderna, Inc. bivalent COVID-19 vaccine or in other safety studies, including the Vaccines Adverse Event Report System. Studies using the Centers for Medicare and Medicaid Services database and the Veterans Affairs database did not reveal an increased risk of ischemic stroke, nor did a review of Pfizer-BioNTech's global safety database or other countries' data, CDC and FDA said.

Ongoing Evaluations

FDA and CDC are continuing to evaluate data on the signal and plan to discuss their latest findings at the 26 January FDA Vaccines and Related Biological Products Advisory Committee, but they emphasized that "the totality of the data current suggests that it is very unlikely that the signal in VSD represents a true clinical risk."

The agencies argued their notice, despite the lack of confirmation of a safety concern thus far, was done in the name of public trust and transparency.

"Transparency and vaccine safety are top priorities for the FDA and CDC. Posting about this signal, and describing our assessment that this does not pose a health risk is exemplary of this. Both agencies want to underscore our continued confidence in the safety and effectiveness of the vaccines, and our hope is that trough our transparency – the public will as well."

However, the way the information was conveyed, led to questions about the agencies' true commitment to transparency.

'A Rorschach Test'

"I think the mistake they make is not having some kind of public discussion of it today or yesterday or whatever. Preferably not five o'clock on Friday before a long weekend," said Diana Zuckerman, blaming in part confusing language in the FDA and CDC webpage update, along with a lack of more proactive and formal public communication, for news headlines that more strongly pointed to a stroke link than the totality of the agency communication suggests.

"When I look at the CDC thing and knowing how this works, I'm like wow, there's a lot of ambivalence in this article. You know, it's not clear. It kind of is a Rorschach test in the eyes of the beholder," said Zuckerman, who is the President of the National Center for Health Research.

"This is the problem. They don't want to be asked questions. They want to control the narrative, so to speak, and they can't control the narrative. And by trying to control it, they're getting the very mistrust that they say they don't want," Zuckerman added.

The lack of a stronger media presence from top agency officials on the issue and the missing pieces of data also led to criticism from Rick Bright, who previously served as the Deputy Assistant Secretary for Preparedness and Response and the Director of the Biomedical Advanced Research and Development Authority.

"Completely irresponsible, yet it's what we've come to expect from the current CDC Director. Another missed opportunity to educate and do the right thing," Bright tweeted.

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From: "Forshee, Richard" <[redacted]
To: "CBER Research Central [redacted]
Cc: "Menschik, David" <[redacted]
Subject: Clearance for manuscript
Date: Mon, 26 Jul 2021 20:13:28 -0000
Importance: Normal
Attachments: mrna_vaccine_6_mo-_tables_and_figures_714.docx;
mRNA_COVID19_vaccine_safety_6_mo_draft_721_clean.docx;
mRNA_COIVD19_vaccine_six_month_safety_review_Clearance_Form.pdf
Inline-Images: image001.png; image002.jpg; image003.jpg; image004.jpg; image005.jpg; image006.jpg

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Hello,

OBE has cleared the attached manuscript.

Thanks,

Richard Forshee, Ph.D.
Acting Deputy Office Director, CBER/OBE

Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Analytics and Benefit-Risk Assessment Team
U.S. Food and Drug Administration
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

From: "Forshee, Richard" [redacted]
To: "Anderson, Steven" [redacted]
Subject: FW: [EXTERNAL] 6 month safety review
Date: Thu, 22 Jul 2021 22:18:36 -0000
Importance: High
Attachments: mRNA_COVID19_vaccine_safety_6_mo_draft_721_clean.docx; mrna_vaccine_6_mo-_tables_and_figures_714.docx

---

Dear Steve,

I think this is an excellent report on the VAERS and v-safe surveillance during the first six months the m-RNA vaccines were on the market. I think you should at least review the abstract, and I recommend sharing it with Peter and Celia for situational awareness.

I'm going to clear it tomorrow.

Thanks,
--Rich

From: Menschik, David <[redacted]
Sent: Thursday, July 22, 2021 3:05 PM
To: Alimchandani, Meghna <[redacted]
Cc: Forshee, Richard [redacted]
Subject: FW: [EXTERNAL] 6 month safety review
Importance: High

Hi Meghna,

Kerry and Deb were able to clear today and forwarding to you for clearance. CDC has asked for this to be cleared by tomorrow if possible.
Copying Rich for his awareness and assuming the office level review will go to him

Best,
David

From: Thompson, Deborah [redacted]
Sent: Thursday, July 22, 2021 2:40 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review

Hi David,

Thanks for the chance to review. The manuscript looks good!

Please find the signed clearance form attached.

Best,

Deb

From: Menschik, David [redacted]
Sent: Thursday, July 22, 2021 1:10 PM
To: Thompson, Deborah [redacted]
Subject: RE: [EXTERNAL] 6 month safety review

Thanks!

From: Thompson, Deborah [redacted]
Sent: Thursday, July 22, 2021 1:02 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review

Hi David,

Yes, will do.

Thanks,

Deb

From: Menschik, David [redacted]
Sent: Thursday, July 22, 2021 1:00 PM
To: Thompson, Deborah [redacted]
Subject: FW: [EXTERNAL] 6 month safety review

Hi Deb,

Can you please use the attached form?
(Jane B was not available to clear this)

Thanks,
David

From: Welsh, Kerry [redacted]
Sent: Thursday, July 22, 2021 12:02 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review

Hi David,

No clearance issues. Here's the signed clearance form.

Best,
Kerry

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Wharton, Melinda (CDC/DDID/NCIRD/OD)" [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
Subject: FW: slides
Date: Fri, 16 Dec 2022 13:28:06 +0000
Importance: Normal
Attachments: VSD_Bivalent_and_Ischemic_Stroke_Dec_15_2022,_1771_v2.pptx

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Feel free to use these slides to brief folks in CDC or to share with selected CDC staff but please treat as confidential.
Thanks.
Tom

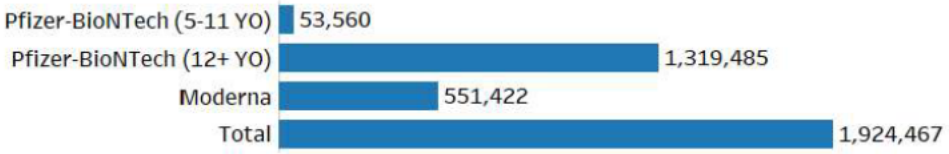
VSD:
Ischemic Stroke – following
Covid-19 Pfizer Bivalent Booster Dose

Data through Dec 10, 2022 week 1771
65+

Eric S. Weintraub – CDC/ISO/VSD
Nicky Klein – Northern California Kaiser
Kristin Goddard – Northern California Kaiser
Ned Lewis – Northern California Kaiser

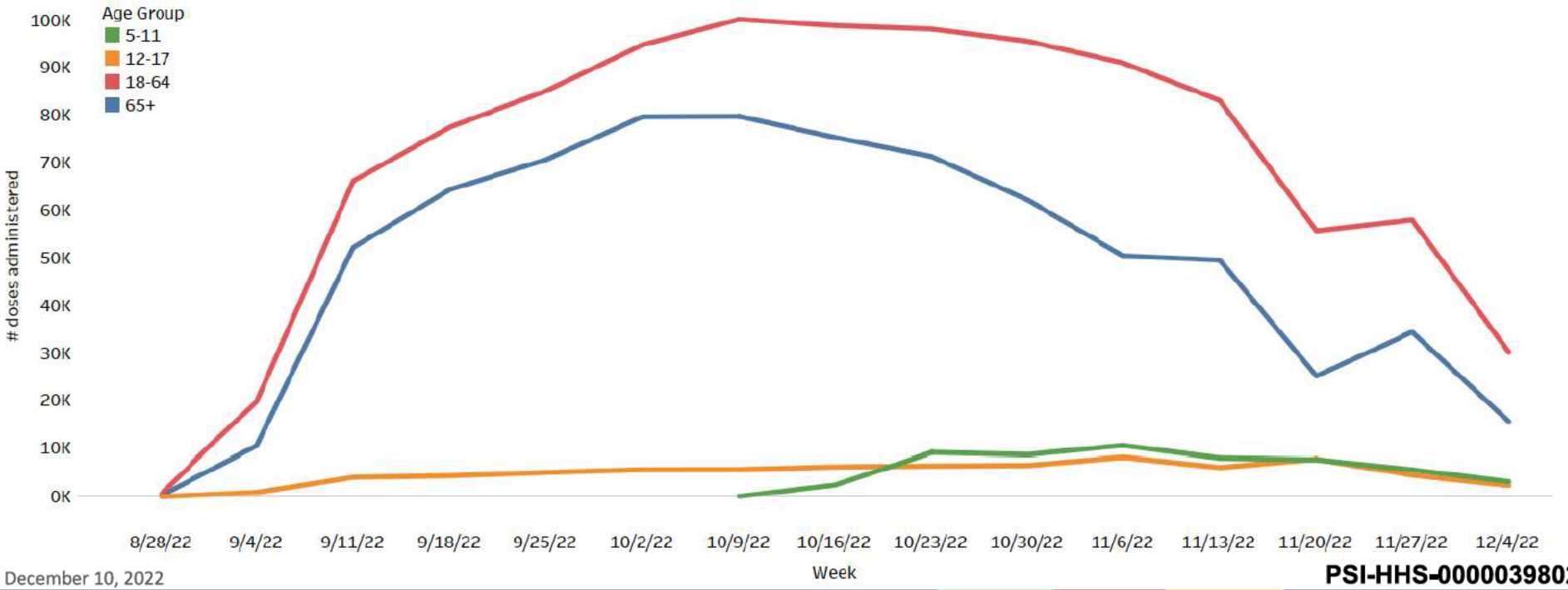
Bivalent Booster Uptake

Number of bivalent booster doses administered, by vaccine type



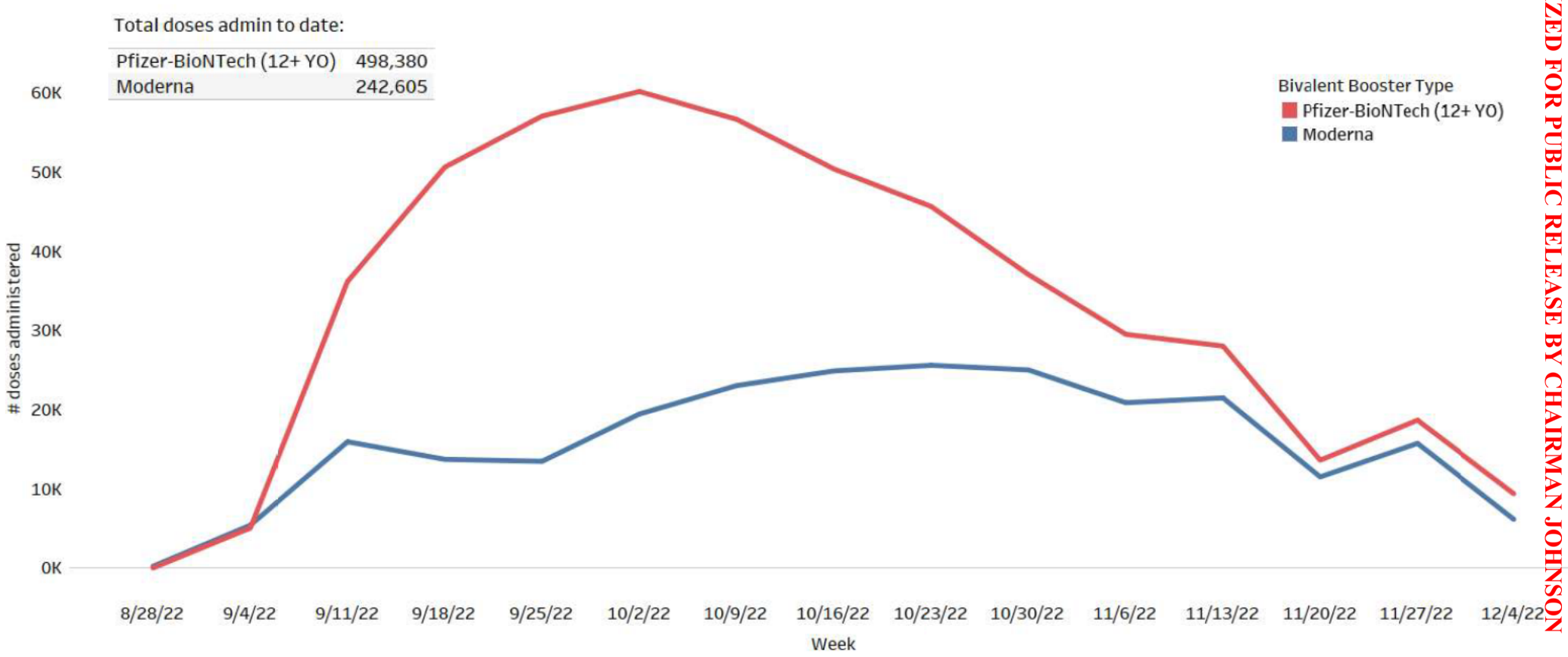
Number of bivalent booster doses administered, by age group

Number of bivalent booster doses administered over time, by age group



Data through December 10, 2022

Number of bivalent booster doses administered over time among persons aged 65+, by vaccine type



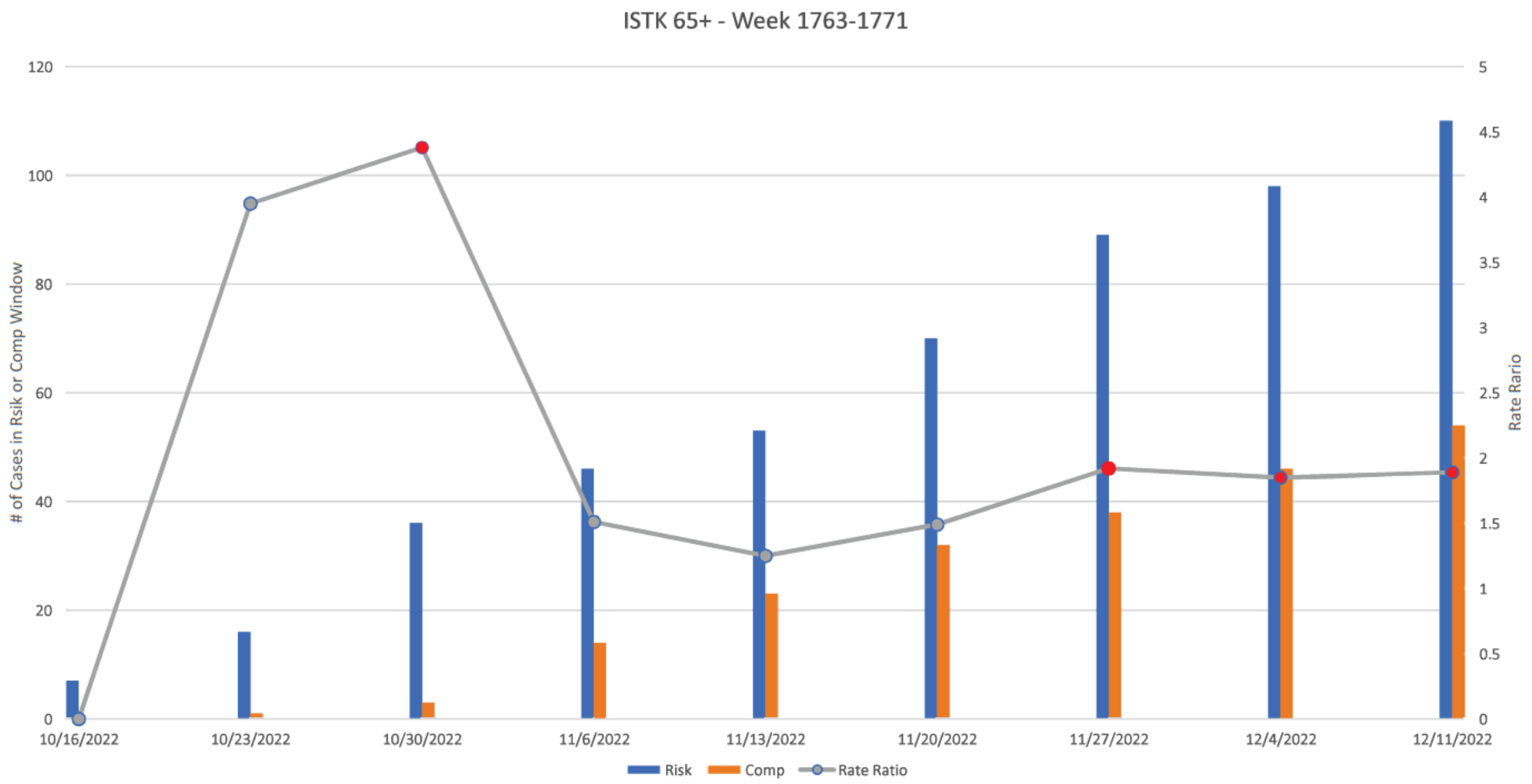
Data through December 10, 2022

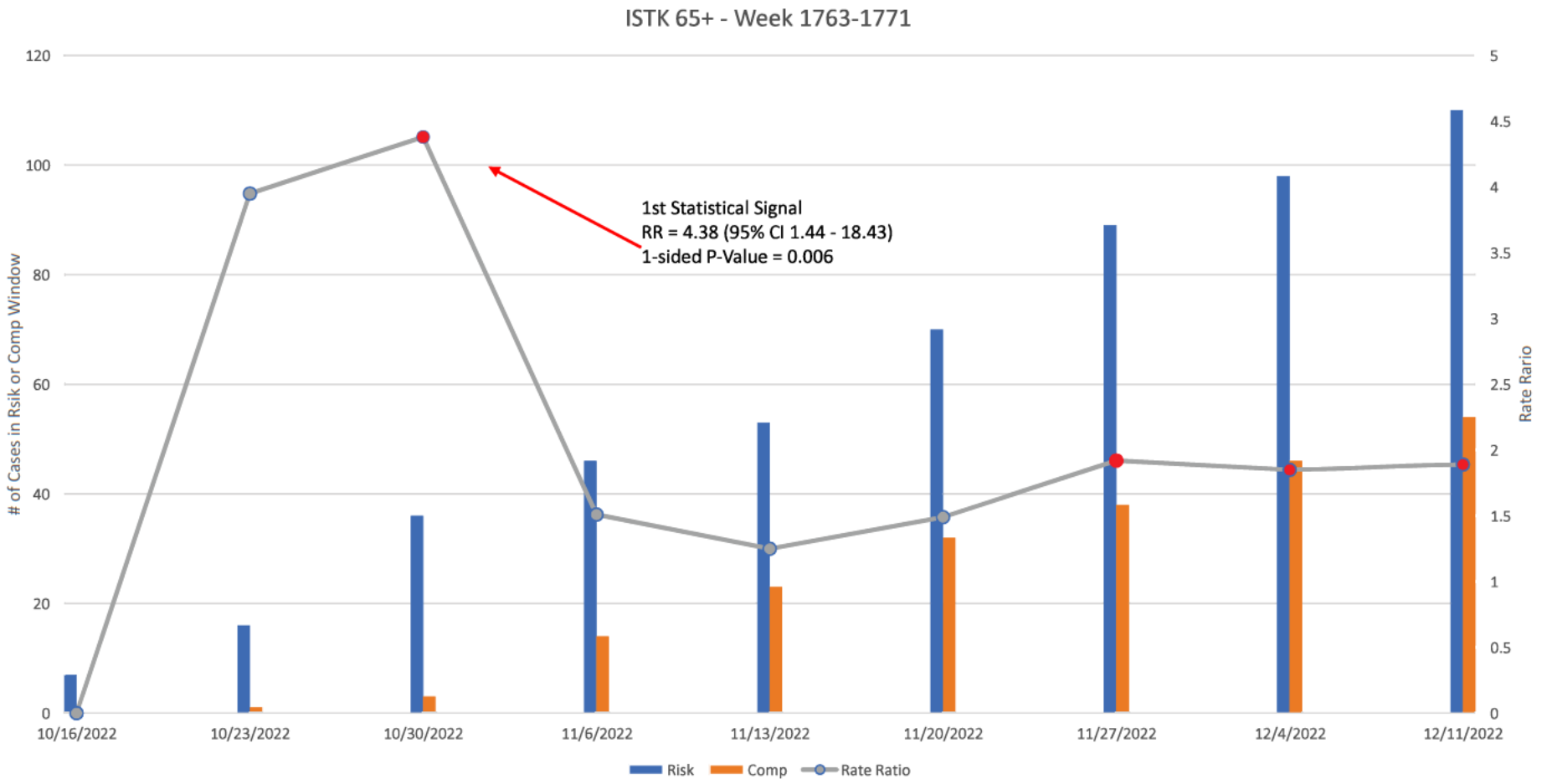
VSD RCA Ischemic Stroke Definition

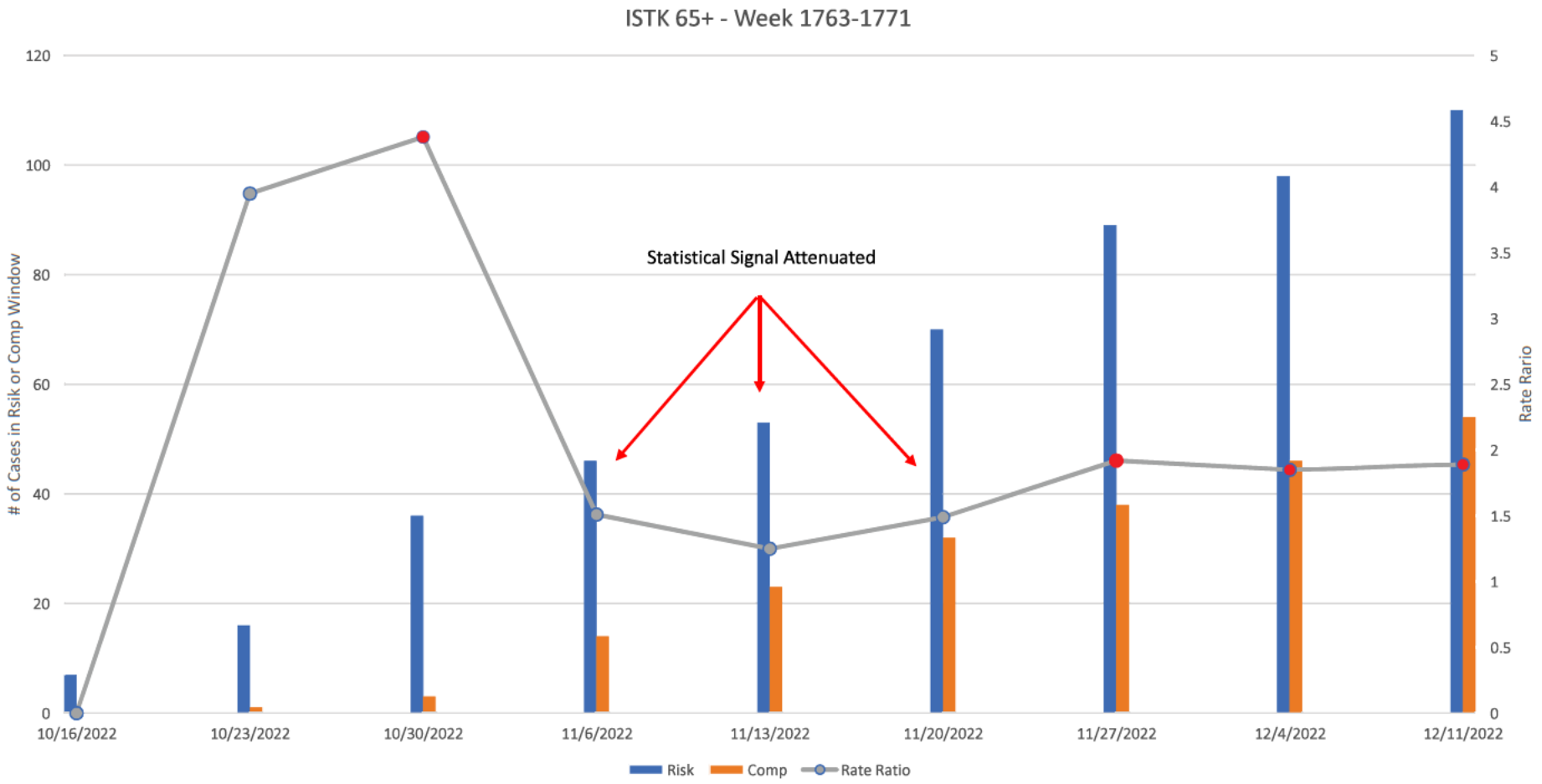
ICD-10 CODES TO FIND INCIDENT CASES	ICD-10 CODES FOR LOOKBACK TO ADJUST ONSET DATE (in all settings)	ICD-10 CODES - TO DETECT PREVALENCE (history of, in all settings)	ICD-10 CODES - OTHER CAUSE EXCLUSIONS (in all settings)
Stroke, ischemic (settings = Emergency, Inpatient)	**Codes to adjust Stroke, ischemic onset (if seen within 1 day before case)**	**Stroke, ischemic - Review for Prevalence - 1ST EVER**	**Other possible causes of Stroke, ischemic**
G45.8 Other transient cerebral ischemic attacks and related syndromes G45.9 Transient cerebral ischemic attack, unspecified I63.* Cerebral infarction	**Adjust onset date if occurs in the 1 day prior to incident case:** Z92.82 Status post administration of tPA (rtPA) in a different facility within the last 24 hours prior to admission to current facility R51.* Headache R47.* Speech disturbances, not elsewhere classified R29.810 Facial weakness R53.1 Weakness R42.* Dizziness and giddiness R41.82 Altered mental status, unspecified R40.4 Transient alternation of awareness G81.9* Hemiplegia, unspecified H53.9 Unspecified visual disturbance H53.13* Sudden visual loss	**Exclude if occurs EVER prior to incident case:** Z86.73 Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits I69.* Sequelae of cerebrovascular disease	**Exclude if COVID-19 in the last 30 days prior to incident case (not including same day):** FIRST COVID-19 DIAGNOSIS **OR** FIRST COVID-19 POSITIVE LAB TEST **Exclude if occurs in the time period noted prior to incident case (not including same day):** I48.* Atrial fibrillation and flutter (if seen EVER prior to incident case) I21.* Acute myocardial infarction (if seen within 28 days prior to incident case) S15.* Injury of blood vessels at neck level (if seen within 1 day prior to incident case) I74.* Arterial embolism and thrombosis (if seen within 1 day prior to incident case) D57.* Sickle-cell disorders (if seen EVER prior to incident case) D68.5* Primary thrombophilia (if seen EVER prior to incident case)

