From: "Nair, Narayan" <[redacted]
To: "Bazel, Samaneh" <[redacted], "Jankosky, Christopher *" <[redacted], "Jason, Christopher" <[redacted]
Subject: RE: f/u on 8Y male with stroke and Left vertebral artery dissection (Pfizer bivalent notable cases for Jan/Feb)
Date: Tue, 04 Apr 2023 15:33:07 -0000
Importance: Normal
Inline-Images: image001.png; image002.png; image003.jpg; image004.jpg; image005.jpg; image006.jpg; image007.jpg

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Yes, it is reassuring that we have not seen a pattern of these type of injuries after millions of doses given to children.

Narayan

From: Bazel, Samaneh <[redacted]
Sent: Tuesday, April 4, 2023 8:25 AM
To: Nair, Narayan <[redacted] Jankosky, Christopher * <[redacted] Jason, Christopher [redacted]
Subject: RE: f/u on 8Y male with stroke and Left vertebral artery dissection (Pfizer bivalent notable cases for Jan/Feb)

Thank you for your insight Chris,

I've never heard of such an event in children, so unusual. Judging from the fair number of kids I saw during clinical practice with periorbital petechiae post vomiting or cough, I agree that it can be pretty forceful, not to mention that kids experience so many injuries that aren't even observed or the child doesn't even mention to the parent (I was one of those kids!). But given that injuries and vomiting are ubiquitous in children, it makes me question underlying predisposition in this case as well, such as the family history or the connective tissue diseases you mentioned. I recently heard that EDS is very underdiagnosed.

I wish we had the notes for the subsequent hospitalizations to see further workup. But I agree that from the limited information and the temporal sequence of events, the role of vaccine can't be ruled out.

Thanks again,
-Sam

From: Nair, Narayan [redacted]
Sent: Tuesday, April 4, 2023 7:10 AM
To: Jankosky, Christopher * [redacted] Bazel, Samaneh [redacted] Jason, Christopher [redacted]
Subject: RE: f/u on 8Y male with stroke and Left vertebral artery dissection (Pfizer bivalent notable cases for Jan/Feb)

Thanks, this is super helpful.

Narayan

From: Jankosky, Christopher * <[redacted]
Sent: Monday, April 3, 2023 8:30 PM
To: Nair, Narayan [redacted] Bazel, Samaneh [redacted] Jason, Christopher [redacted]
Subject: RE: f/u on 8Y male with stroke and Left vertebral artery dissection (Pfizer bivalent notable cases for Jan/Feb)

Good afternoon all,

Interesting case. My thoughts:

1. A recent publication from Japan discussed two elderly patients, who after their first COVID vaccine, had a rupture of pre-existing Vertebral Artery dissecting aneurysms ("ruptured immediately after the administration of different mRNA anti-COVID-19 vaccines. In both cases, caliber irregularity of the VA was retrospectively identified on MRA before vaccination, suggesting that unruptured VA dissection had already developed. Then, these VADAs ruptured immediately after the vaccination."), and the authors propose that inflammation may have played a role. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9119691/#:~:text=In%20this%20paper%2C%20we%20report,%2D1273%20COVID%2D19%20vaccine. No evidence that the 8 year old had any pre-existing abnormality, and an autoimmune mechanism for causation after the 4th COVID vaccine dose (in addition to a prior COVID infection) is a little unusual, since already exposed to spike protein and other vaccine constituents on multiple occasions. Still possible, though, for the 8 year old to have some unusual predisposition to arterial dissection, based on a relatively unusual family history in sister and father.
2. Nausea and vomiting the day of vaccination is important, and I will come back to this later.
3. "Vertebral artery dissection, like arterial dissection elsewhere, is a result of blood entering the media through a tear in the intima of the vertebral artery. It is potentially lethal and can be difficult to diagnose clinically and radiologically." - https://radiopaedia.org/articles/vertebral-artery-dissection?lang=us#:~:text=CT%20and%20CT%20angiography%20(CTA,often%20with%20some%20surrounding%20stranding)
4. Etiology https://radiopaedia.org/articles/vertebral-artery-dissection?lang=us#:~:text=CT%20and%20CT%20angiography%20(CTA,often%20with%20some%20surrounding%20stranding)

- blunt trauma (most common)
- antecedent neck manipulation or other sudden movements [5,10]
- spontaneous

- fibromuscular dysplasia (FMD)
- connective tissue diseases [2]
  - Ehlers-Danlos disease
  - Marfan's disease
  - pseudoxanthoma elasticum

