From: "Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
To: "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Shay, David (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Olson, Christine (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Kim, Sehwa (Susan) (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Broder, Karen (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Sharma, Andrea J. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: Monthly Status Report - Lukos 15135
Date: Tue, 11 Apr 2023 15:43:45 +0000
Importance: Normal
Attachments: Mar_23_Lukos_Monthly_Report.docx
Inline-Images: image001.png

FYI

From: Brian McKibben <[redacted]>
Sent: Tuesday, April 11, 2023 11:40 AM
To: Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Alldredge, Berta (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: MSR

Berta/Bonita,

See attached monthly status report. Please let me know if you have any questions.

Thanks
Brian

Brian McKibben
Director of Operations, Lukos
[redacted]

From: "Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
To: "Olson, Christine (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Sharma, Andrea J. (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Shay, David (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Kim, Sehwa (Susan) (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Broder, Karen (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: Lukos Feb Monthly Report
Date: Wed, 8 Mar 2023 18:18:10 +0000
Importance: Normal
Attachments: Feb_23_Lukos_Monthly_Report.docx
Inline-Images: image001.png

FYI - Lukos monthly status report is attached for Feb 2023.

Thanks,

Bonita
404-498-0646

From: Alldredge, Berta (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, March 8, 2023 12:48 PM
To: Brian McKibben <[redacted]>
Cc: Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) <[redacted]>; laura.hedrick[redacted]
Subject: RE: Lukos Feb Monthly Report

Received, thank you.

From: Brian McKibben <[redacted]>
Sent: Wednesday, March 8, 2023 12:46 PM
To: Alldredge, Berta (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) <[redacted]>; laura.hedrick[redacted]
Subject: Lukos Feb Monthly Report

Berta,

See attached MSR for February.

Please acknowledge receipt.

Have a great day.

Thanks
Brian

Brian McKibben
Director of Operations, Lukos
[redacted]

From: "Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
To: "Kim, Sehwa (Susan) (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Broder, Karen (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Olson, Christine (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Shay, David (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Sharma, Andrea J. (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: Monthly Report - Lukos 15135
Date: Tue, 28 Feb 2023 15:01:40 +0000
Importance: Normal
Attachments: Jan_23_Lukos_Monthly_Report.docx
Inline-Images: image001.png

FYI

From: Brian McKibben <[redacted]>
Sent: Wednesday, February 8, 2023 12:49 PM
To: Alldredge, Berta (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: monthly report

Berta,

Please see attached monthly report for review. Let me know if you have any questions.

Also, I do not intend to send any more hiring updates. We consider the contract transitioned. We are currently not 100% manned, but we have the positions hired and are just waiting for CDC Public Trust approval. I suspect with a 63 person contract we will usually have a bit of natural turnover.

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:	March 8, 2023
Contract ID:	15135
Reporting Period:	February 1 – February 28, 2023

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

a. Accomplishments

Task	Outcome/Accomplishment
Total Assigned cases (all abstractors)	• 16,607 Cumulative
Total Incomplete/No Abstraction Status (awaiting medical records)	• 487
February Assigned abstraction cases	• 1,977
February Completed abstraction/adjudication cases	• 1,392
Onboarding/Training new hires	• All active abstractors are trained and functioning independently

b. Status of on-going projects

Project	Status
Shoulder Injury after Vaccine Administration (SIRVA)	• New project • 3 abstractors assigned, trained, and accepting assignments • 612 cases assigned
Death Project	• New project • Project coordinators worked with CDC staff to update abstraction form in REDCap • 12 abstractors selected • Pilot completed with 2 abstractors and feedback used to modify abstraction form • Anticipated start date 3/6/2023 with almost 18,000 cases to be reviewed
Coagulopathy Project	• 794 cases assigned; additional 1,450 cases pending for 3/2023
Monkeypox Abstraction	• 98 reports with 2 completed abstractions; project continuing through Mar 2023 (at least)
Pregnancy	• Ongoing abstraction of 628 cases for mother and infant AESI's
Bivalent COVID/ Influenza Co-Administration project	• Ongoing project • 129 newly assigned cases
Stroke Project	• Ongoing project • 118 additional cases assigned with 75% completion rate in preparation for Advisory

	Committee on Immunization Practices meeting February 22-24, 2023
Quality Control	• De-duplication of cases underway

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
None identified	

II. Task 3 CISA Physicians: February 2023

a. Accomplishments

Task	Outcome/Accomplishment
Clinical on-call assignments	• Available for consultations/projects during assigned hours

Case/Work Assignments
(Cases include - Triage only, Clinician Assist, Enhanced inquiry, mini consult, or Full consult)
 	
• CISA's research coordination
  ○ eClearance of abstracts, presentation slides and manuscripts
  ○ DQHP clearance of concept proposals (CP)
  ○ Follow-up on the regulatory requirement and sevier 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
 	
• Shoulder Inquiry Related to Vaccine Administration (SIRVA) working group
• Note taking:
  ○ Meeting of the advisory committee on immunization practices (ACIP) – 2/24/2023
Vaccines and related biological products advisory committee (VRBPAC) meeting – 2/28/2023
 	
Participate in and take notes on CISA IgA nephropathy consult
 	
Participate in and take notes on CISA HHE consult
	• cases/inquiries 19 completed/in-progress
	
	• Submitted and got cleared through eclearance
	  1. Apnea after 2-month Vaccinations in Hospitalized Preterm Infants: A Randomized Clinical Trial
	  2. Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple Clinic-Based Interventions: a Randomized Controlled Trial (NCT04772755)
	  3. Surveillance for multisystem inflammatory syndrome in U.S. children aged 5-11 years who received Pfizer-BioNTech COVID-19 vaccine, November 2021March 2022
	  4. Evaluation of association of anti-PEG antibodies with anaphylaxis after mRNA COVID-19 vaccination
	
	• Submitted and got cleared through DQHP share point:
	  1. Preventing Post-Vaccination Presyncope and Syncope in Adolescents Using Simple, Clinic-based Interventions
	  2. Evaluation of association of anti-PEG antibodies with anaphylaxis after mRNA COVID-19 vaccination'
	  3. Apnea after 2-month Vaccinations in Hospitalized Preterm Infants: A Randomized Clinical Trial
	• Assessed severity and their relationship to study product of reported SAEs
	• Reviewed SIRVAs reported to VAERS
	• ACIP and VRBOC notes

Night coverage as scheduled	• 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:	• IgA nephropathy case – consult ○ Presented consult

(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 2 month vaccines – ○ 1 part of response sent – waiting for further clinical information for second response • Meningoencephalitis following mening and tdap vaccination – going to consult • ITP following COVID-19 infection – clinician assist • Lethargy after Kinrix and Proquad – enhanced inquiry
Trainings/education:	• Attended the National Vaccine Advisory Committee Meeting on February 2 and February 3 • Attended 2 CISA case consults • Monthly Loyal Source Team meeting • Attended NCEZID Virtual All Hands Meeting • Attended CDC Moving Forward Webinar (Workforce Priority Actions) • Attended CDC Moving Forward Webinar (Policy and Strategy Priority Actions) • DTaP/DT and Tdap/Td Vaccines Continuing Education Session • Influenza Continuing Education Session • Attended 3 days of ACIP meetings • Attended FDA VRBPAC meeting • Attended NCEZID DEIBA Council's Roundtable: What the World (and our workplace) Needs Now is LOVE: DEIBA--What LOVE Looks Like!
Special Meetings	
Standard calls - CISA AM/PM calls and CISA site calls	• Discuss daily cases/inquiries on the CISA tracker
NVAC (National vaccine advisory committee) meeting (2/2, 2/3) CDC ACIP meeting (2/22-2/24) FDA VRBAC meeting- RSV vacc (2/28- 3/1)	discussion of covid vaccine myocarditis risks -discussion of Mpox Jynneos vaccine myocarditis risks -discussion of safety and efficacy of two RSV vaccines
COCA Call on Feb 09	• Evaluating and Supporting Children and Adolescents with Post-COVID Conditions
CISA WG2 Issues Discussion	• Influenza Evid Topic on
CISA COVID Babies Research Study Meetings	• Ongoing research meeting
CISA Moving Forward Webinar on 2/1	• MOVING follow-up

CISA Research Coordination Standing Meeting
CISA (Vanderbilt) Call, Monday – Thursday 10:00am ET
CISA (Vanderbilt) Call, Friday 10:30am ET
CISA RZV and allV4 Standing Call
CISA COVID Babies/CISA COVID Peds Standing Study Call
CISA Admin Call with Duke University Medical Center
  ○ Shingrix/Flu SAE Discussion
  ○ COVID/Flu
	• Discussion:
	  1. Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children (pending)
	  2. Safety of Pediatric COVID-19 Vaccination (NCT05157191)
	  3. Simultaneous mRNA COVID-19 and Quadrivalent Inactivated Influenza Vaccine (IIV4) Vaccination Study (NCT05028361)
	  4. A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Pregnant Women (NCT04826640)
	Safety of Simultaneous Vaccination With Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4) (NCT05007041)

Scheduling/Coordination between CDC and Contractor Physician	Ongoing
View 2023 Koplan Global Leadership in PH Lecture: COVID-19 in Africa	

b. Status of on-going projects

Project	Status
Suspect cardiac arrest consult -date set for consult -review literature -prepare for VAERS search **Steven-Johnsons syndrome post flu vaccination** -communicate with inquirer -review materials in VAERS report **Inadvertent MMR vaccine administration in immunocompromised child** -presented to leadership -prepare presentation to entire CISA team **Deep dive allergy project** -analyze data and summarize results -work on excel data sheet	• Ongoing • Ongoing • Ongoing • Ongoing
1. *Manuscript: Reporting patterns of vaccine adverse events by reporter type in the Vaccine Adverse Event Reporting System (VAERS) Reports of Shoulder Inquiry Related to Vaccine Administration in the Vaccine Adverse Event Reporting System, 2018-2022*	• Data review and analysis
MOVING Project	• Immunocompromised Patient Guidance
Clinical Coordinator Role	• Working with CDC supervisors and Medical Officers
MOVING study, 1 year follow up interviews	• Attend several meetings, spent time contacting providers to setup interviews, participate in interviews with cardiologists, enter survey answers in RedCap database, enter data on Excel tracker for MOVING Study • Total # of cases to work through= 17 cases
Review of Serious Adverse Event (SAE) reports of Simultaneous RZV and aIIV4 Vaccination Study	• Assessment of SAE
COVID adult study	• Active participation in call and review of meeting minutes
COVID vaccine research studies	• Ongoing
CISA COVID Babies Research Study	• Ongoing meeting every other week
Pregnancy Registry COVID-19 Vaccine Study Review and assess Maternal COVID study SAE	• Ongoing; Started participating in meetings

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
none	

d. Accomplishments

Task	Outcome/Accomplishment
Clinical on-call assignments	• Available for consultations/projects during assigned hours
Case/Work Assignments *(Cases include - Triage only, Clinician Assist, Enhanced inquiry, mini consult, or Full consult)*	• 12 (twelve) cases/inquiries completed/in-progress
Night coverage as scheduled	• Completed trainings during night coverage when not actively receiving EOC calls. • Provided written response and communication with provider
• Coordinated CISA's research portfolio ○ eClearance ○ Regulatory requirement ○ Safety (SAE) ○ Action items • HHE and DTaP Consult Planning for Feb 8 Note taking for the vaccines and related biological products advisory committee (VRBPAC) meeting	• Submitted for clearance ○ Outcomes of Myocarditis after mRNA COVID-19 Vaccination ○ Effects of SARS-CoV-2 on the Young Heart: COVID and MIS-C and Vaccines...oh my! • Assess severity of reported SAEs and their relationship to study product
Onboarding/Training new hires	• Read all referenced publications from CISA site calls. • For practice, attempted to replicate recent inquiry response/soaps to see if I got same results for VAERS and Pub. Med searches. • Did Cybercare readings and meetings. • Read many "Continuing Education" sites. • Reviewed mpox/Jynneos
Trainings/education	• Listened to Ebola: Clinical Presentation, Evaluation, and Infection Prevention • *Pink Book Web-on-Demand Series:* completed several and obtained CE credit on TEO • Review of IOM 2012 materials • Review of ICC precautions and contraindications for vaccines • Papers shared by the team related to blue leg syndrome, IgA nephropathy, guidance on dtap and pertussis immunizations, up to date information related to cases • Review MMWRs: safety monitoring of bivalent COVID-19 mRNA booster doses among children aged 5-11 years; vaccine coverage by age 24 months; epidemiology of human mpox worldwide; reasons for not/receiving bivalent COVID-19 booster vaccination among adults
Special Meetings	
Standard calls - CISA AM/PM calls and CISA site calls	• Discuss daily cases/inquiries on the CISA tracker
Attended FDA VRBPAC meeting 1/26/23	• Took notes on COVID-19 epi, strategies for future boosters, and listened to committee discussion on updating vaccination strategies • Listened to presentations on current vaccine safety issues
COCA Call: Updates to COVID-19 Testing and Treatment for the Current SARS-CoV-2 Variants	• Up to date on COVID-19 epi and current variants, CDC testing guidance, and NIH and IDSA COVID-19 treatment guidelines
CISA WG2 Issues Discussion	• Influenza Evid Topic on
CISA COVID Babies Research Study Meetings	• Ongoing research meeting
Advisory Commission on Childhood Vaccines (ACCV)	• Updates on childhood vaccination

CISA Research Coordination Standing Meeting CISA (Vanderbilt) Call, Monday – Thursday 10:00am ET CISA (Vanderbilt) Call, Friday 10:30am ET CISA RZV and aIIV4 Standing Call CISA COVID Babies/CISA COVID Peds Standing Study Call CISA Admin Call with Duke University Medical Center ○ Shingrix/Flu SAE Discussion ○ COVID/Flu VRBPAC meeting, January 26, 2023	• Discussion: 5. Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children (pending) 6. Safety of Pediatric COVID-19 Vaccination (NCT05157191) 7. Simultaneous mRNA COVID-19 and Quadrivalent Inactivated Influenza Vaccine (IIV4) Vaccination Study (NCT05028361) 8. A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Pregnant Women (NCT04826640) Safety of Simultaneous Vaccination With Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4) (NCT05007041)
Scheduling/Coordination between CDC and Contractor Physician	Ongoing

e. Status of on-going projects

Project	Status
Manuscript: Reporting patterns of vaccine adverse events by reporter type in the Vaccine Adverse Event Reporting System (VAERS)	• Discussed on the data analysis plan
MIS-C projects for < 5yo age	• Completed two PPT presentations for future adjudication of MIS-C cases <5 yo
MOVING study, 1 year follow up interviews	• Attend several meetings, set up DCIPHER, DCIPHER 101 training, send emails to providers to setup interviews, participate in interviews with cardiologists, enter survey answers in RedCap database, enter data on Excel tracker for MOVING Study
Clinical Coordinator Role	• Working with CDC supervisors and Medical Officers
Allergy deep dive	• Review and analyze cases of anaphylaxis after covid vaccines reported in VAERS - ongoing
Review of Serious Adverse Event (SAE) reports of Simultaneous RZV and aIIV4 Vaccination Study	• Assessment of SAE
COVID adult study	• Active participation in call and review of meeting minutes
COVID vaccine research studies	• Ongoing
CISA COVID Babies Research Study	• Ongoing meeting every other week
Inadvertent MMR vaccine administration in immunocompromised child -prepare powerpoint document summarizing the case and followup information -review the power point document with CDC physician and revise according to suggested changes -prepare presenting to CISA leadership	• Ongoing

f. 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	• 38 initial abstractions completed (counted at the dyad level)
Medical record re-abstractions	• 8 re-abstractions
Medical record "backfills"	• 13 Backfilled records
HTN review	• 14 records were reviewed for hypertensive disorders during pregnancy
Abstraction-re-abstraction Comparison	• Completed comparison tool for 17 records for the January comparison tool
Medical record reconciliation	• Completed reconciliation for 13 records for the January comparison tool
ICD-10 Vpoint	• Assignment of ICD-10 codes to infant conditions for approximately 3000 participants (1000 each per Lukos clinician)
ICD-10 Vpoint tier 1.5 review QC	• Review of CDC FTE clinician's assignment of ICD-10 codes to infant conditions for approximately 2800 records (split between 3 Lukos clinicians)
ICD-10 Vpoint for multiples	• Assignment of ICD-10 codes to infant conditions for approximately 255 participants who had a multiple gestation pregnancy
Clinical adjudication of birth defects with medical record data (medical record abstraction [MRA] Vpoint)	• Provided specific feedback on changes needed in a Microsoft Access tool that was developed to aid in the clinical adjudication of birth defects-changes were agreed upon and adopted • For round 2/7/23 adjudicated 63 records • For round 2/14/23 adjudicated 34 records
Quality control checks	• Reviewed data for all pregnancies with multiple gestation for whom medical records were abstracted to ensure consistency of data abstraction across fetuses/infants. Specific QC variables addressed: Date of birth and pregnancy outcome; Diagnosis dates for BD
Birth defect paper appendix	• Wrote appendix of infant conditions for paper being written on birth defects
Resolution of performance review	• 2 Lukos clinicians under review have been retained

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
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
NICU admission, Infant Hospitalization analysis	• Meeting weekly with data analysts from Abt Associates to discuss and direct the analysis of the NICU admission & Infant hospitalization project-ongoing
Risk of stillbirth following maternal COVID-19 vaccination	• Analysis completed; a draft has been written; waiting for review by OB SME; still ongoing

1. Hypertensive disorders during pregnancy & COVID-19 vaccination 2. Maternal ICU admission among a cohort of vaccinated pregnant people	• Completing medical record abstractions • SOP for HTN comparison is being developed • Ongoing
Infant NICU admission, infant hospitalization, and neonatal mortality	• Working with Abt Associates to direct the analysis; still ongoing • Progress being made on draft of analysis • All records for infant deaths have been abstracted
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
Performance review feedback process and metrics	• We are beginning documentation of all meetings held between Lukos clinicians and CDC so as to document feedback and action plans delivered. • Meetings between Lukos Team Lead and CDC FTEs and Program leadership have been proposed in order to obtain more specified and directive feedback. Lukos Team Lead is waiting for decision regarding occurrence of meetings and scheduling. Meeting still has not occurred.
Determination of need for cell phone for Lukos clinician in order to participate in interviews for extended infant follow up (IFU)	• Pending decision from CDC leadership of purchase of a cell phone for clinician (most important functions being ability to text participants and having a number to provide participants to call clinician back). • Unknown solution at this time. Anticipate calling to begin at the end of March 2023 or early April 2023

IV. Manning

	COVID	Required	On hand
Task 2	VAERS physicians (OASIS Medical Officer 2022)	40	35*
Task 4	VAERS project coordinator (OASIS Program Mgr. 2022)	1	1
Task 3	CISA physicians (OASIS Medical Officer 2022)	8	8
Task 5	Pregnancy medical officer/epidemiologist (OASIS Epi VI 2022)	1	1
Task 6	Pregnancy clinician (OASIS Medical Officer 2022)	3	2*
	Monkeypox/Other		
Task 2	VAERS physicians (OASIS Medical Officer 2022)	6.75	6.75
Task 4	VAERS project coordinator (OASIS Program Mgr 2022)	0.25	.25

Task 3	CISA physicians (OASIS Medical Officer 2022)	2	2
Task 5	Pregnancy medical officer/epidemiologist (OASIS Epi VI 2022)	0.25	.25
Task 6	Pregnancy clinician (OASIS Medical Officer 2022)	0.75	.75
	Totals	**63**	**57**

* Denotes new hire identified – waiting on CDC Public Trust approval

Monthly Status Report **Lukos, LLC**

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

Date:	April 11, 2023
Contract ID:	15135
Reporting Period:	March 1 – March 31, 2023

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

a. Accomplishments

Task	Outcome/Accomplishment
Total Assigned cases (all abstractors)	• 23,217 Cumulative
Total Incomplete/No Abstraction Status (awaiting medical records)	• 508
March Assigned abstraction cases	• 3,272
March Completed abstraction/adjudication cases	• 3,338
Onboarding/Training new hires	• All 42 active abstractors are trained and functioning independently • 4 new G2S contractors to onboard April 2023

b. Status of on-going projects

Project	Status
AESI < 18	• Ongoing project • 1 abstractor assigned • 13 new cases assigned; 12 completed
Myocarditis all ages	• Ongoing project • 4 abstractors assigned • 39 new cases assigned; 64 completed
Thrombotic Thrombocytopenia Syndrome (TTS)	• Ongoing project • 3 abstractors assigned • 74 new cases assigned; 95 cases completed
Guillain Barre' Syndrome (GBS)	• Ongoing project • 1 abstractor assigned • 14 new cases assigned; 17 completed
Guillain Barre' Syndrome adjudication	• Ongoing project • 1 abstractor assigned • 11 new cases assigned; 11 abstractions completed
Shoulder Injury after Vaccine Administration (SIRVA)	• Ongoing project • 3 abstractors assigned, trained, and accepting assignments • 612 total cases assigned; 346 completed
Death Project	• Ongoing project • 12 abstractors assigned and trained • 2116 new cases assigned; 2049 completed

Coagulopathy Project	• Ongoing project • 12 abstractors assigned • 922 new cases assigned; 765 completed
Monkeypox Abstraction	• 6 reports with no additional completed abstractions • 1 abstractor assigned • Project completed
Pregnancy	• Ongoing project • 2 abstractors assigned • 661 total cases for mother and infant AESI's; 557 cases completed
Bivalent COVID/ Influenza Co-Administration project	• Ongoing project • 3 abstractors assigned • 129 newly assigned cases; all completed
Stroke Project	• Completed project • 15 outstanding 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 underway • Project development begun in collaboration with CDC staff to embed process of quality checks into workflows through reeducation and peer review of cases

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
None identified	
Quality Control	• De-duplication of cases underway

II. Task 3 CISA Physicians: March 2023

a. Accomplishments

Task	Outcome/Accomplishment
Clinical on-call assignments	• Available for consultations/projects during assigned hours

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
  ○ eClearance of abstracts, presentation slides and manuscripts
  ○ DQHP clearance of concept proposals (CP)
  ○ 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
 	
• Shoulder Inquiry Related to Vaccine Administration (SIRVA) working group
• Note taking:
  ○ Meeting of the advisory committee on immunization practices (ACIP)
  ○ Vaccines and related biological products advisory committee (VRBPAC) meeting
VARES search for search of anaphylaxis reports after influenza vaccines in VAERS and egg allergy and determining based on the Brighton Collaboration case definitions and classification
 	
• Attended FDA VRBPAC meeting
• Immunization Safety Office (ISO)All-Hands Meeting
• Attended CDC all hands meeting
• Attended the SARS-CoV-2: Doing Science in Dog Years conference
• Attended NCEZID Operational Readiness Listening Session
• Attended March 16th Microbial Ecology themed journal club presented by members of DHQP's Microbial Ecology workgroup
• Attended VAERS Search Tool Lunch and Learn
• Attended Case Consultation: ITP following Pfizer COVID-19 vaccine
• Monthly Loyal Source Team meeting
• NCEZID DEIBA Roundtable: Women's History Month--Telling Our Stories, Telling Our Truth
	• cases/inquiries 6 completed/in-progress
	
	• Available for consultations and other task assigned
	• Submitted and got cleared through DQHP share point:
	  1. Concept Proposal: Exploring Mechanisms of Intussusception in Infants Receiving Rotavirus Vaccine
	• Submitted and got cleared through eclearance
	  1. Manuscript: Evaluation of association of anti-PEG antibodies with anaphylaxis after mRNA COVID-19 vaccination
	• Assessed severity and their relationship to study product of reported SAEs
	• Reviewed SIRVAs reported to VAERS
	• ACIP and VRBOC notes
	• VAERS search
	
	Brighton Collaboration case definitions and classification of anaphylaxis after influenza vaccines reported to VAERS
	
	• FDA review and manufacturer presentations on Pfizer and GSK RSV vaccines. Safety issues include GBS, ADEM, and atrial fibrillation.
	• ISO meeting- ISO Director, media Policy, CMO, Mpox, VAERS Team, CISA Project Team, and Vaccine Safety Datalink Team updates

Night coverage as scheduled	• 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)	• IgA nephropathy case – consult
	  ○ Presented consult
	• ADEM following 2 month vaccines –
	  ○ 1 part of response sent – waiting for further clinical information for second response
	• Meningoencephalitis following mening and tdap vaccination – going to consult
	• ITP following COVID-19 infection – clinician assist
	• Lethargy after Kinrix and Proquad – enhanced inquiry
	
	• IgA nephropathy case – consult
	  ○ Presented consult
	• ADEM following 2 month vaccines –
	  ○ 1 part of response sent – waiting for further clinical information for second response
	• Meningoencephalitis following mening and tdap vaccination – going to consult
	• ITP following COVID-19 infection – clinician assist
	• Lethargy after Kinrix and Proquad – enhanced inquiry