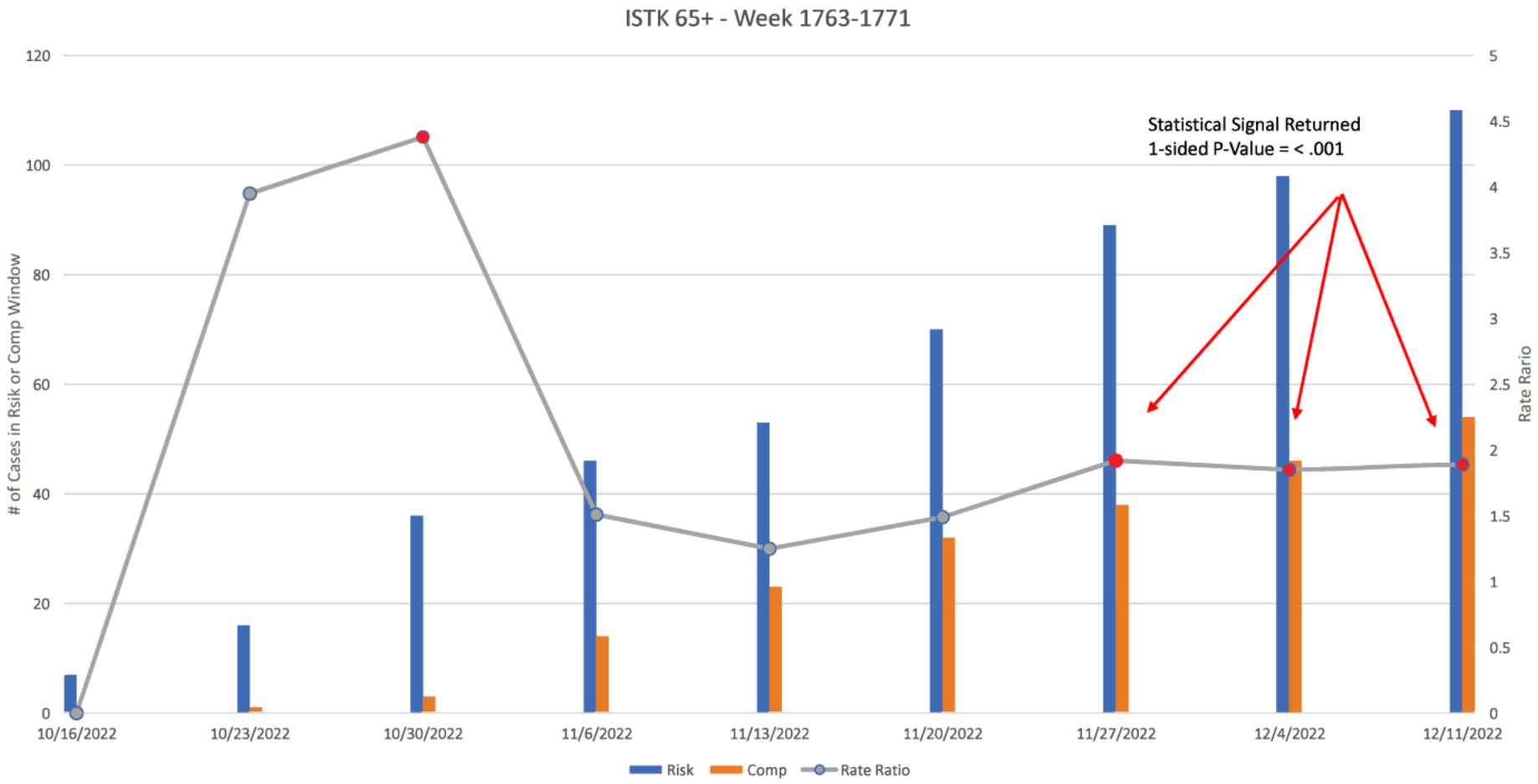
VSD COVID-19 RCA Analyses:

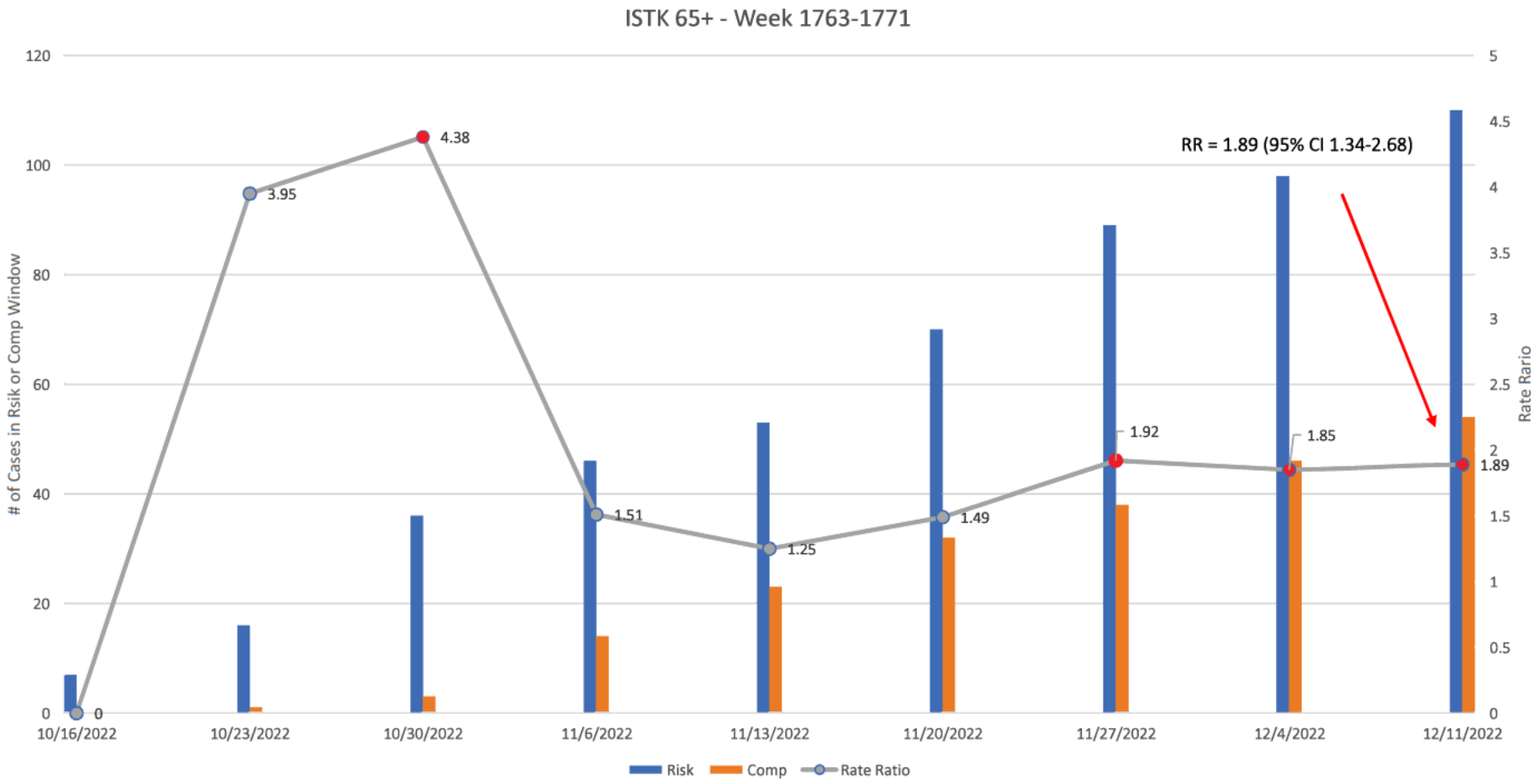
Ischemic stroke in the 1-21-day risk interval following bivalent Pfizer booster vaccination in people 65+ years of age compared to the 22-42 days following bivalent Pfizer booster vaccination



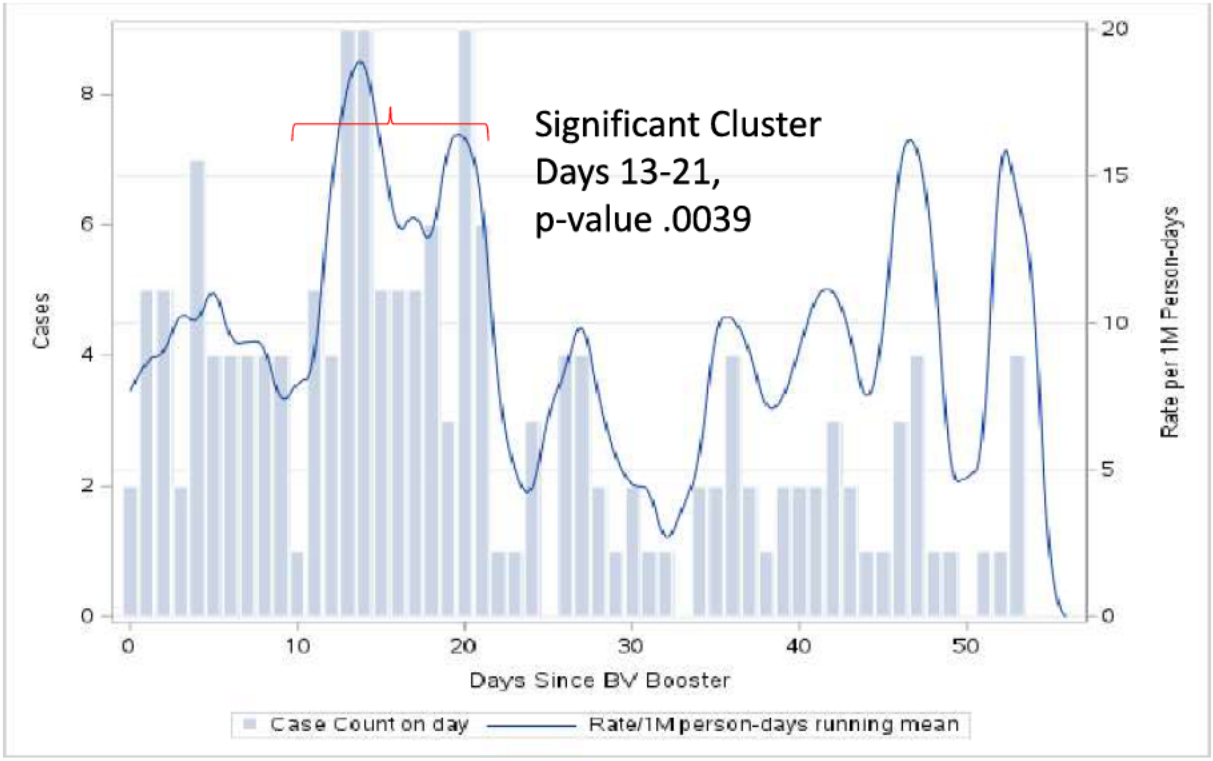




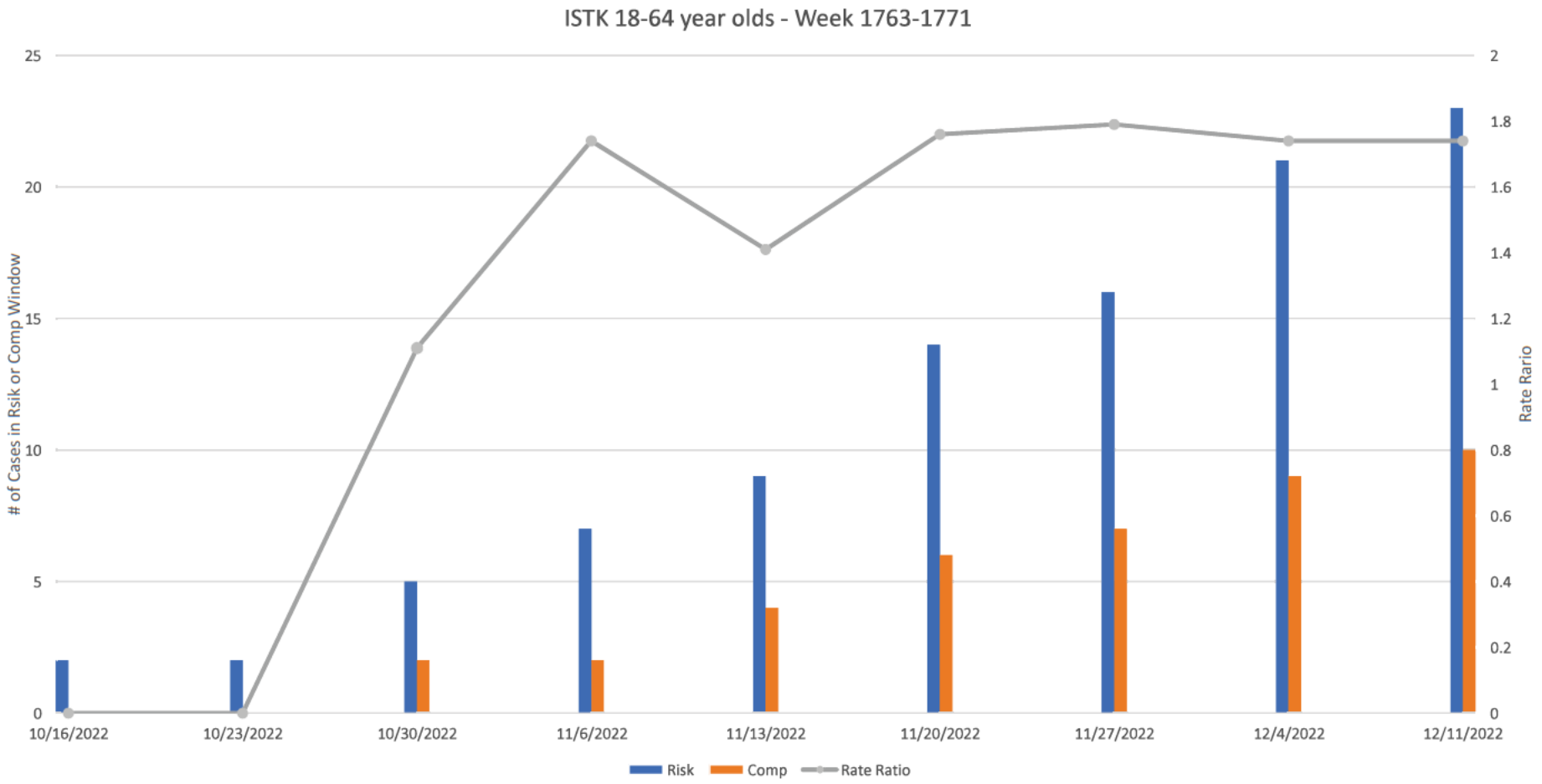


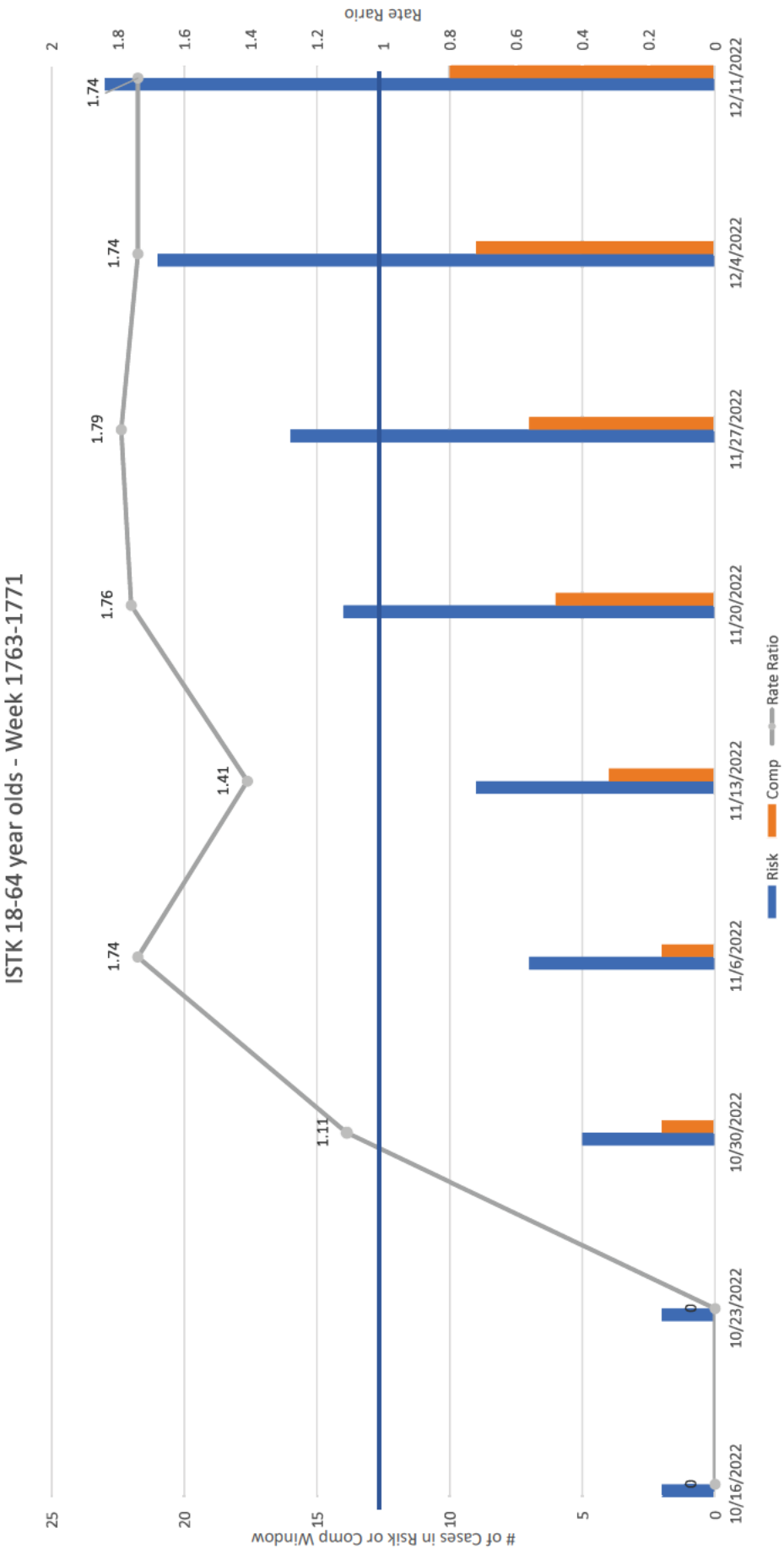


Temporal Scan – Pfizer, 65+



Ischemic Stroke
Data through Dec 10, 2022
week 1771
18-64 years of age





ISTK Bivalent RCA Summary – data through Dec 10, 2022

Analysis Parameters					Informative Counts and Follow-up				Nominal Analysis				Sequential Analysis	
Outcome Event	Age Group	Risk Interval Days	Comp Interval Days	Vaccine	Risk Events	Comp Events	Risk Fwp (days)	Comp Fwp (days)	Rate Ratio	95% Lower CI	95% Upper CI	P-value	1-sided P-Value	Signal 1-sided p < 0.01
ISTK	18-64y	1-21	22-42	Both mRNA	31	18	85516	72788	1.25	0.68	2.33	0.474	0.284	no
			22-42	Pfizer	23	10	45286	38741	1.74	0.81	3.91	0.16	0.107	no
			22-42	Moderna	8	8	8468	7191	0.67	0.23	1.95	0.461	0.847	no
	65+y	1-21	22-42	Both mRNA	149	83	559745	523791	1.55	1.17	2.06	0.002	0.001	yes
			22-42	Pfizer	110	54	273597	262868	1.89	1.34	2.68	<.001	<.001	yes
			22-42	Moderna	38	29	61375	51210	1.02	0.62	1.7	0.935	0.519	no

Ischemic Stroke and Pfizer Bivalent Summary

- 65+ Statistical signal consistent for past 3 weeks (RR-1.89 95% CI – 1.34 – 2.68), 1 sided p-value <.001
    - Significant Temporal clustering, days 13-21
    - No elevations or statistical signals for 65+ for primary and first booster
    - Preliminary work does not appear to be driven by confounding with COVID-19 Disease, but the VSD is currently improving our algorithm which was based upon incident covid-19 disease definition only
- 18-64 year old's – an increased risk is identified, but not signaling. (RR 1.74) (currently would be underpowered probably to look at finer age categories)

- Next Steps – chart review questions:
    - NCK has reviewed 24 cases in the 11-21 days post Pfizer in 65+, PPV (21/24 were real incident ISTK 88%)
    - Onset date didn't shift for many
    - 62% did have flu vaccine co-admin on the same day – Fluzone HD is the predominant vaccine administered to the 65+ in VSD (79%)
        - New models will be ran adjusting for coadministration of flu vaccine and also stratifying by coadministration for flu vaccine

Extra Slides

ISTK RCA Primary Series Summary 65+ – data through May 2022

Analysis Parameters					Informative Counts and Follow-up				Analysis			
Outcome	**Vaccine**	**Risk Window**	**Comp Window**	**Dose**	**Risk Events**	**Comp Events**	**Risk Fwp (days)**	**Comp Fwp (days)**	**Rate Ratio**	**95% Lower CI**	**95% Upper CI**	**P-value**
ISTK	Primary Series	1-21	22-42	Both Doses	399	218	1852593	984378	1.09	0.89	1.33	0.4
			22-42	Dose 1	199	215	474162	639936	1.19	0.9	1.56	0.221
			22-42	Dose 2	199	202	853250	807229	1.04	0.83	1.31	0.714

ISTK RCA First Booster Summary 65+ – data through Sept 2022

Analysis Parameters					Informative Counts and Follow-up								
Outcome	**Primary**	**Extra Covariates**	**Risk Window**	**Comp Window**	**Risk Events**	**Comp Events**	**Risk Fwp (days)**	**Comp Fwp (days)**	**Rate Ratio**	**95% Lower CI**	**95% Upper CI**	**P-value**	**1-sided P-value**
Stroke, ischemic	Pfizer	None	1-21	22-42	116	168	320298	421118	0.86	0.67	1.11	0.246	0.89
		TSPS	1-21	22-42	116	166	245295	272222	0.88	0.68	1.13	0.306	0.862
		TSPS HR	1-21	22-42	115	166	154715	170250	0.86	0.67	1.12	0.264	0.882
		TSPS CvdHx	1-21	22-42	115	163	210826	246366	0.89	0.69	1.15	0.368	0.833

TSPS- Time Since Primary Series
HR – High Risk for Covid
CvdHx – Covid-19 Disease History

VSD COVID-19 RCA Analysis -- Bivalent Boosters AMI – week 1771

VSD COVID-19 RCA Analysis -- Bivalent Boosters 5+ years of Age															
Summary of Concurrent Comparator Analyses															
Analysis Parameters					Informative Counts and Follow-up				Nominal Analysis					Sequential Analysis	
Outcome	Age	Risk	Comp	Vaccine	Risk	Comp	Risk	Comp	Exact	Rate Ratio	95% Lower	95% Upper	P-value	1-sided	Signal
Event	Group	Interval	Interval	Type	Events	Events	Fwp	Fwp	Analysis	Estimate	Conf Limit	Conf Limit		P-valu	1-sided
		Days	Days				(days)	(days)							p < 0.01
AMI	18-64y	1-21	22-42	Both mRNA	30	21	101592	91309	Yes	1.11	0.62	2.01	0.733	0.422	no
			22-42	Pfizer	18	19	52939	49573	Yes	0.8	0.4	1.57	0.513	0.798	no
			22-42	Moderna	11	2	8832	7024	Yes	4.01	0.95	27.38	0.059	0.05	no
		1-42	43-84	Both mRNA	43	10	220818	92344	Yes	1.62	0.8	3.54	0.192	---	---
			43-84	Pfizer	30	10	113839	52591	Yes	1.29	0.6	2.92	0.536	---	---
			43-84	Moderna	11	0	15272	5146	Yes	.	0.85	.	0.074	---	---
	65+y	1-21	22-42	Both mRNA	95	68	337345	329510	Yes	1.31	0.95	1.82	0.099	0.058	no
			22-42	Pfizer	68	53	177550	190078	Yes	1.32	0.9	1.92	0.152	0.089	no
			22-42	Moderna	26	14	27710	21375	Yes	1.5	0.77	3.01	0.238	0.152	no
		1-42	43-84	Both mRNA	135	60	847298	487726	Yes	1.02	0.74	1.43	0.898	---	---
			43-84	Pfizer	95	47	441449	324728	Yes	1.14	0.78	1.69	0.497	---	---
			43-84	Moderna	35	13	63056	20460	Yes	0.8	0.41	1.62	0.508	---	---

From: "Wharton, Melinda (CDC/DDID/NCIRD/OD)" [redacted]
To: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
Cc: "Helfand, Rita (CDC/DDID/NCEZID/OD)" [redacted]
Subject: RE: proposed note to Center
Date: Thu, 15 Dec 2022 23:13:44 +0000
Importance: Normal

Thanks Tom. Would it be possible to either get the slides from this afternoon to review, or for Eric to run thru them for me again tomorrow?

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Thursday, December 15, 2022 5:35 PM
To: Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Helfand, Rita (CDC/DDID/NCEZID/OD) [redacted]
Subject: FW: proposed note to Center

FYSA. This is what will be going up to our center.

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)
Sent: Thursday, December 15, 2022 5:31 PM
To: Bell, Michael MD (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: proposed note to Center

See my suggestions below:

Dan, Deb;

Monitoring in the Vaccine Safety Datalink (VSD) has detected a statistical signal for bivalent Pfizer COVID-19 booster vaccination and ischemic stroke in 65yo and older recipients. The signal has persisted for several weeks now with a rate ratio (similar to relative risk) of around 1.9 with 95% CIs that do not include 1. You'll recall that VSD does ongoing analyses of EHR data from several integrated healthcare organizations to detect associations for pre-specified clinical outcomes. The VSD team is working with site investigators to conduct additional analyses to further assess the finding and confirm the signal. It will require confirmation over the coming weeks, especially since the parallel CMS data monitored at FDA are not showing a signal for Pfizer COVID-19 bivalent boosters and ischemic stroke, although the CMS data are limited at this point. FDA analyses are ongoing and more data are expected in the coming weeks. It is important to note that the finding of a statistical signal does not necessarily mean a finding of an increased risk. Signal assessment analyses can further evaluate for a causal association.

Wanting you to be aware given the WH and HHS intense push to increase uptake of the booster in that age group. Based on the current data, excess cases of ischemic stroke are estimated to be ~10/100,000. Given the co-administration of high dose flu vaccine (~40% of Bivalent recipients are getting both), that is being assessed as a potential factor as well. VSD monitoring is also detecting an elevated rate ratio for bivalent Pfizer COVID-19 booster vaccination and ischemic stroke in 18-64 yo but it has not yet reached the threshold for a statistical signal. No similar signal has been seen for Moderna, though uptake in VSD is less and later. FDA is aware per above, and an ACIP COVID-19 Vaccine Safety Technical WG call is scheduled in January to present the VSD and FDA CMS findings.

From: Bell, Michael MD (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Thursday, December 15, 2022 4:57 PM

To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: proposed note to Center

Dan, Deb;
Our Vaccine Safety Datalink (VSD) team has identified a possible association between Bivalent Pfizer booster and ischemic stroke in 65yo and older recipients. You'll recall that VSD does ongoing analyses of data from several HMOs to detect associations with clinical conditions. It will require confirmation over the coming weeks, especially since the parallel CMS data monitored at FDA are not showing that association so far. FDA analyses are ongoing as well.
Wanting you to be aware given the WH and HHS intense push to increase uptake of the booster in that age group. Excess cases of ischemic stroke is estimated to be ~10/100,000.
Given the co-administration of high dose flu vaccine (~40% of Bivalent recipients are getting both), that is being assessed as a potential factor as well.
No similar signal seen for Moderna, though uptake is less and later.

FDA is aware per above, and a VAST call is scheduled in January. (TOM: what does VAST stand for??)

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted] "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Shay, David (CDC/DDID/NCIRD/ID)" [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Fri, 3 Dec 2021 14:33:08 +0000
Importance: Normal

Sorry- In addition to FYI-
I did just speak to him on the phone for a while and he went through more details about his reasoning.

What do you all think?

I'm going through the paper now to see what would need to be removed and happy to connect with all of you this afternoon to discuss briefly if you have time.