5. A case report from 2000 provides a good summary on vertebral artery dissection in children: "Posterior circulation strokes are rare in children, but vertebrobasilar dissection is one of the more common causes of this rare entity. Arterial dissections have been classified in the literature as either traumatic or spontaneous, although in many cases trivial trauma may not be recognized. Neck exercises, coughing, sneezing, rapid head turning, swimming, judo, painting the ceiling, and bicycle riding have all been noted to be potentiators of vertebral artery dissection."... "Playing different sports, sudden head turning, and amusement rides have been associated with vertebral artery dissection in children." ... "The signs and symptoms of this unusual entity can be subtle and intermittent over a period of days to weeks; thus, making it very difficult to recognize." https://journals.lww.com/pec-online/fulltext/2000/06000/recognizing_vertebral_artery_dissection_in.14.aspx#:~:text=The%20most%20commonly%20reported%20symptoms,same%20side%20as%20the%20dissection. During my neurology residency I was on the team managing a young man with a vertebral artery dissection similar to this case, and in hindsight the only precipitating event was him having played in a local baseball game the day before, and that was the best underlying "traumatic event" (which I suppose would distinguish it from being in the spontaneous category).
6. What is the prognosis for people with cervical artery dissection? Cleveland Clinic answer: "Cervical artery dissections typically heal very well, returning the vessel to normal. This process usually occurs within the first three to six months." https://my.clevelandclinic.org/health/diseases/16857-cervical-carotid-or-vertebral-artery-dissection#outlook--prognosis
7. Thus the CT angiogram evidence of a dissected left vertebral artery, in conjunction with the clinical history of symptoms beginning approximately 70 days earlier, is plausible.
8. Important to get back to the nausea and subsequent single episode of vomiting the day of vaccination, with first possible symptoms of vertebral dissection the following day (the first TIA). It is not uncommon to have a series of potentially traumatic neck movements during vomiting. When all of the possibilities are considered, this causative mechanism may rise towards the top. Current Comirnaty package insert listed moderate vomiting in 0.4% of adolescents 12 through 15 years of age after second dose Comirnaty, compared to 0.1% after second dose placebo. "Any vomiting" was 2.6% Comirnaty, 1.1% placebo. Comirnaty package insert, table 6.

I am in general agreement with Sam's comments from the March 30th sender, that "Based on the temporal relationship, the association between the event transient ischemic attack with BNT162B2, BNT162B2 OMI BA.4-5 cannot be fully excluded. The causal association between the event Cerebrovascular accident, Vertebrobasilar artery dissection and the suspect drug cannot be excluded. Based on the current available limited information in the case provided, the causal association between the events Cerebellar infarction, Hemiparesis and the use of suspect product BNT162B2, BNT162B2 OMI BA.4-5 cannot be fully excluded."

Hopefully this helps, let me know if you have any questions or want to touch base on the phone,

Thanks,
Chris

From: Nair, Narayan [redacted]
Sent: Saturday, April 1, 2023 6:02 AM
To: Jankosky, Christopher * [redacted]; Bazel, Samaneh [redacted]; Jason, Christopher [redacted]
Subject: FW: f/u on 8Y male with stroke and Left vertebral artery dissection (Pfizer bivalent notable cases for Jan/Feb)

Hi Chris,
I was wondering if you could review the case below and give your thoughts. Perhaps we could speak by phone when you are available. Feel free to reach out to Sam and Chris Jason if you have some questions.

From: Bazel, Samaneh [redacted]
Sent: Friday, March 31, 2023 3:58 PM
To: Jason, Christopher [redacted]
Cc: Alimchandani, Meghna [redacted]; Nair, Narayan [redacted]
Subject: RE: f/u on 8Y male with stroke and Left vertebral artery dissection (Pfizer bivalent notable cases for Jan/Feb)

Hi Chris,

I reviewed the latest updates (Received March 30th) for this case and tried to piece the different reports together with the summary as below. I only saw scanned physician notes/labs (HCP report # [redacted]) for the 12/23/22 hospitalization and not subsequent hospitalizations on 1/28/23 or 2/23/23.

8 yr old male patient with no prior medical history received 2 doses of Pfizer primary vaccine series on the following dates: 18Nov2021, 15Dec2021. He then developed Covid-19 infection on April 20, 2022. He received a monovalent booster dose on 16Sep2022. He then received a Pfizer Bivalent booster (dose #4) on: 12/15/2022. One physician note says he also received influenza vaccine with the Pfizer booster dose, but I don't see it in VAERS.

He developed 3 episodes of TIA, with onset of first event 2 days after the booster dose: 17dec2022; 20dec2022; 23dec2022, symptoms consisting of transient left arm and left leg weakness and numbness, lasting 10 to 15 minutes, which self-resolved.