Trainings/education:	• Attended the National Vaccine Advisory Committee Meeting on February 2 and February 3 • Attended 2 CISA case consults • Monthly Loyal Source Team meeting • Attended NCEZID Virtual All Hands Meeting • Attended CDC Moving Forward Webinar (Workforce Priority Actions) • Attended CDC Moving Forward Webinar (Policy and Strategy Priority Actions) • DTaP/DT and Tdap/Td Vaccines Continuing Education Session • Influenza Continuing Education Session • Attended 3 days of ACIP meetings • Attended FDA VRBPAC meeting • Attended NCEZID DEIBA Council's Roundtable: What the World (and our workplace) Needs Now is LOVE: DEIBA--What LOVE Looks Like!
Special Meetings	
Standard calls - CISA AM/PM calls and CISA site calls	• Discuss daily cases/inquiries on the CISA tracker
Special meetings attended • CISA AM management huddle, Monday, Wednesday and Friday - 8:30am ET ▪ Morning huddle, Monday – Friday 9:00am ET ▪ CISA Research Coordination Standing Meeting (Internal) ▪ CISA (Vanderbilt) Call, Monday – Thursday 10:00am ET • CISA (Vanderbilt) Call, Friday 10:30am ET • CISA Research calls with Duke	• Attend review of key leadership/management updates • Discussed cases (inquiries) and exchange experiences. • Discussed CISA's research portfolio issues (internal) • Discussion: 1. Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children (pending) 2. Safety of Pediatric COVID-19 Vaccination (NCT05157191) 3. Simultaneous mRNA COVID-19 and Quadrivalent Inactivated Influenza Vaccine (IIV4) Vaccination Study (NCT05028361) 4. A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Pregnant Women (NCT04826640)

SIRVA review meeting	Safety of Simultaneous Vaccination With Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4) (NCT05007041
ITP consults (3/30)	listen to case presentation -listen to various causes of thrombocytopenia -listen to analysis of the case
CISA inquiry: ADEM following immunization with MMR, varicella, and influenza vaccines	• Enhanced inquiry • Partial response sent Awaiting specialty consultation prior to further discussion; reached out to provider
CISA inquiry: ITP following MMR	• Enhanced Inquiry • Attended additional meeting with CDC SMEs • Final response sent • Redcap closed
CISA inquiry: GBS following COVID-19 vaccine	• Consult
V safe Extended Follow Up Project	• Attended meeting regarding organization of data entry Still in planning phase--awaiting further instructions
Scheduling/Coordination between CDC and Contractor Physician	Ongoing

b. Status of on-going projects

Project	Status
1. *Manuscript: Reporting patterns of vaccine adverse events by reporter type in the Vaccine Adverse Event Reporting System (VAERS) Reports of Shoulder Inquiry Related to Vaccine Administration in the Vaccine Adverse Event Reporting System, 2018-2022*	• Data review and analysis
Suspect cardiac arrest consult -review CDC data -review literature -prepare for VAERS search	-ongoing
Steven-Johnsons syndrome post flu vaccination -communication with inquirer -review materials in VAERS report	-ongoing
Inadvertent MMR vaccine administration in immunocompromised child -communications about presentation -presentation to entire CISA team	-ongoing
Deep dive allergy project -analyze data and summarize results -work on excel data sheet -meet with CDC physician	-ongoing
MOVING Project	

	• Immunocompromised Patient Guidance
Clinical Coordinator Role	• Working with CDC supervisors and Medical Officers
MOVING study, 1 year follow up interviews	• Attend several meetings, spent time contacting providers to setup interviews, participate in interviews with cardiologists, enter survey answers in RedCap database, enter data on Excel tracker for MOVING Study • Total # of cases to work through= 17 cases
Review of Serious Adverse Event (SAE) reports of Simultaneous RZV and aIIV4 Vaccination Study	• Assessment of SAE
2 going to consult which involves significant time in scheduling, meetings and independent work on VAERS search and presentation	• Ongoing
CISA COVID Babies Research Study	• Ongoing meeting every other week
Pregnancy Registry COVID-19 Vaccine Study Review and assess Maternal COVID study SAE	• Ongoing; Started participating in meetings
Review and assess Maternal COVID study SAE	• completed
Draft section of new research study proposal and review entire proposal	• ongoing
Review CISA research study VaST presentation	• completed
Start Good Clinical Practice CITI training	• ongoing

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	• 41 initial abstractions completed (counted at the dyad level)
Medical record re-abstractions	• 17 re-abstractions
Medical record "backfills"	• 66 Backfilled records
HTN review	• 97 records were reviewed for hypertensive disorders during pregnancy
Abstraction-re-abstraction Comparison	• Completed comparison tool for 33 records for the March comparison tool
Medical record reconciliation	• Completed reconciliation for 20 records for the January comparison tool
ICD-10 Vpoint	• Assignment of ICD-10 codes to infant conditions for approximately 175 participants (these are records that were missed from original assignment by MRA data cleaning)
ICD-10 Vpoint reviews for records missed	• Provided specific feedback on changes needed in a Microsoft Access tool that was developed to aid in the clinical adjudication of birth defects- changes were agreed upon and adopted • For round 3/1/23 adjudicated 175 records
Quality control checks	• Reviewed data for all pregnancies with multiple gestation for whom medical records were abstracted to ensure consistency of data

	abstraction across fetuses/infants. Specific QC variables addressed: Date of birth and pregnancy outcome; Diagnosis dates for BD
Hypertension Comparison Tool Pilot	• 3 Lukos clinicians performed comparison of 29 records concentrating specifically on the hypertension form in REDCap to initiate and evaluate areas of process improvement for future on-going HTN comparison
Communication with CDC Pregnancy Registry leadership	• Established clear expectations from CDC Pregnancy Registry leadership regarding core work hours during the day, process of flexing hours, and process of how to notify Lukos team lead and CDC Pregnancy Registry leadership of last minute needs for sick time/other PTO last minute needs.

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
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
NICU admission, Infant Hospitalization analysis	• Collaboration with Abt Associates to discuss and direct the analysis of the NICU admission & Infant hospitalization project-ongoing • New decision was made on 3/20/23 that the data we have needs to be cleaned and a new dataset may need to be created. Paper on hold while process improvement continues
1. Hypertensive disorders during pregnancy & COVID-19 vaccination 2. Maternal ICU admission among a cohort of vaccinated pregnant people	• Completing medical record abstractions • SOP for HTN comparison developed • Ongoing Comparison processes specifically reconciled by new Lukos clinician
Infant NICU admission, infant hospitalization, and neonatal mortality	• Working with Abt Associates to direct the analysis; still ongoing • All records for infant deaths have been abstracted • New decision was made on 3/20/23 that the data we have needs to be cleaned and a new dataset may need to be created. Paper on hold while process improvement continues
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
Performance review feedback process and metrics	• We are beginning documentation of all meetings held between Lukos clinicians and

	CDC so as to document feedback and action plans delivered. • Lukos team lead continues to work with CDC Pregnancy registry leadership on how to communicate performance feedback more effectively while mitigating the amount of emails/communication placed on Lukos Director of Operations.
Determination of need for cell phone for Lukos clinician in order to participate in interviews for extended infant follow up (IFU)	• Pending decision from CDC leadership of purchase of a cell phone for clinician (most important functions being ability to text participants and having a number to provide participants to call clinician back). • Unknown solution at this time. Anticipate calling to begin at the end of March 2023 or early April 2023- unknown status of need

Monthly Status Report **Lukos, LLC**

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

Date:	Feb 8, 2023
Contract ID:	15135
Reporting Period:	January 1 – January 31, 2023

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

a. Accomplishments

Task	Outcome/Accomplishment
Total Assigned cases (all abstractors)	• 14,630 Cumulative
Incomplete/No Abstraction Status (awaiting medical records)	• 1,737
Assigned abstraction cases	• 1196
Completed abstraction/adjudication cases	• 1512
Onboarding/Training new hires	• Trained 5 new VAERS clinicians/abstractors

b. Status of on-going projects

Project	Status
Coagulopathy Project	• 712 cases assigned; additional 1300 anticipated for 2/2023
Monkeypox Abstraction	• 61 reports with 5 abstractions; project continuing through Feb 2023 (at least)
Pregnancy	• Continued abstraction of 556 cases for mother and infant AESI's
Bivalent COVID/ Influenza Co-Administration project	• Ongoing project; 168 newly assigned
Stroke Project	• 110 cases assigned in response to enhanced signal for ischemic stroke after Pfizer bivalent vaccine; 67% completed that supported a joint FDA/CDC position statement and presentation to VRBPAC on January 26, 2023
Quality Control	• All new clinicians are assigned an experienced mentor who reviews practice cases and 100% of their newly assigned cases are reviewed for accuracy before completion • 3 clinicians met criteria for independent abstraction without case review by mentor • 6 clinicians continue to be in training

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
Lengthy training of some clinicians without improvement in abstraction performance	• Will continue to support and provide feedback; will not advance to independent abstraction until abstraction accuracy consistently demonstrated

II. Task 3 CISA Physicians

a. Accomplishments

Task	Outcome/Accomplishment
Clinical on-call assignments	• Available for consultations/projects during assigned hours
Case/Work Assignments *(Cases include - Triage only, Clinician Assist, Enhanced inquiry, mini consult, or Full consult)*	• 12 (twelve) cases/inquiries completed/in-progress
Night coverage as scheduled	• Completed trainings during night coverage when not actively receiving EOC calls. • Provided written response and communication with provider
• Coordinated CISA's research portfolio ○ eClearance ○ Regulatory requirement ○ Safety (SAE) ○ Action items • HHE and DTaP Consult Planning for Feb 8 Note taking for the vaccines and related biological products advisory committee (VRBPAC) meeting	• Submitted for clearance ○ Outcomes of Myocarditis after mRNA COVID-19 Vaccination ○ Effects of SARS-CoV-2 on the Young Heart: COVID and MIS-C and Vaccines...oh my! • Assess severity of reported SAEs and their relationship to study product
Onboarding/Training new hires	• Read all referenced publications from CISA site calls. • For practice, attempted to replicate recent inquiry response/soaps to see if I got same results for VAERS and Pub. Med searches. • Did Cybercare readings and meetings. • Read many "Continuing Education" sites. • Reviewed mpox/Jynneos
Trainings/education	• Listened to Ebola: Clinical Presentation, Evaluation, and Infection Prevention • *Pink Book Web-on-Demand Series:* completed several and obtained CE credit on TEO • Review of IOM 2012 materials • Review of ICC precautions and contraindications for vaccines • Papers shared by the team related to blue leg syndrome, IgA nephropathy, guidance on dtap and pertussis immunizations, up to date information related to cases • Review MMWRs: safety monitoring of bivalent COVID-19 mRNA booster doses among children aged 5-11 years; vaccine coverage by age 24 months; epidemiology of human mpox worldwide; reasons for

	not/receiving bivalent COVID-19 booster vaccination among adults
Special Meetings	
Standard calls - CISA AM/PM calls and CISA site calls	• Discuss daily cases/inquiries on the CISA tracker
Attended FDA VRBPAC meeting 1/26/23	• Took notes on COVID-19 epi, strategies for future boosters, and listened to committee discussion on updating vaccination strategies • Listened to presentations on current vaccine safety issues
COCA Call: Updates to COVID-19 Testing and Treatment for the Current SARS-CoV-2 Variants	• Up to date on COVID-19 epi and current variants, CDC testing guidance, and NIH and IDSA COVID-19 treatment guidelines
CISA WG2 Issues Discussion	• Influenza Evid Topic on
CISA COVID Babies Research Study Meetings	• Ongoing research meeting
Advisory Commission on Childhood Vaccines (ACCV)	• Updates on childhood vaccination
CISA Research Coordination Standing Meeting CISA (Vanderbilt) Call, Monday – Thursday 10:00am ET CISA (Vanderbilt) Call, Friday 10:30am ET CISA RZV and aIIV4 Standing Call CISA COVID Babies/CISA COVID Peds Standing Study Call CISA Admin Call with Duke University Medical Center ○ Shingrix/Flu SAE Discussion ○ COVID/Flu VRBPAC meeting, January 26, 2023	• Discussion: 1. Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children (pending) 2. Safety of Pediatric COVID-19 Vaccination (NCT05157191) 3. Simultaneous mRNA COVID-19 and Quadrivalent Inactivated Influenza Vaccine (IIV4) Vaccination Study (NCT05028361) 4. A Prospective Observational Study to Evaluate the Safety of COVID-19 Vaccination in Pregnant Women (NCT04826640) Safety of Simultaneous Vaccination With Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4) (NCT05007041)
Scheduling/Coordination between CDC and Contractor Physician	Ongoing

b. Status of on-going projects

Project	Status
Manuscript: Reporting patterns of vaccine adverse events by reporter type in the Vaccine Adverse Event Reporting System (VAERS)	• Discussed on the data analysis plan
MIS-C projects for < 5yo age	• Completed two PPT presentations for future adjudication of MIS-C cases <5 yo
MOVING study, 1 year follow up interviews	• Attend several meetings, set up DCIPHER, DCIPHER 101 training, send emails to providers to setup interviews, participate in interviews with cardiologists, enter survey answers in RedCap database, enter data on Excel tracker for MOVING Study
Clinical Coordinator Role	• Working with CDC supervisors and Medical Officers
Allergy deep dive	• Review and analyze cases of anaphylaxis after covid vaccines reported in VAERS - ongoing
Review of Serious Adverse Event (SAE) reports of Simultaneous RZV and aIIV4 Vaccination Study	• Assessment of SAE

COVID adult study	• Active participation in call and review of meeting minutes
COVID vaccine research studies	• Ongoing
CISA COVID Babies Research Study	• Ongoing meeting every other week
Inadvertent MMR vaccine administration in immunocompromised child -prepare powerpoint document summarizing the case and followup information -review the power point document with CDC physician and revise according to suggested changes -prepare presenting to CISA leadership	• Ongoing

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	• 100 initial abstractions completed (counted at the dyad level)
Medical record re-abstractions	• 24 re-abstractions
HTN review	• 15 records were reviewed for hypertensive disorders during pregnancy
Abstraction-re-abstraction Comparison	• Completed comparison tool for 94 records for the January comparison tool
Medical record reconciliation	• Completed reconciliation for 24 records
Extended follow-up planning	• Abstractors began interviews
NICU admission, Infant Hospitalization analysis	• Met bi-weekly with data analysts from Abstraction Associates to discuss and direct the analysis of the NICU admission & Infant hospitalization project
Clinical adjudication of birth defects with medical record data	• Provided specific feedback on changes needed in a Microsoft Access tool that was developed to aid in the clinical adjudication of birth defects • Met and discussed 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
Quality control checks	• Reviewed data for all pregnancies with multiple gestation for whom medical records were abstracted to ensure consistency of data abstraction across fetuses/infants. Specific QC variables addressed: Date of birth and pregnancy outcome; Diagnosis dates for BD

Delivery facility Data Acquisition	• Clinicians were given 300 records with unknown delivery facility information (specifically fax number, but also email or phone if fax unavailable) • Contact information was obtained and given to CNI for medical records requests

b. Status of on-going projects

Project	Status
V-safe pregnancy registry extended follow-up	• Starting interviews in mid-November; ongoing
Risk of stillbirth following maternal COVID-19 vaccination	• a draft was written and submitted after OB SME review; paper returned for revision and edits are being made; ongoing
1. Hypertensive disorders during pregnancy & COVID-19 vaccination 2. Maternal ICU admission among a cohort of vaccinated pregnant people 3. Birth Defects among cohort of infants with maternal vaccination	• Completing medical record abstractions; ongoing • Developing standard operating procedure (SOP) for HTN comparison; ongoing
Infant NICU admission, infant hospitalization, and neonatal mortality	• Working with abstractors to direct the analysis; ongoing • Progress being made on draft of analysis; ongoing • All records for infant deaths have been abstracted
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; ongoing
Review of medical records for birth defect adjudication	• Ongoing
Clinical Review of Birth defects	• Ongoing
Medical record abstraction and abstraction	• Ongoing
Onboarding of newly hired clinician	• Clinician is working through clearance process and awaiting issuance of smartcard and laptop; scheduled to start in March; training materials being developed by Registry Medical Officer as materials specific to Pregnancy Registry are not yet available; ongoing
Performance review	• 2 clinicians in review process; ongoing

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
Abstractors unclear on how individual quality audits impact outcome data and their performance. • Program Manager awaiting meeting with CDC leadership • Performance review process ongoing	• CDC program leadership to provide more specified overview of use of quality tool, impact to outcome data… • Begin documentation of all meetings held between contract clinicians and CDC to document feedback and action plans for any improvements needed.

IV. Manning

	COVID	Required	On hand
Task 2	VAERS physicians (OASIS Medical Officer 2022)	40	37*
Task 4	VAERS project coordinator (OASIS Program Mgr. 2022)	1	1
Task 3	CISA physicians (OASIS Medical Officer 2022)	8	8
Task 5	Pregnancy medical officer/epidemiologist (OASIS Epi VI 2022)	1	1
Task 6	Pregnancy clinician (OASIS Medical Officer 2022)	3	2*

	Monkeypox/Other		
Task 2	VAERS physicians (OASIS Medical Officer 2022)	6.75	6.75
Task 4	VAERS project coordinator (OASIS Program Mgr 2022)	0.25	.25
Task 3	CISA physicians (OASIS Medical Officer 2022)	2	2
Task 5	Pregnancy medical officer/epidemiologist (OASIS Epi VI 2022)	0.25	.25
Task 6	Pregnancy clinician (OASIS Medical Officer 2022)	0.75	.75
	Totals	**63**	**59**

* Denotes new hire identified – waiting on CDC Public Trust approval

From: "Goldstein, Robert (CDC/OD/OCS)" <[redacted]>
To: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Helfand, Rita (CDC/DDID/NCEZID/OD)" <[redacted]>, "Griffis, Kevin (CDC/OD/OADC)" <[redacted]>
Cc: "Berger, Sherri (CDC/OD/OCS)" <[redacted]>
Subject: CDC/FDA discussion
Date: Sat, 21 Jan 2023 16:05:30 +0000
Importance: Normal
Attachments: Booster_analysis_012323.pptx; Updated_Posting_Draft_01202023_CDC.docx

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Tom, Rita, and Kevin,

We are hoping to pull together this group with folks from FDA at 5:30pm tonight to discuss the attached slides and statement. We need to confirm this time will work for FDA and can send an invite out afterwards.

If you have additional edits to the statement, feel free to share before the call.

-Robbie

U.S. FOOD & DRUG ADMINISTRATION

Update on COVID-19 Vaccine Safety

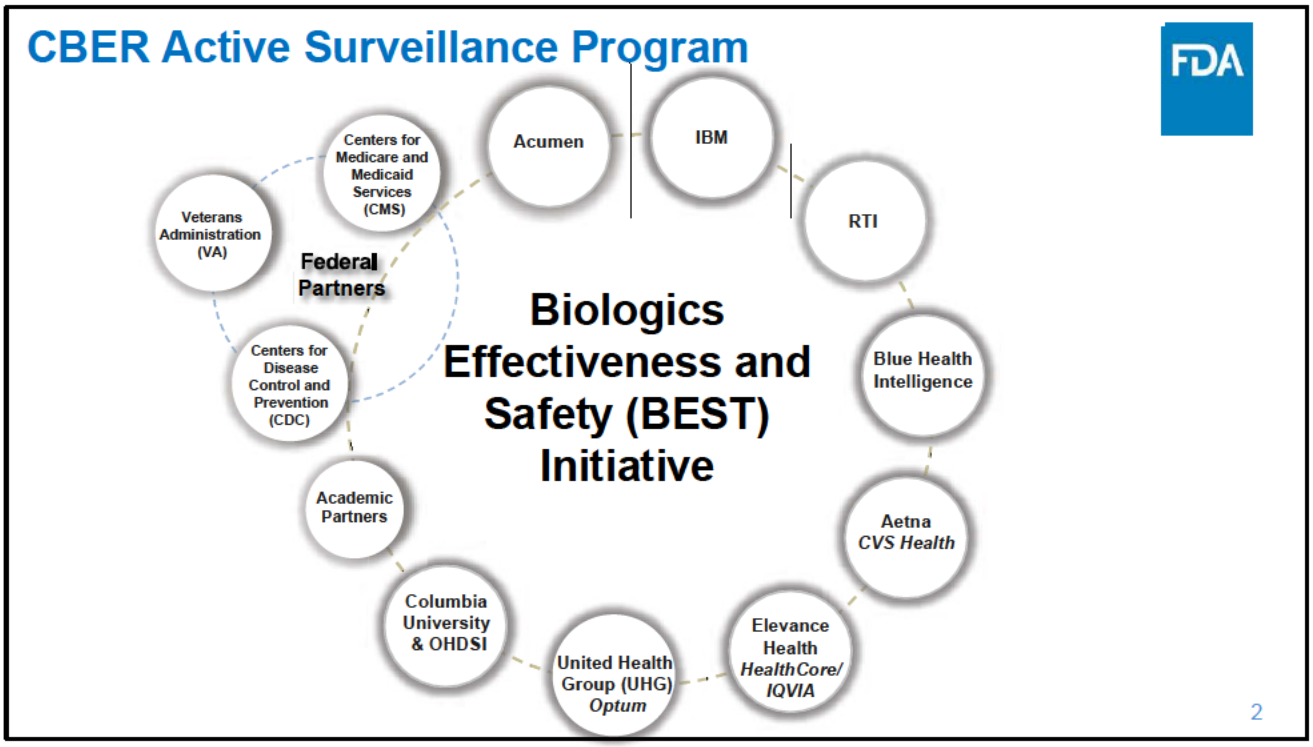
Presentation currently includes bivalent results with the following data cuts:

CMS - data through 12/24

HCI - data through 11/7

CVS - data through 10/31

Optum data are not currently included



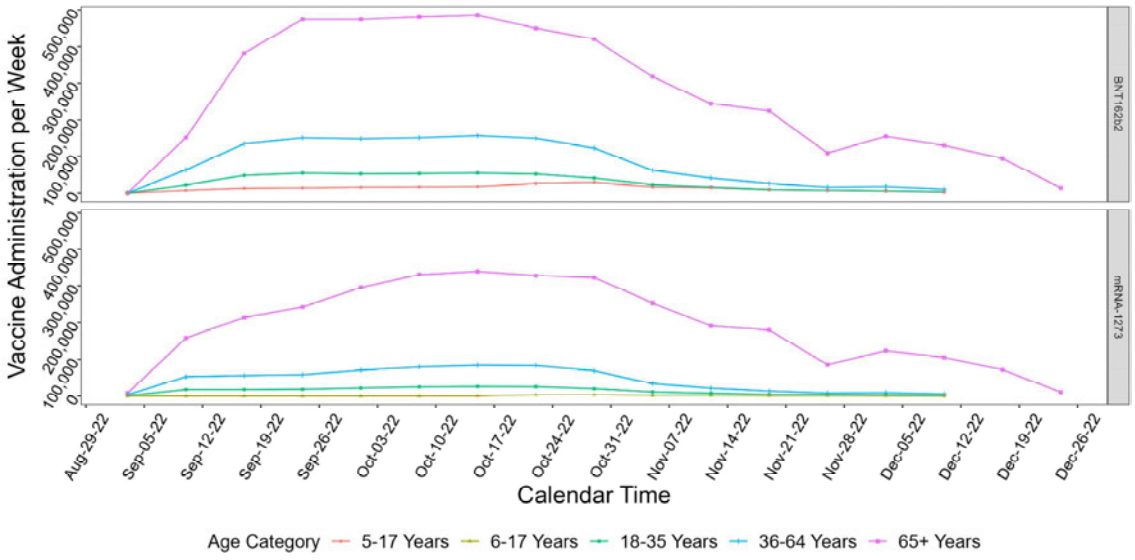
BEST Initiative Data Sources

Data Source*	Database Type	No. Patients Covered (Millions)	Time Period Covered
CMS- Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
MarketScan Commercial (IBM)	Claims	65	2016 - present
Blue Health Intelligence	Claims	93	2016 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	31	2017 - present
HealthCore	Claims	70	2010 - present
CVS Health	Claims	41	2018 - present
OneFlorida Clinical Research Consortium - Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium - EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims - EHR	Linked EHR Claims	25	2007 – 2020

*Data lag varies based on data source, ranges from a few days to a few months.