Thanks,
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Friday, December 3, 2021 9:30 AM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted]; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]; Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Shay, David (CDC/DDID/NCIRD/ID) [redacted]
Subject: FW: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

FYI

Hannah

From: Menschik, David [redacted]
Sent: Friday, December 3, 2021 9:29 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted] Baer, Bethany (FDA/CBER) [redacted]
Cc: Shay, David (CDC/DDID/NCIRD/ID) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Hi Hannah,

Bethany and I have reviewed the comments from the Lancet ID Reviewers, and we agree with Reviewer #5's comment that disproportionality analysis is extremely limited when the background database has such a high proportion of reports involving the vaccine of interest. We acknowledged this in the limitations and understand that there is a considerable bias toward the null when using our data mining methods in this current, unprecedented situation. Therefore, we agree with the Lancet ID editor's comments on page 1 that it would be best to remove the disproportionality analysis from this paper. As the disproportionality analysis was the only aspect of this paper that Bethany and I were involved in, it would be most appropriate to remove Bethany and me from authorship on the paper.

Best,
David and Bethany

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, December 01, 2021 4:24 PM
To: Menschik, David [redacted] Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Importance: High

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear David and Bethany
I hope you are both well. I'm writing with news that we've received an invitation to **revise** the 6 month mRNA safety manuscript from The Lancet ID.

I'm attaching a document of their comments with our team's draft responses in red and **some specific flags in tracked changes for you re: data mining and questions about death 'causality'.**

Also attached is a tracked changes updated copy of the version that was submitted to them (and also revised to remove one duplicate myocarditis death report since submission), that I will clean for submission to them for your reference.

They have asked for comments by December 7- I apologize for the tight deadline, but if you're able to **send your feedback by COB Friday, 12/3**, that would be excellent- if you need more time, of course, let me know.

All the very best,
Hannah

From: [redacted] **On Behalf Of** Phoebe Hall
Sent: Tuesday, November 23, 2021 11:03 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: Your Submission THELANCETID-D-21-02703

Manuscript: THELANCETID-D-21-02703, Safety Monitoring of mRNA Vaccines Administered During the Initial 6 Months of the U.S. COVID-19 Vaccination Program: Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe

Dear Dr. Rosenblum,

Thank you for submitting your manuscript to *The Lancet Infectious Diseases*.

Your submission has now been assessed by external advisers and discussed by the Editorial team. We would like to invite you to REVISE your paper in light of the editorial and reviewers' comments below.

Please be aware that an invitation to revise does not imply acceptance. Our target revision time is 10 working days for normal track.

Comments to the Author:

We wonder whether the paper would be better if the inferential analyses were removed from the paper given concerns from the reviewers about the comparison of expected with observed mortality (which we note is based on a preprint and not adequately described in the Methods) and the disproportionality analysis. Please justify their inclusion if you wish to keep them in the paper.

Editorial points - IMPORTANT:

- The following points list items that **must be included before considered** further. Addressing them at this stage reduces the risk of errors and delays later.
- Please read the requirements below carefully and consult me or https://www.thelancet.com/preparing-your-manuscript, for further details or clarification if needed.
- Please note that not every point below will be relevant to your manuscript.

Authorship and reporting guidelines:

1. Please check that all author name spellings and affiliations are correct.
2. Please indicate any authors who are full professors.
3. Please list the highest degree for each author (one degree only, please).
4. Please follow the appropriate EQUATOR network reporting guidelines and include the corresponding checklist(s). These include: CONSORT reporting guidelines for randomised trials (http://www.consort-statement.org), STROBE for observational studies, PRISMA for systematic reviews, STARD for diagnostic studies, CHEERS for economic evaluations and RECORD for routinely collected health data. *Lancet* specific guidelines for reporting RCT and systematic reviews and meta analyses are available here:
http://www.thelancet.com/pb/assets/raw/Lancet/authors/Rctguidelines.pdf
https://thelancet.com/pb/assets/raw/Lancet/authors/metaguidelines.pdf

Title/summary:

5. Please ensure that the title of the paper is non-declamatory (i.e, it describes the aim of the study rather than the findings) and that it includes a description of the study type (e.g. a randomised controlled trial).
6. Please limit the summary to pre-defined primary endpoints and safety endpoints.
7. For RCTs, please state the trial registration number.

Methods:

8. At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit.
9. Please explain any deviations from the protocol.
10. Please ensure that all outcomes specified in the protocol (including all secondary outcomes) are reported in the manuscript. If there are any secondary endpoints that cannot be included please mention these explicitly and explain why and where they will be made available.
11. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses were post-hoc.
12. Please use rINNs for drug names. For genes and proteins, authors can use their preferred terminology so long as it is in current use by the community, but should provide the preferred name from Uniprot (http://www.uniprot.org/uniprot/) for proteins and HUGO (http://www.genenames.org) for genes at first use to assist non-specialists.
13. For drug studies, please ensure that details of doses, route of delivery, and schedule are included.

Results:

14. For the main outcome measures, please include a result for each group, plus a point estimate (eg, RR, HR) with a measure of precision (e.g, 95% CI) for the absolute difference between groups, in both the Summary and the main

Results section of the paper.

15. p-values should be given to two significant figures, but no longer than 4 decimal places (e.g. p<0.0001).
16. Please provide absolute numbers to accompany all percentages. Percentages should be rounded to whole numbers unless the study population is very large (>1000 individuals).
17. Please give 95% confidence intervals for hazard ratios/odds ratios.
18. For means, please provide standard deviation (or error, as appropriate).
19. Please provide interquartile ranges for medians.
20. Please provide numbers at risk for Kaplan-Meier plots and ensure that plots include a measure of effect (e.g, log-rank p); estimates should be reported with 95% CIs.

Discussion:

21. Please ensure that the Discussion contains a section on limitations of the study.

Additional requirements:

22. Please provide the text, tables, and figures in an editable format (eg, EPS files, PowerPoint files, depending on software used to produce them. If figures are composed of photographs or other images, high resolution files (300dpi or greater) should be provided. More information can be found here: https://www.thelancet.com/for-authors/forms?section=artwork.
23. References should be in Vancouver style. For references with six authors or fewer, all authors should be listed. For those with seven or more authors, only the first three authors and 'et al' should be listed. Please ensure that reference numbering throughout the manuscript is not inserted with electronic referencing software, such as Endnote, as this is incompatible with our production system (if used, please convert to normal text before resubmission). If the references “move” from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. All web references should have the exact date they were last accessed. With your revised submission please enclose copies of any papers cited as being 'in-press', along with a copy of the acceptance letter from the journal. References that are "submitted" should be removed and citations in the text replaced with "(unpublished data; authors)".
24. If accepted, only 5-6 non-text items (figures, tables, or panels) can be accommodated in the main paper; additional material can be provided in a web appendix. Please indicate which items can go in a web appendix.
25. Please provide a research in context panel with 3 parts: Evidence before this study (which includes a description of how you searched for evidence and how you assessed the quality of that evidence); Added value of the study; and Implications of all the available evidence.
26. At the end of the manuscript, please provide a Contributors statement that summarises the contribution of each author to the work. *The Lancet’s* journals require that more than one author has verified the underlying data in all research articles. Please state which author(s) have accessed and verified the data, and which author(s) were responsible for the decision to submit the manuscript.
27. At the end of the manuscript please summarise the declaration of interests for each author.
28. In the Contributors section list at least two authors who accessed and verified all the data.
29. If your author line has more than 20 authors, we very strongly encourage the use of a study group name. Collaborators' names and affiliations may be listed at the end of the paper or in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a list of names of all study group members presented as a two-column table in Word. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to appear on PubMed. The table will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly.
30. Please note our guideline length for research articles is 3500 words and 30 references. For RCTs, the text can be expanded to 4500 words.
31. All research articles must contain a data sharing statement, to be included at the end of the manuscript. For more information on these required statements see the Data sharing section of the Information for Authors (https://thelancet.com/pb-assets/Lancet/authors/tlid-info-for-authors.pdf) and (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31282-5/fulltext)

32. Please ensure that the funding source is stated in the Acknowledgement section.

Reviewers' Comments:

Note that reviewer numbers are allocated by the system at invitation and not at completion of reviews, so some numbers might be missing.

- In your point-by-point reply to the reviewers', please indicate the text changes which have been made (if any) and the line number on the tracked changes manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.]
- Please do not use boxes for responses as this slows assessment.
- When interpreting editorial points made by reviewers, please remember that we will edit the final manuscript if accepted.

Reviewer #2: Thank you very much for the opportunity to review this manuscript. The authors reviewed and summarised adverse events reported after COVID-19 vaccination with two mRNA vaccines based on reports from two vaccine-specific pharmacovigilance systems in the US, the Vaccine Adverse Events Reporting System and the active surveillance system v-safe.

The manuscript is very well written and provides important insight to spontaneously reported adverse events following mRNA vaccination, which should be available to a wide audience. With the broad rollout of mRNA COVID-vaccines in the US and worldwide, these results are reassuring and provide important information for the risk-benefit assessment of these vaccines.

Major comments:
* The reviewers missed some important information on selection bias in v-safe. Is it possible to compare the included participants to non-respondents? This would give important insight into the representativeness of the resulting data
* The authors present disproportionality measures for mortality from VAERS. It feels like a missed opportunity not to report these also for the other pre-specified AESI. Is this possible?
* The analyses of v-safe are purely descriptive. Is there any disproportionality or further analysis planned from this database?

Minor comments:
-Methods, p. 7 paragraph 1, line 5. What are the pre-specified AESI? Please provide a reference or refer to table 2 where the results for the AESI are presented.
-Discussion, p. 11 paragraph 2, line 1: "more health impact was reported […] received mRNA-1273 versus BNT162b2". While this is an interesting and relevant finding to report, there may have been differences (e.g. in terms of underlying comorbidities) between the patient collectives receiving the different vaccines. It might be worth considering adding a sentence in the discussion/limitations to highlight that this finding from spontaneous reports should not be interpreted in that one mRNA vaccine is "safer" than the other.
Table 1, Table 5: Race and Ethnicity are reported. The term "Unknown ethnicity", which is further split into subgroups entitled "White", "Black", "Asian" etc. is confusing for the reader as "unknown" should not have subgroups. Consider to rename or merge with "Non-Hispanic" if this refers to the same ethnic subgroups.

Reviewer #3: This is a very important report of the first 6 months of mRNA vaccine rollout as capture through the passive and active surveillance system.
The major limitations of this approach is not knowing the denominator and not knowing what portion of the population is being missed or not included because of the nature of how the data is being collected.
This is underscored by the demographics which show that both for passive surveillance and the active reports through V-safe the populations represented are largely White women between the ages of 18-60.
Realizing that many of the reactions both reactogenic and other are occurring in this demographic there is also the very real affect that this is reporting artifact and that we do need to understand to a much better extent what types of events are occurring in the populations not represented well is Vsafe in particular. This might be an opportunity on how to develop Vsafe into a program that is more inclusively represents age, sex and race. This is

captured in VSafe and VAERS does not capture race information. Perhaps trying to give some representative demographics (e.g. 6% of respondents are Blacks although they represent 12% of the US population). It would also be interesting to see if there are any geographic differences in where reports come from across the United States - by State, level of education and insured versus uninsured)
Otherwise I think the findings are important but somewhat expected in terms of the reactogenic symptoms higher in age <65 and women
Supplemental tables 2,3 and 4 are important but has vaccination disproportionately reduced death in COVID related morbidities in educated Whites.
The report is important and should be published and I guess I am thinking about this more in terms of the next steps for both VSafe and VAERS but particularly VSafe to be representative of the US population and more inclusive across age, race, sex, level of education and socioeconomic status. For the targeted reports of interest (myopericarditis, anaphylaxis) it would be helpful to see the data broken down by age and sex.
Although not the goal of Vsafe clearly important if socioeconomically disadvantage and uninsured individuals are vaccine hesitant because of fear of reactogenic events that would cause them to have unpaid time off work or visits to the ER.

There is a lot of data represented in this report but also of interest to know what happened with reporting of events as the vaccine rollout matured. Is it possible to show data from the first 3 months versus second 3 months. Women were more likely to be over-represented during the initial three months in view of healthcare rollout. It would be of interest if the reporting of any of the events including reactogenic events changed as time went on and there was more societal familiarity with these.

Reviewer #4: These are important data to publish as full transparency around AEs is necessary for public trust in vaccination and ending the pandemic. My questions and clarifications are as follows:
MAJOR COMMENTS
1. P5: Cause of death had ICD codes, covid related, or unknown but what about causality assessment to the vaccines? Is no standardized causality assessment performed? If not, wht not? The only mention of "vaccine related" is in supplemental table 3 and denotes only 4 deaths related to the vaccine, but what is the precedent for this very narrow definition? All AEs reported to FDA at minimum are marked unrelated, related, or possibly related. Causality assessments used in safety research can further refine.
2. P5/P7/Table 4: It is not at all clear to me that this is a fair or valid comparison to make. Deaths reported to VAERS are considered potentially related to the vaccine by reporters and not all deaths in vaccinated individuals are reported to VAERS. The comparison to all-cause mortality in vaccinated individuals appears flawed. Death within days of vaccination has a high suspicion of causality and deaths from other causes would not be expected to be spontaneously reported to VAERS. Background mortality rates from all causes are not surprisingly higher —the reporting of deaths to VAERS are only for deaths suspected potentially from the vaccine. I don't think this comparison is valid and to me, it undermines the message of transparency. It assumes when we as clinicians are reporting deaths, we do so indiscriminately but we don't. I considered the method of EB data mining with e EB05>2 a stronger way to assess any safety outliers in this paper and perhaps more focus should be placed on those methods and findings.
3. Regarding the death reports, it is critically important to specifically address whether any deaths were from the two known related serious AEs: anaphylaxis or myocarditis. This requires specific data and mention in the manuscript. Deaths from these within a reasonable time frame post vaccination would be causal. Really all of the special interest AEs in Table 2 would be useful to indicate deaths for transparency.

MINOR COMMENTS
4. P5: Is there a basis for the definition of serious used? Is this standard from prior vaccines?
5. P6: Time from vaccination to reported death is referred to as "onset interval" but is perhaps better described as latency?
6. VSD studies should also be mentioned in the discussion (Nicola Klein et al JAMA) as these provide more valid comparator groups for severe outcomes.
7. The increased reactogenicity symptoms are interesting in the younger/female. Did pregnancy impact this at all? higher or lower in the pregnant female compared to similar age non pregnant female?
8. The healthcare utilization and out of work time is impressive—were there any demographic predictors

associated with needing healthcare resource use or out of work?
9. Supp Table 2- Other is such a large category—what comprised other? Can anaphylaxis and myocarditis be added here?
10. Can any modelling of associated factors for severe outcomes or high reactogenicity be performed?

Reviewer #5: This article provides a picture of reports of AEFI in the first six months of utilization of mRNA COVID-19 vaccines in the United States. I think that similar reports are highly desirable to reassure the population about vaccine safety and therefore priority is high. However, in the attempt of providing more information, the study goes beyond the simple description of reports from VAERS and providing a survey of data collected by v-safe. Unfortunately, the authors made this step without providing important information to the readers. With the current information I cannot establish whether and to what extent the results deserve to be discussed with more caution.
Specific comments
Introduction (page 3) "We reviewed VAERS and v-safe […] vaccines were administered". Instead of providing a simple descriptive report of the data collected in these two databases the authors 1) calculated a rate of report of death and compared that with that expected in an unspecified vaccinated population and 2) performed a disproportionality analysis. These are objectives to be declared in the and text and in the abstract.
For the above mentioned analysis the authors did not included in the methods important information.
For the disproportionality analysis we have no information on the dataset. What were the vaccines included in the dataset? What was the proportion of COVID-19 vaccines? For the latter question, the authors reported in the limitation that in the analyzed period (we know only that they included reports up to June 14th, 2021 but we have not the initial date) the great majority of reports was for the vaccines of interest. If this proportion is over 90% the possibility of identifying a signal was likely close to zero. So, why performing such an analysis?
For the comparison of mortality rates we have not information about the comparator: does it refers to mortality following immunization with any vaccine? From the reference number 20 it seems that this rate was calculated (how?) only for COVID-19 vaccines? So what is the rationale for this comparison? Estimating the under-reporting of fatal cases? Estimating the number of reports over a mortality for any cause that was attributed to vaccines (not accidental) by reporters? What was the period in which mortality was calculated in the reference? 14 days after vaccination or longer? In summary, I think that these two rates cannot be compared or should be interpreted in a different way, at least with the details of information provided by the authors.
Page 7: "there were 4,496 reports of death…." Were all these reports from US? Did the VAERS include reports from other countries? I suppose these fatal cases have been occurred all in the US since the authors used this number to estimate the reporting rate for fatal cases using the number of doses of vaccines administered in the US. If this is the case, it should be clearly stated.
Page 8: "During the analytic period, 7,914,583 mRNA COVID-19 vaccine recipients […]". How many patients dropped out after the initial enrolment? In case the drop-out is quite high (as I suppose) the authors should compare the population included in the analysis with the population dropped out to check for a possible selection that could have had an impact on the results.
Page 10 "Analysis of deaths reported to VAERS demonstrated lower than expected reported mortality rates compared to background mortality rates". Besides my doubt about comparability given the lack of essential information, why the authors wrote "than expected"? I would have bet whatever I have that the rate was lower than that estimated for a background mortality for two reasons: 1) under-reporting and 2) background mortality include death for any cause while VAERS includes only deaths that have been somehow associated with the immunization. The authors included an interpretation similar to mine in the "limitations" section. So they likely expected this results as well.

Reviewer #6: Thank you for the opportunity to review this paper. It is an interesting an important piece of research.

I would like to have seen very clear research questions rather than a broad aim of "We review VAERS and v-safe data during the first 6 months of the U.S. vaccination program, when >298 million doses of mRNA COVID-19 vaccines were administered."

There is a lot of data so I would like to see a a STROBE Statement—Checklist of items that should be included

in reports of cohort studies, and a CONSORT style flow chart showing for each vaccine the flow e.g. Overall recipients at dose 1, then at dose 2, and how many recipients reported through VAERS and how many completed V-safe survey reports from days 0-7 - split by vaccine type. This will make it easier to follow the tables.

All VAERS reports for mRNA vaccines were submitted and processed from December 14, 2020 through June 14, 2021, inclusive of any interval from vaccination to event report. Could this mean that some recipients were not followed up for the full 6 weeks post dose, e.g. had their vaccine in early June?

Vsafe participants receive text messages that link to web-based health check-in surveys following vaccination, initially daily (days 0-7), then at longer intervals post vaccination. The system resets to the initial survey frequency after entry of another dose. Does this mean that the information relates to either dose 1 or dose 2.

Table 1: I would recommend this table only show the descriptive characteristics of the vaccine recipients, not the the outcomes e.g. Reports, Signs or symptoms most frequently reported, nonserious, and Signs or symptoms most frequently reported, serious. Linking to above, this should be by dose (e.g. Table 5 could replace this). Did all those who are presented in Table 5 as having first dose, then be those who also had their second does e.g. for BNT162b2 vaccine second doses=1,861,599 from 2,150,068 who had first dose - or are could these be a different groups?

Table 2 shows the Reports (as in Table 1) and Reports of adverse events of special interest. It should also include Signs or symptoms most frequently reported, nonserious, and Signs or symptoms most frequently reported, serious (as presented in Table 2).

Deaths were recorded as in the 7 days and 42 days (6 weeks) post vaccination - needs to split by dose 1 and 2. Time interval to death following vaccination was available for 4,119 reports (92·1%); median time interval was 10·0 days (range: 0—161 days). The greatest number of death reports occurred on day 1 (10·5%) and day 2 (7·0%) following vaccination (Supplemental Figure 1). There are clear differences between vaccines here. This might be better as a Kaplan Meier plot and as there are apparent differences by vaccine type - could survival analysis be done here to compare them, adjusting for characteristics and allowing for censoring.

Of the 4,472 reports of deaths analyzed, 2,087 (46·7%) were reported following BNT162b2 and 2,385 (53·3%) following mRNA-1273 - should any statistical comparison made here, adjusting by recipient characteristics? e.g. Females accounted for 42·6% of reported deaths (can this be split by vaccine type), and adjustments are needed as in Table 1 44.0% and 41.4% of the recipients were female.

During the analytic period, VAERS received and processed a total of 340,522 reports: 164,669 following BNT162b2 and 175,816 following mRNA-1273 vaccination (Table 1). Were these individual participants or could one recipient report more than once? How many recipients did not report e.g. had no side effects?

During the analytic period, 7,914,583 mRNA COVID-19 vaccine recipients enrolled in v-safe and completed at least one post-vaccination health survey during days 0-7 (Table 5). What is this as a proportion? A total of 6,775,515 participants completed at least one survey during day 0-7 after dose (3,455,778 following BNT162b2; 3,319,737 following mRNA-1273). Why do these numbers not match?

A clear limitation of this data is a lack of analysis on the time from vaccine (dose 1 and/or dose 2), and time to side effect or adverse event. Also a lack of statistical comparison between the vaccines as there are some differences - however if the aim is not to compare vaccines, splitting the sessions by vaccine might make the paper easier to read.

TECHNICAL INFORMATION:

When you submit the revised paper, please provide the following:

1. One "clean" copy of your manuscript
2. One copy where your changes are highlighted (tracked changes).
3. A separate, point by point response to the editorial and referee comments typed immediately following each specific point above. Please do not use boxes for responses.
4. Any images and/or tables (even if no revisions have been made).

Please do NOT include a copy of your original manuscript. All text files should be supplied as MS Word files.

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To submit your revised manuscript, please visit *The Lancet Infectious Diseases's* Online Submission and Peer Review Website at: https://www.editorialmanager.com/thelancetid/ and enter your username and password.

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After you have entered your account details, remember to click the 'Author' button. You will see a menu item call 'Submission Needing Revision'. You will find your submission record there.

We ask all authors of, and all contributors (including medical writers and editors) to specify their conflicts of interest (if any) and individual contributions to a manuscript under consideration at *The Lancet Infectious Diseases*. *The Lancet Infectious Diseases* will not publish any articles unless we have a completed author statement form, conflict of interest form, and the signatures of all authors. Please sign and complete the author statement form and the ICMJE conflicts of interest statement form, and either upload the signed copies in to EM with your manuscript, or scan and email to [redacted] In addition, please also include written consent of any cited individual(s) noted in acknowledgements or personal communications.

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The editors may use such information as a basis for editorial decisions and will publish such disclosures if they are believed to be important to readers in judging the manuscript.

In summary, the signed statements we require are:

- Authors' contribution and signatures
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Yours sincerely,

Phoebe Hall
Senior Editor

The Lancet Infectious Diseases

From: "Wharton, Melinda (CDC/DDID/NCIRD/OD)" [redacted]
To: "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
Subject: RE: slides
Date: Fri, 16 Dec 2022 13:36:49 +0000
Importance: Normal

Probably but not until January.

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, December 16, 2022 8:35 AM
To: Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: slides

Do you think that VaST needs to see this before Jan 23?

From: Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Sent: Friday, December 16, 2022 8:33 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: slides

Thanks – can I share with Sara O.? (I just talked to her.) Think the risk of stroke post COVID is relevant for risk-benefit assessment.

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Friday, December 16, 2022 8:28 AM
To: Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: FW: slides

Feel free to use these slides to brief folks in CDC or to share with selected CDC staff but please treat as confidential.
Thanks.
Tom

From: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24
Date: Tue, 21 Feb 2023 19:00:06 +0000
Importance: Normal
Inline-Images: image001.png

Adding edit dropped in this suggestion earlier.
Karen

From: Broder, Karen (CDC/DDID/NCEZID/DHQP)
Sent: Tuesday, February 21, 2023 1:51 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

What about

- Cause of the increased rate ration is unclear; potential contributing factors include simultaneous administration of **bivalent COVID-19 booster** and influenzas vaccine (most VSD participants aged≥ 65 years received high-dose influenza vaccine in 2022-23 season) or unmeasured confounding.

Karen

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Tuesday, February 21, 2023 1:44 PM
To: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

Fine, but keep in mind that high-dose was mostly administered to 65+ y/o in VSD so that could be confounding by indication. VSD providers appear to have followed the preferential recommendations for HD in the elderly.

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Tuesday, February 21, 2023 1:40 PM
To: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: VaST assessment - draft slides for ACIP Feb 24

I wanted you to see this email exchange.

From: Edwards, Kathryn [redacted]
Sent: Tuesday, February 21, 2023 1:24 PM
To: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Daley, Matt [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted] Lee, Grace [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda

(CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

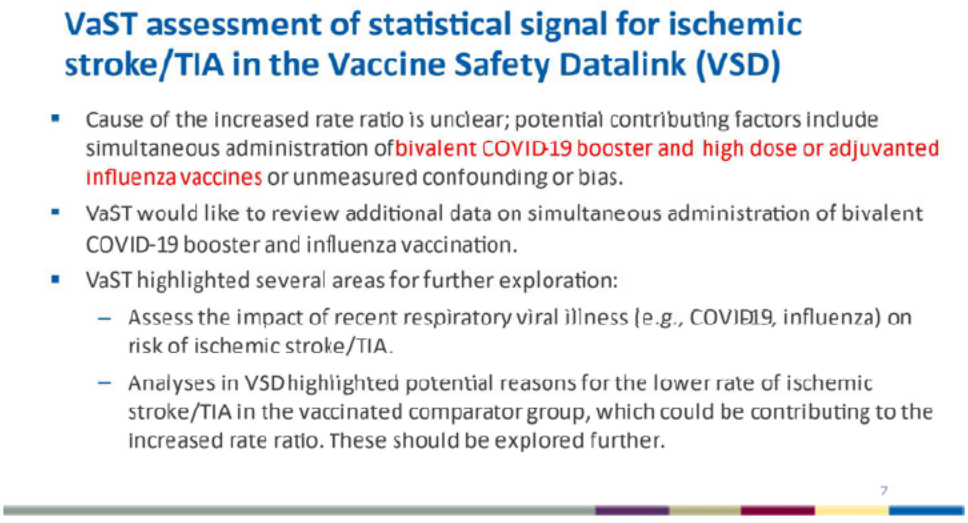
Yes, it was almost all high dose. I really think that needs to be added because it definitely was not associated with all influenza vaccines, only the high dose.

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Tuesday, February 21, 2023 11:41 AM
To: Edwards, Kathryn [redacted] Daley, Matt [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted] Lee, Grace [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

Good suggestion. I think it was almost all high dose and will add that after checking with ISO

From: Edwards, Kathryn [redacted]
Sent: Tuesday, February 21, 2023 12:38 PM
To: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Daley, Matt [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted] Lee, Grace [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

I am fine with all this but would add that the influenza administration was high dose or adjuvanted and not all flu vaccines. I have copied my edits to that slide for you to consider.



VaST assessment of statistical signal for ischemic stroke/TIA in the Vaccine Safety Datalink (VSD)

- Cause of the increased rate ratio is unclear; potential contributing factors include simultaneous administration of bivalent COVID-19 booster and high dose or adjuvanted influenza vaccines or unmeasured confounding or bias.
- VaST would like to review additional data on simultaneous administration of bivalent COVID-19 booster and influenza vaccination.
- VaST highlighted several areas for further exploration:
  - Assess the impact of recent respiratory viral illness (e.g., COVID19, influenza) on risk of ischemic stroke/TIA.
  - Analyses in VSD highlighted potential reasons for the lower rate of ischemic stroke/TIA in the vaccinated comparator group, which could be contributing to the increased rate ratio. These should be explored further.

7

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Tuesday, February 21, 2023 11:24 AM
To: Daley, Matt [redacted] Edwards, Kathryn [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted] Lee, Grace [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted];

Riley, Laura [redacted]; Schechter, Robert [redacted]; Talbot, H. Keipp [redacted]; Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

Dear all,

Thanks again for everyone's comments. In a meeting today with VaST chairs and ISO, some additional changes were made for accuracy, wording consistency with other presentations in the session, and clarity. We also deleted slide 4. Attached is draft version 3.