Per neurologist's note: he developed nausea and vomited once later the same day of the vaccine and was fine after, and the first TIA episode was the next day in school.
He was taken to ER on the day of the third event on 23dec2022. Had normal exam, normal labs including hypercoagulable workup, negative Covid 19 PCR, normal head CT on 12/23/22. 12/23/22 MRI showed: "several small acute infants measuring less than 1 cm, in the left posterior cerebellum and additional punctate acute infarct in the left occipital lobe subcortical white matter." 12/24/22 MRI: "three infarctions in the cerebellum and one in the occipital lobe." 12/24/22 MRA was normal. Factor V Leiden, PT gene mutation tests were normal. Discharged after 2 days with one month of baby Aspirin.

Then experienced more episodes of (? 4 times)TIA (VAERS reports don't have details) on 28Jan2023 and 23Feb2023.
Labs from 2/25/2023 WNL, MRI: "three infarctions in the cerebellum and one in the occipital lobe" **CTA: "Dissection of left vertebral artery" (71 days post vaccination).**

PMH: Unremarkable but per ER notes: "worsening headaches over the last several months but no persistent headaches or morning headaches. Otherwise no visual disturbance, facial weakness, or other changes." This was also reported in the neurologist's note "intermittent frontal headaches and some behavior changes over the past year."

FH is notable for sister with brain cavernous malformation, s/p neurosurgical resection with onset of post-op epilepsy, and father with two small benign brain tumors which are followed with serial brain MRIs.

Per VAERS report: "As of 24Mar2023, it was reported that reporter considered the Pfizer product had a causal effect to the adverse event was no. Event cerebellar infarct required visit in emergency room, physician office, intensive care unit. Patient symptoms had now been attributed to a dissection of left vertebral artery unrelated to the vaccine."

March 30th Sender's Comments: "Follow-up attempts are completed. No further information is expected. Based on the temporal relationship, the association between the event transient ischemic attack with BNT162B2, BNT162B2 OMI BA.4-5 cannot be fully excluded. The causal association between the event Cerebrovascular accident, Vertebrobasilar artery dissection and the suspect drug cannot be excluded. Based on the current available limited information in the case provided, the causal association between the events Cerebellar infarction, Hemiparesis and the use of suspect product BNT162B2, BNT162B2 OMI BA.4-5 cannot be fully excluded. The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to regulatory authorities, Ethics Committees, and Investigators, as appropriate., Linked Report(s) : US-PFIZER INC-PV202300017285 Same patient, drug/ different dose, AE;"

Please let me know if I need to do anything else.

Thanks,
-Sam

From: Jason, Christopher [redacted]
Sent: Monday, March 27, 2023 2:07 PM
To: Bazel, Samaneh [redacted]
Subject: RE: f/u on 8Y male with stroke (Pfizer bivalent notable cases for Jan/Feb)

I would review the medical records first. IF you are having VAERS portal issues may Deb would we willing to send you a PDF of medical records or you can wait until your access is restored

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From: Bazel, Samaneh [redacted]
Sent: Monday, March 27, 2023 2:02 PM
To: Jason, Christopher [redacted]
Subject: FW: f/u on 8Y male with stroke (Pfizer bivalent notable cases for Jan/Feb)

Hi Chris,

Please see Deb's messages below about the 8 YO with strokes. Do I need to send this to Narayan as well, or informing you is enough?

BTW, I can't access VAERS portal for individual case f/u. I called ERIC and a technician and his supervisor couldn't help me. I just sent an email to the VAERS support group so waiting to hear back from them.

Thanks,
-Sam

From: Thompson, Deborah [redacted]
Sent: Monday, March 27, 2023 10:46 AM
To: Bazel, Samaneh [redacted]
Subject: RE: Pfizer bivalent notable cases for Jan/Feb

Thanks, Sam. The case has three different report numbers: [redacted] (MFR report), [redacted] (MFR report), and [redacted] (HCP report now linked to [redacted]). The medical records obtained by the VAERS contractor follow-up are under [redacted]. It doesn't seem likely that we'll get any additional follow-up. It would be good to update leadership.

Thanks,

Deb

From: Bazel, Samaneh [redacted]
Sent: Monday, March 27, 2023 10:34 AM
To: Thompson, Deborah [redacted]
Subject: RE: Pfizer bivalent notable cases for Jan/Feb

Thanks Deb,

I'll call ERIC this afternoon after my meetings. Trying to see if I can reset my password in the meantime. But will let you know if any problems.

So, do you think this is a final report, or just keep checking each week? Also do we need to update leadership?