3

COVID-19 Bivalent mRNA Vaccines Doses Administered By Age Group



Data cuts: CMS data through 12/2022, CVS data through 10/2022, HealthCore data through 11/2022, Optum data through 12/2022

4

COVID-19 Bivalent mRNA Vaccines Safety Monitoring

- **Study Design:** Rapid Cycle Analysis (RCA) near real-time surveillance
  - No causal association established
- **Population:** 0-4/5 years, 5/6-17 years, 18-64 years*, ≥65 years
- **Exposure:** mRNA-1273.222 and BNT162b2 COVID-19 vaccines
  - Bivalent booster: original SARS-CoV-2 virus and Omicron variants BA.4 and BA.5.
- **Statistical Method**: MaxSPRT
- **Comparator:** Historical rates

*For the myocarditis/pericarditis outcome, the study population was additionally split into 18-35 and 36-64year age groups.

5

Note that results for 0-5/6 years old are not included in presentation as monitoring is still being set up for this population

Adverse Events Monitored

Adverse Events Monitored in Adult and Pediatric Populations	
Acute Myocardial Infarction	Hemorrhagic Stroke
Anaphylaxis	Immune Thrombocytopenia
Appendicitis	Multisystem Inflammatory Syndrome
Bell's Palsy	Myocarditis/Pericarditis (Myo-/Pericarditis)*
Common Site Thrombosis with Thrombocytopenia	Narcolepsy
Disseminated Intravascular Coagulation	Non-hemorrhagic Stroke
Deep Vein Thrombosis	Pulmonary Embolism
Encephalitis/Encephalomyelitis	Transverse Myelitis
Guillain-Barre Syndrome	Unusual Site Thrombosis (Broad) with Thrombocytopenia

Adverse Events Monitored in Pediatric Populations Only
Seizure/Febrile Seizure
Kawasaki Disease
Multisystem Inflammatory Syndrome in children (MIS-C)

*This includes 4 myo-/pericarditis outcome definitions varying care settings (all settings vs. IP/OP-ED) and risk windows (1-7 vs. 1-21 days)
These AEs have not been associated with COVID-19 vaccines based on available pre-licensure evidence.

6

Multisystem Inflammatory Syndrome in children (MIS-C) was in the previous version

Signals Detected

Adverse Event (AE)	Medicare Population[1] (Ages 65+)	Adult Population[2] (Ages 18-64)	Pediatric Population[2] (Ages 5-17/6-17)
Acute Myocardial Infarction	No	No	Descriptive Only
Anaphylaxis	No	No	No
Appendicitis	No	No	No
Disseminated Intravascular Coagulation	No	No	No
Deep Vein Thrombosis	No	No	No
Bell's Palsy	No	No	No
Encephalomyelitis/Encephalitis	No	No	No
Guillain-Barré Syndrome	No	No	Descriptive Only
Hemorrhagic Stroke	No	No	Descriptive Only
Myocarditis/Pericarditis	No	BNT162b2 Bivalent (18-35)	No
Common Site Thrombosis with Thrombocytopenia	No	No	No
Uncommon Site Thrombosis with Thrombocytopenia Syndrome	No	No	Descriptive Only
Narcolepsy	No	No	No
Non-Hemorrhagic Stroke	No	No	No
Pulmonary Embolism	No	No	No
Transverse Myelitis	No	No	Descriptive Only
Immune Thrombocytopenia	No	No	No
Febrile Seizures	N/A	N/A	Descriptive Only
Seizures/Convulsions	N/A	N/A	No
Kawasaki disease	N/A	N/A	Descriptive Only
Multisystem Inflammatory Syndrome	Descriptive Only	Descriptive Only	Descriptive Only

1. Data cuts: CMS 12/2022
2. Data cuts: CVS Health data through 10/2022; HealthCore data through 11/2022, Optum data through 12/2022

AEs and the associated vaccine brand with a safety signal are noted.
***N/A** indicates neither descriptive monitoring nor sequential testing is being conducted in the indicated age group for a given AE. **NO** indicates that a safety signal has not been detected. **Descriptive Only** indicates sequential testing is not being conducted in the indicated age group for a given AE.*

7

Concomitant Influenza Vaccination

- Approximately 3.5 million doses of the Pfizer-BioNTech bivalent vaccine have been administered in the CMS database in individuals 65 years and older
- Rate of influenza vaccination is about 40%, majority either high dose or adjuvanted
- Further work to be done to segment out the different influenza vaccine types administered with the COVID-19 vaccines
- No signal seen at this time for non-hemorrhagic stroke

8

International Reports Have Not Signaled for Stroke

- FDA contacted other regulators around the work to learn whether anyone had seen safety signals for stroke, vascular events, or thromboembolic events
- No regulatory body reported a signal that any of these events may be associated with mRNA bivalent COVID-19 vaccines
- The following bodies specifically reported that they had not seen a signal: Israel, Japan, Germany, EMA, Italy, UK, and Canada

9

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 old
- Among adults 65 years and older, several AEs have completed the surveillance period. No signal at this time for non-hemorrhagic stroke
- Signal detection studies do not establish a causal relationship and further evaluation of signals is required in more robust studies.

10

Updated Jan. 23, 2023

Update from CDC & FDA Indicates that the Bivalent COVID-19 Booster Vaccine Remains Safe for Use in Persons Aged 65 Years and Older

Additional evidence has now been evaluated regarding the safety of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Multiple international databases that were queried are not showing a safety signal for ischemic stroke. Further analysis of data from the CMS database continues to show no evidence of a signal for ischemic stroke. ~~And a~~Additional analyses of data from CDC's Vaccine Safety Datalink indicate there may be other factors that are contributing to the signal that was observed ~~and that it does not represent a true safety risk~~. Both CDC & FDA will continue to closely monitor the safety of the COVID-19 vaccines and will keep the public informed of their findings. As stated previously, these data and analyses will be discussed at the upcoming January 26 meeting of the FDA's Vaccines and Related Biological Products Advisory Committee.

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

From: "Kroop, Seth (CDC/DDID/NCEZID/DHQP)" <[redacted]>
To: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Goldstein, Robert (CDC/OD/OCS)" <[redacted]>, "Coffin, Nicole (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Crouse, Amanda (CDC/DDID/NCEZID/OD)" <[redacted]>, "Goodman, Jeremy A. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Nordlund, Kristen (CDC/OD/OADC)" <[redacted]>
Subject: RE: questions
Date: Tue, 17 Jan 2023 13:24:36 +0000
Importance: Normal
Attachments: Communications_Plan_-_Signal_CDC_1.12.2023.7pm.docx
Inline-Images: image001.png

Thanks Tom.

Adding @Goodman, Jeremy A. (CDC/DDID/NCEZID/DHQP) from my team here.

Jeremy: could you work from the cleared rollout attached plus some of the additional info below to craft some draft answers. Work with Tom as well, then I'll take a look and we'll definitely want OD to take a look as well before sending anything back.

I've copied the Congressional staff questions here, so that you can see that they are asking for specific numbers…

- **Q: How many cases of strokes have been detected? What is the threshold that triggers a signal? We recognize this is a rate not a number so it would be good to explain that and put the magnitude of what's been detected into perspective. Several staff asked for specific numbers.**

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 13, 2023 6:23 PM
To: Kroop, Seth (CDC/DDID/NCEZID/DHQP) [redacted]; Goldstein, Robert (CDC/OD/OCS) <[redacted]>; Coffin, Nicole (CDC/DDID/NCEZID/DHQP) <[redacted]; Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Cc: Nordlund, Kristen (CDC/OD/OADC) <[redacted]>
Subject: RE: questions

I previously replied to some iteration of this email chain but here is some additional follow-up. Below you can see the actual numbers and the rate ratios for the primary analysis. These are 'informative case counts' meaning you have to match a risk event patient with a similar patient in the comparison window, so it is a bit of an oversimplification to say there have been 130 stroke/TIA cases in 65+ y/o people following 550K Pfizer bivalent boosters in the 1-21 day risk interval, but that number is probably pretty close. With regard to signaling, once we establish that we have detected a statistical signal, the analysis has signaled and you can't un-signal per se. We do continue to monitor after a signal and calculate the rate ratio, 95% confidence interval, and apply a p=0.01 statistical significance. If the rate ratio attenuates that would be reassuring. But as you can see, the current p-value is 0.005.

I agree with Robbie that it might not be a good idea to get into actual numbers unless we are specifically asked for specific numbers.

Ischemic stroke PRIMARY analysis: Bivalent booster concurrent comparator RCA

1–21-day risk interval, 22–42-day comparison interval

Analysis Parameters		Informative Case Counts		Nominal Analysis			Sequential Analysis	
Age Group	Vaccine	Risk Events	Comp Events	Rate Ratio	95% Lower CI	95% Upper CI	1-sided p-Value	Signal 1-sided p <0.01
18-64 years	Pfizer	33	23	1.34	0.77	2.36	0.183	no
	Moderna	11	13	0.65	0.27	1.52	0.89	no
65+ years	**Pfizer**	**130**	**92**	**1.47**	**1.11**	**1.95**	**0.005**	**yes**
	Moderna	57	49	1.12	0.75	1.67	0.323	no

Data through Jan 8, 2023

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From: Kroop, Seth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 13, 2023 3:32 PM
To: Goldstein, Robert (CDC/OD/OCS) <[redacted]>; Coffin, Nicole (CDC/DDID/NCEZID/DHQP) <[redacted]>; Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; Nordlund, Kristen (CDC/OD/OADC) <[redacted]>
Subject: RE: questions

Thanks Nicole and Robby. Amanda—do you want to pull from that cleared rollout that Nicole shared, and perhaps Tom could write up those sentences Robbie describes below?

From: Goldstein, Robert (CDC/OD/OCS) <[redacted]>
Sent: Friday, January 13, 2023 3:30 PM
To: Coffin, Nicole (CDC/DDID/NCEZID/DHQP) <[redacted]>; Kroop, Seth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; Nordlund, Kristen (CDC/OD/OADC) <[redacted]>
Subject: RE: questions

Tom may be best able to craft a paragraph about the methods. I would hesitate to say the specific numbers because they change week-to-week as more data come in.

What we need is to (in plain language) describe how a rate ratio works and what statistical test is done to show when an elevated rate ratio is significantly different.

From: Coffin, Nicole (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 13, 2023 3:28 PM
To: Kroop, Seth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; Goldstein, Robert (CDC/OD/OCS) <[redacted]>; Nordlund, Kristen (CDC/OD/OADC) <[redacted]>
Subject: RE: questions

+Tom S and Robbie G, who addressed a bit of this on the call.

Tom/Robbie – possible to provide the number of cases surveyed and bit about ischemic stroke being under .05%, plus give a comparison to how that played out with myocarditis.

Seth/Amanda – no need to send follow-ups through OADC. Can use the attached to address Q/As and work directly with Robbie and Tom for technical questions not covered.

Thanks,
~Nicole

Nicole Coffin, MA
Deputy Associate Director for Communications (Acting), CDC

From: Kroop, Seth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 13, 2023 3:05 PM
To: Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Cc: Coffin, Nicole (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: questions

Yes, that would be helpful. OD will have the pen on this issue.

From: Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Sent: Friday, January 13, 2023 3:04 PM
To: Kroop, Seth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Coffin, Nicole (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: questions

Got it, thank you. Will re-direct them unless I hear otherwise from you both.

Amanda

From: Kroop, Seth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 13, 2023 3:01 PM
To: Crouse, Amanda (CDC/DDID/NCEZID/OD) [redacted]
Cc: Coffin, Nicole (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: questions

All of the communications and analysis has been driven by OD. Adding Nicole Coffin here. OD would have the responsive information or other details on what they are able to say.

From: Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>
Sent: Friday, January 13, 2023 2:47 PM
To: Kroop, Seth (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: questions

Hi Seth,

See question below that came up on several congressional calls earlier today. Could you please work on some responsive language that we could share with CDCW?

Thanks,
Amanda

From: Klingbeil, Martin (CDC/OD/CDCWO) <[redacted]>
Sent: Friday, January 13, 2023 1:08 PM
To: Crouse, Amanda (CDC/DDID/NCEZID/OD) <[redacted]>; Miedema, Gregory (CDC/DDID/NCEZID/OD) [redacted]; Gwynn,

Melanie (CDC/DDID/NCEZID/OD) <[redacted]>
Subject: FW: questions

Follow-up from calls that just happened – we need to draft a TP that explains how the threshold works (what rate of cases exceeds it, about how long does the signal need to remain over the threshold to warrant review).

Can you work with DHQP and ISO on this? See below.

Thanks,
Martin

From: Greaser, Jennifer (CDC/OD/CDCWO) <[redacted]>
Sent: Friday, January 13, 2023 1:04 PM
To: Klingbeil, Martin (CDC/OD/CDCWO) <[redacted]>
Subject: questions

Multiple staff asked the threshold question (McCarthy, E&C minority, HELP majority, and Eshoo)

Can we have program draft a Q&A on this?

Q: How many cases of strokes have been detected? What is the threshold that triggers a signal?

We recognize this is a rate not a number so it would be good to explain that and put the magnitude of what's been detected into perspective. Several staff asked for specific numbers.

Jennifer Greaser
CDC Washington Office
www.cdc.gov/washington
[redacted]

Confidential, Draft, Pre-Decisions, January 12, 11:30am

WEB POSTING

Suggested Title:

Suggested Posting Date: Friday, January 13

Transparency and vaccine safety are top priorities for the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). U.S. government agencies use multiple, complementary safety monitoring systems to help detect possible safety signals for vaccines and other medical countermeasures as early as possible and to facilitate further investigation, as appropriate. Often these safety systems detect signals that could be due to factors other than the vaccine itself.

All signals require further investigation and confirmation from formal epidemiologic studies. When one system detects a signal, the other safety monitoring systems are checked to validate whether the signal represents an actual concern with the vaccine or if it can be determined to be of no clinical relevance.

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 22-44 following vaccination.

This preliminary signal has not been identified with the Moderna COVID-19 Vaccine, Bivalent. There also may be other confounding factors contributing to the signal identified in the VSD that merit further investigation. Furthermore, it is important to note that, to date, no other safety systems have shown a similar signal and multiple subsequent analyses have not validated this signal:

- A large study of updated (bivalent) vaccines (from Pfizer-BioNTech and Moderna) using the Centers for Medicare and Medicaid Services database revealed no increased risk of ischemic stroke
- A preliminary study using the Veterans Affairs database did not indicate an increased risk of ischemic stroke following an updated (bivalent) vaccine
- The Vaccine Adverse Event Reporting System (VAERS) managed by CDC and FDA has not seen an increase in reporting of ischemic strokes following the updated (bivalent) vaccine
- Pfizer-BioNTech's global safety database has not indicated a signal for ischemic stroke with the updated (bivalent) vaccine
- Other countries have not observed an increased risk for ischemic stroke with updated (bivalent) vaccines

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, as we have in the past, when one of our safety monitoring systems detects a signal. 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.

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

Commented [GK(1]: The title of the July 2021 FDA posting was: "Initial Results of Near Real-Time Safety Monitoring of COVID-19 Vaccines in Persons Aged 65 Years and Older"
Griffis, Kevin (CDC/OD/OADC)
2023-01-12 18:50:00

currently eligible to receive an updated (bivalent) vaccine. Staying up-to-date with vaccines is the most effective tool we have for reducing death, hospitalization, and severe disease from COVID-19, as has now been demonstrated in multiple studies conducted in the United States and other countries:

- Data have shown an updated COVID-19 vaccine reduces the risk of hospitalization from COVID-19 by nearly 3-fold compared to those who were previously vaccinated but have not yet received the updated vaccine.
- Data have shown that the updated COVID-19 vaccine also reduces the risk of death from COVID-19 by nearly 19-fold compared to those who are unvaccinated.
- Other preliminary data from outside the U.S. have demonstrated more than 80% protection against severe disease and death from the bivalent vaccine compared to those who have not received the bivalent vaccine.

Overall safety data for the bivalent COVID-19 vaccines are available here.

Once again, **no change is recommended in COVID-19 vaccination practice**, which can be found here.

TOUGH QUESTIONS AND ANSWERS

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

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

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

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

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

- We need to distinguish the signal observed here from the determination of any associated safety risk. Though a preliminary signal has been identified, multiple other lines of evidence suggest that this signal may not be confirmed on further evaluation, and thus, the totality of the evidence does not suggest a true safety risk exists at this time that should change clinical practice.

- Currently, the signal is slightly elevated but stable/persistent. The rate ratios seen so far are significantly lower than statistical signals seen for issues like myocarditis.
- This statistical signal has a slightly elevated rate ratio (a measure of relative risk) that has just exceeded our pre-specified threshold for statistical significance. Similar findings have not been observed in other vaccine safety monitoring systems in the United States and have not been observed in other global monitoring programs. Additional analyses are underway to evaluate if this finding represents a true clinical risk. At this point there is insufficient information to conclude a true health risk exists.

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

- Scientists are working to determine if this is a true association.
- Our analyses become more stable with more data. We're hopeful to have a clearer picture from the assessment and more data in the coming weeks.
- In January, CDC and FDA will share updates to the assessment in planned upcoming vaccine safety meetings, including with ACIP's COVID-19 Vaccine Working Group and FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). CDC and FDA have already briefed the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST).

When did CDC first notice this signal?

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

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

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

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

- CDC is continuing to monitor VSD data weekly and explore potential data-related explanations for the statistical signal.
- When CDC identified a potential signal in mid-December, CDC:
    - assessed data quality, including diagnostic codes and comparison groups
    - began comparing data to other monitoring systems, including FDA (CMS data) and VA
    - conducted a temporal scan analysis to assess clustering of cases following vaccination
    - examined if the rates between the two groups were caused by decreased risk in the comparison window or increased risk in risk window, or combination of both
- By mid-February, CDC will:
    - review cases to confirm diagnoses and better characterize the cases (i.e., if ischemic strokes reported were actually transient ischemic attacks, also known as TIAs),
    - continue to conduct weekly temporal scan analysis,
    - conduct sub-analyses of different segments (strata) of the population,
    - develop statistical models that stratify by confounding factors (e.g., comorbidities or other conditions, risk factors, vaccine uptake patterns, coadministration of other vaccines),
    - review more data as it continues to accumulate weekly and exploring potential data-related explanations for the signal,

  - evaluate the signal further in other data systems (i.e., in CMS, VA), and
  - communicate findings on CDC's website and other communication channels.
- In the next several months, there is consideration for expanding chart reviews and conducting additional medical record reviews confirming the case diagnosis, onset date, and if the cases had any documented history of COVID-19 disease.
- FDA may conduct a definitive study using appropriate epidemiologic study designs such as self-controlled or other designs.

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

- SEE ANSWER ABOVE.
- CDC hopes to assess all factors listed above by mid-February 2023.
- Signal assessment analyses and supplementary analyses in the data system where the signal was detected are underway. The timeline for these assessments will take weeks. The timeline for formal epidemiologic studies in other data systems will take months.
- Additional expected data will make the assessment stronger. CDC will continue to update on its assessment of whether a causal association between bivalent booster vaccine and ischemic stroke exists.

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

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

Has stroke and COVID-19 vaccinations been studied previously?

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

Should people with a family history of stroke be concerned?

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

What is CDC doing about this?

- CDC is currently conducting additional analyses. Signal assessments typically take weeks to months. CDC hopes to have a clearer picture of the signal by mid-February.
- For the issue of stroke, relative risk is particularly difficult to parse out as ischemic stroke was already common in the U.S population prior to the introduction of COVID-19 vaccines.

- CDC has notified the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST) and will brief the COVID-19 Vaccines Work Group and Vaccines and Related Biological Products Advisory Committee (VRBPAC) later in January, as scheduled. These groups advise on the safety, development, and administration of vaccines and are critical to the risk assessment process.

What is FDA doing about this?

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

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

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

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

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

- Check whether comparison groups are defined appropriately
- Check other analyses that use a different control group (e.g., concurrent vs. historical) or compare with a different vaccine
- Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window
- Evaluate the signal further in other data systems (i.e., in CMS, VA). Other signal detection and assessment systems exist, such as CDC's v-safe (signal detection only), the FDA's CMS collaboration and BEST, VA near real-time sequential monitoring, and DoD's DMSS.
- Conduct a definitive study using appropriate epidemiologic study designs (e.g., logistic regression analysis)

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

- CDC evaluates the benefits of COVID-19 vaccines through multiple methodologies, employing various methods and using information collected through different surveillance platforms or electronic health records, among other avenues. In addition, COVID-19 vaccines continue to undergo the most comprehensive and intense safety monitoring in U.S. history. These data are presented and discussed through ongoing benefit-risk analyses to both the ACIP COVID-19 vaccines Work Group and the public ACIP meetings. These analyses have continued to demonstrate that COVID-19 vaccination is the single best way to protect people from serious COVID-19 illness and the benefits continue to outweigh the risks. As with all emerging data for the vaccines, CDC and ACIP will continue to evaluate the balance of benefits and risks for COVID-19 vaccines.

What is an ischemic stroke?

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

###

From: Bruce H Fireman <[redacted]>
To: "Weintraub, Eric (CDC/DDID/NCEZID/DHQP)" <[redacted]>, Ousseny Zerbo <[redacted]>, "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>, NICOLA P KLEIN <[redacted]>, Ned Lewis <[redacted]>, Kristin Goddard <[redacted]>
Subject: RE: Two things
Date: Tue, 10 Jan 2023 21:39:19 +0000
Importance: Normal
Inline-Images: image001.png

Hi Tom,

I'm writing to clarify something in the email sent an hour or so ago.

I didn't mean to promise that we now plan to conduct any particular additional re-analysis,
such as the analysis that Dr Jha apparently is suggesting (omitting data from the earliest weeks of our bivalent booster surveillance).

I was just saying that there are a number of potentially informative ways of examining the available data, and we are doing some of them, as we try to understand the signal that we're seeing.

Two more clarifications:

1. I agree with your responses to Goldstein. I was just adding a few thoughts…i didn't mean to imply that any of my comments should be added into your response to Goldstein (or any response to Jha or Califf).

2. Regarding the concern about the earliest boosted vaccinees – concern that we can't adequately adjust for ways that these people may be especially risky or especially health-seeking:

   Due to our design, the very first people to get the bivalent booster are NOT now informative during their risk interval because no comparators are yet available. However, they ARE informative during their comparison interval when they are compared with vaccinees boosted a few weeks later. Therefore, any bias from these people who were boosted earliest may be in the opposite direction from what Dr Jha may expect.

Best, Bruce

From: Bruce H Fireman
Sent: Tuesday, January 10, 2023 12:06 PM
To: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) <[redacted]>; Ousseny Zerbo <[redacted]>; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; NICOLA P KLEIN <[redacted]>; Ned Lewis <[redacted]>; Kristin Goddard <[redacted]>
Subject: RE: Two things

Here are some additional comments on these two things.

1. Yes, we can re-analyze the data in a number of ways that may be informative regarding potential sources of bad data or confounding or other kind of bias. One potentially informative analysis could -- as Dr Jha suggests -- omit data from the earliest weeks we started using the bivalent booster. We can also look at whether the stroke "signal" is stronger or non-existent in subgroups defined by concomitant receipt of a hi-dose flu shot, or by age group, or VSD site, or by available stroke risk factors.

   We can also re-analyze the ischemic strokes after omitting the TIAs, and we can also examine more closely the risk over time of possibly-related outcomes such as AMI, VTE, and PE. We can also interpret available comparisons with unboosted individuals who were eligible for boosting, and with unvaccinated individuals, and with boosted vaccinees during other times post-vaccination. And we can re-analyze the data using alternative methods that have a somewhat different profile of strengths and limitations.

   We are already doing, and interpreting, many such re-analyses, and sooner or later we may do many others. Such analyses should help us assess whether the signal we are seeing is due to a real safety concern or else some kind of data problem or bias. And if there is a real safety concern, it may help us identify who and when: is it only a problem with concomitant hi-dose flu? How transient is any period of possibly elevated risk, etc.

This is how we are supposed to be conducting our RCA according to our protocol.

2. Yes, a Bonferroni correction could be done and it would greatly reduce the chance of a false positive signal (a Type I error). A Bonferroni correction would greatly reduce the power of our vaccine safety surveillance. It would greatly attenuate our power to detect any real adverse effects of vaccination, and therefore the amount of reassurance we can ever appropriately offer. The current signal--regarding risk of ischemic stroke during the second and third week after a Pfizer booster – would not "signal" if the threshold is Bonferroni-adjusted. Also, Bonferroni isn't the only way to account for multiple testing, but the dependencies among our outcome events, and the fact that some of them are very rare (eg. GBS) complicate adjustments that would take less severe a toll on our power to notice any real safety concerns that may arise.

We are NOT saying that the current stroke signal is especially strong or robust. We are examining it further, and we hope others look into it with good relevant data (other than the data that is already available to us).

Sooner or later, we may confidently ascertain that the signal was due mainly to data problems (the data are still somewhat unsettled, to an unknown extent), or to problems with our boosted concurrent comparators, or to other sources of confounding. But we now are conducting our safety monitoring according to a good, reasonable protocol, and we are examining a signal that we see.