Lauri

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Monday, February 20, 2023 11:25 AM
To: Edwards, Kathryn [redacted]; Matthew Daley [redacted]; Lee, Grace [redacted]
Cc: Hopkins, Bob [redacted] Lisa A Jackson [redacted]; Jennifer L Nelson [redacted]; McNally, Veronica [redacted] Patricia Whitley-Williams [redacted]; Riley, Laura [redacted]; Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

In the attached are responses to Kathy's helpful comments and edits.

Thanks to all for reviewing. As soon as I have feedback from ISO on slide 4, I will send an updated clean version.

Lauri

From: Edwards, Kathryn [redacted]
Sent: Monday, February 20, 2023 11:15 AM
To: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Matthew Daley [redacted] Lee, Grace [redacted]
Cc: Hopkins, Bob <hopkinsroberth [redacted] Lisa A Jackson <Lisa.A.Jackson [redacted] Jennifer L Nelson [redacted]; McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted]; Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: Re: VaST assessment - draft slides for ACIP Feb 24

Thx

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From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Monday, February 20, 2023 10:12:58 AM
To: Edwards, Kathryn [redacted]; Matthew Daley [redacted] Lee, Grace <GMLee [redacted]
Cc: Hopkins, Bob [redacted] Lisa A Jackson [redacted] Jennifer L Nelson [redacted] McNally, Veronica [redacted]; Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda

(CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

Hemorrhagic stroke is a separate prespecified outcome in VSD.

From: Edwards, Kathryn [redacted]
Sent: Monday, February 20, 2023 10:23 AM
To: Matthew Daley [redacted] Lee, Grace [redacted]
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Hopkins, Bob [redacted] Lisa A Jackson [redacted] Jennifer L Nelson [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: Re: VaST assessment - draft slides for ACIP Feb 24

I talked with my hypertension colleagues, and they said that poorly controlled hypertension leads to hemorrhagic stroke. Could the two vaccines together make you hypertensive? Unlikely. K

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From: Matthew Daley [redacted]
Sent: Monday, February 20, 2023 8:34:07 AM
To: Lee, Grace [redacted] Edwards, Kathryn [redacted]
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Hopkins, Bob [redacted] Lisa A Jackson [redacted] Jennifer L Nelson [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: RE: VaST assessment - draft slides for ACIP Feb 24

Hello all.
Can we confirm (perhaps with Tom S) the answer to Kathy's question about hemorrhagic stroke? Examined and no signal, versus not examined, in VSD and other systems? Agree with Kathy's suggestions.
Thanks,
Matt

From: Lee, Grace [redacted]
Sent: Monday, February 20, 2023 6:00 AM
To: Edwards, Kathryn [redacted]
Cc: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Matthew Daley [redacted] Hopkins, Bob [redacted] Lisa A Jackson [redacted] Jennifer L Nelson [redacted] McNally, Veronica [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Schechter, Robert [redacted] Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: Re: VaST assessment - draft slides for ACIP Feb 24

Thanks Lauri and Kathy. Agree with Kathy's suggestions.
Best

Grace

On Feb 20, 2023, at 4:00 AM, Edwards, Kathryn [redacted] wrote:

Thanks so much Lauri. I have added some questions, comments and some suggested rewording.

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, February 19, 2023 4:25 PM
To: Daley, Matt [redacted]; Edwards, Kathryn [redacted]; Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted]; Lee, Grace [redacted]; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]; McNally, Veronica [redacted] Patricia Whitley-Williams [redacted]; Riley, Laura [redacted]; Schechter, Robert [redacted]; Talbot, H. Keipp [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: VaST assessment - draft slides for ACIP Feb 24

Dear all,

Attached is the short (9 slides) draft VaST presentation for the ACIP meeting on Feb 24. There are 2 slides for ischemic stroke/TIA, 1 slide for myocarditis/pericarditis, and 1 slide for VaST future plans.

Let us know if there are any comments or edits by Wednesday.

Lauri and Melinda

[**WARNING** : This email came from an external source. Please treat this message with additional caution.]
<VaST_ACIP 02_24_2023_draftke.pptx>

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted] "Liu, Ruiling (CDC/NIOSH/WTCHP)" [redacted], "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted] "Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted], "Strid, Penelope (CDC/DDNID/NCCDPHP/DRH)" [redacted], "Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP)" [redacted], "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted], "Myers, Tanya R. (CDC/DDID/NCEZID/DHQP)" [redacted] "Hause, Anne M. (CDC/DDID/NCEZID/DHQP)" [redacted] "Menschik, David (FDA/CBER)" <David.Menschik[redacted], "Baer, Bethany (FDA/CBER)" <Bethany.Baer[redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted], "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Shay, David (CDC/DDID/NCIRD/ID)" [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
Subject: 6 month mRNA safety review posted to medRxiv
Date: Thu, 28 Oct 2021 15:06:11 +0000
Importance: Normal

Good morning all,
I'm writing to let you know that the medRxiv version of the 6 month mRNA safety review has posted.
The link is here: https://www.medrxiv.org/content/10.1101/2021.10.26.21265261v1

Our submission is being processed by The Lancet Infectious Diseases – will keep you updated on that status.

Thanks so very much for all of your work on this for the past 6 months!
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Monday, October 25, 2021 10:26 AM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]; Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted] Menschik, David (FDA/CBER) <David.Menschik[redacted]>; Baer, Bethany (FDA/CBER) <Bethany.Baer[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: 6 month safety review for journal submission- please fill out author contribution by noon 10/26
Importance: High

Good morning co-authors:

The manuscript reviewing six months of mRNA safety data is ready for submission to Lancet ID. Before submission could you please:

1) Review your affiliation, name, and degree on the attached version's title page. Lancet ID only allows use of one degree, so if you have multiple, I had to choose one. Please correct me if I did not choose your intended degree.

2) Complete the attached Author contribution form. I selected roles for each of you- if you agree with this designation please sign the form and send back to me. If you wish to edit your roles, that's fine- just let me know.

3) Only if you have not filled out the ICMJE COI form already, please send me back a copy.

If you can complete these tasks ASAP or by **noon tomorrow, 10/26**, I'd be very grateful!

Thanks everyone and thank you so much for all of your work on this.

All the best,
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Friday, October 22, 2021 9:52 AM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted]; Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted] Menschik, David (FDA/CBER) [redacted]; Baer, Bethany (FDA/CBER) [redacted]; Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: 6 month safety review-COI form- please fill out and send back by COB 10/21

Good morning all,
Attached is a copy of the clean version that is being submitted for posting to medRxiv.
Thanks to all of you for your hard work on this.

Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Wednesday, October 20, 2021 6:16 PM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP [redacted] Menschik, David (FDA/CBER) [redacted]; Baer, Bethany (FDA/CBER) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: 6 month safety review-COI form- please fill out and send back by COB 10/21

Dear co-authors,

Thanks so so much for all of your hard work and feedback on the 6 month safety review manuscript. The paper has been through CDC and FDA clearance, and is in final revision stages. Our plan is to submit to the medRxiv pre-print server, to be followed by journal submission shortly therefore.

I will send a revised draft for all of you to review in the next day or two- **in the meantime, could you please complete and return the attached COI form with your name, the date and any disclosures by COB tomorrow, 10/21/21?**

Thanks so very much,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

HPV Team, Viral Vaccine-Preventable Diseases Branch
Division of Viral Diseases, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

From: "Cunningham, Fran (Associate Chief Consultant, PBM)" [redacted]
To: "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted] "Wharton, Melinda (CDC/DDID/NCIRD/OD)" [redacted]
Subject: RE: VaST
Date: Mon, 20 Mar 2023 15:39:54 +0000
Importance: Normal

Hi Lauri – Thanks. We are continuing our monitoring of the bivalent vaccine both through RCA and for ischemic stroke as full studies. We can summarize where we are to date with the analysis if you'd like and send along as slides or just plan to present the updated information and full study results to the ACIP Workgroup once completed which should be within the next month or so. I can also plan to update the VA ADERS data for both the monovalent and bivalent as part of the minutes regardless. I'll be happy to do whatever will work best for the group!

Thanks,
Fran

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, March 17, 2023 3:29 PM
To: Cunningham, Fran (Associate Chief Consultant, PBM) [redacted]
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted]
Subject: [EXTERNAL] VaST

Dear Fran,

At present, our last VaST call is planned for March 27, at which time the VSD will give their summary presentation.
You gave a summary of VA monitoring data to VaST in November 2022 (we initially thought we were going to transition the COVID-19 vaccine safety data review to the ACIP COVID-19 Vaccines Work Group at the end of 2022). However, I know the VA has more data and, of course, all of the vaccine safety monitoring is ongoing. I think that further data could be presented to the ACIP COVID-19 Vaccines Work Group after the transition occurs, or you can share slides to be distributed to VaST before the end of March.

The VA has been such a vital member of VaST and I wanted to make sure you were aware of the planned transition.

Regards,
Lauri

Lauri Markowitz, MD
VaST Co-Lead
CDC COVID-19 Response, Vaccine Task Force
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

From: "Cunningham, Fran (Associate Chief Consultant, PBM)" [redacted]
To: "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
Subject: RE: VaST minutes
Date: Fri, 13 Jan 2023 17:22:19 +0000
Importance: Normal

Hi Lauri! This looks good. I made a few edits below, highlighted in red. Have a great weekend!

Veterans Affairs (verbal update) – Dr. Fran Cunningham (VA)
Dr. Cunningham provided a verbal update on adverse events following bivalent vaccines in the VA active surveillance system. The overall uptake for bivalent vaccine was slower than anticipated – 377k Moderna and 376k Pfizer-BioNTech doses administered. The historical comparator analysis includes events in the 1-21 day window, except for anaphylaxis which is 1 day. The rate ratio was < 1 for ischemic stroke/TIA following Moderna and Pfizer-BioNTech bivalent booster vaccine. The rate ratio was also < 1 among persons aged ≥ 65 years (Moderna: 277k; Pfizer-BioNTech: 264k). VA is now working on a companion surveillance analysis using target trial emulation method for bivalent vaccines, comparing mRNA vaccinees to a non-vaccinated population as well as those who received influenza vaccine only and those who received both influenza and bivalent vaccines. VA is also conducting a bivalent vaccine cohort study to assess pertinent outcomes (including AMI, ischemic stroke) using continuous VA users only, adjusting for relevant baseline co-morbid conditions.

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, January 12, 2023 3:44 PM
To: Cunningham, Fran (Associate Chief Consultant, PBM) [redacted]
Subject: [EXTERNAL] VaST minutes

Hi Fran,
Can you look over this short paragraph. Does this look right to you?
Thank you!
Lauri

Veterans Affairs (verbal update) – Dr. Fran Cunningham (VA)
Dr. Cunningham provided a verbal update on adverse events following bivalent vaccines in the VA active surveillance system. The overall uptake for bivalent vaccine was slower than anticipated – 377k Moderna and 376k Pfizer-BioNTech doses administered. The historical comparator analysis includes events in the 1-21 day window, except for anaphylaxis which is shorter. The rate ratio was < 1 for ischemic stroke/TIA following Moderna and Pfizer-BioNTech bivalent booster vaccine. The rate ratio was also < 1 among persons aged ≥ 65 years (Moderna: 277k; Pfizer-BioNTech: 264k). VA is now working on a target trial emulation method for bivalent vaccines, comparing mRNA vaccinees to a non-vaccinated population for different combinations/cohorts.

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted] "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted] "Shay, David (CDC/DDID/NCIRD/ID)" [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: FW: Your Submission THELANCETID-D-21-02703R1
Date: Thu, 23 Dec 2021 15:00:45 +0000
Importance: High
Attachments: THELANCETID-D-21-02703_R1.pdf

Hi all,
Another holiday- another Lancet revision! 😊
There are many minor issues in the comments (attached PDF) and some in the email below, but the main issue I have highlighted in yellow below. The editor would like the mortality analysis removed entirely and more explanation about VAERS added.

I know many are already on leave, and I will be out next week through 1/4/22. Revisions are due back **1/10** so hopefully it will work to all connect during the first week of January about next steps. I'll send a Teams invite and share another document for editing shortly.

Hope everyone is getting some rest during the next few weeks!

Hannah

From: [redacted]
<[redacted]> **On Behalf Of** Phoebe Hall
Sent: Thursday, December 23, 2021 9:43 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: Your Submission THELANCETID-D-21-02703R1

Manuscript: THELANCETID-D-21-02703R1, Safety Monitoring of mRNA Vaccines Administered During the Initial 6 Months of the U.S. COVID-19 Vaccination Program: Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe

Dear Dr. Rosenblum,

Thank you for submitting your manuscript to *The Lancet Infectious Diseases*.

Your submission has now been assessed by external advisers and discussed by the Editorial team. We would like to invite you to REVISE your paper in light of the editorial and reviewers' comments below:

Please be aware that an invitation to revise does not imply acceptance. Our target revision time is 10 working days (due Jan 10), although please let me know if you will need a few extra days because of absences during the holiday period.

Comments to the Author:
We do not entirely agree with all of the points raised by reviewer 6. The point about baseline and multiple reporting of symptoms is a limitation of VAERS not of the paper or analysis. We don't mind that table 1 includes outcome data because it's describing the reasons why reports were submitted and these outcomes are the reasons.

We do not think that a comparison by dose and vaccine type would be appropriate because of the spontaneous reporting nature of VAERS.

We do, however, agree that the mortality analysis is not appropriate. The method is barely described and it's based on a non-peer-reviewed preprint. We think it is questionable whether a spontaneous reporting system should be used for this sort of analysis. Finally, how are we supposed to interpret the findings? The rates of deaths are way below the expected rates in the population, for which we cannot think of an explanation, other than it's not appropriate to use the reporting system for this analysis. We'd prefer that you remove this analysis.

For our readers, it would be helpful if you could describe in the paper the reasons why VAERS was established in the first place and the limitations of this sort of adverse event reporting system. Please also say whether this first 6 months of adverse event surveillance highlighted any safety signals that led to further investigation (myocarditis?), and if so what were the conclusions of those investigations.

Finally, please carefully address the editorial points below and the comments on your manuscript in the attached PDF. The points below were not addressed in the previous revision.

Editorial points - IMPORTANT:

- The following points list items that **must be included before considered** further. Addressing them at this stage reduces the risk of errors and delays later.
- Please read the requirements below carefully and consult me or https://www.thelancet.com/preparing-your-manuscript, for further details or clarification if needed.
- Please note that not every point below will be relevant to your manuscript.

Authorship and reporting guidelines:

1. Please check that all author name spellings and affiliations are correct.
2. Please indicate any authors who are full professors.
3. Please list the highest degree for each author (one degree only, please).
4. Please follow the appropriate EQUATOR network reporting guidelines and include the corresponding checklist(s). These include: CONSORT reporting guidelines for randomised trials (http://www.consort-statement.org), STROBE for observational studies, PRISMA for systematic reviews, STARD for diagnostic studies, CHEERS for economic evaluations and RECORD for routinely collected health data. *Lancet* specific guidelines for reporting RCT and systematic reviews and meta analyses are available here:
   http://www.thelancet.com/pb/assets/raw/Lancet/authors/Rctguidelines.pdf
   https://thelancet.com/pb/assets/raw/Lancet/authors/metaguidelines.pdf

Title/summary:

5. Please ensure that the title of the paper is non-declamatory (i.e, it describes the aim of the study rather than the findings) and that it includes a description of the study type (e.g. a randomised controlled trial).
6. Please limit the summary to pre-defined primary endpoints and safety endpoints.
7. For RCTs, please state the trial registration number.

Methods:

8. At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit.
9. Please explain any deviations from the protocol.
10. Please ensure that all outcomes specified in the protocol (including all secondary outcomes) are reported in the manuscript. If there are any secondary endpoints that cannot be included please mention these explicitly and explain why and where they will be made available.

11. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses were post-hoc.
12. Please use rINNs for drug names. For genes and proteins, authors can use their preferred terminology so long as it is in current use by the community, but should provide the preferred name from Uniprot (http://www.uniprot.org/uniprot/) for proteins and HUGO (http://www.genenames.org) for genes at first use to assist non-specialists.
13. For drug studies, please ensure that details of doses, route of delivery, and schedule are included.

Results:

14. For the main outcome measures, please include a result for each group, plus a point estimate (eg, RR, HR) with a measure of precision (e.g, 95% CI) for the absolute difference between groups, in both the Summary and the main Results section of the paper.
15. p-values should be given to two significant figures, but no longer than 4 decimal places (e.g. p<0.0001).
16. Please provide absolute numbers to accompany all percentages. Percentages should be rounded to whole numbers unless the study population is very large (>1000 individuals).
17. Please give 95% confidence intervals for hazard ratios/odds ratios.
18. For means, please provide standard deviation (or error, as appropriate).
19. Please provide interquartile ranges for medians.
20. Please provide numbers at risk for Kaplan-Meier plots and ensure that plots include a measure of effect (e.g, log-rank p); estimates should be reported with 95% CIs.

Discussion:

21. Please ensure that the Discussion contains a section on limitations of the study.

Additional requirements:

22. Please provide the text, tables, and figures in an editable format (eg, EPS files, PowerPoint files, depending on software used to produce them. If figures are composed of photographs or other images, high resolution files (300dpi or greater) should be provided. More information can be found here: https://www.thelancet.com/for-authors/forms?section=artwork.
23. References should be in Vancouver style. For references with six authors or fewer, all authors should be listed. For those with seven or more authors, only the first three authors and 'et al' should be listed. Please ensure that reference numbering throughout the manuscript is not inserted with electronic referencing software, such as Endnote, as this is incompatible with our production system (if used, please convert to normal text before resubmission). If the references “move” from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. All web references should have the exact date they were last accessed. With your revised submission please enclose copies of any papers cited as being 'in-press', along with a copy of the acceptance letter from the journal. References that are "submitted" should be removed and citations in the text replaced with "(unpublished data; authors)".
24. If accepted, only 5-6 non-text items (figures, tables, or panels) can be accommodated in the main paper; additional material can be provided in a web appendix. Please indicate which items can go in a web appendix.
25. Please provide a research in context panel with 3 parts: Evidence before this study (which includes a description of how you searched for evidence and how you assessed the quality of that evidence); Added value of the study; and Implications of all the available evidence.
26. At the end of the manuscript, please provide a Contributors statement that summarises the contribution of each author to the work. *The Lancet's* journals require that more than one author has verified the underlying data in all research articles. Please state which author(s) have accessed and verified the data, and which author(s) were responsible for the decision to submit the manuscript.
27. At the end of the manuscript please summarise the declaration of interests for each author.
28. In the Contributors section list at least two authors who accessed and verified all the data.

29. If your author line has more than 20 authors, we very strongly encourage the use of a study group name. Collaborators' names and affiliations may be listed at the end of the paper or in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a list of names of all study group members presented as a two-column table in Word. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to appear on PubMed. The table will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly.
30. Please note our guideline length for research articles is 3500 words and 30 references. For RCTs, the text can be expanded to 4500 words.
31. All research articles must contain a data sharing statement, to be included at the end of the manuscript. For more information on these required statements see the Data sharing section of the Information for Authors (https://thelancet.com/pb-assets/Lancet/authors/tlid-info-for-authors.pdf) and (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31282-5/fulltext)
32. Please ensure that the funding source is stated in the Acknowledgement section.

Reviewers' Comments:

Note that reviewer numbers are allocated by the system at invitation and not at completion of reviews, so some numbers might be missing.

- In your point-by-point reply to the reviewers', please indicate the text changes which have been made (if any) and the line number on the tracked changes manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.]
- Please do not use boxes for responses as this slows assessment.
- When interpreting editorial points made by reviewers, please remember that we will edit the final manuscript if accepted.

Reviewer #5: The authors provided a satisfactory reply to my queries. I have no more comments.

Reviewer #6: There are still no clear research questions.
A STROBE statement is now included.
There is still an issue with baseline (how many had no symptoms) and multiple reporting of symptoms.
There is no comparison of dose or vaccine type.
Table 1 still includes outcome data.
I still do not think that the analysis of mortality is robust. As median has been quoted, it should be possible to use cox regression to adjust for age and gender.

TECHNICAL INFORMATION:

When you submit the revised paper, please provide the following:

1. One "clean" copy of your manuscript
2. One copy where your changes are highlighted (tracked changes).
3. A separate, point by point response to the editorial and referee comments typed immediately following each specific point above. Please do not use boxes for responses.
4. Any images and/or tables (even if no revisions have been made).

Please do NOT include a copy of your original manuscript. All text files should be supplied as MS Word files.

Please also supply the word count for the body of your paper and your abstract (word count for the body of your paper should not include abstract, references, figures or tables).

To enable readers to better appreciate research findings and to encourage full and transparent reporting of outcomes, *The Lancet* family journals offer to publish a webaddress in accepted paper that links to the study's protocol on the author's institutional website (see Lancet 2009; 373: 992). This is particularly encouraged for randomised controlled trials, but is welcome for all types of research.

To submit your revised manuscript, please visit *The Lancet Infectious Diseases's* Online Submission and Peer Review Website at: https://www.editorialmanager.com/thelancetid/ and enter your username and password.

Your username is: Your username is: [redacted]
If you need to retrieve password details, please go to: click here to reset your password

After you have entered your account details, remember to click the 'Author' button. You will see a menu item call 'Submission Needing Revision'. You will find your submission record there.

We ask all authors of, and all contributors (including medical writers and editors) to specify their conflicts of interest (if any) and individual contributions to a manuscript under consideration at *The Lancet Infectious Diseases*. *The Lancet Infectious Diseases* will not publish any articles unless we have a completed author statement form, conflict of interest form, and the signatures of all authors. Please sign and complete the author statement form and the ICMJE conflicts of interest statement form, and either upload the signed copies in to EM with your manuscript, or scan and email to [redacted] In addition, please also include written consent of any cited individual(s) noted in acknowledgements or personal communications.

The Lancet Infectious Diseases's requirements are described in more detail at the Information for Authors page at: https://www.thelancet.com/pb-assets/Lancet/authors/tlid-info-for-authors.pdf

The editors may use such information as a basis for editorial decisions and will publish such disclosures if they are believed to be important to readers in judging the manuscript.

In summary, the signed statements we require are:

- Authors' contribution and signatures
- Signed Conflict of interest statement for ALL authors

Please also check whether you need to provide the following:

- Signed copyright permissions for previously published material
- Signed consent from individuals cited in the Acknowledgements
- Signed consent for use of cited personal communications
- Signed patient's consent and permission to publish (if not already submitted)

Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" <[redacted]>
To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" <[redacted], "Liu, Ruiling (CDC/NIOSH/WTCHP)" <[redacted], "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" <[redacted], "Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR)" <[redacted], "Strid, Penelope (CDC/DDNID/NCCDPHP/DRH)" <[redacted], "Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP)" <[redacted], "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" <[redacted], "Myers, Tanya R. (CDC/DDID/NCEZID/DHQP)" <[redacted], "Hause, Anne M. (CDC/DDID/NCEZID/DHQP)" <[redacted], "Menschik, David (FDA/CBER)" <David.Menschik[redacted], "Baer, Bethany (FDA/CBER)" <Bethany.Baer[redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted], "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted], "Shay, David (CDC/DDID/NCIRD/ID)" <[redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" <[redacted]>
Subject: 6 month safety review for journal submission- please fill out author contribution by noon 10/26
Date: Mon, 25 Oct 2021 14:25:47 +0000
Importance: High
Attachments: mRNA_6mo_safety_review-2021-10-25_CLEAN_LancetID.docx; coi_disclosure_6mosafety.docx; tlid-author-signatures_6_month.pdf

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Good morning co-authors:

The manuscript reviewing six months of mRNA safety data is ready for submission to Lancet ID. Before submission could you please:

1) Review your affiliation, name, and degree on the attached version's title page. Lancet ID only allows use of one degree, so if you have multiple, I had to choose one. Please correct me if I did not choose your intended degree.

2) Complete the attached Author contribution form. I selected roles for each of you- if you agree with this designation please sign the form and send back to me. If you wish to edit your roles, that's fine- just let me know.

3) Only if you have not filled out the ICMJE COI form already, please send me back a copy.

If you can complete these tasks ASAP or by **noon tomorrow, 10/26**, I'd be very grateful!

Thanks everyone and thank you so much for all of your work on this.

All the best,
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Friday, October 22, 2021 9:52 AM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) <[redacted]; Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]; Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]; Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted]; Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted]; McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted]; Menschik, David (FDA/CBER) <David.Menschik[redacted]; Baer, Bethany (FDA/CBER) <Bethany.Baer[redacted]

Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: 6 month safety review-COI form- please fill out and send back by COB 10/21

Good morning all,
Attached is a copy of the clean version that is being submitted for posting to medRxiv.
Thanks to all of you for your hard work on this.

Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Wednesday, October 20, 2021 6:16 PM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted]
Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted]
Menschik, David (FDA/CBER) [redacted] Baer, Bethany (FDA/CBER) [redacted]
Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: 6 month safety review-COI form- please fill out and send back by COB 10/21

Dear co-authors,

Thanks so so much for all of your hard work and feedback on the 6 month safety review manuscript. The paper has been through CDC and FDA clearance, and is in final revision stages. Our plan is to submit to the medRxiv pre-print server, to be followed by journal submission shortly therefore.

I will send a revised draft for all of you to review in the next day or two- **in the meantime, could you please complete and return the attached COI form with your name, the date and any disclosures by COB tomorrow, 10/21/21?**

Thanks so very much,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

HPV Team, Viral Vaccine-Preventable Diseases Branch
Division of Viral Diseases, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

From: Nathan S [redacted]
To: Lauri Markowitz [redacted]
Subject: Re: washington post
Date: Fri, 13 Jan 2023 15:32:40 -0500
Importance: Normal
Attachments: Extensive_review_affirms_safety_of_covid_booster_after_signal_of_possible_risk_-_The_Washington_Post.pdf

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Here's the PDF

On Jan 13, 2023, at 3:20 PM, Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] wrote:

Extensive review affirms safety of covid booster after signal of possible risk - The Washington Post

The Washington Post

Extensive review affirms safety of covid booster after signal of possible risk

A deep dive into several large databases has failed to confirm the preliminary information, according to the CDC and FDA

By Laurie McGinley and Lena H. Sun
January 13, 2023 at 2:30 p.m. EST

A vaccine safety monitoring system in late November picked up a signal that the updated Pfizer coronavirus vaccine booster was possibly linked to an increased risk of strokes in people 65 and older. But a deep dive into several large databases failed to confirm the preliminary information, leading federal health officials to conclude the risk is extremely low — and probably nonexistent, those officials said Friday.

The Centers for Disease Control and Prevention, whose system detected the early signal, and the Food and Drug Administration, which also assesses vaccine safety, have decided there is no need to change the recommendation that everyone 6 months and older should stay up to date with their coronavirus vaccinations, including those 5 and older who are eligible for the updated booster, according to agency officials who discussed the situation on background.

The early signal involved the bivalent booster — which targets the original virus and omicron subvariants and became available starting in September — that is made by Pfizer and its German partner, BioNTech. It did not apply to Moderna's updated booster, officials said.

Government vaccine safety experts have combed through databases containing millions of records in the United States and consulted with regulators in other countries but so far have not found any indication that the statistical signal represents a clinical risk to patients. They said they would continue to analyze the data.

“We have looked at the totality of the evidence and there are no concerns at this time that this represents a true safety signal,” an FDA official said.

The FDA official said the government’s sensitive vaccine-safety systems are like a radio whose volume is turned up high. Sometimes, when listening, “like with a radio, you are going to hear some static in the background,” the official said, adding it does not mean someone is talking. Chances are “this is just static, and not someone real talking.”