From: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Tuesday, January 10, 2023 9:41 AM
To: Ousseny Zerbo <[redacted]>; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; NICOLA P KLEIN <[redacted]>; Ned Lewis <[redacted]>; Bruce H Fireman <[redacted]>; Kristin Goddard <[redacted]>
Subject: RE: Two things

No it's never been done – however, we have used different thresholds for "priority outcomes" – for h1n1 – GBS was .05, all others .01 etc.

For the thimerosal and neuro studies as well, the expert panel all agreed to not use Bonferroni adjustments and allow the each finding to be interpreted vs masking any potential associations by an extremely small threshold.
But in general to answer your question – NO, the vsd has never applied a Bonferroni like correction to RCA. An additional key reason why is as well, is often we are conducting RCA analyses on automated data. A "statistical" signal brings the outcome to our attention to further evaluate and usually conduct chart reviews to validate the outcome of interest. It is not reasonable for any system to conduct real time chart reviews of every outcome under surveillance, so this allows us some flexibility on how we utilize our resources efficiently.

From: Ousseny Zerbo <[redacted]>
Sent: Tuesday, January 10, 2023 12:31 PM
To: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) <[redacted]>; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; NICOLA P KLEIN <[redacted]>; Ned Lewis <[redacted]>; Bruce H Fireman <[redacted]>; Kristin Goddard <[redacted]>
Subject: RE: Two things

This looks good to me, but I will let Bruce and Ned talk. In past RCAs, have you ever applied Bonferroni correction to the p value after a signal is detected? If not maybe it could be pointed out.
Thank you
Ousseny

From: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Tuesday, January 10, 2023 8:59 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; NICOLA P KLEIN <[redacted]>; Ned Lewis <[redacted]>; Bruce H Fireman <[redacted]>; Kristin Goddard <[redacted]>; Ousseny Zerbo <[redacted]>
Subject: RE: Two things

Look good to me, I'll defer to NCK team.

Ned and I were also just discussing – the very first people vaccinated, ie in the first 3 weeks are essentially not informative anyway, because there aren't any people during this time period that are eligible to be in the comparison window yet (essentially there has to be at least 1 day of comparison time in the stratums of interest for the analyses to officially start).

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Tuesday, January 10, 2023 11:53 AM
To: NICOLA P KLEIN <[redacted]>; Ned Lewis <[redacted]>; Bruce H Fireman <[redacted]>; Kristin X. Goddard <[redacted]>; ousseny.x.zerbo [redacted]
Cc: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: FW: Two things
Importance: High

Thoughts on my responses?

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)
Sent: Tuesday, January 10, 2023 11:37 AM
To: Goldstein, Robert (CDC/OD/OCS) <[redacted]>
Subject: RE: Two things

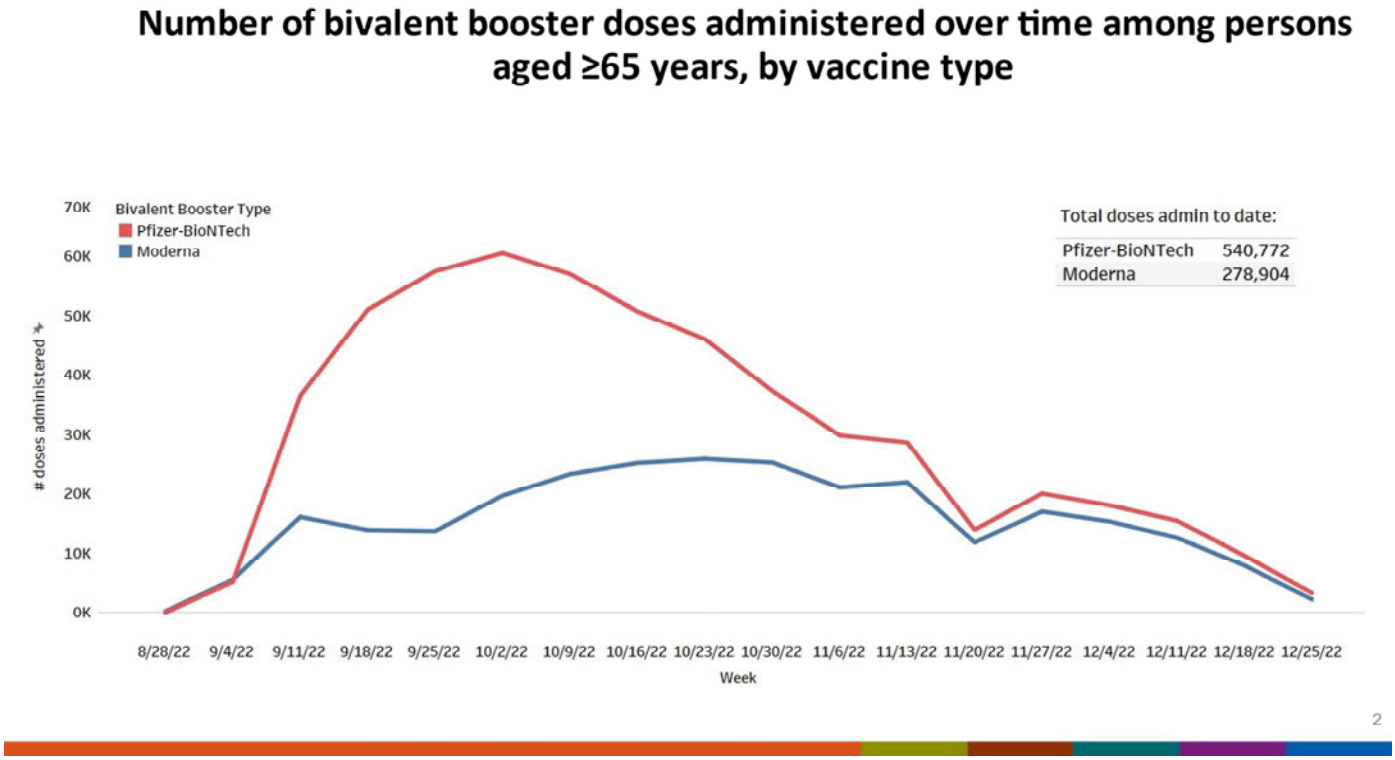
I'll f/u to see if the VSD analysts have any additional comments re: #2.

From: Goldstein, Robert (CDC/OD/OCS) <[redacted]>
Sent: Tuesday, January 10, 2023 11:16 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: Two things

Tom,

Two things:

1. Yesterday, Dr. Jha asked about redoing the analysis without the first few weeks of data. While I think you answered the question as to why this is not what would be done, he is asking if this analysis could be done. Would it be possible to do so?
   It could be done but it wouldn't be a valid signal assessment sub-analysis. From the graph below, if we restricted that data by excluding observations prior to 11/27 when the persistent signal started we would essentially be excluding the overwhelming majority of the informative data and we would end up with sparse data, small numbers, and unstable point estimates (which would almost certainly be non-statistically significant b/c the current estimates are barely significant). I am concerned that this would be viewed as an example of slicing the data to get an intended result. Furthermore, it would eliminate the option of looking at concomitant flu vaccination.



2. There are continued questions about Bonferonni corrections. Is it possible to get a written response from the ISO statistician (and maybe others at FDA in this space) as to why this does not work with the current methodology of VSD?

I think it's best to go straight off the protocol (Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink (cdc.gov), which was written with the investigators: "The sequential methods used in this analysis will permit us to maintain an overall one-sided type I error rate of 0.05 across the multiple tests performed for each outcome, subgroup, and statistical method combination. We recognize that while the sequential methods will account for the repeated weekly analyses for each outcome/subgroup combination, it does not account for the numerous statistical tests across the different combinations that will be performed during this RCA. While this may increase the probability of a false positive result, all signals will be evaluated by VSD vaccine safety experts following an established protocol (described in a separate section below)." It's not that a statistical correction for multiplicity of outcomes won't work with VSD methodology. Any adjustment that will raise the statistical threshold for signaling will reduce the likelihood of false signals. It's more about the balance between sensitivity versus specificity and concept of erring on the side of sensitivity when it comes to monitoring and detecting safety signals. RCA is basically a screening methodology and a surveillance activity and we are willing to (theoretically) accept a certain level of false positives to ensure we don't miss true positives. Adjusting for multiplicity of outcomes in vaccine safety surveillance risks over adjusting and potentially setting up a methodology that might systematically fail to find true safety signals.

-Robbie

Table 2: SME Technical Review: Recommended redaction for of Exemptions 4, 5 and 6 (proprietary commercial interest, pre-decisional/deliberative/ and *mosaic identity* of patients, outside healthcare providers or institutions).

FOIA No. _____

DHQP/ISO SME: _____

Page(s) (Per FOIA pdf package)	Item to Redact	Rational for Protection	Comments
Example 2	University of Tennessee Lab, Michael Whit	Business Proprietary & Personal Privacy (CISA AoC)	Exemption 6 – located at bottom of the page

From: "Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR)" <[redacted]>
To: "Starling, Doneshia (CDC/DDID/NCEZID/DHQP) (CTR)" <[redacted]>, "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: RE: medical records for reports of ischemic stroke after bivalent mRNA COVID-19 vaccine
Date: Wed, 28 Dec 2022 21:51:24 +0000
Importance: Normal
Inline-Images: image001.png

Doneshia,

The abstractors will be assigned the cases tomorrow morning. There are 53 total; some already have medical records. They are all Stroke AESI. I have asked the abstractor to request records first and enter comment: "High Priority" in the comment box.

Quick question: if PII is missing, do you want the abstractors to try to obtain it as they usually would or will the medical records team?

Thanks!

Best regards,

Carol

Carol W. Ennulat MBA, PA-C DDID/NCEZID/DHQP (CTR)
VAERS Project Coordinator/Clinician, Centers for Disease Control and Prevention
Lukos, LLC
[redacted]

Do NOT send any confidential medical records to this email account. Please submit them to [redacted] or fax to [redacted] and include the VAERS record number provided in the subject line of thie email. Thank you!

From: Starling, Doneshia (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Sent: Wednesday, December 28, 2022 3:24 PM
To: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: medical records for reports of ischemic stroke after bivalent mRNA COVID-19 vaccine

Sounds good 😊

Doneshia Starling
Program Coordinator
Eagle Health Analytics, LLC
Center for Disease Control and Prevention
[redacted]

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, December 28, 2022 3:24 PM
To: Starling, Doneshia (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Cc: Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: medical records for reports of ischemic stroke after bivalent mRNA COVID-19 vaccine

Thanks, Doneshia. In truth, I won't be sending requests – but if you receive any from the abstraction team(s) noting that the report is of ischemic stroke after bivalent vaccine, you'll know to prioritize it. 😉 Thanks again!

- John

From: Starling, Doneshia (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Sent: Wednesday, December 28, 2022 3:05 PM
To: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: medical records for reports of ischemic stroke after bivalent mRNA COVID-19 vaccine

Hi John,

I have received your email. Yes, please send any priority request to us and our team will be sure to process them immediately.

Thank you,

Doneshia Starling
Program Coordinator
Eagle Health Analytics, LLC
Center for Disease Control and Prevention
[redacted]

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, December 28, 2022 2:56 PM
To: Starling, Doneshia (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Cc: Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: medical records for reports of ischemic stroke after bivalent mRNA COVID-19 vaccine

Hi Doneshia,

I hope the holiday season has been treating you well!

I understand you're the coordinator for medical record acquisition. We've received a high priority request from leadership to assess reports in VAERS of ischemic stroke – specifically, to confirm such reports by medical documentation (e.g., hospital records). I understand that for routine work, there's a bit of a delay or backlog? I just wanted to clarify that any requests for medical records pertaining to abstraction of ischemic stroke after bivalent vaccine should take top priority, ahead of all other requests. There aren't many such reports, and we plan to complete such efforts in the next couple of weeks – then it's back to business as usual. 😉

Please let me know if you have any questions. Thanks in advance!

- 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, [redacted]
Atlanta, GA 30333
[redacted]

From: "Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR)" <[redacted]>
To: "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: RE: Team Meeting Tuesday
Date: Fri, 13 Jan 2023 15:21:09 +0000
Importance: Normal
Inline-Images: image001.png

Certainly!

I did that last month and will make it a standing item moving forward

Best regards,

Carol

Carol W. Ennulat MBA, PA-C DDID/NCEZID/DHQP (CTR)
VAERS Project Coordinator/Clinician, Centers for Disease Control and Prevention
Lukos, LLC
[redacted]

Do NOT send any confidential medical records to this email account. Please submit them to [redacted] or fax to [redacted] and include the VAERS record number provided in the subject line of thie email. Thank you!

From: Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 13, 2023 9:58 AM
To: Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: Team Meeting Tuesday

Hi Carol,

I don't have any updates. Can you provide a summary of the progress for the projects or activities the group is involved with? for: coagulopathy, deaths, ischemic stroke, anything of note in AESI but just if unusual, coadministration of bivalent-flu vaccine project, pregnancy

But just general things, I don't want you to do extra work, this is just for everyone so that the whole group is aware of the projects going on and their progress

Thanks

Pedro

From: Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Sent: Friday, January 13, 2023 9:27 AM
To: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: Team Meeting Tuesday

Good morning Ruth and Pedro!

Do either of you have any agenda items for our meeting Tuesday 10 am?

Have a great long weekend!

Best regards,

Carol

Carol W. Ennulat MBA, PA-C DDID/NCEZID/DHQP (CTR)
VAERS Project Coordinator/Clinician, Centers for Disease Control and Prevention
Lukos, LLC
[redacted]

Do NOT send any confidential medical records to this email account. Please submit them to [redacted] or fax to [redacted] and include the VAERS record number provided in the subject line of thie email. Thank you!

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 <[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: "Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR)" <[redacted]>
To: "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: RE: additional reports of ischemic stroke to abstract -- ADDITIONAL REPORTS
Date: Tue, 10 Jan 2023 13:23:23 +0000
Importance: Normal
Inline-Images: image001.png

Good morning!

Will assign them today!

Have a great day!

Best regards,

Carol

Carol W. Ennulat MBA, PA-C DDID/NCEZID/DHQP (CTR)
VAERS Project Coordinator/Clinician, Centers for Disease Control and Prevention
Lukos, LLC
[redacted]

Do NOT send any confidential medical records to this email account. Please submit them to [redacted] or fax to [redacted] and include the VAERS record number provided in the subject line of thie email. Thank you!

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Tuesday, January 10, 2023 8:11 AM
To: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>; Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Subject: RE: additional reports of ischemic stroke to abstract -- ADDITIONAL REPORTS
Importance: High

Hi folks,

At Tom's request, I had Paige do a refresh on these reports, current as of Jan 6. Please see below an additional 22 reports of ischemic stroke. Please assign and abstract as best as you can. At the least, we'll count them as preliminary reports – but if we can abstract them by COB Friday, all the better. Thanks!

- John

2547029
2548970
2548981
2549516
2549670
2550206
2550245
2551969
2449682
2458284
2459191
2459203
2459210
2459528
2491976
2492041
2517497
2524382
2525595
2537283
2545614
2549516

From: Su, John (CDC/DDID/NCEZID/DHQP)
Sent: Friday, January 6, 2023 10:40 AM
To: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Moro, Pedro (CDC/DDID/NCEZID/DHQP) [redacted]; Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Subject: RE: additional reports of ischemic stroke to abstract

No – just do the best you can; we'll report out what we have as of Jan 13. But we can continue abstraction until we've abstracted all reports for which we have records.

- John

From: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 6, 2023 10:34 AM
To: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>; Ennulat, Carol (CDC/DDID/NCEZID/DHQP) (CTR) <[redacted]>
Subject: RE: additional reports of ischemic stroke to abstract

does this change the turnaround date of Jan 13?

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Friday, January 6, 2023 10:25 AM
To: Moro, Pedro (CDC/DDID/NCEZID/DHQP) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: additional reports of ischemic stroke to abstract

Hi folks,

Please add the below reports to the list to abstract and/or request records. I was able to confirm that most were after bivalent vaccine. Thanks!

- John

VAERS_ID
2440868
2486017
2475449
2471039
2524255
2521980
2535384
2536025
2529696
2511323
2468381
2472773
2473226
2476816
2484903
2486182
2487250
2487250
2487292
2487805
2488430
2491998
2498681
2500017
2506519
2508589
2509220
2511323
2511323
2513947
2523180
2533269
2536545
2536857
2536868
2539874
2540577
2541906
2543266
2544586

From: "Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
To: "Shay, David (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Olson, Christine (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Sharma, Andrea J. (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Kim, Sehwa (Susan) (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Broder, Karen (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Alldredge, Berta (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: April Monthly Status Report - Lukos Clinical Contract 15135
Date: Tue, 9 May 2023 13:45:10 +0000
Importance: Normal
Attachments: Apr_23_Lukos_Monthly_Report.docx
Inline-Images: image001.png

Lukos Monthly Status Report attached for your info.

Bonita
404-498-0646

From: Brian McKibben <[redacted]>
Sent: Tuesday, May 9, 2023 9:32 AM
To: Alldredge, Berta (CDC/DDID/NCEZID/DHQP) <[redacted]>; Johnson, Bonita C. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: laura.hedrick[redacted]
Subject: April Monthly Status Report

Berta/Bonita,

See attached MSR for April. 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:	May 9, 2023
Contract ID:	15135
Reporting Period:	April 1 – April 30, 2023

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

a. Accomplishments

Task	Outcome/Accomplishment
Total Assigned cases (all abstractors)	• 26,258 Cumulative
Total Incomplete/No Abstraction Status (awaiting medical records)	• 595
April Assigned abstraction cases	• 3,041
April Completed abstraction/adjudication cases	• 3,854
Onboarding/Training new hires	• 4 new contractors were oriented • 1 new abstractor is now taking “live cases” • 3 new abstractors receiving practice cases

b. Status of on-going projects

Project	Monthly Status
AESI < 18	• Ongoing project • 1 abstractor assigned • 11 new cases assigned; 196 completed
Myocarditis all ages	• Ongoing project • 4 abstractors assigned • 39 new cases assigned; 94 completed
Thrombotic Thrombocytopenia Syndrome (TTS)	• Ongoing project • 3 abstractors assigned • 71 new cases assigned; 77 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 • 16 new cases assigned; 16 adjudications completed
Shoulder Injury after Vaccine Administration (SIRVA) Need Liza	• Ongoing project • 3 abstractors assigned • 615 total cases assigned; 475 completed
Death Project	• Ongoing project • 12 abstractors assigned and trained • 2320 new cases assigned; 2325 completed

Coagulopathy Project	• Ongoing project • 12 abstractors assigned • 500 new cases assigned; 576 completed
Monkeypox Abstraction	• 1 report with 1 additional completed abstraction • 1 abstractor assigned
Pregnancy	• Ongoing project • 2 abstractors assigned • 10 total new cases for mother and infant AESI's; 116 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	• Ongoing project • 6 abstractors • 59 additional cases assigned to prepare for ACIP meeting; 58 cases completed
GBS following PCV20 vaccine	• New project • 2 abstractors assigned • 11 newly assigned cases; 4 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 • Knowledge assessment quiz administered to all abstractors; 15/36 (42%) of abstractors did not attain passing score of 75% • Re-Education/Re-training PowerPoint recorded with input from CDC leadership and released for abstractor review • Plan reassignment of quiz to assess if knowledge gaps are improved with re-education • Second phase is dual abstraction to compare performance of abstractors to encourage similar work method; to begin May 2023

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
Part-time Project Coordinator began maternity leave	• Burden of role will fall to FT Project Coordinator; CDC leadership assisting in some tasks
Re-Education Project	• If re-education does not produce desired improvement in knowledge scores, uncertain as to next steps for additional re-training

II. Task 3 CISA Physicians: March 2023

a. Accomplishments

Task	Outcome/Accomplishment
Clinical on-call assignments	• Available for consultations/projects during assigned hours

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
  ○ eClearance of abstracts, presentation slides and manuscripts
  ○ DQHP clearance of concept proposals (CP)
  ○ 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
• Shoulder Inquiry Related to Vaccine Administration (SIRVA) working group
 	
• Lit review for pediatric GBS and pediatric meningoencephalitis case, Review of new ICC COVID-19 vaccine guidelines
 	
• Literature review, ICC, ACIP, VAERS, vaccine package inserts, Pink book, National Academies Press, MMWR, publications in chats, reviewed some RedCap entries, read all email in response box, read immunocompromise and live virus vaccine safety powerpoint slides, read on-call resources entries.
	• cases/inquiries 7 completed/in-progress
	
	• Available for consultations and other task assigned
	
	• Submitted and got cleared concept proposals, abstracts, presentations, and manuscripts through:
	  ○ DQHP science office (share point)
	  ○ CDC eclearance
	
	• Assessed severity and their relationship to study product of reported SAEs
	
	• Identify action items for follow up from standing and ad hoc research calls with Duke and Vanderbilt Universities
	
	• Reviewed SIRVAs reported to VAERS

Night coverage as scheduled	• 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 2 month vaccines – ○ 2nd part sent as enhanced inquiry • Meningoencephalitis following mening and tdap vaccination – consult presentation completed • GBS following COVID-19 vaccination dose #2 – moving towards consult • 1 case (GBS) going to consult which involves significant time in scheduling, meetings, and independent work on VAERS search and literature presentation • 1 case- 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 • 1 case in progress, part enhanced inquiry with possible second part full consult • Lit review, ACIP, package inserts, Pinkbook • Emails to clinician • SOAP note revisions • CISA inquiry: GBS following COVID-19 vaccine • Planned consult in May • Several preliminary VAERS searches completed with varying results; participated in meetings to narrow VAERS search strategy, participated in executive meeting where decision made to delegate VAERS search to VAERS team • Read through similar cases on VAERS, Compiled Power Point of CDC studies on safety of COVID-19 vaccine and studies of GBS following COVID-19 and other vaccines to be presented during consult • Pediatric patient with SOB and chest pain s/p 2 doses of 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 • 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	• Attend review of key leadership/management updates • Discussed cases (inquiries) and exchange experiences. • Discussed CISA's research portfolio issues • Updates on COVID-19 vaccine program and safety updates. • Updates on V-safe after vaccination health checker, data and work group considerations, and clinical considerations updates. • Covered public comment and committee discussion note taking • Sessions on Chronic Diseases, Public Health Surveillance, HIV and Sexually Transmitted Infections, Respiratory Diseases, One health, Vaccine-Preventable Diseases, Langmuir Lecture, Notes

• 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 • 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 • 1-2 meetings for MOVING project • Immunocompromised patient project – meeting and presentation • Multiple meetings for meningoencephalitis consult preparation • FDA meeting for protein based vaccines • EIS meetings x 2 days • Attended ACIP meeting • Attended EIS conference virtually • Recombinant protein-based COVID-19 vaccine workshop	from the Field, COVID-19 Surveillance and Response, TB, and Lake- Breaking reports
• Participate in COVID maternal study meeting • Participate in COVID adult study meeting • Participate in RZV and flu study meeting • Participate in 2 CISA research coordination meetings • Participate in CISA study administration meeting • Meet with Dr. Broder and Geta and confirm form 308b submissions • Listen to and provide feedback on Dr. Broder's PAHO presentation • Review and assess updated info for COVID/flu study SAE • Review and assess RZV/Fluad study SAE • Continue Good Clinical Practice CITI training • Attended DHQP Work In Progress Seminar	• Learned about current investigations in DHQP, including antimicrobial resistance monitoring, transmission of New Delhi Metallo-B-Lactamase Producing E coli Among Dogs at an Animal Rescue Facility, Investigation of the First Cluster of Candida auris cases among pediatric patients in the United States, and the effect of the coronavirus pandemic on antibiotic use among hospitalized adults in Indonesia and the Philippines
V safe Extended Follow Up Project	• Attended meeting regarding organization of data entry Still in planning phase--awaiting further instructions
Scheduling/Coordination between CDC and Contractor Physician	Ongoing

b. Status of on-going projects

Project	Status
1. *Manuscript: Reporting patterns of vaccine adverse events by reporter type in the Vaccine Adverse Event Reporting System (VAERS)* 2. *Manuscript: Reports of Shoulder Inquiry Related to Vaccine Administration in the Vaccine Adverse Event Reporting System, 2018-2022*	• VEAR search, Data review and analysis
• MOVING project •	
Suspect cardiac arrest consult months after covid bivalent vaccine -Review previous vaccine advisory meeting presentations for data available -prepare power point presentation for consult -Review 108 reports from Vaccine Adverse Events Reports System (VAERS) search -In depth review of 3 reports from the VAERS medical reports that has similarity to the consult case -Complete redcap entry for the case	VAERS search was done on 4/14 Fri 4pm -108 reports from VAERS was reviewed from 4/15 Sat to 4/17 Mon -Three in depth VAERS report review was done on 4/17 Mon to 4/18 Tuesday -**Official consult was done on 4/19 Wed** -database entry (Redcap) for the case was completed 4/19 Thurs
Steven-Johnsons syndrome (SJS) after exposure to flu vaccine, tyelnol and a possible infection in a 7 year old girl -Review general literature on pediatric SJS -Review publications from CDC regarding SJS from Vaccine Adverse Event Reporting systems (VAERS) -Review publication from CDC regarding SJS for nasal flu vaccine in Vaccine Safety Database -Prepare clinical summary and literature and other information for the case to be discussed by academic vaccine experts -further communicate with provider to set up meeting with academic experts	-Review of 6 publications done on 4/19 Thurs -Review of CDC's 3 publications done on 4/20 Thurs -Review of FDA medical watch document done on 4/20 Fri -Clinical summary with literature review and references (SOAP sent on 4/20 Fri) -**Case was presented to academic (CISA) experts on 4/24 Mon** -further communication to provider was done on 4/24 Mon
Rash after Bexsero Meningococcal B vaccine in 11 year old boy -communications with the provider to obtain clinical information	Inquiry received 4/6 The case was worked from 4/6 – 4/13

-Did readings on the UpToDate medical database about meningococcal vaccine schedule and requirements -Did reading on the immunization contraindication and precaution for meningococcal vaccines -Did reading on MMWR (CDC publication) on meningococcal disease and vaccines -write draft response for the provider using a previous skin rash/ hive template -went through multiple rounds of review and edits with various CDC physicians	**Response was sent to the provider on 4/13**
Hives after MMRV and other vaccines in a 5-year-old boy	The case was worked from 3/13 to 4/6 The case was presented to CISA experts on 3/15 **Response was sent to the provider on 4/6**
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 • Participate in and take notes on 2 CISA full consults: ○ Meningoencephalitis • Myocarditis • CISA inquiry: ADEM following immunization with MMR, varicella, and influenza vaccines • Project on Immunization schedule/document for adult and child vaccine recommendations based on CDC guidelines.	• Enhanced inquiry • Re-presented to CISA (2 parts) • Ongoing
MOVING Project	Ongoing • Immunocompromised Patient Guidance
Clinical Coordinator Role	• Working with CDC supervisors and Medical Officers
MOVING study, 1 year follow up interviews	• Attended initial meeting to work on future project for 5- 11 yo patients
2 going to consult which involves significant time in scheduling, meetings and independent work on VAERS search and presentation	• Ongoing

CISA COVID Babies Research Study	• Ongoing meeting every other week
Pregnancy Registry COVID-19 Vaccine Study Review and assess Maternal COVID study SAE	• Ongoing
Draft section of new research study proposal and review entire proposal	• ongoing
Start Good Clinical Practice CITI training	• ongoing

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	• 155 initial abstractions completed (counted at the dyad level)
Medical record re-abstractions	• 40 re-abstractions
Medical record "backfills"	• 42 Backfilled records
HTN review	• 157 records were reviewed for hypertensive disorders during pregnancy
Abstraction-re-abstraction Comparison	• Completed comparison tool for 41 records for the March comparison tool
Medical record reconciliation	• Completed reconciliation for 34 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 12 records
Hypertension Comparison Tool	• 1 Lukos clinician performed comparison of 178 records concentrating specifically on the hypertension form in REDCap to initiate and evaluate areas of process improvement for future on-going HTN comparison; based off of pilot performed in March

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
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
Orientation of new clinician	• SS oriented CH on preg registry specific tasks • SS reviewed work done by CH the following week • SS provided feedback to CH • SS remains primary liaison between CH and CDC leadership- CLOSED

c. Challenges/barriers and proposed solutions

Challenges/barriers	Proposed solutions
Determination of need for cell phone for Lukos clinician in order to participate in interviews for extended infant follow up (IFU)	• Pending decision from CDC leadership of purchase of a cell phone for clinician (most important functions being ability to text participants and having a number to provide participants to call clinician back). • Confirmed via email 5/5/23 that CDC will be issuing a cell phone to S. Sheets. Email from Bonita Johnson- CLOSED

From: "Prigodich, Cheryl (CDC/OCOO/OSSAM/OD)" <[redacted]>
To: "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Bruce, Sherrie (CDC/DDID/NCEZID/DPEI)" <[redacted]>, "Graham, D'Artonya (CDC/OCOO/OD)" <[redacted]>, "Miller, Elaine R. (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Cc: "Gallego, Ruth (CDC/DDID/NCEZID/DHQP)" <[redacted]>
Subject: RE: Nurses needed
Date: Thu, 18 Feb 2021 21:09:06 +0000
Importance: Normal
Inline-Images: image001.png; image002.png; image003.png

Great thanks. Please don't hesitate if we need to do something.

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, February 18, 2021 4:07 PM
To: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>; Graham, D'Artonya (CDC/OCOO/OD) <[redacted]>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: Nurses needed

Hi Cheryl,

Thanks! We'll assume Melanie can start on Mar 1, and we'll keep working on the red tape in the meantime. Thanks again for your help!

- John

From: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Sent: Thursday, February 18, 2021 3:58 PM
To: Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) [redacted]; Graham, D'Artonya (CDC/OCOO/OD) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: Nurses needed

Melanie's supervisor informed me that she did not get a request through CDC Responder. I don't want to hold things up on our end, so if you're able to push it through, you can utilize this email as supervisor approval!

Cheryl Prigodich, MPH
Deputy Director
Office of Safety, Security, and Asset Management (OSSAM)
Office of the Chief Operating Officer
[redacted]

OSSAM Office of Safety, Security, and Asset Management

From: Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>
Sent: Thursday, February 18, 2021 9:02 AM
To: Graham, D'Artonya (CDC/OCOO/OD) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>; Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: Nurses needed

Thanks D'Artonya! If you could, let's go ahead and process through the system as "sent to supervisor for approval" – that will give Cheryl an opportunity to see the official record of Melanie's approval. Thanks

From: Graham, D'Artonya (CDC/OCOO/OD) [redacted]
Sent: Thursday, February 18, 2021 8:32 AM
To: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>; Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>
Subject: RE: Nurses needed

All,
I sent the request to Melanie's supervisor, Wednesday, February 17, 2021, for approval. However, I am using this email chain as approval will set Melanie as "Ready for Activation" within CDC-R.

Please let me know if you require additional assistance.

D'Artonya Graham
[redacted]
Vaccine Task Force (VTF) – Ops Coordinator
2019 Novel Coronavirus Response
Roll-Off 3/5/2021

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, February 17, 2021 4:27 PM
To: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>; Graham, D'Artonya (CDC/OCOO/OD) <[redacted]>
Subject: RE: Nurses needed

Hi Cheryl,

Will do. Thanks!

- John

From: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Sent: Wednesday, February 17, 2021 4:19 PM
To: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>; Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>; Graham, D'Artonya (CDC/OCOO/OD) <[redacted]>
Subject: RE: Nurses needed

Thanks! We have a few people out on response activities (including our MO), so please feel free to reach out to me directly if there's a hang up on our end anywhere

---

From: Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, February 17, 2021 4:10 PM
To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>; Graham, D'Artonya (CDC/OCOO/OD) <[redacted]>
Subject: RE: Nurses needed

Hi all,

I've asked our ops chief to submit a name request via CDC Responder. My understanding is that once entered, we should be set. Thanks for your willingness to have Melanie assist with this very important activity!

Best regards,

John

John R. Su, M.D., Ph.D., M.P.H.
Lead, VAERS Team
CAPT, U.S. Public Health Service
NCEZID/ Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
1600 Clifton Road, [redacted]
Atlanta, GA 30329-4027
[redacted]

From: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, February 17, 2021 3:07 PM
To: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>
Subject: RE: Nurses needed

Hi Cheryl,

Yes-we followed up with Melanie and her start date is March 1.
I am adding John Su, VAERS team lead, but he notified the appropriate staff and I think we are all set. (John-please confirm).
We are so happy to have Melanie coming!

Thanks,
Elaine

From: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Sent: Wednesday, February 17, 2021 2:59 PM

To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>
Subject: RE: Nurses needed

Hey Elaine!

I wanted to follow up to see if you all would like to move forward with a response assignment for Melanie. I know she is very interested and could be available to start on 3/1. Please let me know how I can assist to help make that happen!

Cheryl Prigodich, MPH
Deputy Director
Office of Safety, Security, and Asset Management (OSSAM)
Office of the Chief Operating Officer (OCOO)
[redacted]

OSSAM Office of Safety, Security, and Asset Management

From: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, February 11, 2021 3:31 PM
To: Lagarde, Melanie (CDC/OCOO/OSSAM/OHSO) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Subject: RE: Nurses needed

Great-I will send an invite.
Best,
Elaine

From: Lagarde, Melanie (CDC/OCOO/OSSAM/OHSO) <[redacted]>
Sent: Thursday, February 11, 2021 3:30 PM
To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>; Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Subject: RE: Nurses needed

Hi Elaine,
Thank you! I look forward to it!

I can be available for a call tomorrow morning or any time tomorrow, at your convenience.

Looking forward to meeting you and your team.

Kind regards,
Melanie

Melanie Carmel Lagarde, DNP, MPH, RN, CHES
Centers for Disease Control and Prevention (CDC)
CDC Occupational Health Clinic
[redacted]

Email: [redacted]

From: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, February 11, 2021 2:28 PM
To: Lagarde, Melanie (CDC/OCOO/OSSAM/OHSO) <[redacted]>
Cc: Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: FW: Nurses needed

Hi Melanie,
We look forward to having you deploy with us!
Please let me know when we can have a short call of introduction with you.
Thanks,
Elaine

Elaine R. Miller, RN, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, GA
[redacted]

From: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP)
Sent: Thursday, February 11, 2021 2:26 PM
To: Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>; Gallego, Ruth (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: RE: Nurses needed

Thank you Sherrie-will do!

From: Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>
Sent: Thursday, February 11, 2021 2:18 PM
To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>
Subject: RE: Nurses needed

Hi Elaine – great!

OK, please reach out directly to her, confirm her start and end date and then have your team ops coordinator or staffing coordinator enter the request officially into CDCResponder. Her supervisor is ready to approve whenever it officially comes through the system.

From: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, February 11, 2021 2:12 PM
To: Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>
Subject: RE: Nurses needed

Hi Sherrie,
Sorry for the delay-I have been in meetings since I got your email.
Yes-we would definitely like to add Melanie to our team.
We are flexible about the dates, but need her as soon as she is available.
I can call you when I get out of my current meeting, which should be in a few minutes.

Thank you,
Elaine

From: Bruce, Sherrie (CDC/DDID/NCEZID/DPEI) <[redacted]
Sent: Thursday, February 11, 2021 2:08 PM
To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>
Subject: FW: Nurses needed
Importance: High

Hi Elaine and John – hope you are doing well. We are recruiting Melanie for another team and she is immediately available. Please confirm if you're planning to add her to your team so I can let the other team know they need to look for someone else. If so, do you have dates in mind? Thanks

---

From: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD)
Sent: Thursday, February 11, 2021 12:36 PM
To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>; Lagarde, Melanie (CDC/OCOO/OSSAM/OHSO) <[redacted]>
Subject: RE: Nurses needed

I have an employee who is interested. Her resume is attached and I have cc'd her. Please let us know if you have any questions.

From: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, February 11, 2021 12:28 PM
To: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>
Subject: RE: Nurses needed

Hi Cheryl,
It is 100% telework.
If you have more questions and would like to discuss, please let me know.
Thanks,
Elaine

From: Prigodich, Cheryl (CDC/OCOO/OSSAM/OD) <[redacted]>
Sent: Thursday, February 11, 2021 12:11 PM
To: Miller, Elaine R. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Su, John (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>
Subject: FW: Nurses needed

Is this detail telework? Or in person?

From: Newsome, Kimberly (CDC/DDNID/NCBDDD/DHDD) <[redacted]>
Sent: Thursday, February 11, 2021 11:53 AM
To: CNWG (CDC) <[redacted]>
Subject: Nurses needed

CDC Nurses needed for 30–90 day detail for COVID-19 Vaccine Safety Monitoring, beginning now

CDC's Immunization Safety Office needs nurses for a COVID-19 vaccine safety detail, anticipated for the months of February through June 2021, and possibly longer. The detail will primarily focus on responding to public inquiries about the safety of COVID-19 vaccines, and medical abstraction on adverse events following COVID-19 vaccination. Activities include initial intake and screening of vaccine safety inquiries, responding to inquiries, triaging inquiries to office subject matter experts, record keeping, and descriptive analysis of the types of inquiries received, as well as medical abstraction of vaccine adverse event reports. Minimum requirement of 30 days, but prefer 60–90 days. Commissioned Corps nurses may be able to earn clinical hours for work on inquiries from healthcare providers. No after-hours work (e.g., no nights or weekends) will be required. Supervisory approval for Civil Service personnel is required.

Desired skills

Background in nursing and public health
Good written and oral communication skills
Basic working knowledge of Microsoft Office Suite (e.g., Word, Excel)
Knowledge of vaccines and vaccine safety helpful, but not necessary

If interested, or if you need more information, please contact Elaine Miller ([redacted]) or John Su ([redacted])

From: "Griffis, Kevin (CDC/OD/OADC)" <[redacted]>
To: "Walensky, Rochelle (CDC/OD)" <[redacted]>
Subject: Fwd: Next steps for rollout?
Date: Thu, 12 Jan 2023 12:24:59 +0000
Importance: Normal
Attachments: Communications_Plan_-_Signal_KJ_(SC_535pm)_KJ_WH.docx
Inline-Images: image001.png

Get Outlook for iOS

From: Jones, Kamara (HHS/ASPA) <[redacted]>
Sent: Wednesday, January 11, 2023 8:35:21 PM
To: Berger, Sherri (CDC/OD/OCS) <[redacted]>; Cha, Stephen (HHS/IOS) <[redacted]>
Cc: Goldstein, Robert (CDC/OD/OCS) <[redacted]>; Griffis, Kevin (CDC/OD/OADC) <[redacted]>
Subject: RE: Next steps for rollout?

CDC,

See attached. Edits reflected from the WH. They don't want to see this document again. They do want to see a reactive and a list of all the reporters we plan to brief. I think their best edit is their comment about making the point that we've been using surveillance systems for years for vaccines unrelated to COVID and other medical countermeasures unrelated to COVID. Some of their other edits are overkill. Kevin, I'll call you tomorrow about the SME issue.

Best,

Kamara Jones
Acting Assistant Secretary for Public Affairs
[redacted]

From: Berger, Sherri (CDC/OD/OCS) <[redacted]>
Sent: Wednesday, January 11, 2023 9:06 AM
To: Jones, Kamara (HHS/ASPA) <[redacted]>; Cha, Stephen (HHS/IOS) <[redacted]>
Cc: Goldstein, Robert (CDC/OD/OCS) <[redacted]>; Griffis, Kevin (CDC/OD/OADC) <[redacted]>; Tierney, Julia (FDA/OC) <[redacted]>; Jefferson, Erica <[redacted]>
Subject: Next steps for rollout?

Good morning, we have not received any edits from FDA on this (added here in case they are coming). Will you be adding this to the draft rollout plan this morning and handling review and transmittal to CRT? Thank you, Sherri

Sherri A. Berger, MSPH

Chief of Staff
Centers for Disease Control and Prevention
[redacted]

From: Goldstein, Robert (CDC/OD/OCS) <[redacted]>
Sent: Tuesday, January 10, 2023 7:28 PM
To: Tierney, Julia (FDA/OC) <[redacted]>; Jefferson, Erica (FDA/OC) <[redacted]>
Cc: Berger, Sherri (CDC/OD/OCS) <[redacted]>; Griffis, Kevin (CDC/OD/OADC) <[redacted]>
Subject: Draft Statement, 7:30p

Julie and Erica,

Attached see a revised version of the statement reflecting tonight's conversation. Julie, I left your comments about waiting for Pfizer approval and responded to one when you review.

Rochelle has not yet reviewed, but will do so tonight.

-Robbie

POTENTIAL VSD SAFETY SIGNAL, ISCHEMIC STROKE IN 65+ POPULATIONS OVERVIEW INFORMATION

- **Communication Point of Contact:** Kamara Jones (HHS ASPA), Kevin Griffis (CDC), Erica Jefferson (FDA)

BOTTOM LINE UP FRONT (BLUF)

Following the availability and use of the updated (bivalent) COVID-19 vaccines, a single vaccine safety monitoring system – the Vaccine Safety Datalink – detected a preliminary ~~statistical~~ signal for ischemic stroke in people ages 65 years and older who received the updated Pfizer-BioNTech COVID-19 Vaccine, B~~b~~ivalent ~~mRNA vaccine~~. Other safety monitoring systems have not shown a similar signal to date for this vaccine. Additionally, this preliminary signal has not been identified for the Moderna COVID-19 Vaccine, B~~b~~ivalent ~~mRNA vaccine~~.

CDC and FDA are informing the public of this preliminary signal in an effort to be fully transparent. Such a ~~statistical~~ signal does not definitively mean that the Pfizer-BioNTech COVID-19 V~~v~~accine, Bivalent causes stroke, as it ~~. It~~ could be due to factors other ~~factors~~ than the vaccine itself. Preliminary signals like this indicate that further investigation is necessary to determine whether the signal represents a true health risk. No other safety systems have shown a similar signal and multiple lines of evidence have not substantiated this signal.

The totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk since all of the other systems checked show no signal for risk. ~~At this point there is insufficient information to definitively conclude a health risk exists.~~ CDC and FDA continue to evaluate additional data from other vaccine safety monitoring systems. These data and additional analyses will be discussed at the upcoming January 26 meeting of the Vaccine and Related Biologic Products Advisory Committee.

No change in vaccination practice is recommended. There is overwhelming evidence of the benefits of the COVID-19 vaccines and bivalent boosters in preventing serious outcomes and deaths, especially in medically vulnerable people. We recognize these results may sound concerning, but this finding is preliminary, has not been seen in other monitoring systems, and is undergoing further rigorous assessment COVID-19 vaccination remains recommended for everyone 6 months and older. We continue to encourage all who are eligible – including older Americans – to get vaccinated against COVID-19.

Receiving any of the recommended updated vaccines is the most effective tool we have for reducing death, hospitalization, and severe disease from COVID-19. COVID-19 vaccines will continue to undergo extensive safety monitoring and we will continue to share the data publicly.

TICK TOCK

Date /Time	Activity /Product
Monday, January 9	CDC's VaST (ACIP vaccine safety sub-working group) meets

Commented [JK(1]: This is just a summary of what this is. The external materials are below.
Jones, Kamara (HHS/ASPA)
2023-01-11 14:56:00

Commented [CS(2]: Can we replace this sentence w other language from below? (not new words): "No other safety systems have shown a similar signal and multiple lines of evidence have not substantiated this signal. The totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk since all of the other systems checked show no signal for risk." And lead the next paragraph with: "No change in vaccination practice is recommended." (also language from below)
Stephen Cha
2023-01-11 17:10:00

Commented [JK(3R2]: Done.
Jones, Kamara (HHS/ASPA)
2023-01-11 18:21:00

Thursday, January 12, 19	ACIP's COVID-19 Vaccine Working Group meets
Friday, January 13	CDC and FDA post statement
Friday, January 13	Embargoed briefing (CDC- Dr. Robert Goldstein; FDA – Dr. Robert Califf or Dr. Peter Marks) with trusted reporters (e.g. Helen Branswell, Mike Stobbe, Laurie McGinley etc.)
Friday, January 13	Embargoed briefing with key vaccine experts (e.g. below) • Bill Schaffner • Patsy Stinchfield • Nancy Messonnier • Bonnie Maldonado • Michael Osterholm • Amy Pisani • Peter Hotez • Grace Lee • Walt Orenstein
Friday, January 13	Embargoed Briefing to Congressional Stakeholders Briefing with CDC and FDA SMEs to Congressional Stakeholders (Either Committees of Jurisdiction—HELP, E&C, Appropriations, Leadership OR All-Health LAs)
Friday, January 13	Outreach to state partners • Call with SHOs • Call with state vaccine safety coordinators and immunization directors • Share statement and tough Q/As
Friday, January 13	Outreach to Key Partners • ACIP liaisons • Public health partners • Vaccine partners • Pharmacy A • Clinical partners
Thursday, January 26	FDA's VRBPAC meets, presentations are posted on the web **(public)**

Commented [JK(4]: WH is adamant that this Walensky and Califf do the briefing.
Jones, Kamara (HHS/ASPA)
2023-01-11 19:54:00

Commented [JK(5]: The WH wants to see the complete list.
Jones, Kamara (HHS/ASPA)
2023-01-11 19:52:00

Commented [JK(6]: ASL is adding a section Re: Capitol Hill as we speak.

Jones, Kamara (HHS/ASPA)
2023-01-11 14:55:00

COMMUNICATIONS STRATEGY

Consistent with our commitment to transparency, CDC and FDA plan to post a statement on their websites that explains the preliminary signal and next steps. This will be supplemented with media, public health, state, and clinician outreach and will emphasize that there is no change in recommended COVID-19 vaccination practice. Outreach will include:

- Media: pre-release hold embargoed media briefing with a small group of health reporters who have to explain the preliminary signal and reinforce that the risk-benefit profile for the bivalent vaccines has not changed. Public health and states and Clinicians: share link to statement and hold as needed briefings with key state, provider groups.
- Hill outreach: CDC and FDA SMEs will brief the Hill
    - ASL is working to determine ~~, TBD on~~ whether this is an All-Health LAs briefing or just Committees of Jurisdiction, we will time our briefing to be at the same time or right before or after press briefing, prior to press statement release.

KEY MESSAGES

(We can use what's here to draft a reactive.)

- ~~Throughout the pandemic~~For years, U.S. government agencies have used several safety monitoring systems that ~~allow~~ help us to detect possible vaccine safety signals.
- Signals from these screening safety systems, used for vaccines and a wide array of other medical countermeasures, are suggestions that require investigation and confirmation from formal epidemiologic studies.
-
    - These preliminary signals could be due to other factors than the vaccine itself; further investigation can determine whether the preliminary signal represents a true health risk. The agencies work to investigate quickly to determine whether additional action is needed.
    - An important element of evaluating any ~~statistical~~ preliminary signal is whether other independent data sets confirm the finding.
    - These systems have been useful in identifying potential risks with the COVID-19 vaccines like myocarditis, seen with the mRNA vaccines and thrombosis – blood clots in the circulatory system – with thrombocytopenia syndrome, seen~~m~~ with the Janssen vaccine. In both instances, after further evaluation, we shared more information on these potential risks with the public.
- Recently, one of these vaccine safety monitoring systems – the Vaccine Safety Datalink (VSD) – detected a preliminary signal for ischemic stroke in people ages 65 and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent as a booster dose~~.~~, which triggered a process that has confirmed that there is no evidence of an association with stroke. statistical signal of stroke association.
    - CDC and FDA are working together to determine if this is a true or confirmed association.
    - To date, none of the other safety systems have shown a potential stroke signal for this vaccine.
    - This preliminary signal has not been identified for the Moderna COVID-19 Vaccine, Bivalent.
    - CDC and FDA are informing the public of this preliminary signal in an effort to be fully transparent.
- CDC is conducting an assessment to determine if the statistical signal has identified a true or confirmed association.
- CDC and FDA continue to evaluate additional data from other vaccine safety monitoring systems and will continue to update the public as we learn more.

Commented [JK(7]: From White House

But we found there was no risk?

Jones, Kamara (HHS/ASPA)
2023-01-11 19:58:00

Commented [JK(8R7]: We've deleted the words "potential risk" here.
Jones, Kamara (HHS/ASPA)
2023-01-11 19:58:00

Commented [JK(9]: From White House

What if we did one story, see how it lands, then do the reporter outreach that's broader after that story lands?
Jones, Kamara (HHS/ASPA)
2023-01-11 19:57:00

Commented [JK(10]: From the White House
Jones, Kamara (HHS/ASPA)
2023-01-11 20:00:00

Commented [JK(11]: From the White House

○Are there other examples to include that also point to false flags so people can understand the value of the signals?

Jones, Kamara (HHS/ASPA)
2023-01-11 20:02:00

Commented [JK(12]: From White House

What does this involve?

Jones, Kamara (HHS/ASPA)
2023-01-11 20:05:00

Commented [SDAE13]: What does this involve?
Salcido, Dori A. EOP/WHO
2023-01-11 18:46:00

WEB POSTING

Suggested Title:

Suggested Posting Date: Friday, January 13

Vaccine safety and transparency areis a top prioritiesy for the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). Throughout the pandemicFor years, U.S. government agencies have utilized multiple, complementary safety monitoring systems to help detect possible vaccine safety signals for vaccines and other medical countermeasures as early as possible and to facilitate further investigation, as appropriate. From time to time, these safety systems detect signals that could be due to factors other than the vaccine itself.