The review is happening as the pandemic grinds on, with hospitalizations and deaths rising and an increasingly frustrated White House urging Americans to get the booster to bolster their protection. Uptake remains low: Only 16 percent of people 5 and older and only 39 percent of those 65 and older, the most vulnerable group, have received the booster, according to the CDC.

The CDC and FDA described the early signal in a statement updating their websites Friday afternoon. The signal set off an intense debate among officials about whether and how to release the information. CDC officials argued for releasing it, while some other officials, including at the FDA, were concerned that putting out unconfirmed data would fuel anti-vaccine sentiment and scare older Americans into avoiding the boosters. Ultimately, the agencies decided to release the information in the hopes that transparency “will build confidence,” said a CDC official.

The signal was detected in the Vaccine Safety Datalink, a collaboration between CDC and about a dozen health-care organizations with electronic health records on 12 million people. As part of routine monitoring for possible adverse events, officials noticed late last year that they were picking up indications of higher-than-expected stroke risk, officials said.

Among about 550,000 people 65 and older who had already been vaccinated and received a booster dose of the Pfizer bivalent vaccine, 130 people had strokes in the first three weeks after getting the shot. No deaths have been reported. That finding raised a question because it suggested that people who received the bivalent were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22 through 44 following vaccination.

The findings prompted officials to look for similar findings. CDC officials conducted a different analysis in the Vaccine Safety Datalink system, using the same data but different methodology, and were not able to replicate the finding. Officials also searched other systems, including those of Medicare, the Department of Veterans Affairs and Pfizer's global surveillance network. Regulators in other countries, including Israel, also were consulted, but no evidence of similar findings emerged, the officials said.

The statement from the two agencies said the government uses multiple systems to detect potential safety problems and that "often these safety systems detect signals that could be due to factors other than the vaccine itself."

The statement said, "Although the totality of the data currently suggests that it is very unlikely that the signal ... represents a true clinical risk, we believe it is important to share this information with the public."

Kit Longley, a spokesman for Pfizer, said the company and its partner, BioNTech, have been made aware of the "limited reports" of stroke. "There is no evidence to conclude that ischemic stroke is associated with the use of the companies' covid-19 vaccines," Longley said in an emailed statement. He added that about 550 million doses of the companies' omicron-targeted bivalent shot have been delivered globally, and about 30 million in the United States.

Safety experts say that safety signals occur frequently; if they don't, the system might not be sensitive enough. But there is a difference between signals and genuine safety risks. One of the reasons officials believe strongly there is not a safety risk is because they have not been able to come up with a plausible reason why such a problem would occur now — given the huge number of vaccines that have been administered worldwide since the end of 2020 — or why a problem would affect the Pfizer-BioNTech booster and not Moderna's. Both shots use mRNA technology.

Public health experts say it's important for the health agencies to be as transparent as possible about possible adverse events. If the information is not presented, public health agencies could be accused of hiding data. But such reports can be misinterpreted as causal when they are not.

The agencies said they will continue to evaluate data from the systems and will discuss the data and additional analyses at the FDA's previously scheduled Jan. 26 meeting with its vaccine advisers.

The Vaccine Safety Datalink has electronic health data that includes the kind of vaccine given to patients, the dates of vaccination and other vaccinations administered on the same day. It uses information on illnesses diagnosed at doctors' offices, in emergency rooms and in hospitals.

The system set up to monitor coronavirus vaccine safety is the most extensive in U.S. history.

In 2021, the system detected a link between the Johnson & Johnson vaccine and a rare but potentially deadly blood clotting and bleeding syndrome called thrombosis with thrombocytopenia, or TTS. The data prompted the FDA to impose new restrictions last May, saying only people who were unable or refusing to get other vaccines should receive the Johnson & Johnson shot.

There have also been concerns about the mRNA vaccines and the possible risk of a rare condition known as myocarditis, inflammation of the heart muscle, in adolescent and young men. But federal health officials have said data show the known risks of covid-19 illness and its related, possibly severe complications far outweigh the potential risks.

In previous investigations of the Johnson & Johnson vaccine and links to blood clots, and possible risks of myocarditis, officials found stronger signals as they searched additional safety databases. But that was not the case in this instance.

“Here, as we continue to dig … it’s disappearing rather than becoming stronger,” the FDA official said.

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted] "Shay, David (CDC/DDID/NCIRD/ID)" [redacted] "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: FW: Your Submission THELANCETID-D-21-02703
Date: Tue, 23 Nov 2021 17:47:08 +0000
Importance: High

Hi all,
See below- we have an opportunity to revise and resubmit to Lancet ID.
I'm a bit overwhelmed by the breadth of the comments, but I'll start looking at them in detail today and tomorrow and circulate something for everyone to look at. They seem to be mostly focused on how we did the death comparisons, but also some of the limitations of v-safe…
They are "due" in 10 days (the website lists December 7th) and I realize it's not great timing with Thanksgiving but nonetheless I'll get working on this ASAP!

Hannah

From: [redacted]
<[redacted] **On Behalf Of** Phoebe Hall
Sent: Tuesday, November 23, 2021 11:03 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: Your Submission THELANCETID-D-21-02703

Manuscript: THELANCETID-D-21-02703, Safety Monitoring of mRNA Vaccines Administered During the Initial 6 Months of the U.S. COVID-19 Vaccination Program: Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe

Dear Dr. Rosenblum,

Thank you for submitting your manuscript to *The Lancet Infectious Diseases*.

Your submission has now been assessed by external advisers and discussed by the Editorial team. We would like to invite you to REVISE your paper in light of the editorial and reviewers' comments below.

Please be aware that an invitation to revise does not imply acceptance. Our target revision time is 10 working days for normal track.

Comments to the Author:
We wonder whether the paper would be better if the inferential analyses were removed from the paper given concerns from the reviewers about the comparison of expected with observed mortality (which we note is based on a preprint and not adequately described in the Methods) and the disproportionality analysis. Please justify their inclusion if you wish to keep them in the paper.

Editorial points - IMPORTANT:

- The following points list items that **must be included before considered** further. Addressing them at this stage reduces the risk of errors and delays later.
- Please read the requirements below carefully and consult me or https://www.thelancet.com/preparing-your-manuscript, for further details or clarification if needed.
- Please note that not every point below will be relevant to your manuscript.

Authorship and reporting guidelines:

1. Please check that all author name spellings and affiliations are correct.
2. Please indicate any authors who are full professors.
3. Please list the highest degree for each author (one degree only, please).
4. Please follow the appropriate EQUATOR network reporting guidelines and include the corresponding checklist(s). These include: CONSORT reporting guidelines for randomised trials (http://www.consort-statement.org), STROBE for observational studies, PRISMA for systematic reviews, STARD for diagnostic studies, CHEERS for economic evaluations and RECORD for routinely collected health data. *Lancet* specific guidelines for reporting RCT and systematic reviews and meta analyses are available here:
   http://www.thelancet.com/pb/assets/raw/Lancet/authors/Rctguidelines.pdf
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Title/summary:

5. Please ensure that the title of the paper is non-declamatory (i.e, it describes the aim of the study rather than the findings) and that it includes a description of the study type (e.g. a randomised controlled trial).
6. Please limit the summary to pre-defined primary endpoints and safety endpoints.
7. For RCTs, please state the trial registration number.

Methods:

8. At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit.
9. Please explain any deviations from the protocol.
10. Please ensure that all outcomes specified in the protocol (including all secondary outcomes) are reported in the manuscript. If there are any secondary endpoints that cannot be included please mention these explicitly and explain why and where they will be made available.
11. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses were post-hoc.
12. Please use rINNs for drug names. For genes and proteins, authors can use their preferred terminology so long as it is in current use by the community, but should provide the preferred name from Uniprot (http://www.uniprot.org/uniprot/) for proteins and HUGO (http://www.genenames.org) for genes at first use to assist non-specialists.
13. For drug studies, please ensure that details of doses, route of delivery, and schedule are included.

Results:

14. For the main outcome measures, please include a result for each group, plus a point estimate (eg, RR, HR) with a measure of precision (e.g, 95% CI) for the absolute difference between groups, in both the Summary and the main Results section of the paper.
15. p-values should be given to two significant figures, but no longer than 4 decimal places (e.g. $p<0.0001$).
16. Please provide absolute numbers to accompany all percentages. Percentages should be rounded to whole numbers unless the study population is very large (>1000 individuals).
17. Please give 95% confidence intervals for hazard ratios/odds ratios.
18. For means, please provide standard deviation (or error, as appropriate).
19. Please provide interquartile ranges for medians.
20. Please provide numbers at risk for Kaplan-Meier plots and ensure that plots include a measure of effect (e.g, log-rank p); estimates should be reported with 95% CIs.

Discussion:

21. Please ensure that the Discussion contains a section on limitations of the study.

Additional requirements:

22. Please provide the text, tables, and figures in an editable format (eg, EPS files, PowerPoint files, depending on software used to produce them. If figures are composed of photographs or other images, high resolution files (300dpi or greater) should be provided. More information can be found here: https://www.thelancet.com/for-authors/forms?section=artwork.
23. References should be in Vancouver style. For references with six authors or fewer, all authors should be listed. For those with seven or more authors, only the first three authors and 'et al' should be listed. Please ensure that reference numbering throughout the manuscript is not inserted with electronic referencing software, such as Endnote, as this is incompatible with our production system (if used, please convert to normal text before resubmission). If the references “move” from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move. All web references should have the exact date they were last accessed. With your revised submission please enclose copies of any papers cited as being 'in-press', along with a copy of the acceptance letter from the journal. References that are "submitted" should be removed and citations in the text replaced with "(unpublished data; authors)".
24. If accepted, only 5-6 non-text items (figures, tables, or panels) can be accommodated in the main paper; additional material can be provided in a web appendix. Please indicate which items can go in a web appendix.
25. Please provide a research in context panel with 3 parts: Evidence before this study (which includes a description of how you searched for evidence and how you assessed the quality of that evidence); Added value of the study; and Implications of all the available evidence.
26. At the end of the manuscript, please provide a Contributors statement that summarises the contribution of each author to the work. *The Lancet's* journals require that more than one author has verified the underlying data in all research articles. Please state which author(s) have accessed and verified the data, and which author(s) were responsible for the decision to submit the manuscript.
27. At the end of the manuscript please summarise the declaration of interests for each author.
28. In the Contributors section list at least two authors who accessed and verified all the data.
29. If your author line has more than 20 authors, we very strongly encourage the use of a study group name. Collaborators' names and affiliations may be listed at the end of the paper or in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a list of names of all study group members presented as a two-column table in Word. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to appear on PubMed. The table will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly.
30. Please note our guideline length for research articles is 3500 words and 30 references. For RCTs, the text can be expanded to 4500 words.
31. All research articles must contain a data sharing statement, to be included at the end of the manuscript. For more information on these required statements see the Data sharing section of the Information for Authors (https://thelancet.com/pb-assets/Lancet/authors/tlid-info-for-authors.pdf) and (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31282-5/fulltext)
32. Please ensure that the funding source is stated in the Acknowledgement section.

Reviewers' Comments:

Note that reviewer numbers are allocated by the system at invitation and not at completion of reviews, so some numbers might be missing.

- In your point-by-point reply to the reviewers', please indicate the text changes which have been made (if any) and the line number on the tracked changes manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.]
- Please do not use boxes for responses as this slows assessment.

- When interpreting editorial points made by reviewers, please remember that we will edit the final manuscript if accepted.

Reviewer #2: Thank you very much for the opportunity to review this manuscript. The authors reviewed and summarised adverse events reported after COVID-19 vaccination with two mRNA vaccines based on reports from two vaccine-specific pharmacovigilance systems in the US, the Vaccine Adverse Events Reporting System and the active surveillance system v-safe.

The manuscript is very well written and provides important insight to spontaneously reported adverse events following mRNA vaccination, which should be available to a wide audience. With the broad rollout of mRNA COVID-vaccines in the US and worldwide, these results are reassuring and provide important information for the risk-benefit assessment of these vaccines.

Major comments:
* The reviewers missed some important information on selection bias in v-safe. Is it possible to compare the included participants to non-respondents? This would give important insight into the representativeness of the resulting data
* The authors present disproportionality measures for mortality from VAERS. It feels like a missed opportunity not to report these also for the other pre-specified AESI. Is this possible?
* The analyses of v-safe are purely descriptive. Is there any disproportionality or further analysis planned from this database?

Minor comments:
-Methods, p. 7 paragraph 1, line 5. What are the pre-specified AESI? Please provide a reference or refer to table 2 where the results for the AESI are presented.
-Discussion, p. 11 paragraph 2, line 1: "more health impact was reported […] received mRNA-1273 versus BNT162b2". While this is an interesting and relevant finding to report, there may have been differences (e.g. in terms of underlying comorbidities) between the patient collectives receiving the different vaccines. It might be worth considering adding a sentence in the discussion/limitations to highlight that this finding from spontaneous reports should not be interpreted in that one mRNA vaccine is "safer" than the other.
Table 1, Table 5: Race and Ethnicity are reported. The term "Unknown ethnicity", which is further split into subgroups entitled "White", "Black", "Asian" etc. is confusing for the reader as "unknown" should not have subgroups. Consider to rename or merge with "Non-Hispanic" if this refers to the same ethnic subgroups.

Reviewer #3: This is a very important report of the first 6 months of mRNA vaccine rollout as capture through the passive and active surveillance system.
The major limitations of this approach is not knowing the denominator and not knowing what portion of the population is being missed or not included because of the nature of how the data is being collected.
This is underscored by the demographics which show that both for passive surveillance and the active reports through V-safe the populations represented are largely White women between the ages of 18-60.
Realizing that many of the reactions both reactogenic and other are occurring in this demographic there is also the very real affect that this is reporting artifact and that we do need to understand to a much better extent what types of events are occurring in the populations not represented well is Vsafe in particular. This might be an opportunity on how to develop Vsafe into a program that is more inclusively represents age, sex and race. This is captured in VSafe and VAERS does not capture race information. Perhaps trying to give some representative demographics (e.g. 6% of respondents are Blacks although they represent 12% of the US population). It would also be interesting to see if there are any geographic differences in where reports come from across the United States - by State, level of education and insured versus uninsured)
Otherwise I think the findings are important but somewhat expected in terms of the reactogenic symptoms higher in age <65 and women
Supplemental tables 2,3 and 4 are important but has vaccination disproportionately reduced death in COVID related morbidities in educated Whites.
The report is important and should be published and I guess I am thinking about this more in terms of the next steps for both VSafe and VAERS but particularly VSafe to be representative of the US population and more

inclusive across age, race, sex, level of education and socioeconomic status. For the targeted reports of interest (myopericarditis, anaphylaxis) it would be helpful to see the data broken down by age and sex.
Although not the goal of Vsafe clearly important if socioeconomically disadvantage and uninsured individuals are vaccine hesitant because of fear of reactogenic events that would cause them to have unpaid time off work or visits to the ER.

There is a lot of data represented in this report but also of interest to know what happened with reporting of events as the vaccine rollout matured. Is it possible to show data from the first 3 months versus second 3 months. Women were more likely to be over-represented during the initial three months in view of healthcare rollout. It would be of interest if the reporting of any of the events including reactogenic events changed as time went on and there was more societal familiarity with these.

Reviewer #4: These are important data to publish as full transparency around AEs is necessary for public trust in vaccination and ending the pandemic. My questions and clarifications are as follows:
MAJOR COMMENTS
1. P5: Cause of death had ICD codes, covid related, or unknown but what about causality assessment to the vaccines? Is no standardized causality assessment performed? If not, wht not? The only mention of "vaccine related" is in supplemental table 3 and denotes only 4 deaths related to the vaccine, but what is the precedent for this very narrow definition? All AEs reported to FDA at minimum are marked unrelated, related, or possibly related. Causality assessments used in safety research can further refine.
2. P5/P7/Table 4: It is not at all clear to me that this is a fair or valid comparison to make. Deaths reported to VAERS are considered potentially related to the vaccine by reporters and not all deaths in vaccinated individuals are reported to VAERS. The comparison to all-cause mortality in vaccinated individuals appears flawed. Death within days of vaccination has a high suspicion of causality and deaths from other causes would not be expected to be spontaneously reported to VAERS. Background mortality rates from all causes are not surprisingly higher —the reporting of deaths to VAERS are only for deaths suspected potentially from the vaccine. I don't think this comparison is valid and to me, it undermines the message of transparency. It assumes when we as clinicians are reporting deaths, we do so indiscriminately but we don't. I considered the method of EB data mining with e EB05>2 a stronger way to assess any safety outliers in this paper and perhaps more focus should be placed on those methods and findings.
3. Regarding the death reports, it is critically important to specifically address whether any deaths were from the two known related serious AEs: anaphylaxis or myocarditis. This requires specific data and mention in the manuscript. Deaths from these within a reasonable time frame post vaccination would be causal. Really all of the special interest AEs in Table 2 would be useful to indicate deaths for transparency.

MINOR COMMENTS
4. P5: Is there a basis for the definition of serious used? Is this standard from prior vaccines?
5. P6: Time from vaccination to reported death is referred to as "onset interval" but is perhaps better described as latency?
6. VSD studies should also be mentioned in the discussion (Nicola Klein et al JAMA) as these provide more valid comparator groups for severe outcomes.
7. The increased reactogenicity symptoms are interesting in the younger/female. Did pregnancy impact this at all? higher or lower in the pregnant female compared to similar age non pregnant female?
8. The healthcare utilization and out of work time is impressive—were there any demographic predictors associated with needing healthcare resource use or out of work?
9. Supp Table 2- Other is such a large category—what comprised other? Can anaphylaxis and myocarditis be added here?
10. Can any modelling of associated factors for severe outcomes or high reactogenicity be performed?

Reviewer #5: This article provides a picture of reports of AEFI in the first six months of utilization of mRNA COVID-19 vaccines in the United States. I think that similar reports are highly desirable to reassure the population about vaccine safety and therefore priority is high. However, in the attempt of providing more information, the study goes beyond the simple description of reports from VAERS and providing a survey of data collected by v-safe. Unfortunately, the authors made this step without providing important information to the

readers. With the current information I cannot establish whether and to what extent the results deserve to be discussed with more caution.

Specific comments

Introduction (page 3) "We reviewed VAERS and v-safe […] vaccines were administered". Instead of providing a simple descriptive report of the data collected in these two databases the authors 1) calculated a rate of report of death and compared that with that expected in an unspecified vaccinated population and 2) performed a disproportionality analysis. These are objectives to be declared in the and text and in the abstract.

For the above mentioned analysis the authors did not included in the methods important information.

For the disproportionality analysis we have no information on the dataset. What were the vaccines included in the dataset? What was the proportion of COVID-19 vaccines? For the latter question, the authors reported in the limitation that in the analyzed period (we know only that they included reports up to June 14th, 2021 but we have not the initial date) the great majority of reports was for the vaccines of interest. If this proportion is over 90% the possibility of identifying a signal was likely close to zero. So, why performing such an analysis?

For the comparison of mortality rates we have not information about the comparator: does it refers to mortality following immunization with any vaccine? From the reference number 20 it seems that this rate was calculated (how?) only for COVID-19 vaccines? So what is the rationale for this comparison? Estimating the under-reporting of fatal cases? Estimating the number of reports over a mortality for any cause that was attributed to vaccines (not accidental) by reporters? What was the period in which mortality was calculated in the reference? 14 days after vaccination or longer? In summary, I think that these two rates cannot be compared or should be interpreted in a different way, at least with the details of information provided by the authors.

Page 7: "there were 4,496 reports of death…." Were all these reports from US? Did the VAERS include reports from other countries? I suppose these fatal cases have been occurred all in the US since the authors used this number to estimate the reporting rate for fatal cases using the number of doses of vaccines administered in the US. If this is the case, it should be clearly stated.

Page 8: "During the analytic period, 7,914,583 mRNA COVID-19 vaccine recipients […]". How many patients dropped out after the initial enrolment? In case the drop-out is quite high (as I suppose) the authors should compare the population included in the analysis with the population dropped out to check for a possible selection that could have had an impact on the results.

Page 10 "Analysis of deaths reported to VAERS demonstrated lower than expected reported mortality rates compared to background mortality rates". Besides my doubt about comparability given the lack of essential information, why the authors wrote "than expected"? I would have bet whatever I have that the rate was lower than that estimated for a background mortality for two reasons: 1) under-reporting and 2) background mortality include death for any cause while VAERS includes only deaths that have been somehow associated with the immunization. The authors included an interpretation similar to mine in the "limitations" section. So they likely expected this results as well.

Reviewer #6: Thank you for the opportunity to review this paper. It is an interesting an important piece of research.

I would like to have seen very clear research questions rather than a broad aim of "We review VAERS and v-safe data during the first 6 months of the U.S. vaccination program, when >298 million doses of mRNA COVID-19 vaccines were administered."

There is a lot of data so I would like to see a a STROBE Statement—Checklist of items that should be included in reports of cohort studies, and a CONSORT style flow chart showing for each vaccine the flow e.g. Overall recipients at dose 1, then at dose 2, and how many recipients reported through VAERS and how many completed V-safe survey reports from days 0-7 - split by vaccine type. This will make it easier to follow the tables.

All VAERS reports for mRNA vaccines were submitted and processed from December 14, 2020 through June 14, 2021, inclusive of any interval from vaccination to event report. Could this mean that some recipients were not followed up for the full 6 weeks post dose, e.g. had their vaccine in early June?

Vsafe participants receive text messages that link to web-based health check-in surveys following vaccination, initially daily (days 0-7), then at longer intervals post vaccination. The system resets to the initial survey

frequency after entry of another dose. Does this mean that the information relates to either dose 1 or dose 2.

Table 1: I would recommend this table only show the descriptive characteristics of the vaccine recipients, not the the outcomes e.g. Reports, Signs or symptoms most frequently reported, nonserious, and Signs or symptoms most frequently reported, serious. Linking to above, this should be by dose (e.g. Table 5 could replace this). Did all those who are presented in Table 5 as having first dose, then be those who also had their second does e.g. for BNT162b2 vaccine second doses=1,861,599 from 2,150,068 who had first dose - or are could these be a different groups?

Table 2 shows the Reports (as in Table 1) and Reports of adverse events of special interest. It should also include Signs or symptoms most frequently reported, nonserious, and Signs or symptoms most frequently reported, serious (as presented in Table 2).

Deaths were recorded as in the 7 days and 42 days (6 weeks) post vaccination - needs to split by dose 1 and 2. Time interval to death following vaccination was available for 4,119 reports (92·1%); median time interval was 10·0 days (range: 0—161 days). The greatest number of death reports occurred on day 1 (10·5%) and day 2 (7·0%) following vaccination (Supplemental Figure 1). There are clear differences between vaccines here. This might be better as a Kaplan Meier plot and as there are apparent differences by vaccine type - could survival analysis be done here to compare them, adjusting for characteristics and allowing for censoring.

Of the 4,472 reports of deaths analyzed, 2,087 (46·7%) were reported following BNT162b2 and 2,385 (53·3%) following mRNA-1273 - should any statistical comparison made here, adjusting by recipient characteristics? e.g. Females accounted for 42·6% of reported deaths (can this be split by vaccine type), and adjustments are needed as in Table 1 44.0% and 41.4% of the recipients were female.

During the analytic period, VAERS received and processed a total of 340,522 reports: 164,669 following BNT162b2 and 175,816 following mRNA-1273 vaccination (Table 1). Were these individual participants or could one recipient report more than once? How many recipients did not report e.g. had no side effects?

During the analytic period, 7,914,583 mRNA COVID-19 vaccine recipients enrolled in v-safe and completed at least one post-vaccination health survey during days 0-7 (Table 5). What is this as a proportion? A total of 6,775,515 participants completed at least one survey during day 0-7 after dose (3,455,778 following BNT162b2; 3,319,737 following mRNA-1273). Why do these numbers not match?

A clear limitation of this data is a lack of analysis on the time from vaccine (dose 1 and/or dose 2), and time to side effect or adverse event. Also a lack of statistical comparison between the vaccines as there are some differences - however if the aim is not to compare vaccines, splitting the sessions by vaccine might make the paper easier to read.

TECHNICAL INFORMATION:

When you submit the revised paper, please provide the following:

1. One "clean" copy of your manuscript
2. One copy where your changes are highlighted (tracked changes).
3. A separate, point by point response to the editorial and referee comments typed immediately following each specific point above. Please do not use boxes for responses.
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The editors may use such information as a basis for editorial decisions and will publish such disclosures if they are believed to be important to readers in judging the manuscript.

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- Signed Conflict of interest statement for ALL authors

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Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Menschik, David" <David.Menschik[redacted]
To: "Markowitz, Lauri (CDC)" <[redacted], "Myers, Tanya R (CDC)" [redacted] "Rosenblum, Hannah (CDC)" [redacted] "Gee, Julianne M (CDC)" <[redacted], "Liu, Ruiling (CDC)" [redacted], "Marquez, Paige L (CDC)" [redacted], "Zhang, Bi C (CDC)" [redacted], "Strid, Penelope (CDC)" [redacted], "Abara, Winston E (CDC)" [redacted], "Mcneil, Michael M (CDC)" [redacted] "Hause, Anne M (CDC)" [redacted], "Baer, Bethany" <Bethany.Baer[redacted], "Su, John (CDC)" [redacted], "Shimabukuro, Tom (CDC)" [redacted] "Shay, David K (CDC)" [redacted]
Subject: RE: [EXTERNAL] RE: 6 month safety review for journal submission- please fill out author contribution by noon 10/26
Date: Mon, 25 Oct 2021 15:16:38 +0000
Importance: Normal
Attachments: tlid-author-signatures_6_month_trm_LM.pdf

I added my signature as well per attached
Thanks,
David

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Monday, October 25, 2021 11:00 AM
To: Myers, Tanya R (CDC) <[redacted]; Rosenblum, Hannah (CDC) <[redacted]; Gee, Julianne M (CDC) [redacted] Liu, Ruiling (CDC) [redacted] Marquez, Paige L (CDC) [redacted] Zhang, Bi C (CDC) [redacted]; Strid, Penelope (CDC) [redacted]; Abara, Winston E (CDC) [redacted]; Mcneil, Michael M (CDC) [redacted] Hause, Anne M (CDC) [redacted] Menschik, David <[redacted] Baer, Bethany [redacted]; Su, John (CDC) [redacted] Shimabukuro, Tom (CDC) [redacted]; Shay, David K (CDC) [redacted]
Subject: [EXTERNAL] RE: 6 month safety review for journal submission- please fill out author contribution by noon 10/26

I added my signature to this form.

From: Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Monday, October 25, 2021 10:41 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]; Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted]; Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]; Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted]; Menschik, David (FDA/CBER) [redacted] Baer, Bethany (FDA/CBER) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) <[redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Shay, David (CDC/DDID/NCIRD/ID) <[redacted]; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: 6 month safety review for journal submission- please fill out author contribution by noon 10/26

Good morning, Hannah,

Attached is the tlid form, signed. I believe I've already returned the COI form, but if I'm mistaken, please let me know.

Kind regards,
Tanya

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Monday, October 25, 2021 10:26 AM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted]; Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted]; Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted]; Menschik, David (FDA/CBER) [redacted]; Baer, Bethany (FDA/CBER) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: 6 month safety review for journal submission- please fill out author contribution by noon 10/26
Importance: High

Good morning co-authors:

The manuscript reviewing six months of mRNA safety data is ready for submission to Lancet ID. Before submission could you please:

1) Review your affiliation, name, and degree on the attached version's title page. Lancet ID only allows use of one degree, so if you have multiple, I had to choose one. Please correct me if I did not choose your intended degree.

2) Complete the attached Author contribution form. I selected roles for each of you- if you agree with this designation please sign the form and send back to me. If you wish to edit your roles, that's fine- just let me know.

3) Only if you have not filled out the ICMJE COI form already, please send me back a copy.