When one system detects a signal, the other safety monitoring systems are checked to validate whether the signal represents an actual concern with the vaccine or if it can be determined to be of no clinical relevance. In other words, signals are suggestions that require further investigation and confirmation from formal epidemiologic studies. Throughout this process, CDC, FDA and the U.S. Department of Health and Human Services have remained committed to transparency, which is why we think it's important to share information about a signal that one of our monitoring systems detected

EXPLAIN HOW SIGNALS ARE REGULARLY USED, AND CITE EXAMPLES OF HOW THERE ARE ALWAYS FALSE FLAGS.

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 regarding 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 has raised a question of whether people 65 and older who have received the Pfizer-BioNTech COVID-19 bivalent vaccine were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22-44 following vaccination.

This preliminary signal has not been identified with the Moderna COVID-19 Vaccine, Bivalent, but fewer doses of that vaccine have been administered and captured in VSD. There also may be other confounding factors contributing to the signal identified in the VSD that merit further investigation. Furthermore, i

It is important to note that to date, no other safety systems have shown a similar signal and multiple lines of evidence have not substantiated this signal:. The totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk since all of the other systems checked show no signal for risk.

- A large study of bivalent vaccines (from Pfizer-BioNTech and Moderna) using the Centers for Medicare and Medicaid Services database revealed no increased risk of ischemic stroke
- A preliminary study using the Veterans Affairs database did not indicate an increased risk of ischemic stroke following a bivalent vaccine
- Pfizer-BioNTech's global safety database has not indicated a signal for ischemic stroke with the bivalent vaccine

Commented [JK(14]: Do we want to say "seven" so folks have a denominator?
Jones, Kamara (HHS/ASPA)
2023-01-11 14:10:00

Commented [JK(15]: From White House

Please add:

Signals from these screening safety systems, used for vaccines and a wide array of other medical countermeasures, are suggestions that require further investigation and confirmation from formal epidemiologic studies.

Commented [JE16]: We can also say, "Occasionally" or "periodically"

Commented [JK(17]: Seems that "associations" and "signals" are synonyms. If so, I'd use the same word

Commented [ML18]: "potential" associations?
Lorrie Mcneil

Commented [TJ19R18]: not sure whether this qualifier is accurate since its association - defer to

Commented [MP20R18]: Agree that this sentence needs editing –tried to make it a bit narrower

Commented [JK(21]: You don't need "possible" given what follows.

Commented [JK(22]: From White House
Jones, Kamara (HHS/ASPA)

Commented [JK(23]: From White House (From Kamara: I honestly think this posting is too long but I'll

Commented [JK(24]: Can we just say "real-time"? I get the desire to be precise but no one will ding us on

Commented [JK(25]: The word trigger is triggering.
Jones, Kamara (HHS/ASPA)

Commented [JK(26]: Deletion from White House
Jones, Kamara (HHS/ASPA)

Commented [ML27]: Would not recommend using bold font here – if read quickly could be misread that

Commented [TJ28R27]: agree - think this is a remnant of a previous draft

Commented [CS(29]: We should bold this and hit this in every talking point along w no change in vax

Commented [TJ30]: Need to run by Pfizer
Tierney, Julia

Commented [JE31R30]: Seeking permission from Pfizer.

- The Vaccine Adverse Event Reporting System (VAERS) managed by CDC and FDA has not seen an increase in reporting of ischemic strokes following the bivalent vaccine
- Other countries have not observed an increased risk for ischemic stroke with bivalent vaccines
-

Although the totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk, we are committed to transparency and think it's important to share this information with the public as we have in the past when one of our surveillance systems detects a signal. ~~The totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk since all of the other systems checked show no signal for risk.~~ 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.

~~At this time, n~~**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, including receipt of a bivalent vaccine, if eligible. Staying up-to-date with vaccines is the most effective tool we have for reducing death, hospitalization, and severe disease from COVID-19, as has now been demonstrated in multiple studies conducted in the United States and other countries:

- Data have shown an updated COVID-19 vaccine reduces the risk of hospitalization from COVID-19 by nearly 3-fold compared to those who were previously vaccinated but have not yet received the updated vaccine.
- Data have shown that the updated COVID-19 vaccine also reduces the risk of death from COVID-19 by nearly 19-fold compared to those who are unvaccinated.
- Other preliminary data from outside the U.S. have demonstrated more than 80% protection against severe disease and death from the bivalent vaccine compared to those who have not received the bivalent vaccine.

Overall safety data for the bivalent COVID-19 vaccines are available here.

Once again, **no change is recommended in COVID-19 vaccination practice**, which can be found here.

TOUGH QUESTIONS AND ANSWERS

CDC: Please use the key messages above to draft a reactive. In addition to the list of reporters, this is the other item that CDC wants to see before this goes out.

TOUGH QUESTIONS AND ANSWERS

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

- Not often. Preliminary signals often emerge as we have more experience with a product and accumulate data. Signals are assessed for further evaluation.
- To date, this particular system, VSD, has identified 1 "true" signal associated with the COVID-19 vaccine (for myocarditis) - meaning a signal that is an actual health risk, albeit a relatively rare one.
    - Preliminary signals from VSD were run through an assessment, including comparing findings to other vaccine safety monitoring systems.
- VSD uses a type of analysis that allows us to conduct near real-time safety monitoring. VSD rates are then assessed weekly. If the rate of adverse events among vaccinated people is higher than among

Commented [TJ32]: Think this should be "bivalent boosters" since uk had different composition
Tierney, Julia
2023-01-10 08:50:00

Commented [CDC33R32]: Leaving this as Julie states, but everywhere else it says bivalent vaccines. Not sure I understand why we can't say vaccines here.
CDC User
2023-01-10 18:04:00

Commented [TJ34R32]: ok to say vaccines. It had been changed to "the bivalent booster" so needed to be changed to reflect different composition in UK
Julie Tierney
2023-01-10 22:47:00

Commented [JK(35]: I moved the transparency line down and added some language from the WH. Feel free to move it back up. Felt like it flowed better here. If you do, the paragraph would look like this.

When one system detects a signal, the other safety monitoring systems are checked to validate whether the signal represents an actual concern with the vaccine or if it can be determined to be of no clinical relevance. **As part of this process, CDC, FDA and the U.S. Department of Health and Human Services have remained committed to transparency, which is why we regularly share information about signals our monitoring systems detected**

Jones, Kamara (HHS/ASPA)
2023-01-11 20:24:00

Commented [CS(36]: We should bold this and hit this in every talking point along w no change in vax practice recommended. That should end every sentence we say on this.
Stephen Cha
2023-01-11 17:17:00

Commented [ML37]: 6 months or 6 years? Should make clear.
Lorrie Mcneil
2023-01-10 21:03:00

the comparison group, it triggers a notice for further investigation into whether the vaccine may be associated with an adverse event. All potential signals are further analyzed to verify the signal and quantify if a true health risk exists.

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

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

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

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

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

- Scientists are working tirelessly to determine if this is a true association.
- Our analyses become more stable with more data. We're hopeful to have a clearer picture from the assessment and more data in the coming weeks.
- In January, CDC and FDA will share updates to the assessment in planned upcoming vaccine safety meetings, including with ACIP's COVID-19 Vaccine Working Group and FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). CDC and FDA have already briefed the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST).

When did CDC first notice this signal?

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

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

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

Commented [JE38]: But it's not perfect and we should include its limitations.
Jefferson, Erica [2]
2023-01-11 15:25:00

Commented [CS(39R38]: Agree—should we clarify that the comparison group is also people who got the vax? CDC should correct, but something like: "VSD compares people who got the vaccine [11-25] days after getting the vaccine to people who got the vaccine [25-40] days after getting the vaccine. More early events as compared to fewer later events is a potential signal for excess events that should be validated in other systems."
Stephen Cha
2023-01-11 17:18:00

Commented [JE40]: We actually haven't. This is an expectation that CDC is now setting. For the J&J and mRNA signals, we did have more time to work through those before communicating to the public.
Jefferson, Erica [2]
2023-01-11 15:26:00

Commented [CS(41R40]: I hear the point. How should we answer this question then? (we are undoubtedly getting it…)
Stephen Cha
2023-01-11 17:35:00

Commented [AS42]: This is a pretty broad statement I don't think we should make it.
Anderson, Steven
2023-01-11 13:05:00

Commented [GR(43]: This could use FDA input on their prospective epidemiologic studies. We need to know which systems they are using, the timeline for their analysis, and the expected outcomes.
Goldstein, Robert H (CDC)
2023-01-10 12:52:00

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

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

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

- SEE ANSWER ABOVE.
- CDC hopes to assess all factors listed above by mid-February 2023.
- Signal assessment analyses and supplementary analyses in the data system where the signal was detected are underway. The timeline for these assessments will take weeks. The timeline for formal epidemiologic studies in other data systems will take months.
- Additional expected data will make the assessment stronger. CDC will continue to update on its assessment of whether a causal association between bivalent booster vaccine and ischemic stroke exists.

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

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

Has stroke and COVID-19 vaccinations been studied previously?

Commented [GR(44]: Can FDA add in here what they have done to evaluate for stroke? They have this as a pre-specified endpoint.
Goldstein, Robert H (CDC)
2023-01-10 12:57:00

- Yes. CDC performs safety monitoring of vaccines to assess and identify serious outcomes. Clinical trials for the bivalent booster did not show serious safety concerns. An interim analysis of 6.2 million

people (all ages) who received the primary series of the vaccine found no significant associations between vaccination with mRNA COVID-19 vaccines and selected serious health outcomes, including stroke, 1 to 21 days after vaccination. CDC typically conducts retrospective analyses for specific adverse outcomes if signals are detected through surveillance systems.

- FDA has routinely evaluated 'Hemorrhagic' and 'Non-hemorrhagic' stroke 1-28 days following vaccination as part of its COVID-19 Vaccine Safety Surveillance efforts. This monitoring evaluates 16 or more outcomes for adult patients who received the primary series, monovalent boosters and bivalent boosters. FDA has found no signals for stroke in any of our analyses.

Should people with a family history of stroke be concerned?

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

What is CDC doing about this?

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

What is FDA doing about this?

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

Commented [GR(45]: We need an answer from FDA here.
Goldstein, Robert H (CDC)
2023-01-10 13:00:00

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

Commented [GK(46]: CDC developing answer
Griffis, Kevin C (CDC)
2023-01-10 16:46:00

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

- The Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office, integrated health care organizations, and networks across the U.S. The VSD started in 1990 and continues today to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization. As of September 28, 2022, there are 13 VSD sites that provide clinical, methodological, and data expertise; 11 are data providing sites.
- The VSD uses electronic health data from participating sites to monitor and assess the safety of vaccines. This includes information on vaccines: the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day. The VSD also uses information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays.

- The VSD conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). When there are new vaccines that have been recommended for use in the United States or if there are changes in how a vaccine is recommended, the VSD will monitor the safety of these vaccines.
- The VSD has a long history of monitoring and evaluating the safety of vaccines. Since 1990, investigators from the VSD have published many studies to address vaccine safety concerns.
- VSD does ongoing analyses of electronic health record (EHR) data from several integrated healthcare organizations to detect associations for pre-specified clinical outcomes.
- VSD uses validated methods to conduct near real-time sequential safety monitoring called Rapid Cycle Analysis (RCA). Findings of associations in RCA are considered statistical signals; further refinement of the analysis needs to occur once a statistical signal is identified to verify the signal and quantify the risk if a true signal exists.
- The following steps are taken to assess a signal identified in RCA:
    - Check data quality, especially of diagnostic codes
    - Review charts to confirm or exclude cases as true incident cases; 'quick' chart reviews (i.e., incident physician diagnosed case with symptom onset in risk window) can generally be performed within several days
    - Check inputs, 'background incidences' (i.e., temporal trends)
    - Check whether comparison groups are defined appropriately
    - Check other analyses that use a different control group (e.g., concurrent vs. historical) or compare with a different vaccine
    - Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window
    - Evaluate the signal further in other data systems (i.e., in CMS, VA). Other signal detection and assessment systems exist, such as CDC's v-safe (signal detection only), the FDA's CMS collaboration and BEST, VA near real-time sequential monitoring, and DoD's DMSS.
    - Conduct a definitive study using appropriate epidemiologic study designs (e.g., logistic regression analysis)

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

- CDC evaluates the benefits of COVID-19 vaccines through multiple methodologies, employing various methods and using information collected through different surveillance platforms, electronic health records, or prospective studies. In addition, COVID-19 vaccines continue to undergo the most comprehensive and intense safety monitoring in U.S. history. These data are presented and discussed through ongoing benefit-risk analyses to both the ACIP COVID-19 vaccines Work Group and the public ACIP meetings. These analyses have continued to demonstrate that COVID-19 vaccination is the single best way to protect people from serious COVID-19 illness and the benefits continue to outweigh the risks. As with all emerging data for the vaccines, CDC and ACIP will continue to evaluate the balance of benefits and risks for COVID-19 vaccines.

Commented [GR(47]: That show what? I assume you mean VE against severe disease, hospitalization, and death, but we need to say the outcomes that we consider to be benefits here - which may include protection against severe complications from COVID, like stroke, MI, post-COVID Conditions, etc.
Goldstein, Robert H (CDC)
2023-01-10 13:02:00

What is an ischemic stroke?

- Most strokes are ischemic strokes. An ischemic stroke occurs when blood clots or other particles block the blood vessels to the brain. Fatty deposits called plaque can also cause blockages by building up in the blood vessels. During a stroke, parts of the brain become damaged or die. A stroke can cause lasting brain damage, long-term disability, or even death. Some health conditions and lifestyle habits can increase your risk for stroke.
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From: "Wallender, Erika K. (CDC/DDPHSIS/CGH/DPDM)" <[redacted]>
To: "Walensky, Rochelle (CDC/OD)" <[redacted]>
Subject: FYI: F/u on COVID-19 + flu vaccine on stroke
Date: Thu, 25 May 2023 15:54:33 +0000
Importance: Normal
Inline-Images: image001.jpg

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, May 24, 2023 12:18 PM
To: Wallender, Erika K. (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: RE: F/u on COVID-19 + flu vaccine on stroke for Dr. Walensky

Erika,

There are no new data or no new data that would substantially change the basic findings that were presented at ACIP in April mRNA COVID-19 bivalent booster vaccine safety update (cdc.gov). We are continuing to monitor in VSD and assess the signal but most of the assessment we can do has been completed. The key point from VSD surveillance is that the data are insufficient to conclude that that a safety problem exists for ischemic stroke following the Pfizer bivalent vaccine or when the Pfizer bivalent vaccine is simultaneously administered with high-dose or adjuvanted flu vaccines in people ages 65 years and older, and that there may be other factors besides vaccination (e.g., unmeasured confounding) that contributed to the initial findings. FDA has a self-controlled analysis in the CMS data that's in progress and they should have results prior to fall covid and flu vaccination programs. I'm not sure the Epic analysis really changes anything. Happy to discuss if you want.

Tom

Tom Shimabukuro, MD, MPH, MBA
Captain, U.S. Public Health Service
Director
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)
1600 Clifton Road, [redacted] Atlanta, GA 30329
[redacted]

From: Wallender, Erika K. (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Sent: Wednesday, May 24, 2023 11:43 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Subject: F/u on COVID-19 + flu vaccine on stroke for Dr. Walensky

Dear Tom,

I hope this email finds you well. I'm on detail as a science advisor to Dr. Walensky (since Robbie Goldstein's departure).

With the below analysis, it reopened questions about stroke risk in the combo of flu and COVID-19 vaccine. I recall from ACIP that the RR had lost statistical significance but the point estimate was still a bit up around 1.6. Has there been any movement on the studies you mentioned for the other surveillance systems for the coadministration issue? What are your current thoughts on the risk?

Happy to chat briefly if you have time to make sure I understand the nuances.

Thanks so much,
Erika

Erika Wallender, MD, MPH (she/her)
LCDR, U.S. Public Health Service
Senior Science Advisor to the CDC Office of the Director
U.S. Centers for Disease Control and Prevention
[redacted]

From: POLITICO Pro Health Care <[redacted]>
Sent: Wednesday, May 24, 2023 10:02 AM
To: Berger, Sherri (CDC/OD) <[redacted]>
Subject: Pfizer's Covid vaccine does not pose a stroke risk, records review finds

[redacted]

Pfizer's Covid vaccine does not pose a stroke risk, records review finds

BY **BEN LEONARD** | 05/24/2023 10:00 AM EDT

The risk of stroke from the bivalent Pfizer-BioNTech Covid-19 vaccine is lower than that from flu shots, according to millions of patient histories analyzed by the research arm of the electronic health records firm Epic.

Patients getting the monovalent or bivalent vaccines were 9 percent less likely to have a stroke in the 30 days post-vaccination than patients getting the flu vaccine, according to Epic Research data. Patients with a Covid-19 infection were significantly more likely to suffer a stroke during the same period than those who got either Covid vaccine at over 1 percent versus about 0.6 percent.

The Epic data also indicates that people who received the vaccine were not likely to suffer blood clots or other cardiovascular conditions like venous thrombosis and thrombocytopenia.

"These findings align with CDC and FDA reports that these conditions after COVID-19 vaccination remain rare and suggest that bivalent and monovalent COVID-19 vaccinations have similar rates of these diagnoses after vaccination," Epic said in a release.

Why it matters: The CDC and FDA issued a statement in January saying that their surveillance system showed a possible link between the bivalent Pfizer-BioNTech Covid-19 vaccine and strokes in people 65 and over.

At the same time, the agencies said that it was "very unlikely" that the signal the system flagged represented a true clinical risk.

When the agencies issued the statement, Pfizer and BioNTech said there was "no evidence to conclude that ischemic stroke is associated with the use of the companies' COVID-19 vaccines."

The Epic data appears to buttress that assessment, though it didn't break down results by age.

View this article online.

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]>
To: "Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP)" <[redacted]>
Cc: "Fox, Kimberley (CDC/DDID/NCIRD/DBD)" <[redacted]>, "Hicks, Lauri (CDC/DDID/NCEZID/DHQP)" <[redacted]>, "Patel, Anita (CDC/DDID/NCIRD/OD)" <[redacted]>, "Joshi, Namita (CDC/DDPHSIS/CGH/DPDM)" <[redacted]>
Subject: RE: Myocarditis update in director's bullets
Date: Thu, 3 Jun 2021 15:26:52 +0000
Importance: Normal

The VSD sequential monitoring uses a test statistic like a p-value or a log likelihood ratio. We basically set the critical value in advance and if the test statistic exceeds (or falls below) the critical value on a sequential analysis then we have a statistical signal, which may or may not represent a true risk (depending on the results of signal assessment).

In VAERS, the formal statistical testing is done via empirical Bayesian data mining. EB data mining alerts happen when vaccine-AE pairs are reported at least twice as frequently as expected compared to all other vaccine-AE pairs in the VAERS database (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05 >2]).

This stuff is kind of like a foreign language to me. I get it conceptually, but I can't explain the mathematical details.

From: Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP) <[redacted]>
Sent: Thursday, June 3, 2021 10:54 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Fox, Kimberley (CDC/DDID/NCIRD/DBD) <[redacted]>; Hicks, Lauri (CDC/DDID/NCEZID/DHQP) <[redacted]>; Patel, Anita (CDC/DDID/NCIRD/OD) <[redacted]>; Joshi, Namita (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: RE: Myocarditis update in director's bullets

Is there a quantitative way you can define a VSD statistically significant signal for me. Director wants something more meaty to understand what that means.

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, June 3, 2021 10:48 AM
To: Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP) <[redacted]>
Cc: Fox, Kimberley (CDC/DDID/NCIRD/DBD) <[redacted]>; Hicks, Lauri (CDC/DDID/NCEZID/DHQP) <[redacted]>; Patel, Anita (CDC/DDID/NCIRD/OD) <[redacted]>; Joshi, Namita (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: RE: Myocarditis update in director's bullets

That O v. E is descriptive, so no hard statistical threshold, but the fact that O exceeds E in those 2 age groups and is creeping up in the 25–39 y/o is telling. There is early VSD data that is a bit concerning, but no statistical signals yet.

From: Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP) <[redacted]>
Sent: Thursday, June 3, 2021 10:35 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Fox, Kimberley (CDC/DDID/NCIRD/DBD) <[redacted]>; Hicks, Lauri (CDC/DDID/NCEZID/DHQP) <[redacted]>; Patel, Anita (CDC/DDID/NCIRD/OD) <[redacted]>; Joshi, Namita (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: RE: Myocarditis update in director's bullets

Is there a clear threshold for significance by # of cases?

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Sent: Thursday, June 3, 2021 10:27 AM
To: Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP) <[redacted]>
Cc: Fox, Kimberley (CDC/DDID/NCIRD/DBD) <[redacted]>; Hicks, Lauri (CDC/DDID/NCEZID/DHQP) <[redacted]>; Patel, Anita (CDC/DDID/NCIRD/OD) <[redacted]>; Joshi, Namita (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: RE: Myocarditis update in director's bullets

Attached are slides with the main highlights. Slides 3 and 4 have the main findings and the outcomes.

From: Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP) <[redacted]>
Sent: Wednesday, June 2, 2021 5:19 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Fox, Kimberley (CDC/DDID/NCIRD/DBD) <[redacted]>; Hicks, Lauri (CDC/DDID/NCEZID/DHQP) <[redacted]>; Patel, Anita (CDC/DDID/NCIRD/OD) <[redacted]>; Joshi, Namita (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: RE: Myocarditis update in director's bullets

+ Lauri

From: Daskalakis, Demetre (CDC/DDID/NCHHSTP/DHP)
Sent: Wednesday, June 2, 2021 5:16 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>
Cc: Fox, Kimberley (CDC/DDID/NCIRD/DBD) <[redacted]>; Patel, Anita (CDC/DDID/NCIRD/OD) <[redacted]>; Joshi, Namita (CDC/DDPHSIS/CGH/DPDM) <[redacted]>
Subject: Myocarditis update in director's bullets

Could we add a myocarditis update in the director's bullets for Friday morning? She is interested in having some update of where we are on the statistical significance side of the signal.

Demetre

Demetre C. Daskalakis, M.D., M.P.H.
Deputy Incident Manager and Senior Lead, Equity in COVID Data and Engagement

Director, Division of HIV/AIDS Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD & TB Prevention
Centers for Disease Control and Prevention
1600 Clifton Road, NE [redacted]
Atlanta, GA 30329-4027
[redacted]
Pronouns: He/His/Him

From: "Su, John (CDC/NCEZID/DHQP/ISO)" <[redacted]>
To: "Nair, Narayan (FDA/CBER)" <[redacted]>, "Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO)" <[redacted]>
Cc: "Duffy, Jonathan M. (CDC/NCEZID/DHQP/ISO)" <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper
Date: Fri, 19 Jan 2024 13:56:03 +0000
Importance: Normal
Attachments: tinnitus_after_COVID_vaccination_17_Jan_2024.docx

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You're awesome --- thanks! Please see enclosed.

- John

From: Nair, Narayan <[redacted]>
Sent: Friday, January 19, 2024 8:45 AM
To: Su, John (CDC/NCEZID/DHQP/ISO) <[redacted]>; Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO) <[redacted]>
Cc: Duffy, Jonathan M. (CDC/NCEZID/DHQP/ISO) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Sure, I think we can do that. Do you have the latest draft?

Narayan

From: Su, John (CDC/NCEZID/DHQP/ISO) <[redacted]>
Sent: Thursday, January 18, 2024 3:32 PM
To: Nair, Narayan <[redacted]>; Shimabukuro, Tom (CDC) <[redacted]>
Cc: Duffy, Jonathan M (CDC) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Narayan,

Adding Jon Duffy to this thread, for his awareness.

Also, while I'd indicated Jan 31 as a target date, there's interest in moving this paper forward with haste. Would the end of next week (Jan 26) be doable? Any priority you could put on this ask would be greatly appreciated. Thanks!

- John

From: Nair, Narayan <[redacted]>
Sent: Wednesday, January 17, 2024 11:27 PM
To: Su, John (CDC/NCEZID/DHQP/ISO) <[redacted]>; Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Thanks John. Good to hear from you. We will try and get back to you by the due date.

Narayan

From: Su, John (CDC/NCEZID/DHQP/ISO) <[redacted]>
Sent: Wednesday, January 17, 2024 6:09 PM
To: Nair, Narayan <[redacted]>; Shimabukuro, Tom (CDC) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

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Hi Narayan,

I hope you're keeping warm! It's frosty out there. ❄

I think this paper fell off a lot of radars. We're trying to move this paper forward. I'm working on updating the most current draft with data from VAERS by dose number; I'll send later tonight under separate cover. Please amend with EB data mining language (methods, results). I don't know of a due date per se – would Jan 31 be reasonable? Of course, sooner would be greatly appreciated.

Thanks!

- John

From: Nair, Narayan <[redacted]>
Sent: Friday, December 1, 2023 11:03 AM
To: Shimabukuro, Tom (CDC/NCEZID/DHQP/ISO) <[redacted]>; Su, John (CDC/NCEZID/DHQP/ISO) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Tom and John,
This fell off my radar with competing priorities. Did you have a due date for us to provide comments/edits on this paper?

Narayan

From: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>
Sent: Friday, October 27, 2023 9:25 PM
To: Su, John (CDC) <[redacted]>; Nair, Narayan <[redacted]>; Bazel, Samaneh <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

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.

Agreed. I think we should use the FDA EB data mining and describe the limitations that might be unique to COVID-19 vaccines.

From: Su, John (CDC/NCEZID/DHQP) <[redacted]>
Sent: Friday, October 27, 2023 3:18 PM
To: Nair, Narayan (FDA/CBER) <[redacted]>; Bazel, Samaneh (FDA/CBER) <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi Narayan,

Thanks for the feedback! I'll discuss with Katherine and company. My inclination is to either use existing EB data mining data from FDA, or not – novel methodologies make me uncomfortable if they haven't been vetted or otherwise validated.

- John

From: Nair, Narayan <[redacted]>
Sent: Friday, October 27, 2023 3:04 PM
To: Su, John (CDC/NCEZID/DHQP) <[redacted]>; Bazel, Samaneh (FDA/CBER) <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi John,
She does bring up a good point. As you know, data mining has all the limitations of passive surveillance as well as others. However, during the COVID vaccine era there is an additional limitation. Since most reports received involve COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID-19 vaccine reports contributing substantially to the comparator group. This would could occur in the setting if there was some type of class-effect (e.g., if both mRNA COVID-19 vaccines are associated with the same adverse event).
We were aware of this limitation before and during the pandemic. There are many data mining tools and there was some discussion about utilizing a novel tool to adjust for this. However, we thought it would be problematic to use a brand new, possibly unvalidated tool in the context of an EUA. We ended up using the same EBGM data mining we use for all vaccines and has a long history of use rather than take an experimental approach. As new non-COVID vaccine reports are added we think this limitation will be mitigated to some degree.
As far as the paper goes there are several options to address this:

- We could report our data mining findings and just acknowledge this as a limitation (this is what we have done in other papers)
- We could not include any data mining findings
- You could develop another tool that would compensate for the greater number of COVID vaccine reports. I am not sure how to do this but you would need a statistician with DM experience. This would be beyond our capabilities at FDA.

Narayan

From: Su, John (CDC/NCEZID/DHQP) <[redacted]>
Sent: Thursday, October 26, 2023 9:32 AM
To: Nair, Narayan <[redacted]>; Bazel, Samaneh <[redacted]>
Cc: Shimabukuro, Tom (CDC) <[redacted]>
Subject: [EXTERNAL] RE: FDA coauthor for tinnitus paper

Hi folks,

Please see below email (it was late, and I got a bit confused). I know EB data mining looks at vaccine-event pairs between the vaccine of interest and an adverse event, and compares against all other vaccines in the VAERS database and the same adverse event, to see if a disproportionality beyond an established threshold is present. However, I don't know the methods well enough to address Judy's comments. How do the methods FDA uses address these points? Thanks!

- John

From: Su, John (CDC/NCEZID/DHQP)
Sent: Thursday, October 26, 2023 9:10 AM
To: Maro, Judy <[redacted]>; Yih, Katherine <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>; Nair, Narayan (FDA/CBER) <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

Sorry, I've been juggling a bit and got my coauthors crossed. FDA performs EB data mining for VAERS, and throughout postauthorization safety monitoring for COVID-19 vaccines, has shared with CDC the results. While I'm familiar conceptually with EB data mining, I'll need to discuss with FDA to better understand how the methods they use address the concerns you've raised. Thanks!

- John

From: Su, John (CDC/NCEZID/DHQP)
Sent: Thursday, October 26, 2023 8:59 AM
To: Maro, Judy <[redacted]>; Yih, Katherine <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>; Nair, Narayan (FDA/CBER) <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

Thanks for the feedback. CCing Narayan for awareness. We'll get back to you.

- John

From: Maro, Judy <[redacted]>
Sent: Wednesday, October 25, 2023 11:43 PM
To: Su, John (CDC/NCEZID/DHQP) <[redacted]>; Yih, Katherine <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Hi John –

To do a disproportionality analysis of any kind (EBGM is just one version but they are statistically similar), you need 4 quantities or a typical 2 x 2 contingency table.

So, one would need

Exposure Yes, Disease yes – any specific vaccine + tinnitus reports

Exposure Yes, Disease no – any specific vaccine + non-tinnitus reports

Exposure no, Disease yes – all exposures but for the specific vaccine. In the covid era, this means basically COVID + tinnitus

Exposure no, Disease no – all exposures but for the specific vaccine + non-tinnitus reports. Again, in this era, that means COVID + non-tinnitus

So, for the 17,859, it's important to know how these are spread among what vaccines and to choose the vaccines that you want to examine for a signal. It will be mostly useless to try to make statements about the COVID vaccines because the database will have so many COVID reports that you can't create a comparator. You also need to know what the capture is for the period you are examining of the non-tinnitus reports.

Best
Judy

From: Su, John (CDC/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, October 25, 2023 11:15 PM
To: Maro, Judy <[redacted]>; Yih, Katherine <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

Glad you're able to help. We're hoping for an analysis of reports to VAERS with the MedDRA Preferred Term (PT) "tinnitus" received during Dec 14, 2020 through May 4, 2023. Specifically, if vaccine-pairs for this PT exceed thresholds for statistical significance.

If having counts or a line list would help, we can put you in touch with our senior data manager. We identified 17,859 reports during the analytic period. I can share the latest draft of the manuscript (confidentially, of course) if that would help.

Please let me know if you have any other questions. Thanks!

- John

From: Maro, Judy <[redacted]>
Sent: Wednesday, October 25, 2023 10:19 PM
To: Su, John (CDC/NCEZID/DHQP) <[redacted]>; Yih, Katherine <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Folks,
I'm fairly familiar with EBGM – do you have the numbers that were used?

On including the FDA, I have no objections but want to note that it will involve another clearance chain which will add probably a good amount of time into the timeline.

Happy to help in any way I can,

Best
Judy

From: Su, John (CDC/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, October 25, 2023 11:15 AM
To: Yih, Katherine <[redacted]>

Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>; Maro, Judy <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Sounds great – thanks!

- John

From: Yih, Katherine <[redacted]>
Sent: Wednesday, October 25, 2023 11:11 AM
To: Su, John (CDC/NCEZID/DHQP) <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>; Maro, Judy <[redacted]>
Subject: RE: FDA coauthor for tinnitus paper

Hi John,
If you all think it's important to include this analysis, then it's fine with me to include a couple of co-authors from FDA. (I'm expecting some or all of the VSD sites to propose a co-author, too, so wouldn't want the number of co-authors to get *too* high (for logistical reasons).)
Thanks for checking. Cc-ing Judy Maro, in case she has comments about this plan.
Katherine

From: Su, John (CDC/NCEZID/DHQP) <[redacted]>
Sent: Wednesday, October 25, 2023 10:30 AM
To: Yih, Katherine <[redacted]>
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) <[redacted]>; Moro, Pedro (CDC/NCEZID/DHQP) <[redacted]>
Subject: FDA coauthor for tinnitus paper

Hi Katherine,

We appreciate your continued patience as we work on this paper! Desire has been expressed to include Empirical Bayesian data mining of the VAERS data, which is performed by our colleagues at FDA. If we include those data, we'll need to include coauthors from FDA. Are you okay with this approach? If so, I'll reach out and get them involved. Thanks!

- John

disclosing it.

SMR1.Point32Health.org made the following annotations

SMR1.Point32Health.org made the following annotations

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Investigating Tinnitus after COVID-19 Vaccination:

Findings from the Vaccine Adverse Events Reporting System and the Vaccine Safety Datalink

By Katherine Yih, Jonathan Duffy, Judy Maro, Eric Weintraub, John Su, Pedro Moro, Paige Marquez, Tom Shimabukuro [if many sites opt for a co-author, we might use alphabetical order for all except first and last]

~~October 11, 2023~~January 17, 2024

~~Introduction~~INTRODUCTION

~~Tinnitus after COVID-19 vaccination has emerged as an object of study in the international otolaryngology community.~~ Tinnitus is the perception of ringing or other noise in the ears ~~a condition in which a person perceives a constant sound~~ that does not have an external source. It is a common problem, especially in older adults, and its causes are not fully understood. ~~Tinnitus has been associated with various risk factors, such as exposure to loud noise, but the exact causal mechanisms are unknown. Tinnitus has been reported as an adverse event following COVID-19 vaccines~~Concerns have been raised about a possible association between COVID-19 vaccination and tinnitus.

A clinical trial of the Janssen adenovirus-vectored COVID-19 vaccine, with approximately 22,000 patients in each arm, treatment and placebo, found 6 tinnitus cases within 28 days of vaccination in the vaccine group versus 0 in the placebo group [1]. Although a causal relationship with the Janssen COVID-19 vaccine could not be determined ~~[1]~~, tinnitus is listed as an ~~side effect~~ adverse reaction in the Janssen Emergency Use Authorization fact sheet for ~~recipients and caregivers~~ vaccination providers [~~2~~1].

Tinnitus after COVID-19 vaccination has ~~emerged as an object of study in the international otolaryngology community~~ been the subject of dozens of peer-reviewed publications. Many of the publications ~~about tinnitus following COVID-19 vaccination~~ have been either single case reports [3-7], sometimes addressing a patient's response to a specific treatment [8, 9], or small case series or other small studies [10-15], which limit the ability to assess risk or evaluate causation. The mechanism by

Commented [DJM(1]: I think the paper needs a more generic opening sentence that starts by defining what tinnitus is.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:13:00

Commented [DJM(2]: I would reference the healthcare provider fact sheet instead because it does not use the term "side effect" which is not as precise as using "adverse event." Would restate this to more closely align with the HCP factsheet, "The following adverse reactions have been identified during post-authorization use of the Janssen COVID-19 Vaccine. "
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:17:00

Commented [DJM(3]: Is this too specific? It's of interest to regulators, public health, etc. Maybe delete this sentence and replace by saying something like "this issue has been the subject of several peer reviewed publications."
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:22:00

which tinnitus might result from vaccination is unknown, but suggested modes of action include an immunological pathophysiology [4]; a hypersensitivity reaction with an abnormal autoimmune response or a vasculitic event [10]; damage to hearing organs via thrombotic complications (after receipt of adenovirus-vectored vaccines) [12]; and multisystem inflammation and organ dysfunction [5].

One large observational epidemiologic study using electronic health record data on more than 2.5 million mRNA COVID-19 vaccine recipients found that only 0.038% (95% CI: 0.036%-0.041%) of patients had a new diagnosis of tinnitus within 21 days of Dose 1 receipt and that there was a higher risk of a new tinnitus diagnosis after influenza, Tdap, and pneumococcal vaccinations than after Dose 1 of the COVID-19 vaccine. However, the risk after non-COVID vaccines was evaluated during 2019, and secular trends in healthcare utilization between 2019 and the years of the COVID-19 pandemic may have contributed to the observed difference. These investigators also found a lower risk of a new tinnitus diagnosis after Dose 2 of COVID-19 vaccine than after Dose 1 (RR: 0.80, 95% CI: 0.71-0.91) [16].

Tinnitus has also been documented in patients infected with SARS-CoV-2, and commonly in those with long COVID [17, 18]. One small study of audiological and vestibular symptoms after SARS-CoV-2 infection and COVID-19 vaccination in children concluded that those infected with SARS-CoV-2 had a higher prevalence of tinnitus than the vaccinated [13].

To investigate the possibility of an association between COVID-19 vaccination and tinnitus, we first present the results of a review of reports of tinnitus following COVID-19 vaccines submitted to the Vaccine Adverse Event Reporting System (VAERS) [19]. We then summarize results from the Vaccine Safety Datalink (VSD) of tree-based data-mining with respect to tinnitus, present results of ad hoc temporal scan analyses of tinnitus after COVID-19 and influenza vaccination, and compare tinnitus incidences after COVID-19 vaccines and influenza vaccines.

Commented [YK4]: In this paragraph, we could state which vaccines are included. If it will be only Pfizer, Moderna, and Janssen for both VAERS and VSD, we can state that and say there weren't enough doses of Novavax (or VAERS reports after Novavax) to analyze usefully.
Yih, Katherine
2023-10-11 16:07:00

~~Methods~~METHODS

Vaccine Adverse Event Reporting System (VAERS)

~~a. VAERS reports~~

VAERS is the U.S. passive vaccine safety monitoring system co-managed by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) and is used to detect rare adverse events or changes in adverse event reporting patterns that might suggest a potential safety concern [19]. We identified reports of tinnitus following COVID-19 vaccination received by VAERS during December 14, 2020–May 4, 2023, by searching for reports assigned the Medical Dictionary for Regulatory Activities [20] Preferred Term "tinnitus." Reports were analyzed similarly to previous VAERS analyses of COVID-19 vaccine safety data [21]. Reporting rates for monovalent primary series COVID-19 vaccination (whether with Pfizer-BioNTech mRNA vaccine, Moderna mRNA vaccine, or Janssen vaccine) and for bivalent mRNA COVID-19 vaccination were calculated using doses administered as the denominator [22].

a. Data mining

We used Empirical Bayesian data mining techniques [reference] to identify MedDRA preferred terms that occurred more often than expected compared to all other vaccines in VAERS. Data mining analysis calculates the Empirical Bayes Geometric Mean and a 90% confidence interval (EB05, EB95). An EB05 ≥ 2 indicates a vaccine-event pair occurs at least twice as often as expected, which is used as a threshold for further evaluation of an adverse event [reference].

Vaccine Safety Datalink (VSD)

VSD is a collaboration between the Centers for Disease Control and Prevention (CDC) and XX health care organizations; it was established in 1990 to conduct vaccine safety research and surveillance [McNeil

Commented [DJM(5]: What about data mining? I think the paper should state what the empirical bayesian data mining results were.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:47:00

Commented [SJ(6R5]: FDA will be providing language on EB data mining and results.
Su, John (CDC/NCEZID/DHQP/ISO)
2024-01-18 08:35:00

Commented [BS7R5]: @Nair, Narayan Data mining comment added
Bazel, Samaneh
2024-01-19 11:36:00

Commented [DJM(8]: What about monovalent boosters? Is there a way to include at least dose 3?
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:46:00

Commented [SJ(9R8]: Now added as Table 2.
Su, John (CDC/NCEZID/DHQP/ISO)
2024-01-18 08:35:00

Commented [BS10]: DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. *Am Stat.* 1999; 53:177 – 190.
Bazel, Samaneh
2023-11-22 12:37:00

Commented [BS11]: Szarfman A et al. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Saf.*2002; 25(6):381 – 392.
Bazel, Samaneh
2023-11-22 12:39:00

Commented [DJM(12]: Subsection header for VSD. Can list the different VSD analyses by letter. Need at least one sentence to describe what the VSD data consists of.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:26:00

2014]. These analyses described here used data from eight participating healthcare organizations, including with data on more than 47 million people who received COVID-19 vaccines.

b.a. VSD Tree-based scan statistical analyses

Tree-based scan statistics have been used as a vaccine safety signal detection method for a number of different vaccines, including COVID-19 vaccines [23-25]. Data from the vaccinated study population's medical encounters during post-exposure follow-up are scanned to detect statistically unusual clusters of diagnoses within the ICD-10-CM "tree" of diagnoses or other hierarchical structure of diagnoses. Advantages of this approach are: (1) it is untargeted and broad—health outcomes of interest are not pre-specified; (2) in using a hierarchical structure of diagnoses, the capability exists to find signals for groups of related outcomes rather than only for specific outcomes; and (3) the method formally adjusts for the multiple evaluations entailed in scanning tens of thousands of outcomes and groups of related outcomes. The method, which we call "TreeScan" for short, after the name of the software used [26], comprises a number of different variants. Our signal detection work on COVID-19 vaccines used the tree-temporal variant, which has two additional advantages: (4) it does not require pre-specification of a risk window, rather the method incorporates a temporal scan component to detect temporal clusters of cases on any branch of the ICD-10-CM code tree within the follow-up period, and (5) this variant is self-controlled, which eliminates confounding by characteristics that do not change over the course of follow-up, e.g., sex and chronic disease status. Further, we used the conditional version of the tree-temporal variant, conditioning not only on the number of events observed in each node of the tree during the whole follow-up period but also on the total number of events occurring during the scanning risk window across the entire tree. This model then offers an additional advantage (6) in adjusting for the type of temporal confounding that can occur when there are differences in the volume of general

health care-seeking behavior over the course of follow-up, e.g., more follow-up visits to specialists shortly after compared with longer after vaccination.

In the COVID-19 vaccine ~~studies~~ analyses reported on here, we evaluated the Pfizer-BioNTech, Moderna, and Janssen primary series; monovalent boosters; and bivalent Pfizer-BioNTech and Moderna vaccines. Our primary analyses were restricted to incident (first-in-400-days) diagnoses in either the emergency department or inpatient setting. Outpatient settings were not included out of a concern to minimize false signals and a desire to focus on outcomes serious enough to entail an emergency department or inpatient encounter. However, in supplemental analyses of primary series and bivalent vaccination, outpatient settings were included with emergency department and inpatient settings for incident case ascertainment. Parameters for the temporal scanning component of the tree-temporal variant were set to look for temporal clusters of cases in the branches of the ICD-10-CM tree between 2 days and half the follow-up period in length and occurring anywhere during follow-up. The follow-up period after Dose 1 of the 2-dose Pfizer-BioNTech and Moderna vaccine primary series was Days 1-70, long enough to allow the possibility of signal detection after Dose 2 as well as Dose 1. Follow-up after Janssen, monovalent boosters, and bivalent Pfizer-BioNTech and Moderna vaccines was Days 1-56. The day of index vaccination (Day 0) was not included in the follow-up period in any analysis. The threshold for statistical significance was pre-specified as p=0.01. Further explanation of the method and of the parameters used in the COVID-19 vaccine studies has been published elsewhere [23-25, 27].

TreeScan software [26] was used for these analyses.

~~c.~~b. VSD ~~A~~ad hoc temporal scan analyses

To examine the possibility of a statistical association between COVID-19 vaccination and tinnitus where the cases were not strongly clustered in time and/or extended beyond the follow-up periods used in the TreeScan COVID-19 ~~studies~~analyses, we extracted data on incident (first-in-400-days) tinnitus (**H93.1***)

in any setting out to 140 days after Dose 1 of Pfizer-BioNTech, Moderna, and Janssen. In targeting this one outcome, we eliminated the simultaneous scanning of the rest of the ICD-10 code tree and gained statistical power. For comparison, we did the same for seasonal influenza vaccination. The date range for eligible doses was January 1, 2019, through August 31, 2022, although COVID-19 vaccines were not generally available until 2021; pre-pandemic time was included for influenza vaccination in order to obtain a robust sample size, considering the lower influenza vaccination rates during the pandemic. We then conducted ad hoc temporal scan analyses for each vaccine, using TreeScan software but a different statistical model than for the tree-based scan statistical analyses (see below), looking for the most likely cluster of any length between 2 and 70 days anywhere during the 140 days. For the COVID-19 vaccines, we anchored these 140-day scans on Dose 1 only, not on subsequent doses. For influenza vaccines, we included and anchored on all doses not preceded by another dose in the previous 6 months. Day 0, the day of Dose 1 receipt, was not included in the scans.

The statistical model in the purely temporal scan analysis of a single outcome is different from the one used in the conditional-tree temporal scan. As mentioned in the section above, the ~~latter~~~~TreeScan~~ conditional-tree temporal scan conditions on the overall pattern of outcome occurrence in the entire tree. That is, it assumes the daily contribution of tinnitus cases follows the pattern of the daily contribution of *all* outcomes. In that respect, it is checking the temporal pattern of tinnitus against the overall temporal pattern of outcomes after vaccination, thereby controlling for trends in general healthcare-seeking behavior. In contrast, the ad hoc temporal scan for a single outcome is run without a tree, and there is no overall pattern of healthcare-seeking behavior to check against. Rather, it checks against a uniform pattern. If it detects anything other than a uniform pattern (equal contribution for every day in the follow-up period), then a signal can result. If the pattern of tinnitus follows the pattern of general healthcare-seeking behavior (reflected, for example, in an increase in many kinds of outcomes in the few weeks after vaccination), it would likely not signal in the conditional tree-temporal

scan analysis, whereas it could well signal in the purely temporal scan analysis because the overall pattern would diverge from a uniform pattern.

~~d.~~c. VSD ~~i~~incidence comparisons

Using the data on incident tinnitus in the 140 days after vaccination that were extracted for the temporal scan analyses, we calculated overall tinnitus incidence as well as incidence by age group (18-39, 40-64, and 65+ years of age) after Dose 1 of Pfizer-BioNTech, Moderna, and Janssen, and after influenza vaccines. (We did not subtract days after incident tinnitus from the 140-day follow-up periods of individuals with incident tinnitus, as we did not have time-to-event data by age group, but reducing the denominators in this way would have made a negligible difference in the incidences, considering the much larger numbers of vaccinees without tinnitus.) We used the exact binomial distribution to calculate 95% confidence intervals. To allow crude comparison with tinnitus incidences reported in the literature, we scaled the point estimates and confidence intervals from 140-day follow-up periods to person-years, assuming that the daily risk in the 140 days after vaccination would have remained the same throughout a year.

~~Results~~RESULTS

VAERS

~~a. VAERS reports~~

During December 14, 2020–May 4, 2023, VAERS received 17,859 reports of tinnitus after COVID-19 vaccination (Table 1). Median patient age and time to symptom onset after vaccination were comparable among monovalent and bivalent vaccines. Median patient age ~~(monovalent:~~varied from 52–55 years for monovalent vaccines, and from ~~bivalent:~~ 57–59 years for bivalent vaccines;~~)~~ ~~and~~ median time to symptom onset after vaccination ~~(~~varied from 1–3 days~~)~~ ~~were comparable among monovalent~~

~~and bivalent vaccines.~~. Table 1 summarizes selected demographic characteristics of case patients in tinnitus reports following COVID-19 vaccination. The highest tinnitus reporting rate was after the Janssen vaccine (65.2 per one million doses administered) (Table 2). Reporting rates for bivalent mRNA COVID-19 vaccines were lower than for monovalent vaccines.

Commented [DJM(13]: It's not clear why the medians are being shown as a range of values without looking at the table. Is there some way to indicate that this is referring to different manufacturers/products?
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:39:00

Commented [SJ(14R13]: Please see revised language.
Su, John (CDC/NCEZID/DHQP/ISO)
2024-01-17 18:13:00

Commented [DJM(15]: I would add something about how many were "serious" and if possible how many reported a doctor visit.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:25:00

Table 1. Characteristics of patients experiencing tinnitus after COVID-19 vaccination* reported to the Vaccine Adverse Event Reporting System (VAERS), December 14, 2020–May 4, 2023.

	Monovalent COVID-19 vaccines ~~(primary series)~~				Bivalent COVID-19 vaccines	
Characteristic	**Pfizer-BioNTech (N=9602)**	**Moderna (N=6744)**	**Janssen (N=1592)**	~~Novavax~~Novavax **(N=6)**	**Pfizer-BioNTech bivalent (N=255)**	**Moderna bivalent (N=178)**
Sex						
Female	5357 (59.1%)	4064 (60.3%)	864 (54.3%)	5 (83.3%)	160 (62.8%)	103 (57.9%)
Male	3560 (39.3%)	2607 (38.7%)	679 (42.7%)	1 (16.7%)	90 (35.3%)	69 (38.8%)
Sex not reported	145 (1.6%)	73 (1.1%)	49 (3.1%)	0 (0.0%)	5 (2.0%)	6 (3.4%)
COVID-19 vaccine given alone	8927 (98.5%)	6655 (98.7%)	1586 (99.6%)	6 (100.0%)	216 (84.7%)	150 (84.3%)
Median time to symptom onset in days (interquartile range)	2 (0–8)	2 (0–12)	1 (0–7)	1 (1–2)	2 (1–19)	3 (1–25)
~~Reporting rate per one million vaccine doses administered~~Classified as serious†	1343 (14.8%)~~24.0~~	871 (12.9%)~~29.6~~	219 (13.7%)~~65.2~~	3 (50.0%)	36 (14.1%)~~0.7~~	24 (13.4%)~~0.9~~

*Twenty-two reports had no information on manufacturer of COVID-19 vaccine

†Serious reports include reports of hospitalization, prolongation of existing hospitalization, life-threatening illness, death, permanent disability, and congenital deformity.