If you can complete these tasks ASAP or by **noon tomorrow, 10/26**, I'd be very grateful!

Thanks everyone and thank you so much for all of your work on this.

All the best,
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Friday, October 22, 2021 9:52 AM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted] Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted] Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted]; McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted] Menschik, David (FDA/CBER) [redacted] Baer, Bethany (FDA/CBER) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Shay, David (CDC/DDID/NCIRD/ID) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: 6 month safety review-COI form- please fill out and send back by COB 10/21

Good morning all,
Attached is a copy of the clean version that is being submitted for posting to medRxiv.

Thanks to all of you for your hard work on this.

Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Wednesday, October 20, 2021 6:16 PM
To: Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted]; Liu, Ruiling (CDC/NIOSH/WTCHP) [redacted]; Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]; Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]; Strid, Penelope (CDC/DDNID/NCCDPHP/DRH) [redacted]; Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP) [redacted]; McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]; Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted]; Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted]; Menschik, David (FDA/CBER) [redacted]; Baer, Bethany (FDA/CBER) [redacted]; Su, John (CDC/DDID/NCEZID/DHQP) [redacted]; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Shay, David (CDC/DDID/NCIRD/ID) [redacted]; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <[redacted]>
Subject: 6 month safety review-COI form- please fill out and send back by COB 10/21

Dear co-authors,

Thanks so so much for all of your hard work and feedback on the 6 month safety review manuscript. The paper has been through CDC and FDA clearance, and is in final revision stages. Our plan is to submit to the medRxiv pre-print server, to be followed by journal submission shortly therefore.

I will send a revised draft for all of you to review in the next day or two- **in the meantime, could you please complete and return the attached COI form with your name, the date and any disclosures by COB tomorrow, 10/21/21?**

Thanks so very much,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

HPV Team, Viral Vaccine-Preventable Diseases Branch
Division of Viral Diseases, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Shay, David (CDC/DDID/NCIRD/ID)" [redacted], "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted] "Hause, Anne M. (CDC/DDID/NCEZID/DHQP)" [redacted] "Myers, Tanya R. (CDC/DDID/NCEZID/DHQP)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted] "Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP)" [redacted] "Strid, Penelope (CDC/DDNID/NCCDPHP/DRH)" [redacted] "Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted] "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted], "Liu, Ruiling (CDC/NIOSH/WTCHP)" [redacted], "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: FW: Your Article in The Lancet Infectious Diseases: revised proof
Date: Fri, 4 Mar 2022 14:01:24 +0000
Importance: Normal
Attachments: 21TLID2703_(002).pdf
Inline-Images: image001.png; image002.png; image003.png

Thanks to all of you for a tremendous team effort on the 6 month mRNA VAERS/v-safe paper. I'm attaching the final proof.

The article will be live on Monday, 3/7 at 6:30p EST here: https://www.thelancet.com/journals/laninf/onlinefirst

And to share a separate note I received from the editor:
"I look forward to seeing the coverage. That the vaccines are more dangerous than the virus is one of the most common beliefs behind vaccine hesitancy that I seem to encounter in real life. I hope this paper goes some way to alleviating those concerns."

Hannah

From: Sheen, Katy (ELS-LOW) [redacted]
Sent: Friday, March 4, 2022 6:03 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Blott, Jonathan (ELS-LOW) [redacted]
Subject: Your Article in The Lancet Infectious Diseases: revised proof

Dear Dr Rosenblum,

Please find attached an updated proof of your Article. I have now sent your Article to press and it is scheduled to go live online on The Lancet Infectious Diseases Online First (https://www.thelancet.com/journals/laninf/onlinefirst) at 2330 h (UK time) on March 7.

Many thanks,

Katy (on behalf of Jonathan Blott)

Katy Sheen
Senior Assistant Editor

The Lancet Journals
125 London Wall, London EC2Y 5AS
[redacted]

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted], "Liu, Ruiling (CDC/NIOSH/WTCHP)" [redacted], "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted] "Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted] "Strid, Penelope (CDC/DDNID/NCCDPHP/DRH)" [redacted], "Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP)" [redacted], "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted] "Myers, Tanya R. (CDC/DDID/NCEZID/DHQP)" [redacted], "Hause, Anne M. (CDC/DDID/NCEZID/DHQP)" [redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted] "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Shay, David (CDC/DDID/NCIRD/ID)" [redacted]
Subject: FW: Your Submission THELANCETID-D-21-02703R2
Date: Fri, 14 Jan 2022 18:50:56 +0000
Importance: High
Attachments: THELANCETID-D-21-02703_R2.pdf; mRNA_6mo_safety_LancetID_revision_1_14_22_tracked.docx
Inline-Images: image00001.png

Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) has shared a OneDrive for Business file with you. To view it, click the link below.

mRNA 6mo safety_LancetID_revision_1_14_22_tracked.docx

Very exciting news!!!!!!!!!!!

This 6 month safety manuscript was accepted to *The Lancet Infectious Diseases.*

Thanks to all of you for all of your incredibly hard work on the analysis, writing and rounds of revision.

See attached word document for a few comments that need to be addressed ASAP. Most I'm able to handle but I have tagged you in the comments if I think you can help so you should also be alerted via a separate email.

If you could all please recheck your name spelling and degree on this Word version and let me know if anything looks incorrect. I aim to return this within two work days so please respond by **Tuesday at noon.**

Thank you all so very much!!

Hannah

From: [redacted]
On Behalf Of Phoebe Hall
Sent: Friday, January 14, 2022 11:53 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: Your Submission THELANCETID-D-21-02703R2

Manuscript: THELANCETID-D-21-02703R2, Safety Monitoring of mRNA Vaccines Administered During the Initial 6 Months of the U.S. COVID-19 Vaccination Program: Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe

Dear Dr. Rosenblum,

Thank you for submitting your manuscript to *The Lancet Infectious Diseases*. I am pleased to inform you that we have decided to accept your paper, subject to completion of some final housekeeping tasks. Specifically:

- Please provide numerators and denominators for all of the highlighted percentages in the attached PDF. I realise most of them are provided in the main and supplementary tables, but it is journal policy to include the absolute numbers used to calculate percentages where the percentages are stated.

- Please address any additional comments on the manuscript in the attached PDF (there are 5)

- Please upload written consent from individual(s) cited in the acknowledgements (this can be in the form of an email)

- Please include a Declaration of interests statement at the end of the manuscript (this should reflect the disclosures made in the ICMJE forms)

We would be grateful if you could submit the revision within 2 working days, although please let me know if you will need a few extra days. If you are unable to obtain consent from people cited in the Acknowledgments in that time, you can send it to me in email.

TECHNICAL INFORMATION:

When you submit the revised paper, please provide the following:

1. One "clean" copy of your manuscript
2. One copy where your changes are highlighted (tracked changes).
3. A separate, point by point response to the editorial and referee comments typed immediately following each specific point above. Please do not use boxes for responses.
4. Any images and/or tables (even if no revisions have been made).

Please do NOT include a copy of your original manuscript. All text files should be supplied as MS Word files.

Please also supply the word count for the body of your paper and your abstract (word count for the body of your paper should not include abstract, references, figures or tables).

To enable readers to better appreciate research findings and to encourage full and transparent reporting of outcomes, *The Lancet* family journals offer to publish a webaddress in accepted paper that links to the study's protocol on the author's institutional website (see Lancet 2009; 373: 992). This is particularly encouraged for randomised controlled trials, but is welcome for all types of research.

To submit your revised manuscript, please visit *The Lancet Infectious Diseases's* Online Submission and Peer Review Website at: https://www.editorialmanager.com/thelancetid/ and enter your username and password.

Your username is: Your username is: [redacted]
If you need to retrieve password details, please go to: click here to reset your password

After you have entered your account details, remember to click the 'Author' button. You will see a menu item call 'Submission Needing Revision'. You will find your submission record there.

Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Marks, Peter" [redacted]
To: "Califf, Robert" [redacted] "Tierney, Julia" [redacted]
Subject: FW: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax
Date: Tue, 17 Jan 2023 15:41:02 +0000
Importance: Normal
Inline-Images: image001.png; image002.jpg

Dear Rob and Julie,

Please see below.

Best Regards,
Peter

From: McNeill, Lorrie [redacted]
Sent: Tuesday, January 17, 2023 8:34 AM
To: Marks, Peter [redacted]; Witten, Celia (CBER) [redacted]; Anderson, Steven [redacted]; Forshee, Richard [redacted]
Cc: Frantz-Bohn, Susan [redacted]
Subject: FW: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Good morning, all – under the heading of "damned if you do and damned if you don't," sharing the Pink Sheet article below.

Lorrie

From: Patel, Bharti [redacted]
Sent: Tuesday, January 17, 2023 6:26 AM
To: OC OCOD Contacts [redacted]
Subject: FYI - Pink sheet News - Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

Reassuring Safety Inquiry But Botched Comms Leads To Mixed Headlines For Pfizer Bivalent Vax

- 16 Jan 2023
- **ANALYSIS**
- 
- [redacted]

Executive Summary

US vaccine surveillance systems were triggered, but so far further investigation clears the bivalent COVID vaccine of any new safety concern. CDC and FDA's attempt to control the narrative appears to have backfired, however, making what looks to be a non-issue more controversial than it needed to be due to limited public communication.

Source: Shutterstock

Pfizer Inc./BioNTech SE's bivalent COVID-19 vaccine is under continued investigation over a preliminary safety signal related to strokes in people ages 65, though thus far the signal identified in the Vaccine Safety Datalink has not been confirmed in other monitoring systems, leading regulators to conclude that it is very unlikely the signal represents a true clinical risk.

That news, made public on 13 January, should largely have represented a win for US public health agencies – demonstrating that systems put in place to rapidly warn of potential harms worked by quickly identifying a possible safety concern and leading to the necessary follow up evaluations.

However, the rollout of the information was haphazard and piecemeal leading to confusing headlines (some played up the possible stroke link while others were more cautious) and criticism from public health experts about the lack of transparency, which among other negatives allows anti-vaccine messaging to thrive unchecked.

The potential safety signal was first publicly revealed in a *Washington Post story* that then linked to an update that the US Centers for Disease Control and Prevention and Food and Drug Administration posted quietly on their websites.

The agencies did not more widely notify the press or health care professionals. FDA did not include the update it its daily news roundup on 13 January.

Sparse Details For The Public

Furthermore, the CDC and FDA announcement was fairly sparse in detail, lacking key pieces of information that were present in the Washington Post story, such as the number of strokes identified in the Vaccine Safety Datalink (VSD). The Post story says the VSD picked up the safety signal in late November, another detail not mentioned on the CDC and FDA announcement.

The agencies confirmed to the *Pink Sheet* that VSD identified 130 ischemic strokes out of about 550,000 Pfizer bivalent vaccines administered to people 65 and older. Those strokes took place within the first three weeks of getting the updated vaccine and raised a question of whether people getting the vaccine were more likely to have a stroke in the 21 days following vaccination compared with days 22-44 following vaccination.

VSD conducts near real-time safety monitoring, assessing rates weekly. If the rate of adverse events among vaccinated people in the risk period is higher than among the comparison window, it results in a signal and prompts further investigation into whether the vaccine may be associated with an adverse event, CDC explained.

The signal was not identified with the Moderna, Inc. bivalent COVID-19 vaccine or in other safety studies, including the Vaccines Adverse Event Report System. Studies using the Centers for Medicare and Medicaid Services database and the Veterans Affairs database did not reveal an increased risk of ischemic stroke, nor did a review of Pfizer-BioNTech's global safety database or other countries' data, CDC and FDA said.

Ongoing Evaluations

FDA and CDC are continuing to evaluate data on the signal and plan to discuss their latest findings at the 26 January FDA Vaccines and Related Biological Products Advisory Committee, but they emphasized that "the totality of the data current suggests that it is very unlikely that the signal in VSD represents a true clinical risk."

The agencies argued their notice, despite the lack of confirmation of a safety concern thus far, was done in the name of public trust and transparency.

"Transparency and vaccine safety are top priorities for the FDA and CDC. Posting about this signal, and describing our assessment that this does not pose a health risk is exemplary of this. Both agencies want to underscore our continued confidence in the safety and effectiveness of the vaccines, and our hope is that trough our transparency – the public will as well."

However, the way the information was conveyed, led to questions about the agencies' true commitment to transparency.

'A Rorschach Test'

"I think the mistake they make is not having some kind of public discussion of it today or yesterday or whatever. Preferably not five o'clock on Friday before a long weekend," said Diana Zuckerman, blaming in part confusing language in the FDA and CDC webpage update, along with a lack of more proactive and formal public communication, for news headlines that more strongly pointed to a stroke link than the totality of the agency communication suggests.

"When I look at the CDC thing and knowing how this works, I'm like wow, there's a lot of ambivalence in this article. You know, it's not clear. It kind of is a Rorschach test in the eyes of the beholder," said Zuckerman, who is the President of the National Center for Health Research.

"This is the problem. They don't want to be asked questions. They want to control the narrative, so to speak, and they can't control the narrative. And by trying to control it, they're getting the very mistrust that they say they don't want," Zuckerman added.

The lack of a stronger media presence from top agency officials on the issue and the missing pieces of data also led to criticism from Rick Bright, who previously served as the Deputy Assistant Secretary for Preparedness and Response and the Director of the Biomedical Advanced Research and Development Authority.

"Completely irresponsible, yet it's what we've come to expect from the current CDC Director. Another missed opportunity to educate and do the right thing," Bright tweeted.

Preferential Media Access May Have Backfired

Giving preferential access to one media outlet with limited follow up likely backfired and made people more skeptical of safety work the agencies seem to have handled well, said Peter Lurie, president of the Center for Science in the Public Interest, and former associate commissioner for public health strategy and analysis at FDA.

"The problem is that in the current environment if people can detect attempts to control the story, then people overlay their own interpretations of the reason for that," Lurie said.

"I guess the best way to approach it, if you're in the agency's point of view, is to try to stick with … what you would do, irrespective of the situation to begin with," he said.

"That's your best defense: follow the science, follow your processes, do what you always do," Lurie said.

"I don't see any reason why the release of this information couldn't have been done in the conventional fashion, which is by whatever press release they wanted to put out available to all to all outlets. That would have been the better way, because now people will wonder, justifiably or otherwise."

"It would be concerning if they only quietly let one news outlet know and updated their website. They seem to indicate that they investigated this safety signal further before making it known to the public so they could and should have been more transparent about this," said Reshma Ramachandran an assistant professor at Yale who has previously studied identification of safety signals, regulatory action and any publicity.

"I understand the need to not stoke anti-vax sentiment unnecessarily, but given that FDA has repeatedly stated that they view addressing misinformation a priority, to me, a lesson learned from everything that happened last year for the agency would be to be as transparent as possible to earn the public's trust to do so," Ramachandran said.

"I'm glad they plan to discuss this at their upcoming vaccines advisory committee though."

History of Quiet Moves

This is not the first time the US government has made COVID-19 vaccine safety related updates quietly.

FDA took a low-key approach when it updated vaccine emergency use authorizations to specifically state that sponsors report all incidences of myocarditis and pericarditis, no matter their severity. (Also see "All Myocarditis, Pericarditis Cases With COVID-19 Vaccines Now Must Be Reported To VAERS" - Pink Sheet, 13 Sep, 2022.)

The agency also neglected to put out a public statement or notice when the Moderna vaccine was thought to have a higher risk of myocarditis than the Pfizer/BioNTech vaccine. (Also see "US FDA Tags Moderna COVID-19 Vaccine With Higher Myocarditis Risk Than Pfizer/BioNTech" - Pink Sheet, 1 Dec, 2021.)

FDA was also quieter than CDC when it came to addressing the risk of thrombosis with thrombocytopenia syndrome (TTS) with Janssen Pharmaceutica Inc.'s vaccine. (Also see "ACIP Prefers mRNA COVID-19 Vaccines, But Worries Message May Not Resonate" - Pink Sheet, 16 Dec, 2021.)

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Sharan, Martha (CDC/DDID/NCEZID/DHQP)" [redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Nordlund, Kristen (CDC/OD/OADC)" [redacted] "Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP)" [redacted] "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted] "Vaccine Safety (CDC)" [redacted]
Subject: RE: Reporter inquiry
Date: Thu, 23 Jun 2022 12:28:31 +0000
Importance: Normal
Inline-Images: image001.png

Okay, but the main reason we didn't do PRR is b/c FDA EB data mining is the 'gold standard' for disproportionality analysis so we had a better and more efficient way of doing disproportionality analysis at a time when we were occupied trying to monitor an onslaught of reports. There really isn't a reason for CDC to do PRR if FDA is conducting EB data mining b/c it's basically redundant. Now that we are further along in the pandemic and we better understand some of the limitations of FDA's EB data mining for COVID-19 vaccines we are doing some exploratory work with PRR, but it's still not a major component of our monitoring.

I find some of the statements in the response a bit problematic.

I disagree with this statement: Various technical limitations, including insufficient data, precluded PRR analyses during that time in the vaccination campaign. PRR is a simple (maybe overly simplistic) mathematical calculation. There are no technical limitations to doing PRR, it's easy, and there are plenty of data in VAERS to do PRR whenever we want to and on whichever vaccines we choose. The issue is whether it's a good idea for CDC to do PRR when FDA is doing EB data mining (see below).

I somewhat disagree with this statement: PRR analyses of COVID-19 vaccines early in the vaccination campaign were inappropriate and thus not conducted. It's only inappropriate in the sense that EB data mining is a better test of disproportionality b/c PRR tends to generate all kinds of spurious findings. FYSA, the Uppsala monitoring center in Europe, which is affiliated with WHO, uses PRR and ROR as its primary disproportionality analysis. Also, the statement seems to indirectly imply that it might be appropriate to use PRR now (vs. early), but I would questions whether PRR is appropriate even now. The test still has all its original limitations.

I think the main message should be that FDA's EB data mining supersedes PRR in importance and from the perspective of generating informative data. CDC surveillance focus early on was descriptive analysis of large volumes of data and focusing on adverse events of special interest (e.g., anaphylaxis).

From: Sharan, Martha (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Thursday, June 23, 2022 8:01 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Nordlund, Kristen (CDC/OD/OADC) [redacted] Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Vaccine Safety (CDC) [redacted]
Subject: RE: Reporter inquiry

Hi Tom and John:
I think this reporter is going to need adequate information from CDC to write her piece countering the CHD.
We can point her to ACIP presentations ands studies, but I don't think she's going to be able to build a piece on her own from all that material, especially if she has not been following it.

So, I think the information John provided will be much more helpful. We may need to edit it down just a bit, but I can work on that. I can also reach out to the reporter to get a reading on how much detail she needs.

There have been 2 inquiries about this: AP and Washington Examiner.

Thanks,
Martha

Martha Sharan
Public Affairs
CDC/Division of Healthcare Quality Promotion
[redacted]

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, June 22, 2022 5:42 PM
To: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]; Sharan, Martha (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Nordlund, Kristen (CDC/OD/OADC) [redacted] Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP) [redacted]; Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]; Vaccine Safety (CDC) [redacted]
Subject: RE: Reporter inquiry

Can we just simply point the reporter to the publications website and the ACIP presentations website to demonstrate the monitoring and signal detection/signal assessment activities that have been happening since December 2020. We could also say that PRR is a form of disproportionality analysis and FDA empirical Bayesian data mining is the primary disproportionality analysis used in VAERS. CDC selectively uses PRR as a supplement or complement to FDA's EB data mining.

From: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, June 22, 2022 5:20 PM
To: Sharan, Martha (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Nordlund, Kristen (CDC/OD/OADC) [redacted]; Thompson, PerStephanie (CDC/DDID/NCEZID/DHQP) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Vaccine Safety (CDC) <[redacted]>; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: Reporter inquiry

Hi folks,

Adding PerStephanie to this email, as she's more versed in FOIA matters, and can advise if any details I provide are privileged (ie, shouldn't be released in response to this inquiry). Also adding Paige, who can provide more technical details if I get my facts crossed, and the Vaccine Safety mailbox for tracking purposes. And Tom, for his awareness (it's AP, after all).

The FOIA below mentioned specified analyses of proportionality reporting ratios (PRRs) during February 1, 2021, through Sept. 30, 2021. You might recall that emergency use authorization (EUA) for the mRNA vaccines was granted in December 2020, and EUA for Janssen's vaccine was in March 2021. While there was a considerable reporting volume to VAERS during this time period, preliminary reports of adverse events of special interest (AESIs) were more limited. Thus, during the time period specified, we were early in the vaccination campaign, and insufficient data had accrued during that time for PRR analysis.

Also, selection of appropriate comparator vaccines was a challenge: ideally, PRRs are conducted between vaccines of similar type or technology (e.g., comparing live virus vaccines like MMR and varicella (Varivax), or conjugated vaccines like Prevnar (pneumococcal conjugate vaccine) and the meningococcal conjugate vaccines). No such comparator existed for the mRNA vaccines. We've performed some draft analyses against the influenza vaccines (with no surprising

results – a lot of the tagged adverse events (AEs) were typical of the mRNA vaccines); these draft analyses were performed after the period specified in the FOIA – and again, they were draft, so we wouldn't want to consider them formal analyses.

Lastly, interpretation of PRRs is tricky – the usual threshold we use is 2.0, indicating that a given AE was reported after one vaccine twice as often as after the comparator vaccine(s). As you can imagine, quite a few AEs yield a PRR of 2.0 or greater. This threshold indicates no statistical significance; it's an arbitrary cut point, like selecting a p value of 0.05 (which corresponds to a given outcome in 5 of 100 occurrences, such as 5 heads out of 100 coin flips). In sum, PRRs are noisy and challenging to interpret. To call a PRR of 2 or greater a "safety signal" (as the author of the CHD article does) is a gross overstatement.

CDC (and VAERS specifically) *was* engaged in safety signal analysis during the period specified in the FOIA – but what the CHD author fails to grasp is that "signal detection" is a sum of both quantitative and qualitative analysis. Case in point: thrombosis with thrombocytopenia syndrome (TTS) after Janssen's vaccine was identified during the FOIA period. VAERS contacted the Advisory Committee on Immunization Practices (ACIP) within 3 weeks of initiating use of the vaccine when 6 cases of cerebral venous sinus thrombosis (CVST) with low platelets had been identified. With only 6 cases of CVST, no thromboembolic symptom would flag via PRR, or even Empirical Bayesian data mining, analyses. However, a similar syndrome had been observed after AstraZeneca's vaccine in Europe – and, like Janssen's vaccine, AstraZeneca's vaccine was based on an adenoviral vector. In this case, VAERS identified this safety signal not through quantitative techniques per se, but via pattern recognition.

With the above background, I might suggest the following response:

"The author of the Children's Health Defense article mischaracterized safety signal analysis. In brief, Proportionality Reporting Ratios (PRRs) can be helpful in identifying potential vaccine safety concerns, or "safety signals", but PRRs are a single tool and do not by themselves indicate such safety signals.

PRRs compare the counts of reports of a given adverse event (AE) after one vaccine to after another vaccine (or vaccines). For example, a PRR of 2.0 indicates that a given AE was reported twice as often after one vaccine as after another vaccine(s). A known limitation of the Vaccine Adverse Event Reporting System (VAERS) is that reporting to VAERS can be influenced by numerous factors, including increased public attention or awareness of a given AE. Thus, a PRR by itself does not constitute a safety signal: there can be numerous explanations for why a PRR might be elevated for a given vaccine. PRRs can be helpful tools, but they do not indicate potential safety concerns with a vaccine on their own.

Further, the FOIA requested PRR analyses from early in the COVID-19 vaccination campaign. Various technical limitations, including insufficient data, precluded PRR analyses during that time in the vaccination campaign.

More importantly, CDC has been engaged in safety signal surveillance since COVID-19 vaccines have been in use. During the first month of their availability, data on anaphylaxis after mRNA COVID-19 vaccines were published (including in highly visible journals, like the Journal of the American Medical Association (JAMA)), indicating an observed incidence comparable to after other vaccines. VAERS detected what would become known as thrombosis with thrombocytopenia syndrome (TTS) after Janssen's vaccine, leading to a pause in the use of the vaccine mere weeks after its use was initiated. VAERS reviewed reports of myocarditis after mRNA COVID-19 vaccines during Summer 2021, providing a highly thorough characterization of such reports. These examples indicate that the vaccine safety surveillance systems in use by CDC and FDA identify potential vaccine safety concerns in a timely and effective manner.

In sum, PRR analyses of COVID-19 vaccines early in the vaccination campaign were inappropriate and thus not conducted. However, CDC and FDA have been actively engaged in vaccine safety surveillance ever since COVID-19 vaccines have been in use."

Please let me know what you think, and if you have any comments, feedback, or any questions. Thanks!

- John

From: Sharan, Martha (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, June 22, 2022 12:51 PM
To: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]

Cc: Nordlund, Kristen (CDC/OD/OADC) [redacted]
Subject: FW: Reporter inquiry

Hi John… wanted to check with you on this request from Associated Press. Can you offer a response to this one? I'm cc'ing Kristen, since the request came through her and we don't have a standard response to what the reporter is asking.
Thanks,
Martha

Martha Sharan
Public Affairs
CDC/Division of Healthcare Quality Promotion
[redacted]

Hi,

I'm a fact-checking reporter at The Associated Press. I'm looking into a new post by Children's Health Defense that is being shared on social media, alleging that a FOIA response from CDC shows the agency "admitted it never analyzed the Vaccine Adverse Event Reporting System for safety signals for COVID-19 vaccines":
https://childrenshealthdefense.org/defender/cdc-vaers-covid-vaccine-safety/

The claim appears to center on a request for "proportional reporting ratio" calculations – and a CDC response saying "no PRRs were conducted by CDC."

Could CDC explain what, exactly, was requested in this FOIA request (#22-01479-FOIA)? Has the agency performed any PRRs in relation to the COVID-19 vaccines? Has the agency analyzed VAERS data pertaining to the COVID-19 vaccines in other ways?

Thanks,
Angelo

--

Angelo Fichera
Reporter, News Verification
The Associated Press
[redacted]

From: "Weintraub, Eric (CDC/NCEZID/DHQP/ISO)" [redacted]
To: "Thompson, PerStephanie (CDC/NCEZID/DHQP/OD)" [redacted], "Starrett, Tracie (CDC/NCEZID/DHQP/OD) (CTR)" [redacted], "Su, John (CDC/NCEZID/DHQP/ISO)" [redacted], "McNeil, Michael (CDC/NCEZID/DHQP/ISO)" [redacted], "Moro, Pedro (CDC/NCEZID/DHQP/ISO)" [redacted]
Cc: "Shay, David (CDC/NCEZID/DHQP/ISO)" [redacted], "Ransom, Allen (CDC/NCEZID/DHQP/SB) (CTR)" [redacted], "Mitchell, Elnetta (CDC/NCEZID/DHQP/OD) (CTR)" [redacted], "Goodman, Jeremy A. (CDC/NCEZID/DHQP/OD)" [redacted]
Subject: RE: ADP Review 24-00023-LT (24-00101-FOIA)
Date: Tue, 15 Oct 2024 15:37:52 +0000
Importance: Normal
Attachments: VSD_Final_308d_extension_current_AoC_2024_Final_version.doc

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See attached - **Extension request approved June 2024 – June 2029**

From: Thompson, PerStephanie (CDC/NCEZID/DHQP/OD) [redacted]
Sent: Tuesday, October 15, 2024 9:50 AM
To: Weintraub, Eric (CDC/NCEZID/DHQP/ISO) [redacted]; Starrett, Tracie (CDC/NCEZID/DHQP/OD) (CTR) [redacted]; Su, John (CDC/NCEZID/DHQP/ISO) [redacted]; McNeil, Michael (CDC/NCEZID/DHQP/ISO) [redacted] Moro, Pedro (CDC/NCEZID/DHQP/ISO) [redacted]
Cc: Shay, David (CDC/NCEZID/DHQP/ISO) [redacted]; Ransom, Allen (CDC/NCEZID/DHQP/SB) (CTR) [redacted]; Mitchell, Elnetta (CDC/NCEZID/DHQP/OD) (CTR) [redacted]; Goodman, Jeremy A. (CDC/NCEZID/DHQP/OD) [redacted]
Subject: RE: ADP Review 24-00023-LT (24-00101-FOIA)
Importance: High

Thanks everyone that helped to respond to this set of records. After reviewing the VSD AoC, I noticed that it expired June 2024. Are you in the process of extending the VSD AoC? If so, do we have a timeline. If you have already completed the extension, please provide us a copy to use for this FOIA (by COB today) and processing future FOIAs.