Table 2: Reporting rates for reports of tinnitus after monovalent COVID-19 vaccination received by the Vaccine Adverse Event Reporting System (VAERS) received during December 14, 2020 through May 4, 2023, by manufacturer and dose number

Commented [DJM(16]: Include Novavax for completeness.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:41:00

Commented [DJM(17]: Consider putting this per 10,000 doses to make it the same scale as the VSD results for easy comparison and consistency within the paper. Even though VAERS is per doses and VSD is per person year, using the same scale would still be helpful.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:08:00

Commented [YK18R17]: If desired, we can express post-vaccination incidences in VSD in terms of cases per 10,000 doses (using cases in the 140 days after a dose), including in the graph.
Yih, Katherine
2023-10-11 15:20:00

Commented [DJM(19]: I would like to see this separately for dose 1 and dose 2 for the mRNA vaccines. I wonder if the rates after dose 1 are more comparable to Janssen and that the two dose series is diluting the overall rate.
These rates are not age adjusted. Janssen was only authorized for adults. I would say something in a footnote about the different ages included for each vaccine. I think the tendency will be for readers to try and compare these and it should be clear what the limitations of such a comparison is.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-10 23:44:00

Commented [SJ(20]: Will be reported in a separate table.
Su, John (CDC/NCEZID/DHQP/ISO)
2024-01-17 18:19:00

	BNT162b2			mRNA-1273			Ad26.COV2.S	NVX-CoV2373
Dose Number	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 1
Reporting Rate (per one million doses administered)	2.31	2.51	1.37	1.18	1.55	0.70	5.93	67.8

a. Data Mining

As of 01/12/2024, data mining did not reveal an elevated EB05 (≥ 2.0) for the MedDRA PT, "tinnitus," for Janssen, Novavax, or any monovalent or bivalent Pfizer and Moderna COVID-19 vaccines.

Commented [BS21]: @Nair, Narayan There were no data mining results for tinnitus for any COVID-19 vaccines
Bazel, Samaneh
2024-01-19 11:48:00

VSD

~~b.~~a. Tree-based scan statistical analysis

Table 2 presents the results of primary and supplemental TreeScan analyses of COVID-19 vaccines with respect to tinnitus. In our data, 96% of incident tinnitus cases were seen in the outpatient setting, therefore the supplemental analyses, which included all settings and were conducted for the primary series and the bivalent vaccines, are the most relevant here. No clusters of tinnitus were found in either the primary or the supplemental analyses.

Table 2. Summary of results of TreeScan analyses with respect to tinnitus (H93.1*).

Vaccine	Series	Number of doses	Follow-up period	Primary analysis: Potential cases ascertained in ED and inpatient settings only	Supplemental analysis: Potential cases ascertained in ED, inpatient, and outpatient settings
Pfizer-BioNTech	Primary, follow-up anchored on Dose 1	4,068,513 (Dose 1)	70 days	240 cases No clusters of tinnitus found (p=1)	3779 cases No clusters of tinnitus found (p=0.9999)
Pfizer-BioNTech	Monovalent booster after mRNA COVID-19 vaccination	2,467,865	56 days	121 cases No clusters of tinnitus found (p=1)	This supplemental analysis not done
Pfizer-BioNTech	Bivalent vaccine	979,189	56 days	32 cases No clusters of tinnitus found (p=0.6921)	1220 cases No clusters of tinnitus found (p=1)
Moderna	Primary, follow-up anchored on Dose 1	2,559,563 (Dose 1)	70 days	104 cases No clusters of tinnitus found (p=1)	3053 cases No clusters of tinnitus found (p=1)
Moderna	Monovalent booster after mRNA COVID-19 vaccination	1,873,849	56 days	97 cases No clusters of tinnitus found (p=1)	This supplemental analysis not done
Moderna	Bivalent vaccine	352,509	56 days	15 cases No clusters of tinnitus found (p=1)	454 cases No clusters of tinnitus found (p=1)
Janssen	Primary	417,854	56 days	19 cases No clusters of tinnitus found (p=1)	334 cases No clusters of tinnitus found (p=1)
Janssen	Monovalent booster after Janssen	65,238	56 days	1 case No clusters of tinnitus found (p=1)	This supplemental analysis not done

~~c.~~b. Ad hoc temporal scan analyses

Time-to-event graphs and temporal scan results for tinnitus after Dose 1 of each of three COVID-19 vaccines and after influenza vaccination are shown in Figure 1~~ [ignore second column of graphs, all back pain]~~. For Pfizer-BioNTech, with 4,353,720 vaccinated and 12,277 incident tinnitus cases, the strongest temporal cluster was in Days 33-84, p=0.001, with a relative risk of 1.14. For Moderna, there were 2,572,408 vaccinated and 10,232 incident cases; the strongest cluster was in Days 41-105, p=0.01, with a

Commented [YK22]: I will remove the back pain graphs (in second column of figure) later.
Yih, Katherine
2023-10-11 15:25:00

relative risk of 1.09. There were no statistically significant clusters after Janssen, with 427,895 vaccinated and 1,352 incident cases.

Of mRNA COVID-19 vaccinees, 97% received Dose 2 during the 70 days after Dose 1, and approximately three-quarters of Dose 2s were received within 1 day of the recommended spacing after Dose 1, which was 21 days for Pfizer-BioNTech and 28 days for Moderna. In view of this information, the mostly likely clusters included cases occurring around 12-13 days after Dose 2 and beyond for both Pfizer-BioNTech and Moderna vaccinees.

The temporal pattern for tinnitus after influenza vaccination was different from the pattern after either mRNA COVID-19 vaccine, with more cases soon after influenza vaccination and cases decreasing to a plateau within a few weeks after vaccination. The most likely cluster of tinnitus was in Days 5-36 after influenza vaccination.

~~d.~~c. Incidence comparisons

Overall and age group-specific tinnitus incidences calculated from the number of incident cases ascertained from the 140 days of follow-up and scaled to annual incidences are shown in Figure 2. The all-ages incidences are included to enable crude comparison with incidences reported in the literature but should not be closely compared, as they are not age-standardized and there are differences in age distribution among the four groups of vaccinees.

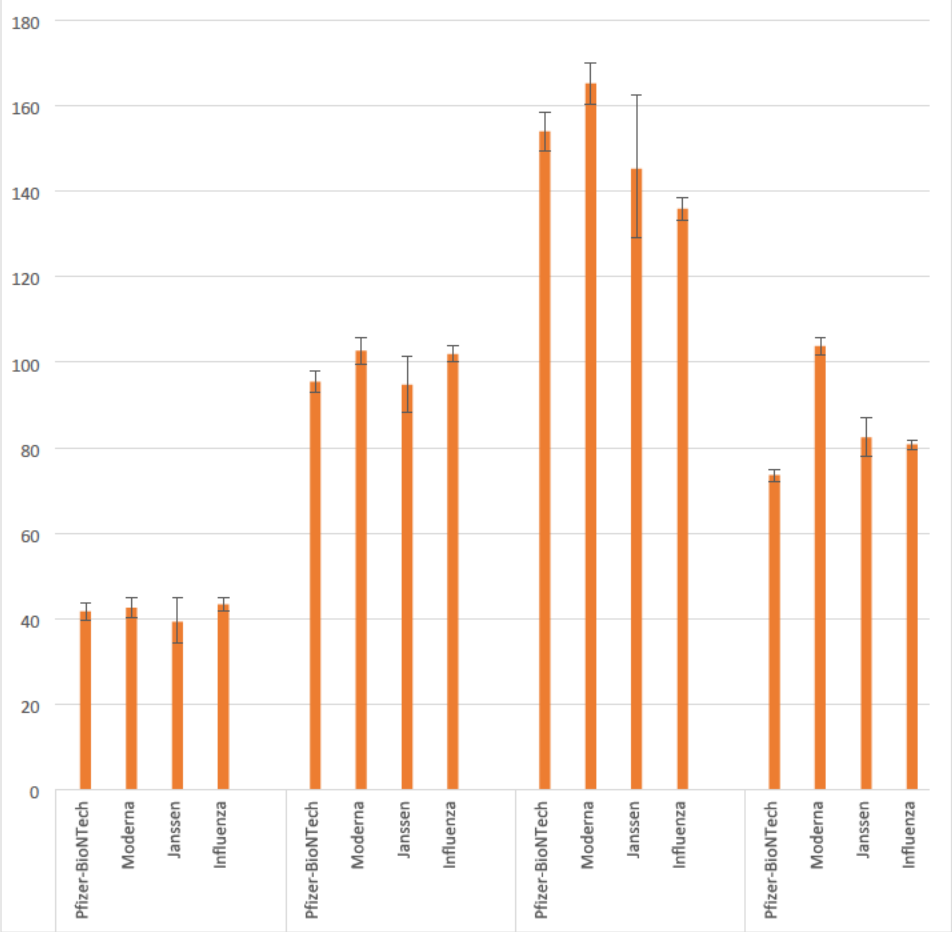

Figure 2. Age-specific and all-ages tinnitus incidences per 10,000 person-years, with exact binomial 95% confidence intervals, calculated and scaled up from 140-day follow-up periods after Dose 1 of each COVID-19 vaccine and after influenza vaccine doses not preceded by another dose in the previous 6 months. The date range for eligible doses was January 1, 2019, through August 31, 2022. The all-ages incidences include events and person-time from vaccinees less than 18 years of age. [Source document: C:\Users\kyih\Documents\TreeScan for COVID-19 vaccines in VSD\Signals, HOIs to check (not AMI) w TTE etc\Tinnitus & hearing loss\Exact binomial confidence for incidence_13Sept2023_KY.xlsx]

Commented [YK23]: We can use per 10,000 doses if desired (using cases in the 140 days after a dose). (I used person-years so as to more easily compare these incidences with those in the literature, but those comparisons aren't terribly comparable and could be stated in the text, without having the figure be in terms of person-years.)
Yih, Katherine
2023-10-11 15:15:00

~~Within the 18-39 year age group, the 95% confidence intervals of the COVID-19 and influenza vaccines all overlap; this is not the case for the other two age groups. In the 40-64-year age group, the incidences after Moderna and influenza vaccination are very similar (with point estimates of 102.7 and 101.9/10,000 person-years, respectively) but somewhat higher than for Pfizer-BioNTech (95.4/10,000 person-years). In the 65+ year age group, the incidence after Moderna (165.2/10,000 person-years) is higher than after Pfizer (154.0/10,000 person-years); both of these are considerably higher than after influenza vaccination (135.9/10,000 person-years). In each of the three age groups, the Janssen 95% confidence interval overlaps with those of the other three vaccines. The all-ages incidences are included to enable crude comparison with incidences reported in the literature but should not be closely compared, as they are not age-standardized and there are differences in age distribution among the four groups of vaccinees.~~

Commented [DJM(24]: I think you can delete most of this. I would just let the graph speak for itself.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:06:00

Discussion

~~This four-part analysis found no compelling evidence of an association~~ Vaccine safety surveillance using pre-specified statistical methods in VAERS and VSD did not signal an association between any brand of COVID-19 vaccin~~eation~~ and tinnitus. Further evaluation of this outcome with additional methods was done in both systems and also did not suggest an increased risk.

Commented [DJM(25]: This statement would be bolstered by inclusion of the VAERS data mining results.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:14:00

Commented [SJ(26R25]: FDA to add EB data mining data; can incorporate language into Discussion.
Su, John (CDC/NCEZID/DHQP/ISO)
2024-01-18 00:46:00

Commented [BS27R25]: @Nair, Narayan Do we need to specify data mining here as well?
Bazel, Samaneh
2024-01-19 11:56:00

VAERS main points:

- Data mining did not signal.
- Reporting rate comparison to background rates not a reliable signaling method for a relatively common non-serious outcome due to potential for underreporting.
- Difference in reporting rate between brands may be confounded by age, etc.
- Is there anything else in reporting pattern that argues against a concern or that is interesting to point out?

The VAERS reporting rates of tinnitus following COVID-19 vaccination appear low, considering the relatively high prevalence of tinnitus in the general population [28]. The reporting rate following Janssen vaccination was higher than that observed following monovalent mRNA COVID-19 vaccination. This higher rate is consistent with the numerical imbalance of tinnitus events observed in the Janssen-vaccinated group compared to the placebo group in the preauthorization clinical trial. ~~This elevated rate is also consistent with tinnitus being listed as an adverse event that has been reported following Janssen vaccination in post-authorization monitoring [1] but not listed as an adverse event in the package inserts for the mRNA COVID-19 vaccines [29, 30].~~ However, it is possible that the higher reporting rate after Janssen is in part due to stimulation of reporting resulting from the information in the Janssen fact sheets [1, 2]. The reporting rates following monovalent mRNA COVID-19 vaccination were higher than following bivalent vaccination, which could be due to a number of reasons other than a truly greater risk after the primary series, e.g., the fact that those receiving the bivalent vaccines were mostly older adults [31], who may have previously experienced onset of tinnitus. The differences in reporting rates observed among different vaccines and in different time periods (i.e., monovalent mRNA COVID-19 vs. bivalent mRNA COVID-19 vaccination periods) could be the result of reporting biases or confounding. Overall, the VAERS data do not provide strong evidence of a safety problem for tinnitus following COVID-19 vaccination.

In the VSD, pre-specified or per protocol tree-based data-mining analysis there was no signal ~~for temporal clustering.~~ With the conditional self-controlled tree-temporal TreeScan variant, we found no temporal clusters of medically attended tinnitus diagnoses in the respective pre-specified follow-up period after each of authorized COVID-19 vaccines studied (70 days after mRNA COVID-19 vaccine Dose 1; 56 days after Janssen, monovalent booster, and bivalent Pfizer-BioNTech and Moderna doses). The ad hoc temporal scans of cases in 140 days of follow-up, which involve no adjustment for overall patterns in post-vaccination healthcare-seeking behavior, found statistically significant 7-9-week-long

Commented [DJM(28)]: I would say that underreporting is expected for a non-serious event such as this. Comparison to background rates would not be a reliable signal detection method for this type of outcome. Would rely more on disproportionate reporting for this.
If you are going to talk about the population rate, would state the rate here.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:16:00

Commented [DJM(29)]: Per my comments on the VAERS table, there are too many differences in age and number of doses between how the brands were used to make this a meaningful comparison. I would focus on the limitations about whey these should not

Commented [DJM(30)]: I would delete this. We don't know what criteria FDA uses to select things to mention in the package inserts / fact sheets for the post-authorization reports.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)

Commented [NN31R30]: Agree with the deletion. Thanks
Nair, Narayan
2024-01-22 11:00:00

Commented [DJM(32)]: Was tinnitus in the original fact sheet or only added later? I don't have a copy of the original at the moment to check.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:22:00

Commented [DJM(33)]: I think the data mining is needed to support this statement. None of the descriptive stuff or reporting rates is very compelling for or against a signal by itself.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)

Commented [BS34R33]: @Nair, NarayanThere were no data mining findings
Bazel, Samaneh
2024-01-19 11:54:00

Commented [NN35R33]: Unfortunately, the absence of a data mining finding does not necessarily mean there is not signal.
Nair, Narayan
2024-01-22 11:01:00

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Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:45:00

clusters of tinnitus after Dose 1 of the mRNA COVID-19 vaccines, with only modestly elevated relative risks. These started on Days 33 and 41 after Pfizer-BioNTech and Moderna, respectively, approximately 12-13 days after Dose 2 would have been received by many of the vaccinees. This pattern was not seen in the case of Janssen, where the sample size was smaller and there was no Dose 2 as part of the primary series~~was recommended~~.

There were some differences among the temporal patterns of tinnitus after the mRNA COVID-19 vaccines and seasonal influenza vaccine. The most likely cluster of tinnitus after influenza vaccination was sooner (Days 5-36) after vaccination than for the mRNA COVID-19 vaccines, with cases dropping to a plateau, a pattern that was not evident with the mRNA COVID-19 vaccines. The significance of the variability in the post-vaccination tinnitus patterns among the mRNA COVID-19 vaccines, the Janssen COVID-19 vaccine, and seasonal influenza vaccine is unclear. These are different vaccines with different schedules, given at different time periods, and possibly given to different kinds of people, complicating interpretation. ~~Based on these findings, we cannot rule out an association between mRNA COVID-19 vaccination and tinnitus,~~ The low relative risk estimates (1.14 for Pfizer-BioNTech and 1.09 for Moderna) observed in the ad hoc temporal scan analysis do not provide compelling evidence to support a causal association between COVID-19 vaccination and tinnitus when considered in the overall context of ~~but considering~~ the lack of associations in the primary and supplemental tree-based scan statistical analyses, ~~the low relative risk estimates (1.14 for Pfizer-BioNTech and 1.09 for Moderna) observed in the ad hoc temporal scan analysis,~~ and the fact that the temporal scan analysis does not adjust for overall patterns of healthcare-seeking behavior~~, there is a lack of compelling evidence overall to support a causal association between COVID-19 vaccination and tinnitus~~.

~~Examination of the incidences does not clarify the picture.~~ The VSD incidence rate analysis provides the best information to compare the different COVID-19 vaccine brands and ~~to~~ influenza vaccine, which has not been generally suspected as a cause of tinnitus. In each age group, the point estimate for the

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Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 00:52:00

Commented [DJM(38]: I think the incidence analysis is the most informative in a way.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 01:48:00

Janssen vaccine ~~, the only one of the three COVID-19 vaccines for which tinnitus is listed as an adverse event in the package insert,~~ was lower than those of the ~~other~~ two mRNA COVID-19 vaccines, although with case and dose counts an order of magnitude lower than for the other two COVID-19 vaccines, the Janssen 95% confidence intervals were relatively wide and overlapped with those of the other COVID-19 vaccines and influenza vaccine. Tinnitus incidence after Moderna was found to be somewhat higher than after Pfizer for the 40-64 and 65+ year old age groups; incidences after both Moderna and Pfizer-BioNTech were higher than after influenza vaccination for the 65+ year group (Figure 2). In a paper on the incidence of clinically significant tinnitus in the UK during 2002-2011 [32], Martinez et al. reported incidences by age group that are 1-2 orders of magnitude lower than the incidences in this study, e.g., 5.4/10,000 person-years (95% CI: 5.3-5.5) overall and 11.4/10,000 person-years (95% CI: 11.0-11.8) for the 60-69-year-old age group, but the outcome is more stringently defined: "a discharge from hospital with a primary diagnosis of tinnitus, or a primary care recording of tinnitus with subsequent related medical follow-up within 28 days." There appeared to be a marked secular increase in annual incidence over the 2002-2011 study period. In a subsequent paper on tinnitus in the UK during 2000-2016 [33], Stohler et al. found an age-standardized incidence of first-time general practitioner-recorded tinnitus of 25.0 per 10,000 person-years (95% CI: 24.6-25.5), also noting an increase in incidence over time. In a more recent global meta-analysis of tinnitus [34], Jarach et al. reported an overall pooled incidence of any tinnitus of 116 per 10 000 person-years (95% CI: 48-283), the 95% confidence interval of which encompasses those of our post-vaccination incidences. However, it is difficult to usefully compare results of studies that use different outcome definitions and are based on populations with different age structures. The VAERS reporting rates and the VSD incidence rates are also not directly comparable due to a number of factors, including 1) ~~lack of a standard risk interval, 2)~~ that VAERS can capture any events ~~and~~ while VSD only captures medically attended events, 2) that VAERS relies on self-reported

Commented [DJM(39]: This has already been mentioned before.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 01:50:00

events while VSD captures all medically attended events in a specified follow-up period, and 3) the lack of a standard risk interval ~~3) etc.~~

VAERS data are subject to the limitations of passive surveillance data in general. Underreporting is typical (particularly for outcomes not involving hospitalization or ED visits), and adverse events soon after vaccination are more likely to be reported than events that occur later. Empirical Bayesian data mining since the inception of COVID-19 vaccines has an additional limitation in which disproportionality scores can be driven towards the null by the unprecedented majority of vaccine reports representing COVID-19 vaccines compared to pre-pandemic reporting. Limitations of the VSD TreeScan, temporal scan, and incidence analyses include the following: (1) events occurring on the day of the index vaccination (Day 0) were not included, (2) the analyses included only medically attended events, (3) the putative cases were not chart-confirmed, (4) the time between symptom onset and the medical encounter where the tinnitus diagnosis code was recorded could not be determined from the data, and (5) the analyses using data from the primary series were anchored on Dose 1, meaning that the timing of tinnitus diagnoses after Dose 2 was merely inferred from aggregate data on compliance with the recommended spacing between Doses 1 and 2 rather than being determined precisely. Novavax was not assessed in the VSD due to a small number of doses administered.

Commented [BS40]: @Nair, Narayan
This is part of your previous email response:
"Empirical Bayesian data mining since the inception of COVID-19 vaccines has an additional limitation in which disproportionality scores can be driven towards the null by the unprecedented majority of vaccine reports representing COVID-19 vaccines compared to pre-pandemic reporting."
Bazel, Samaneh
2024-01-19 11:50:00

Commented [YK41]: This Novavax sentence could go just above the Methods or in the Methods instead of here.
Yih, Katherine
2023-10-11 16:10:00

Tinnitus is complicated to study as a possible adverse reaction to vaccination. It is a common health outcome; prevalence estimates vary but the recent meta-analysis by Jarach et al. reports that tinnitus affects 14% of adults and 24% of older adults globally [34]. There are multiple ~~etiologies and~~ risk factors, including environmental, infectious, neurophysiological, age-related, and trauma-related [35-37]. There can be a delay of variable duration between onset and clinical presentation [35]. Further complicating the study of tinnitus with respect to COVID-19 vaccination is the fact that a large proportion of the U.S. and other populations has been exposed to a COVID-19 vaccine [38], the disease [39], or both.

Conclusions

This study does not provide strong evidence of an association between any of the COVID-19 vaccines and tinnitus. ~~VAERS data suggest a higher reporting rate of tinnitus after Janssen than after the mRNA COVID-19 vaccines, but this could be influenced by the fact that tinnitus after Janssen is mentioned in the Janssen fact sheets and package insert. Tree-based data-mining did not find statistical signals for temporal clustering of tinnitus after any of the COVID-19 vaccines studied. In ad hoc analyses, temporal patterns of tinnitus after administration of the mRNA COVID-19 vaccine primary series were different than patterns after influenza vaccine, but clusters after mRNA COVID-19 vaccines were diffuse. Comparison of post-vaccination age-group-specific incidences among COVID-19 and influenza vaccinees found a consistent ordering of point estimates for the COVID-19 vaccines, with Moderna having a higher post-vaccination incidence of tinnitus than Pfizer, and Pfizer a higher one than Janssen, but some of the respective confidence intervals overlapped, and the position of the influenza vaccine point estimate relative to the others was not consistent among the age groups.~~ These findings do not allow us to definitively exclude the possibility of an association. Nonetheless, the relative risk estimates found in the temporal scans were modest and possibly lower than the risk of tinnitus after contracting COVID-19 disease [13, 17]. ~~A large, targeted, protocol-based study of tinnitus risk after COVID vaccination and after COVID-19 disease, possibly using a case-centered method [40], might further inform our understanding of post-vaccination and post-COVID-19 disease tinnitus.~~ A large, targeted, protocol-based study of tinnitus risk after COVID vaccination and after COVID-19 disease might further inform our understanding of post-vaccination and post-COVID-19 disease tinnitus. However, tinnitus is a common condition in the population, with many varied causes and risk factors, including older age. The high prevalence together with uncertainty around the timing of symptom onset [35, 40] make it a notoriously difficult outcome to study using retrospective designs. ~~The relatively high number and proportion of~~

Commented [DJM(42]: A lot of this seems redundant. Maybe just keep the new ideas and incorporate above.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 02:06:00

Commented [DJM(43]: I would neither highlight this as a main finding due to the limitations, nor repeat it here.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 02:00:00

Commented [DJM(44]: Not sure that RR is a good comparison for different exposures.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 02:07:00

Commented [DJM(45]: Maybe avoid suggesting specific study designs.
Duffy, Jonathan M. (CDC/NCEZID/DHQP)
2023-10-11 02:08:00

Commented [YK46R45]: OK. I'll reinsert the rest of the sentence, though, so that the last two sentences flow logically.
Yih, Katherine
2023-10-11 15:54:00

~~people exposed to COVID-19 in the United States, whether through vaccination or SARS-CoV-2 infection, further complicate evaluations.~~

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From: "Nair, Narayan" <[redacted]>
To: "Debra Yeskey" <[redacted]>
Subject: Slides for tomorrow's meeting
Date: Wed, 18 Oct 2023 20:28:29 -0000
Importance: Normal
Attachments: CEPI_talk_.pptx
Inline-Images: image001.png; image002.jpg; image003.jpg; image004.jpg; image005.jpg; image006.jpg

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Dear Deb,
Sorry for the delay, I was awaiting clearance on these slides.

Narayan Nair, MD (he/him/his)
Division Director

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Office of Biostatistics and Pharmacovigilance
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