Lastly, Tracie is finalizing the review and will be closing by COB.

Many thanks,
-p

From: Weintraub, Eric (CDC/NCEZID/DHQP/ISO) [redacted]
Sent: Tuesday, October 15, 2024 9:05 AM
To: Starrett, Tracie (CDC/NCEZID/DHQP/OD) (CTR) [redacted]; Su, John (CDC/NCEZID/DHQP/ISO) [redacted] McNeil, Michael (CDC/NCEZID/DHQP/ISO) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP/ISO) [redacted]
Cc: Shay, David (CDC/NCEZID/DHQP/ISO) [redacted]; Thompson, PerStephanie (CDC/NCEZID/DHQP/OD) [redacted] Ransom, Allen (CDC/NCEZID/DHQP/SB) (CTR) [redacted]; Mitchell, Elnetta (CDC/NCEZID/DHQP/OD) (CTR) [redacted]; Goodman, Jeremy A. (CDC/NCEZID/DHQP/OD) [redacted]
Subject: RE: ADP Review 24-00023-LT (24-00101-FOIA)

I found no issues with any of the pages being released, given the current level of redacted pages, I think the FOIA office did a good job on this one redacting the pdf etc.

Thanks for the opportunity to review this.

Eric

From: Starrett, Tracie (CDC/NCEZID/DHQP/OD) (CTR) [redacted]
Sent: Tuesday, October 8, 2024 10:02 AM
To: Su, John (CDC/NCEZID/DHQP/ISO) [redacted] Weintraub, Eric (CDC/NCEZID/DHQP/ISO) [redacted] McNeil, Michael (CDC/NCEZID/DHQP/ISO) [redacted]; Moro, Pedro (CDC/NCEZID/DHQP/ISO) [redacted]
Cc: Shay, David (CDC/NCEZID/DHQP/ISO [redacted]; Thompson, PerStephanie (CDC/NCEZID/DHQP/OD) [redacted]; Ransom, Allen (CDC/NCEZID/DHQP/SB) (CTR) [redacted]; Mitchell, Elnetta (CDC/NCEZID/DHQP/OD) (CTR) [redacted] Goodman, Jeremy A. (CDC/NCEZID/DHQP/OD) [redacted]
Subject: FW: ADP Review 24-00023-LT (24-00101-FOIA)
Importance: High

Good morning,

Attached in the document titled *24-00023-LT 3rd Interim Release.pdf* are the results of the Enterprise Search that the FOIA office conducted on your emails.
The FOIA Office has requested ISO to review for PII and/or the release of any sensitive information that may cause the program or agency harm. In your review, if you find information that is required to be protected…please highlight the content and explain your justification in the comment section or add the redactions to the attached *SME Technical Review Identifying Table* for (Pre-Decisional, Mosaic, & Proprietary information). I'll also begin searching for basic PII within the document as well.

Dr. Su, please advise if this should also be forwarded to Dr. Shimabukuro for his review.

Please review the attached FOIA records by **COB Tuesday, Oct. 15**.

Thank you,
Tracie

Tracie Starrett
CACI-INC. | Public Health Analyst (RIM CTR)
CDC, DDID, NCEZID, DHQP
Centers for Disease Control and Prevention
[redacted]

Cover Page

Project name:	**THE VACCINE SAFETY DATALINK PROJECT: COMPREHENSIVE LINKED DATA COLLECTION OF MEDICAL EVENTS AND IMMUNIZATION (THE VSD PROJECT)**

Contact information.

Main Point of Contact:	**Amelia Jazwa**
National Center:	**NATIONAL CENTER FOR PREPAREDNESS, DETECTION, AND CONTROL OF INFECTIOUS DISEASES COORDINATING CENTER FOR INFECTIOUS DISEASES**
Division:	***DIVISION OF HEALTHCARE QUALITY AND PROMOTION***
Address:	***1600 Clifton Road NE, Mailstop H16-3, Atlanta, Georgia 30329***
Phone:	***Amelia Jazwa***
Email:	[redacted]

Table of Contents

Attachments

List all attachments associated with your project or application (Please note some attachments will vary based on the project):
1. Contact Information for VSD CDC and Non-CDC Investigators 2. Letters of Concern from Each MCO 3. Guidelines to Writing Miniproposals for VSD Studies 4. Data Use Agreement 5. Assurance of Confidentiality for Non-CDC/ISO Employees 6. Assurance of Confidentiality for CDC Employees 7. Assurance of Confidentiality for Contractors 8. IRB Approval Letters from Each MCO 9. CDC Human Subjects Determination for the VSD Project 10. NCHS RDC Guidelines

REQUEST FOR EXTENSION OF ASSURANCE OF CONFIDENTIALITY FOR THE VACCINE SAFETY DATALINK PROJECT: COMPREHENSIVE LINKED DATA COLLECTION OF MEDICAL EVENTS AND IMMUNIZATION (THE VSD PROJECT)

DIVISION OF HEALTHCARE QUALITY AND PROMOTION
NATIONAL CENTER FOR PREPAREDNESS, DETECTION, AND CONTROL OF INFECTIOUS DISEASES
COORDINATING CENTER FOR INFECTIOUS DISEASES

Original Application 1/31/2002
Application Amended 7/22/04
Extension Requested 1/29/07 and Finalized 4/10/2009
Amended in 2012
PCU initiated Amendment completed in 2017 (Cybersecurity language added to all AoCs)
Extended June 2019 – June 2024
Extension request approved June 2024 – June 2029

This document is an updated Assurance of Confidentiality for the Vaccine Safety Datalink Project: Comprehensive Linked Data Collection of Medical Events and Immunization (the VSD Project).

A) Purpose of Project

Describe the programmatic purpose(s) of the project including the type of data to be collected and the uses of the information collected. This section is a summary of the project and should be approximately two pages.

Because few vaccine-preventable diseases are currently eradicable, most immunization programs designed to prevent these diseases must be continued indefinitely. No vaccine, however, is perfectly safe. Vaccines are given to healthy individuals, many of whom are children, and therefore a high standard of safety is required. Because vaccinations are administered routinely during childhood, the timing of some of these vaccinations invariably coincide with the onset of childhood illnesses. As vaccinations tend to be memorable events, these illnesses following immunization may be attributed to the vaccine. While some of these reactions may be caused by the vaccine, most are unrelated events occurring after vaccination by coincidence. One important way to minimize vaccine injuries is to foster the development of information systems and databases that will help us monitor and improve our understanding of vaccine safety. Such systems would also stimulate and foster the development and use of safer vaccines. Additionally, such close and ongoing monitoring of vaccine safety might help prevent the loss of

public confidence in immunization programs and the subsequent resurgence of vaccine-preventable diseases, as experienced recently with pertussis and diphtheria in several countries.

Despite the importance of vaccine safety, the Institute of Medicine (IOM) found that serious gaps and limitations exist in both the knowledge and infrastructure needed to study vaccine adverse advents. Among 76 types of vaccine adverse events reviewed by the IOM, the scientific evidence was inadequate to assess definitive vaccine causality for 50 (66%). The IOM also noted that 'if research...[is] not improved, future reviews of vaccine safety will be similarly handicapped.' These gaps in knowledge were attributable to several factors. Prelicensure controlled trials provide only limited safety data because of their relatively small sample size, short duration, and population homogeneity. Postlicensure studies are therefore needed to provide a fuller understanding of the safety of vaccines in general use.

Historically, postlicensure studies of safety have relied on passive surveillance systems such as The Vaccine Adverse Event Reporting System (VAERS). Because of the methodological weaknesses, such as the potential for biased reporting, under-reporting, and lack of denominators or comparison groups, VAERS data are usually not helpful in assessing risk or vaccine causality. Recognizing the need to improve the capability to study the risks of rare vaccine reactions, in 1990, the Centers for Disease Control and Prevention (CDC) formed partnerships with large staff model Managed Care Organizations (MCOs) in order to continually monitor and evaluate vaccine safety through the use of large linked databases (LLDB). LLDBs are the collection of data files linkable by a primary key variable.

Currently, thirteen MCOs and healthcare networks collaborate with the CDC in order to create the Vaccine Safety Datalink (VSD) project. These sites include Kaiser Permanente Washington (KPW), Seattle, WA; Harvard Pilgrim HealthCare Institute (HAR), Boston, MA ; Health Partners Research Institute (HPM), Minneapolis, MN; Kaiser Permanente of Colorado (KPC), Denver, CO; Kaiser Permanente Northwest (NWK), Portland, OR; Kaiser Permanente of Northern California (KPNC), Oakland, CA; Kaiser Permanente of Southern California (KPSC), Los Angeles, CA; Marshfield Clinic Research Institute (MFC), Marshfield, WI; Denver Health (DH), Denver, CO; Kaiser Permanente Mid-Atlantic States (KPMAS), Rockville, MD; Acumen, LLC (Acumen) Burlingame, CA; OCHIN (OCHIN), Portland, OR; and Indiana University/Regenstreif Institute (IU/RI), Indianapolis, IN. Creation of these LLDBs for the VSD has been accomplished both through merging of numerous administrative and clinical databases, including those that capture membership, pharmacy, and laboratory information. These databases allow computerized vaccination records to be linked with extensive computerized medical record information that includes patient demographics as well as birth and death tapes. Thus, information on medical events,

laboratory utilization, demographics and immunization histories are made available in a standardized manner across the participating MCOs. This database provides an economical and rapid means of conducting post-marketing surveillance that allows the evaluation of known and/or suspected associations between immunizations and medical outcomes while reducing under-reporting and recall bias.

Data collected:

For each patient within the VSD MCO sites, medical, pharmaceutical, health care and demographic data are collected, and identification of individuals are encoded by each site with a unique identifier. From 1991-2000, CDC received these data on an annual basis in the form of distinct datasets, comprised of the Constant File, the Enrollment File, the Vaccine File, and the Inpatient File, the Outpatient File, the MCO Birth File, the Mortality File, the Address File, the Geocode File, as well as some additional datasets for specific year or studies. From 2001- to present, CDC no longer receives data from the participating sites. This is largely due to heightened confidentiality concerns and because of the enactment of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Data are still created in the same manner; however, they remain at the sites and CDC is only provided access to these data. Table 1 outlines the types of variables that are collected for each dataset. For some special studies, additional information is also submitted, and includes data on selected procedures, pathogen-specific culture results and other diagnostic tests.

Table 1:

File Name	**Description/Content**
Constant File	Unique identifier, birth date, gender, Medicaid status
Enrollment File	Start and stop dates for enrollment in VSD
Vaccine File	Immunization records, vaccine type, vaccine manufacturer, lot number, date of administration
Inpatient File	Date of hospitalization, length of stay, ICD-9 code, diagnosis type, whether in or outside MCO
Outpatient File	Date of visit, ICD-9 code, diagnosis type, whether in or outside MCO
MCO Birth File	Gestational Age, child's weight, apgar score, race, birth state, birth county, mother's date of birth
Mortality File	Underlying cause of death, date of death
Address File	Zip code

All data collected for VSD up to December 31, 2000, and data that remain at the sites, which includes data after 1/1/2001, undergo a stringent data quality check in order to ensure completeness and accuracy. To further improve data quality, discrepancy checks are implemented to ensure a standardized analytic database.

The cycle files that have been created containing data from after December 31, 2000 utilize a distributed data model (DDM) as a way to access data from CDC to the sites. The DDM is a system that allows MCO data to be assembled and remain at the MCO sites rather than being transferred to CDC on an annual basis. It is a method to access the MCO data through SAS programs submitted to the MCO by data managers. The DDM is a secure method to transfer summary results through SAS programs, logs, and output as well as analytical data sets to the CDC, after full IRB approval.

Data Access

The VSD has developed two methods to permit CDC researchers to securely access the full VSD datasets, Indirect and Direct. With the "Indirect" method, at specified intervals, an MCO computer retrieves "jobs" containing SAS program code from a secure, pre-specified location known as the "hub". Four SAS macros are used to facilitate access of the data and retrieval of SAS logs and output. All transfer of SAS Programs, logs, output, and datasets are encrypted using SSH v2. In the second "Direct" method, CDC researchers access the data files interactively through a secure SAS remote session using SAS Connect. SAS Secure or SSH is used to provide encryption and ensure the security of data transmissions. The 4 SAS macros from the "Indirect" method may still be used, or more typical SAS code submitted using the SAS Log window and ODS, similar to using SAS Windows on the PC, may be used.

Both methods have been functional in a secure environment since May 2004. The DDM permits VSD research to continue using the standardized datasets containing complete vaccination, inpatient and outpatient data. DDM continues to allow access to CDC analysts to conduct studies and evaluate cycle files after 2 years of increasing use by CDC analysts. Confidentiality of individual medical information is maintained. VSD studies utilize limited data sets where only the data necessary to conduct a particular study is used.

Using these data created at the MCOs for VSD, the monitoring of adverse events from vaccination occurs using a two-armed approach. Potential signals of adverse events that have been detected through VAERS, or concerns that have arisen spontaneously (for example, through the media, or through reports at medical conferences or in medical journals) are evaluated by the datasets within the VSD. The second approach to monitoring vaccine-related adverse events is through a near real-time surveillance system whereby data are evaluated using sequential statistical methods to identify predefined adverse events following administration of a newly licensed vaccines or changes in vaccine recommendations. Additionally, as part of a long-term plan to

use the VSD to increase our knowledge base of potential vaccine – medical event associations, specific planned studies are carried out at the CDC and the collaborating MCO sites.

The data collected by and maintained within the Vaccine Safety Datalink Project are of a private and sensitive nature, and could potentially be damaging to an individual's, or family's reputation and their ability to obtain insurance and employment. The medical information provided by the MCOs was provided with the expectation that the protections of the doctor-patient relationship would be maintained. The MCOs are also concerned about incurring competitive harm if their proprietary information, including that related to their practice patterns, is released. The participating MCOs are therefore very protective of these data and are fearful that the data that were formerly provided to the CDC (currently created and located at the sites) might ultimately be obtainable via a Freedom of Information Act (FOIA) appeal. The MCOs feel morally and legally obligated to ensure that these data are used only by the appropriate people for approved purposes. Without an extension of the Assurance of Confidentiality, it is extremely unlikely that these MCOs would continue to participate in the Vaccine Safety Datalink Project.

Period of Time Authorization is Needed For Data Collection:
Data collection in a standardized VSD format began on March 1, 1991, for three MCOs (Group Health Cooperative, Northwest Kaiser Permanente, and Northern California Kaiser Permanente), and on October 1, 1992 for Southern California Kaiser Permanente, and is continuing on for these sites. In 1999, additional MCOs joined the project: Harvard Pilgrim/Harvard Vanguard, HealthPartners Research Foundation (including Marshfield Clinic), and Kaiser Permanente of Colorado. In 2001, Marshfield Clinic joined as a separate site. Data up to December 31, 2000, were sent to CDC from Group Health Cooperative, Health Partners Research Foundation, Kaiser Permanente of Colorado, Marshfield Clinic, Northern California Kaiser Permanente, Northwest Kaiser Permanente, and Southern California Permanente. Health service use and medical information for each patient is routinely collected by each MCO for administrative purposes. These data are computerized and continuously updated by each MCO indexed to individuals by a unique identifier. Such data were initially used primarily for internal MCO administrative and clinical patient treatment purposes but have been adapted for this project.

Previously, the VSD had a contract with American Health Insurance Plans (AHIP). The original contract was with the American Association of Health Plans, now called AHIP. AHIP is charged with the responsibility to establish and maintain an infrastructure of its subcontracted managed care organizations (Group Health Cooperative, Harvard Pilgrim/Harvard Vanguard, Health Partners Research Foundation, Kaiser Permanente of Colorado, Marshfield Clinic, Northern California Kaiser Permanente, Southern California Kaiser Permanente, and Northwest Kaiser Permanente) that allowed scientifically rigorous and efficient monitoring of vaccine safety. In September 2012, the AHIP contract ended and CDC continued the VSD program under an Indefinite Delivery Indefinite Quantity (IDIQ) contract, which remains the current funding mechanism to date. Key participants in the VSD project currently are listed in Attachment 1, "Contact Information for VSD CDC and Non-CDC Investigators."

The VSD was established in 1991 with the understanding by all parties that patient and MCO-identified data were sensitive and needed to be kept confidential. Public interest in the VSD data

prompted the MCOs to seek further assurance from CDC that their confidentiality expectations will be met. As noted in the attached MCO letters sent to CDC in 2001 (Attachment 2), failure to protect their proprietary and patient privacy interests could cause them significant harm and would likely cause the MCOs to withdraw from participation in this critical vaccine safety system. Since these concerns and the potential harm relate to the entire dataset and not just to information collected after issuance of the 308(d) assurance, the 308(d) Assurance of Confidentiality is retroactive to cover all data collected since the beginning of the VSD Project.

B) Justification of Need

Describe why it is important to protect the individual or institution with an Assurance of Confidentiality.

The information submitted to the CDC by the participating MCOs allow the CDC to adequately monitor vaccine safety in a scientifically rigorous manner. Because the MCOs are aware that the CDC as a federal governmental agency must comply with access statutes, such as the Freedom of Information Act, they are deeply concerned about future participation with the VSD if identifying information on the individual or the institution were made available to individuals or organizations outside those participating in the Vaccine Safety Datalink Project.

Within the datasets that have been submitted to the CDC and those that currently remain at the participating MCOs, patients are assigned unique identifiers. Such identifiers, however, do not sufficiently protect either the patient's, or the health plan's, identity to the extent that would permit data sharing with individuals outside the Vaccine Safety Datalink Project. Even though names or addresses are not included in the databases, it is possible to identify many patients by combining a birth date with the dates on which specific kinds of medical care are delivered, or by combining current VSD data with other, public access data that are not under the control of the CDC or VSD. This becomes problematic for individuals with uncommon conditions or for individuals who are prescribed rarely used medications**.** Identification of individuals could have potentially devastating consequences to the individuals as well as to the health plans.

In order to assess the ease with which an outside (non-CDC or non-VSD) person could identify an individual's medical record, one of the funded MCOs conducted the following exercise. They considered a scenario in which the currently collected VSD data files were available on a public access website and that an employee of that MCO was interested in identifying the medical record of a co-worker's child. It would be easy for such an employee to gain information about the child's birth date from non-secure company records or through conversation with unrelated staff members (e.g.; circulation of a birthday card within a company office or access to company administrative files). Additionally, it has been shown that frequently information of a minor medical nature is exchanged (again, office conversation about a child's weekend emergency visit for a sprained ankle, or circulation of a 'get well soon' card for a coworker's child). Given such information however, an employee (or any other interested third party) would – with only minimal sophistication with regards to computing or merging datatapes – be able to identify this

individual child from thousands in the VSD files. In this exercise, a programmer used the Principal Investigator's daughter as a test case. In little time, using only the two pieces of information as outlined above, an analyst quickly found the child's medical record in the VSD file. Once this person's file was found, all of that person's medical history – including information concerning the child's medical visits, diagnoses and pharmacy use - was available for review by this outside person. Conceivably, a third party could then gain all sorts of highly confidential information, including HIV status, test orders for sexually transmitted disease, mental health diagnoses or treatment, etc. Such identification of individuals could have devastating consequences to the individual as well as to the health plan.

In addition to maintaining guarantees of research subject confidentiality, the funded MCOs have understandable concerns over organizational security and proprietary issues, and that the data might be requested in order to create and/or support litigation against them. The data that are created for the VSD contain confidential information on pharmaceutical usage, laboratory utilization, health care utilization and management patterns as well as chronic conditionswhich members are treated. Such information would be very valuable to pharmaceutical companies or other health maintenance organizations who have not otherwise put forth the effort to create this CDC vaccine safety infrastructure. Pharmaceutical companies might use this information to more aggressively market their agents to those who make purchasing decisions for health maintenance organizations as well as to evaluate comparative efficacy of various drug regimens. This could compromise the ability for the organizations to manage their pharmaceutical services. Competing MCOs would be able to have access to strategic information regarding health practices and patterns of care (clinical procedures and guidelines, standards of care, care pathways, and all databases that exist in a form which could describe or reveal such patterns).

Describe why the individual or institution will not furnish or permit access to the information unless an Assurance of Confidentiality is issued.

The VSD project plays an important role in the national vaccine safety infrastructure. The MCOs feel that resolving this issue satisfactorily is their top priority. They believe strongly that their ability to participate in the VSD is predicated on a commitment to protect the confidentiality of both their members as well as their organization. The MCOs believe that they have adhered to specific IRB considerations regarding data use and confidentiality. They have expressed concerns that providing the VSD data outside the CDC may violate specific conditions of IRB approval under which MCOs participate in the VSD. Future participation is contingent upon a continued commitment from the CDC to manage access to VSD datasets in a manner that addresses all issues surrounding confidentiality and proprietary concerns. (See letters from the participating MCOs in Attachment 2 for detailed presentations of their viewpoints and their position that without formal confidentiality protection, their future participation in the VSD project will be doubtful). The 308(d) protection enables CDC to resist compulsory legal demands such as subpoenas and court orders, for such identifying information.

Describe whether or not the information could be obtained with the same degree of reliability from sources that do not require an assurance.

The success of the VSD project is due entirely to the unique established partnerships with the participating MCOs. These MCOs individually create large linked databases for administrative and clinical purposes. Because the MCOs believe that there are confidentiality issues as well proprietary issues associated with the VSD data that they have provided in the past to the CDC and now provide access to the CDC, they would reconsider their participation if the 308(d) protection was not provided. If these actions were to be realized, this would almost assuredly set precedent for other organizations interested in participation with the VSD project. Because no other large managed care organizations or insurance companies with administrative databases would be willing to participate without similar assurances of confidentiality, it would be highly unlikely that the VSD would be able to continue its monitoring activities of vaccine-related adverse events. This would be not only a major loss to the VSD project but to the public health of our nation.

Describe how the information is essential to the success of the particular statistical or epidemiological project and is not duplicative of other information gathering activities of the Department of Health and Human Services.

The very effectiveness of currently available childhood immunizations has decreased the public perception of the threat that vaccine preventable diseases pose to children. However, there has been heightened public concern regarding adverse effects of immunization. The VSD project's ability to adequately monitor vaccine safety in a scientifically rigorous manner cannot be

overstated. It is one of the largest and most diverse databases in the world, and there are no other information gathering activities of the Department that collect this type of medical event information, either individually or linked to immunizations as done within the VSD.

Describe how the issuance of the Assurance of Confidentiality might restrain CDC from carrying out any of its responsibilities.

The extension of the 308(d) Assurance of Confidentiality for VSD data will not restrain the CDC from carrying out any of its responsibilities and duties as a public health institution. Vaccine safety has become an important issue at the congressional level. Also, concerns regarding vaccine safety have recently re-emerged in the media. Public confidence in the CDCs immunization program's efforts would be jeopardized if the VSD did not exist. The VSD project is the only vaccine safety project at CDC that can assess causality and test hypotheses in an effective and economic manner. Through the active surveillance of linking immunization and medical records on MCO members, the VSD project monitors approximately 3% of the total US population. Such assurance will ensure that CDC continues its collaboration with the MCOs so that vaccine safety can be rigorously monitored.

Although the purpose of the VSD is to actively monitor and study vaccine-related adverse events, the infrastructure created by the VSD allows for additional investigations into other vaccination related issues. For example, the diversity in vaccination practices at the participating MCOs permitted an assessment of the effect of the recent change in U.S. polio immunization policy upon vaccination coverage and completeness. Other such ad hoc studies – that have had important policy implications - have included the safety of the second MMR vaccine administered at different ages, and of the safety of inactivated flu vaccine for children. The size of the VSD population may also permit separation of the risks associated with individual vaccine combinations, whether given in the same syringe or simultaneously at different body sites. Such studies are especially valuable in view of the new combined pediatric and adolescent vaccines available and currently in development.

VSD data for ad hoc studies are shared with VSD members at CDC and with the funded MCOs as well as with other CDC (non-VSD) researchers. Some studies, however, seek supplementary information that require additional data collection methods such as chart abstraction, additional computerized data, and telephone interviews. Currently, in order to utilize the VSD data for any analysis, all investigators (VSD members and CDC/non-VSD) must submit a detailed proposal to a VSD proposal review group, which includes the VSD Team Lead, and one designated principal investigator from each MCO. There are specific requirements for each proposal, including specification of (a) principal investigator and collaborators; (b) study summary and hypotheses to be tested; (c) background, methods and analytic strategy; (d) chart abstraction requirements and materials; (e) data management and data quality requirements; (f) any other supplementary study materials; (g) confidentiality protection mechanisms; (h) resource needs; and (i) anticipated timeframe (See Attachment 3, "Guidelines to Writing Miniproposals for VSD Studies"). The proposal is reviewed by this review group and afterwards presented and critiqued to the entire VSD group for their approval.

After VSD approval of the proposal, sites seek the necessary IRB approval from both participating sites and CDC. Limited use data sets, collecting only the necessary data for the study, are collected. Other additional data sources are sought, if needed.

As data collection is completed for an approved study, data and results are transferred to the site leading the study. Data are transferred through secure methods only. The typical method for transferring data is through the VSD Distributed Data Model. The "hub", which is a secure computer located at one of the MCO sites, can also be used for transferring datasets in addition to its purpose in the DDM. Because the "hub" uses encryption and SSH v2 internet protocols, this method is more secure than the previously used secure FTP site. Access to the "hub" is currently maintained by HPM and is limited to up to five CDC programmers and the participating MCOs. Data files as well as SAS logs and output may then be easily transferred from the CDC to the lead site. Individual MCOs login Ids and passwords are not allowed to be shared with other MCOs. Rarely, though, data may be transferred through express mail services.

With the granting of Section 308(d) Confidentiality, potentially identifiable data cannot be shared with researchers outside of the VSD, except as noted below. Currently, the VSD shares data only with the VSD members at the CDC and VSD members at the participating MCOs (See Attachment 1 for a listing of investigators and contact information) as well as other CDC (non-VSD) researchers. The data are only shared when all VSD PIs have approved a specific research proposal. Data has never been shared with non-CDC/non-participating MCO researchers without a formal collaboration. CDC established a VSD Data Sharing Program implemented by the NCHS Research Data Center to allow limited access to VSD data by non-CDC researchers under established protocols.

All researchers who access VSD data must sign a data use agreement (Attachment 4). Occasionally non-CDC employees working at the CDC (guest researchers, visiting fellows, students, contractors, etc.) may be given access to VSD analytical data files or rarely the VSD DDM. Access to the VSD database would be done only under the strict supervision of a CDC employee. These people would be required to sign a 308(d) pledge for non-employees (Attachment 5).

Describe the advantages of assuring confidentiality and how they outweigh the disadvantages.

The advantages of this Assurance of Confidentiality far outweigh any potential disadvantages. The CDC has established excellent ongoing partnerships with the participating MCOs, which have been key to accomplishing the agency's mission in the area of vaccine safety. The VSD has also assisted other PHS agencies (e.g., FDA) in their vaccine safety-related activities. The Assurance of Confidentiality has strengthened CDC's relationship with the MCOs. Moreover, as mentioned earlier, without such an assurance it is very doubtful that the MCOs would continue to participate with VSD project which would seriously affect the national vaccine safety infrastructure.

C) Confidentiality Assurance Statement

Vaccine Safety Datalink Project
Confidentiality Assurance Statement

The Immunization Safety Office (ISO), Centers for Disease Control and Prevention (CDC), in collaboration with a consortium of Managed Care Organizations (MCOs), has been charged with the responsibility to monitor adverse events as a result from vaccination. These MCOs provide data to the CDC for the purpose of actively monitoring and studying vaccine-related adverse events.

The data that are collected for the purposes of VSD are a subset of electronic information that are collected at each MCO on each patient for administrative and clinical purposes. This information includes patient demographic, medical, pharmaceutical, and health care data. The identification of individuals is encoded by each site through the use of a unique identifier. The participating VSD sites maintain these data permanently in longitudinal data files that are used for epidemiologic and health services studies of vaccine safety as well as for public health surveillance and research. ISO, recognizing the sensitivity of the data being furnished by the MCOs, has applied for and obtained an Assurance of Confidentiality to provide a greater level of protection for the data while at the CDC and at each contractor/subcontractor site.

Information received by CDC or its contractors/subcontractors as part of this surveillance system that could lead to direct or indirect identification of patients or MCOs is collected and maintained at CDC under Section 306 of the Public Health Service (PHS) Act (42 USC 242k) with an assurance that it will be held in strict confidence in accordance with Section 308(d) of the PHS Act (42 USC 242m(d)). It will be used only for purposes stated in this Assurance and will not otherwise be disclosed or released, even following the death of patients in this surveillance system. This assurance is effective to cover all data collected for the VSD, including data collected since its inception, in 1991.

Information collected by the CDC will be used without personal identifiers for publication in statistical and analytic summaries and for release in restricted release datasets for research. Every effort will be made to not disclose information to any individual or group that could lead to direct or indirect identification of patients or MCOs. In particular, such information will not be disclosed to: insurance companies; any party involved in civil, criminal, or administrative litigation; agencies of Federal, State or local government; or any other member of the public.

Collected information that could lead to direct or indirect identification of patients or MCOs will be kept confidential and aside from VSD project employees, their contractors/subcontractors, guest researchers, fellows (and the like), and qualified researchers (i.e., non-VSD CDC employees and researchers utilizing the NCHS Research Data Center), no one will be allowed to see or have access to the information. CDC employees, contractors/subcontractors, and non-

employees will be required to handle the information in accordance with procedures outlined in the CDC Staff Manual of Confidentiality and to follow the specific procedures documented in the Confidentiality Security Statement for this project. Qualified researchers will be required to sign a detailed data use agreement to gain access to restricted release data and will only be allowed limited access comparable to that provided in the NCHS Research Data Center and as provided under protocols for a VSD Research Data Center (Attachment 10).

D) Confidentiality Security Statement

Confidentiality Security Statement
Vaccine Safety Datalink Project (VSD)

The Immunization Safety Office, has applied for an extension of the 308(d) Assurance of Confidentiality for the project entitled "The Vaccine Safety Datalink Project" (VSD). Because of this Assurance, documents and files containing information that could be used to identify a patient or MCO either directly or indirectly will be considered confidential materials and will be safeguarded to the greatest extent possible. Because the data are highly sensitive, and have 308(d) protection, the security requirement is rated as high. It is the moral and legal responsibility of each VSD and contract/subcontract staff member working on the VSD Project to protect the right to confidentiality of the patients and MCOs that are part of the project. Computerized health service use and medical information for each patient collected at each of the contract/subcontractor sites for administrative and clinical purposes are indexed to individuals by a unique identifier. Data up to 2000 have been submitted to the CDC annually to be merged into larger datasets. Data files containing data after December 31, 2000 reside at each participating VSD site in which CDC only has access to these data. This document describes the procedures and practices that VSD intends to use to protect the confidentiality of the data collected and accessed as part of this surveillance project.

VSD and contractor/subcontractor staff are required at all times to maintain and protect the confidential records that may come into their presence and under their control. To assure that they are aware of this responsibility and the penalties for failing to comply, each CDC/VSD staff member working on the project must read and sign a Nondisclosure Agreement (CDC 0.979), assuring that all information identifying an individual patient or MCO will be kept confidential and will be used only for epidemiologic or statistical purposes.

The VSD Technical Steward is Amelia Jazwa, MSPH; and the VSD Business Steward is Bonita Johnson.

Attachment 6 is the Nondisclosure Agreement that all CDC/VSD staff on the project will sign. Attachment 7 is the Contractor's Pledge of Confidentiality. All contractor/subcontractor employees from the participating MCOs with access to the data will be required to sign this contractor pledge. Originals of these documents will be retained by ISO. Attachment 5 is the Non-Employee Confidentiality Pledge. All non-employees (guest researchers, fellows, students, trainee, employee of a Federal Agency other than CDC, etc.) who will have access to the data will be required to sign this confidentiality pledge. These originals will be retained by VSD at ISO.

The following are a set of security guidelines that both CDC and contractor/subcontractor staff as well as non-employees will follow to promote a secure surveillance system. Any changes to this Security Statement will be transmitted to the CDC Confidentiality Advisor.

Restrictions on Use of Information and Safeguarding Measures:

- Information received in the course of conducting VSD will be used only for the purposes of carrying out the project and will not be divulged or made known in any manner except as necessary for the project, without written approval from the CDC Technical and/or Business Steward and private investigators at the contractor/subcontractor sites.

Contractors/subcontractors collect records or data containing names and social security numbers for individual patients. They are to remove these identifiers before creation of each dataset.

- VSD/CDC staff will not receive any personal identifying information on patients, but will receive potentially identifying geographic data (e.g., zipcode, county, census tract) and demographic data (e.g., date of birth and death), which is now protected by 308(d). Staff working on the project is not to discuss or divulge any identifying information about project participants to anyone other than the MCO from which the data came or authorized project staff on a "need to know" basis to conduct official business. In general conversation outside the workplace, neither the identifying information nor the nature of the data collected should be discussed in any detail.

- If a contractor/subcontractor inadvertently fails to remove personal identifiers of individual patients before forwarding data files to VSD, project personnel will remove the personal identifiers from the file, delete the original file with personal identifiers, and remind contractor/subcontractor personnel to remove the personal identifiers in the future.

- A unique identifying number is assigned to each patient at the contractor/subcontractor site before accessed by CDC. Any files which map the assigned number to identifying information maintained by the MCO will not be shared with the CDC or other participating MCOs and organizations.

- When not in use by authorized project staff, all hard copy material and physical media containing confidential data will be stored in locked containers, file cabinets, or rooms. Access to locked storage areas will be limited to authorized project staff. This procedure will apply to all physical media containing confidential data, including printouts, diskettes, CDs, tapes or cartridges (or any other electronic media). Staff working with confidential materials during data handling will have access only to the materials that they are currently processing. When confidential records are in use, they must be kept out of sight of persons not authorized to work with these records.

- Except as needed for operational purposes, photocopies of confidential data are not to be made. If photocopies are necessary, care should be taken that all copies and originals are recovered from the copy machines and work areas. All confidential paper records will be destroyed as soon as operational requirements permit by shredding the documents.

Analytical data files, SAS logs and output, and any other output will be transferred primarily through a secure computer maintained at one site, known as the "hub". Transfers will be made using encryption methods and SSH v2 internet protocols. Rarely, data may also be transferred via express mail.

- VSD staff at CDC and at the contracting/subcontracting sites is responsible for protecting all confidential data from eye observation, from theft, or from accidental loss or misplacement due to carelessness. All reasonable precautions will be taken to protect confidential project data.

- All staff currently working on the VSD project have received training in 308(d) confidentiality safeguarding procedures. Training is conducted by VSD/CDC staff, and 308(d) pledges are obtained. As new staff come on board, training will be conducted by the VSD Technical Steward.

Enhanced Protection of Computerized Files:

All data will be protected in confidential computer files. The following safeguards are implemented to protect VSD files so that the accuracy and the confidentiality of the data can be maintained:

- Computer files containing programs, documents, or confidential data will be stored in computer systems that are protected from accidental alteration and unauthorized access. Computer files will be protected by password systems, controlled sharing, and routine backup procedures.

- Data are transferred through secure methods only. The typical method for transferring data is through the VSD Distributed Data Model. The "hub", which is a secure computer located at one of the MCO sites, can also be used for transferring electronic files in addition to its purpose in the DDM. Because the "hub" uses encryption and SSH v2 internet protocols, this method is more secure than the previously used secure FTP site. Access to the "hub" is currently maintained by HPM and is limited to up to five CDC programmers and the participating MCOs. Data files as well as SAS logs and output may then be easily transferred from the CDC to the lead site. Individual MCOs login Ids and passwords are not allowed to be shared with other MCOS. Rarely, though, data may be transferred through secure mail services.

- Previous VSD cycles are located at CDC on the internal network drives and two PCs, which are firewall protected. Only users at CDC can access these datafiles. In order to receive access to these data, users must submit a formal request to the technical steward assigned to VSD. Once access is granted, users receive read-only group rights on which data are password protected.

The CDC LAN complies with several Federal policies, statutes, regulations, and other directives for the collection, maintenance, use, and dissemination of data, including the Department of Health and Human Services Automated Information Systems Security Program and the Computer Security Act of 1987 (Public Law 100-235). Additionally, the LAN is in compliance with the CDC's ITSO Security Policy. Security features implemented include

- user ID and password protection, mandatory password changes; limited logins; user rights/file attribute restrictions and virus protection. The network is backed up on tape every night and weekly tapes are stored off site.

- Employees from the contracting/subcontracting sites will only be granted access to the data files after a signed Contractor Pledge of Confidentiality is received by the VSD Technical Steward, Amelia JazwaMSPH; and the VSD Business Steward, Bonita Johnson. CDC/VSD employees must sign the Nondisclosure Agreement prior to project participation or access to project data.

Dissemination of Project Results

VSD contractors/subcontractors will be supplied with a confidential report of results. Individual patients will receive no report from VSD. In VSD publications, participating sites are acknowledged. Study participants are not identified in any VSD publication.

There are several primary intended uses for VSD data. The first use is for national vaccine safety surveillance, which occurs by using a two-armed approach. In the first arm, potential signals of adverse events that have been detected through the Vaccine Adverse Event Reporting System (VAERS), or concerns that have arisen spontaneously (through the media, or through reports at medical conferences or in medical journals) are evaluated within the VSD. In the second arm. near real-time surveillance system whereby data are evaluated using sequential statistical methods to identify predefined adverse events following administration of a newly licensed vaccines or changes in vaccine recommendations. The second intended use of VSD data is to increase our knowledge of potential vaccine-medical event associations. These studies are carried out at the CDC and at the contract/subcontract sites. The methods of data publication and confidentiality risks are similar to those for surveillance. Studies to increase our knowledge of potential vaccine-medical event associations are also conducted by non-contract researchers who are deemed qualified by the VSD research protocol review committee. Release of data files to researchers would require them to sign a data use agreement that prohibits subsequent release or publication in a way that would enable deductive identification of an individual or MCO.

Records Disposition for the National Archives and Records Administration

After the end of the project, if the records are determined to be permanently valuable, a public use data tape will be sent to the National Archives and Records Administration (NARA). This transfer will be done in accordance with the May 1996 agreement stating that CDC will transfer to NARA all permanent data sets in accordance with approved schedules contained in part IV of the CDC Records Control Schedule B_321, with the exception of identifying information collected under an assurance of confidentiality agreement as specified under the Public Health Service Act, Sections 301(d) and 308(d).

If 308(d) records for this project are being sent to the Federal Records Center for temporary storage (in which CDC maintains control of the data), they must be clearly identified as 308(d) protected records. The SF 135 should state: "This accession contains records protected by a

confidentiality assurance under Section 308(d) of the PHS Act." The boxes should have a label stating: "This accession contains records protected by a confidentiality assurance under Section 308(d) of the PHS Act. The records can be released only to authorized staff from the Immunization Safety Office.

CDC Human Subjects Review:
This project has been determined by the CIO ADS to be active surveillance of vaccine adverse events and is not considered research. Each project site has been approved by their local IRB. These MCOs seek IRB approval in order to satisfy the individual MCO's requirements about the use of their own patient-level information in any data analysis. This application packet includes documentation from CDC stating that VSD Project as a whole is not considered research (Attachment 9) and letters from each contract/subcontract site documenting local IRB approval (Attachment 8).

E) Research/ Non-Research Determination

Please include supporting documentation as an attachment.

- Please state the research determination for the activity as being either research or non-research. Please include the appropriate human research protection document supporting the determination. **VSD projects received Non-Research Determinations, since most activities are surveillance, i.e., using data to assess problems of public health importance**.

This section should also include a PRA determination. If it is determined that PRA does not apply, please include the reasoning given for this determination. **PRA does not apply since VSD surveillance data are secondary data.**

This section should also include if the Privacy Act applies to this project and a Privacy Impact Assessment (PIA) if applicable. **The Privacy Act does not apply.**

Attachments

List all attachments associated with your project or application (Please note some attachments will vary based on the project):
1. Contact Information for VSD CDC and Non-CDC Investigators 2. Letters of Concern from MCOs 3. Guidelines to Writing Miniproposals for VSD Studies 4. Data Use Agreement 5. Assurance of Confidentiality for Non-CDC/ISO Employees 6. Assurance of Confidentiality for CDC Employees 7. Assurance of Confidentiality for Contractors 8. IRB Approval Letters from MCOs 9. CDC Human Subjects Determination for the VSD Project 10. NCHS RDC Guidelines

Attachment 1
Contact Information for Non-CDC VSD Investigators:

NCK
Nicola Klein, MD, PhD
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Fax: [redacted]
Email: [redacted]

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Joshua T.B. Williams, MD
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KPC
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Email: [redacted]

OCHIN
Teresa Schmidt, PhD
Mailing Address: [redacted]
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

Attachment 3: Miniproposals for VSD Studies

From: Julianne Gee, MPH, Project Officer for the Vaccine Safety Datalink Project, Immunization Safety Office, Office of the Chief Science Officer, Office of the Director

To: Interested Parties

Since 1991, the Centers for Disease Control and Prevention (CDC) has collaborated with several health maintenance organizations (HMOs) to develop the VSD project to improve the monitoring of vaccine safety in the U.S. The scope of the project has been expanded to examine a variety of other vaccine-related questions. Because the automated vaccination, medical outcome, and covariate database infrastructure created by the VSD project lends itself to potentially answering other important research questions, the VSD principal investigator team has agreed that concept papers for all research questions be entertained and reviewed by the VSD group. If the concept is approved, proposals will be requested. Please note that approval by HMO-specific Institutional Review Boards (IRBs) is required before each study is initiated. The VSD principal investigator team should also have the opportunity to review and comment on any resulting manuscript.

The suggested format for a study idea to be introduced to the VSD Project is through a 2-3 page concept paper. If this concept is approved, then a proposal will be requested.

The proposal should include:

1. Proposed study title
2. Proposed investigator and collaborators. One or more members of the ISO, should be a principal co-investigator/collaborator.
3. Summary of the study(a brief, concise sentence)
4. Hypotheses to be tested and research questions
5. Brief background information including public health importance of the issue.
6. Methods, including preliminary studies, automated data elements needed, analytical strategy, manual chart abstraction required and logistics.

7. A description of confidentiality protection mechanisms is required. In order to ensure the confidentiality of individual-level data collected for the VSD project, CDC has obtained an Assurance of Confidentiality under Section 308(d) of the Public Health Service Act (42 U.S.C. 242m(d)) for VSD data. Before access is granted to VSD data, all researchers are required to sign a Data Use Agreement and a Nondisclosure Agreement specifying their compliance with the 308(d) regulations.

8. Anticipated problems/difficulties (especially any data not currently collected by the VSD)

9. Resource needs (personnel, funding, etc) of the applicant and requested of the VSD project

10. Data Management needs and identification of CDC Data Manager.

11. Anticipated time frame from commencement of the project to manuscript submission.

Attachment 4

VSD Data Use Agreement

It is of the utmost importance to ensure the confidentiality of individuals from the contracting sites when patient information is entered into a database for the purpose of establishing a research resource and to ensure the confidentiality of the MCOs participating in the VSD. In order to protect this data, CDC has obtained an Assurance of Confidentiality under Section 308(d) of the Public Health Service Act (42 U.S.C. 242m(d)), which provides that this data can only be used for the purpose for which it was obtained. In utilizing data on such individuals or MCOs for research purposes, it is absolutely necessary to insure, to the extent possible, that uses of such data will be limited to research; any effort to determine the identity of any reported cases or establishment, or to use the information for any purpose other than for health statistical reporting and analysis, would be prosecuted to the full extent of the law.

The Immunization Safety Office (ISO) does all it can to assure that the identity of data subjects and MCOs cannot be disclosed. All direct identifiers, as well as characteristics that might lead to identifications, are omitted from the dataset. Nevertheless it may be possible in rare instances, through complex analysis and with outside information to ascertain from the dataset the identity of particular persons. Considerable harm could ensue if this were done.

In order for the ISO to provide a restricted dataset to you, it is necessary that you agree to the following provisions.

1. I will not use nor permit others to use the data in any way other than for statistical reporting and analysis;

2. I will not release nor permit others to release the data sets or any part of them to any person except with the written approval of ISO;

3. I will not attempt to link nor permit others to link the data set with individually identifiable records from any other CDC or non-CDC data set;

4. I will not attempt to use the data sets or permit others to use them to learn the identity of any person or establishment included in any set; and

5. If the identity of any person or establishment should be discovered inadvertently, then

    a) no use will be made of this knowledge,
    b) the Director of the ISO will be notified of the incident,
    c) the information that would identify an individual or establishment will be safeguarded or destroyed as requested by ISO, and
    d) no one else will be informed of the discovered identity.

In addition, I will make every effort to release all statistical information in such a way as to avoid inadvertent disclosure. For example:

$ No data on an identifiable case or MCO should be derivable through subtraction or other calculation from the combination of tables in a given publication.

$ No data should permit disclosure when used in combination with other known data.

Your signature indicates your agreement to comply with the above stated requirements:

Name: _____

Title _____

Organization _____

Date _____

Attachment 5

Safeguards for Individuals and Establishments
Against Invasions of Privacy
(308(d) Assurance of Confidentiality for Non-CDC/ISO employees)

I, as a non-CDC Employee (Guest Researcher, Visiting Fellow, Student, Trainee, etc.) may be given access to personally identifiable data that is covered that is covered by Section 308(d) of the Public Health Service Act (42 U.S.C. 242m). As a condition of this access, I am required to comply with the following safeguards for individuals and establishments against invasions of privacy.

1. **I agree to be bound by the following assurance:**

   In accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m), all respondents are assured that their responses will be kept confidential. No information obtained in the course of this activity will be disclosed in a manner in which the individual or establishment supplying the information or described in it is identifiable, unless the individual or establishment has consented to such disclosure, to anyone other than authorized staff of CDC.

2. **I agree to maintain the following safeguards to assure that confidentiality is protected and to provide for the physical security of the records:**

   To preclude observation of confidential information by persons not authorized to have access to the information on the project, I shall maintain all records that identify individuals or establishments or from which individuals or establishments could be identified in locked containers or protected computer files when not under immediate supervision by me or another authorized member of the project. The keys or means of access to these containers or files are not to be given to anyone other than CDC authorized staff. I further agree to abide by any additional requirements imposed by CDC for safeguarding the identity of individuals and establishments.

My signature below indicates that I have carefully read and understand this agreement and the assurance, which pertains to the confidential nature of the study records. As a(n) (_____) (visiting scientist, guest researcher, fellow, trainee, etc.), I understand that I am prohibited from disclosing any such confidential information that has been obtained under this project to anyone other than authorized staff of CDC. I understand that any disclosure in violation of this Confidentiality Pledge is likely to lead to termination of my employment, fellowship or training experience with ISO as well as other penalties.

_____

(Typed/Printed Name)

_____

(Signature)

_____

(

Attachment 6

NONDISCLOSURE AGREEMENT

(*308(d) Assurance of Confidentiality for CDC Employees*)

The success of CDC's operations depends upon the voluntary cooperation of States, of establishments, and of individuals who provide the information required by CDC programs under an assurance that such information will be kept confidential and be used only for epidemiological or statistical purposes.

When confidentiality is authorized, CDC operates under the restrictions of Section 308(d) of the Public Health Service Act which provides in summary that no information obtained in the course of its activities may be used for any purpose other than the purpose for which it was supplied, and that such information may not be published or released in a manner in which the establishment or person supplying the information or described in it is identifiable unless such establishment or person has consented.

I am aware that unauthorized disclosure of confidential information is punishable under Title 18, Section 1905 of the U.S. Code, which reads:

- **Whoever, being an officer or employee of the United States or of any department or agency thereof, publishes, divulges, discloses, or makes known in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus, or to the identity, confidential statistical data, amount or source of any income, profits, losses, or expenditures of any person, firm, partnership, corporation, or association; or permits any income return or copy thereof or any book containing any abstract or particulars thereof to be seen or examined by any person except as provided by law; shall be fined not more than $1,000, or imprisoned not more than one year, or both; and shall be removed from office or employment.**

- **I understand that unauthorized disclosure of confidential information is also punishable under the Privacy Act of 1974, Subsection 552a (l) (1), which reads:**

- **Any officer or employee of any agency, who by virtue of his employment or official position, has possession of, or access to, agency records which contain individually identifiable information the disclosure of which is prohibited by this section or by rules or regulations established thereunder, and who knowing that disclosure of the specific material is so prohibited, willfully discloses the material in any manner to any person or**

agency not entitled to receive it, shall be guilty of a misdemeanor and fined not more than $5,000.

- **My signature below indicates that I have read, understood, and agreed to comply with the above statements.**

_____ _____

Typed/Printed Name **Signature**

_____

Center/Institute/Office

Date

CDC 0.979 5-83

Attachment 7

Safeguards for Individuals and Establishments Against Invasions of Privacy
(*308(d) Assurance of Confidentiality for Contractors*)

In accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m), the contractor is required to give an assurance of confidentiality and to provide for safeguards to assure that confidentiality is maintained.

To provide this assurance and these safeguards in performance of the contract, the contractor and subcontractor shall:

1. **Be bound by the following assurance:**

Assurance of Confidentiality

In accordance with Section 308(d) of the Public Health Service Act (42 U.S.C. 242m), the Director, CDC, assures all participating establishments or individuals that the confidentiality of the records they release to ISO will be maintained by the contractor, subcontractor, and CDC and that no information obtained in the course of this activity may be disclosed in a manner in which the particular establishment or individual supplying the information or described in it is identifiable, unless such establishment or individual has consented to such disclosure, to anyone other than authorized staff of CDC.

2. **Maintain the following safeguards to assure that this confidentiality is protected by the contractor/subcontractor's employees and to provide for the physical security of the records:**

a. After having read the above assurance of confidentiality, each employee of the contractor/subcontractor participating in this project is to sign the following pledge of confidentiality:

I have carefully read and understand the CDC assurance, which pertains to the confidential nature of all records to be handled in regard to these studies. As an employee of the contractor/subcontractor I understand that I am prohibited by law from disclosing any such confidential information, which has been obtained under the terms of this contract/subcontract to anyone other than authorized staff of CDC.

b. To preclude observation of confidential information by persons not employed on the project, the contractor/subcontractor shall maintain all confidential records that identify individuals or establishments or from which individuals or establishments could be identified under lock and key.

Specifically, at each site where these items are processed or maintained, all confidential records that will permit identification of individuals or establishments are to be kept in locked containers when not in use by the contractor's employees.

The keys or means of access to these containers are to be held by a limited number of the contractor/subcontractor's staff at each site. When confidential records are being used in a room, admittance to the room is to be restricted to employees pledged to confidentiality and employed on this project. If at any time the contractor/subcontractor's employees are absent from the room, it is to be locked.

c. The contractor/subcontractor and his professional staff will take steps to insure that the intent of the pledge of confidentiality is enforced at all times through appropriate qualifications standards for all personnel working on this project and through adequate training and periodic follow-up procedures.

3. In a statement sent to the establishments or individuals asked to supply information, inform in clear and simple terms:

a. That the collection of the information by CDC and its contractor is authorized by Section 306 of the Public Health Service Act (42 U.S.C. 242k);

b. Of the purpose or purposes for which the information is intended to be used, any plans for disclosures of information in a form that would permit the identification of an establishment or individual, and a statement that the records will be used solely for epidemiological or statistical research and reporting purposes;

c. That no information collected under the authority of Section 306 of the Public Health Service Act (42 U.S.C. 242k) may be used for any purpose other than the purpose for which it was supplied, and such information may not be published or released in other form if the particular individual or establishment supplying the information or described in it is identifiable to anyone other than authorized staff of CDC, unless such establishment or individual has consented to such release.

4. Release no information from the data obtained or used under this contract/subcontract to any person except authorized staff of CDC.

_____

(Typed/printed Name)

_____

(Signature)

_____

(Date)

From: "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: data refresh -- bivalent booster dose
Date: Wed, 25 Jan 2023 16:36:49 +0000
Importance: Normal
Attachments: VAERS_COVID19_BIVALENT_Ischemic_Stroke_Death_Linelist_Ages_5_and_older_08.31.2022_to_01082023.xml

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Hey John,
I have 115 deaths in my bivalent dataset for vaccinated 08/31/2022 to 01/08/2023, not 110. Of the 115 deaths, 7 are ischemic strokes (attached line list).

In regards to the 40 ids you listed, were did you get them. I only have 33 of them in my data. The other 7 are not listed as bivalent. Should I just give you the 33 ids?

From: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, January 25, 2023 9:47 AM
To: Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: data refresh -- bivalent booster dose
Importance: High

Hi Paige,

Two asks:

1. For deaths reported after bivalent vaccine (n=110), how many were of ischemic stroke? (ie, would you please run the same search we did for ischemic stroke, but applied to these 110 reports)
2. Please send me the detailed line list for the below list of VAERS IDs

Tom needs these data for VRBPAC, so as soon as possible would be greatly appreciated. Thanks!

- John

2440868
2454631
2459749
2462038
2470311
2472938
2474245
2475449
2475627
2477910
2480512
2484385
2487101
2487324
2488430
2488686
2488712

2489819
2493564
2496859
2499563
2500002
2500533
2508589
2510921
2511821
2512797
2513747
2516891
2519874
2521980
2523180
2524255
2524382
2529696
2535384
2536545
2536857
2548970
2549516

From: Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Tuesday, January 10, 2023 11:21 AM
To: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: data refresh -- bivalent booster dose

Hey John- Did you find out what ages to include in the bivalent analysis? I went ahead and refreshed it for 5+ Pfizer and 6+ Moderna, just in case. Here is the descriptive stats

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From: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Monday, January 9, 2023 3:48 PM
To: Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: data refresh -- bivalent booster dose
Importance: High

Hi Paige,

Also, Tom was wanting a refresh of reports after bivalent mRNA COVID-19 booster dose. Please rerun the same usual query, with the same output (e.g., descriptive data and line list), current as of Jan 8, 2023. Please get to me ASAP – I need to get slides to him by Friday. Thanks!

- John

John R. Su, M.D., Ph.D., M.P.H.
CAPT, U.S. Public Health Service
Acting Deputy Director
Immunization Safety Office
Centers for Disease Control and Prevention
1600 Clifton Road, MS H17-3
Atlanta, GA 30333

[redacted]

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