Thanks,
-Sam

From: Thompson, Deborah [redacted]
Sent: Monday, March 27, 2023 10:26 AM
To: Bazel, Samaneh [redacted]
Subject: RE: Pfizer bivalent notable cases for Jan/Feb

Hi Sam,

Yes, I went into the VAERS Portal and searched for the various IDs I have for that case and looked for any updates:

VAERS Document Images									
VAERS ID Print	VAERS ID	Consolidated Severity	Document #	TAG #	Date Received	Form Type	Doc # Print	Page	Zoom in
	[redacted]	Serious	[redacted]	1	1/4/2023	Initial Report - 15 Day		1	
			[redacted]	1	2/1/2023	Follow Up - 15 Day		1	
			[redacted]	1	3/2/2023	Follow Up - 15 Day		1	
			[redacted]	1	3/24/2023	Follow Up - 15 Day		1	

You will definitely want to have access to the VAERS portal. Please let me know if you have any questions.

Thanks!

Deb

From: Bazel, Samaneh [redacted]
Sent: Monday, March 27, 2023 9:50 AM
To: Thompson, Deborah [redacted]
Subject: RE: Pfizer bivalent notable cases for Jan/Feb

Thanks so much, Deb!

I can't find the updated report in BO. Do you just use the VAERS portal to follow up on individual cases? I haven't used the portal in a while and I can't access it, so need to call ERIC.

-Sam

From: Thompson, Deborah [redacted]
Sent: Monday, March 27, 2023 9:36 AM
To: Bazel, Samaneh [redacted]
Subject: RE: Pfizer bivalent notable cases for Jan/Feb

Hi Sam,

FYI, I checked in VAERS for updates on the report of the 8 year old who experienced TIA/stroke post-bivalent vaccination (VAERS [redacted]. The VAERS report from the company now indicates "Patient's symptoms have now been attributed to a dissection of left vertebral artery" and "The reporter considered "three tia

events (17dec2022; 20dec2022; 23dec2022)/four occurrences of transient ischemic attacks (tias)", "strokes", "three infarctions in the cerebellum and one in the occipital lobe/several small acute infarcts in lt posterior cerebellum. additional acute infarct in left occipital subcortical white matter", "weakness on left side" and "dissection of left vertebral artery" not related to BNT162b2, BNT162b2 omi ba.4-5." The sender comments from the company indicate "The causal association between the event Cerebrovascular accident, Vertebrobasilar artery dissection and the suspect drug cannot be excluded."

Thanks,

Deb

From: Bazel, Samaneh [redacted]
Sent: Tuesday, March 7, 2023 9:46 AM
To: Thompson, Deborah [redacted]
Subject: RE: Pfizer bivalent notable cases for Jan/Feb

Hi Deb,

Yes, I included the 8 yo with TIA in my EUA memo. Did you guys discuss it as a group and contact the sponsor for more information about it, or just waiting for more info when it comes?

Also, when you say you will follow the cases below, do you just search those case numbers in VAERS portal once a week?

Thanks,
-Sam

From: Thompson, Deborah [redacted]
Sent: Tuesday, March 7, 2023 9:37 AM
To: Bazel, Samaneh [redacted] Jason, Christopher [redacted]
Cc: Niu, Manette [redacted] Welsh, Kerry [redacted]
Subject: Pfizer bivalent notable cases for Jan/Feb

Hi Sam,

I'm not sure if it's been decided who will complete the quarterly bivalent ISR for Pfizer, but FYI, I've listed potentially notable deaths/cases below for Jan/Feb. The next ISR will be for Jan-Mar 2023. I can follow-up on the cases below for the ISR, regardless of who completes it. VAERS reports [redacted] and [redacted] and [redacted] below are regarding the 8-year old male who experienced TIA/cerebellar infarct – this case is in the sponsor's cumulative AE summary.

Pfizer-BioNTech COVID-19 Bivalent Vaccine Surveillance

<u>February 2023</u>

Notable US Deaths

ID	Age (years)	Sex	Adverse Event	Summary
[redacted]	13	F		Patient with PMH IRON DEFICIENCY; TYPE 1 DIABETES MELLITUS; VITAMIN D DEFICIENCY experienced tachycardia, chest pain, EKG changes; Referral Cardiology, ED visit, Death. Onset 18-days post-vax, died 22 days post-vax 3rd dose. *<u>Reviewer comment:</u> Limited clinical details preclude further assessment at this time. Await medical records. No mention of autopsy.*

Notable US Reports

ID	Age (years)	Sex	Adverse Event	Summary
[redacted]	39	F	CVST	Patient with no PMH and no meds, 2-3 days after shot developed progressive headache and neck pain, progressive and had imaging almost a month later. Dural venous sinus thrombosis, treated with anticoagulation. Despite anticoagulation, 6 weeks later had submassive PE that had an acute and chronic component. Unresponsive to thrombolytics and thrombectomy attempt. Required ECMO, still hospitalized. MRI brain and CT showing venous sinus thrombosis, 11/17.

				Reviewer comment: Re-review if medical records become available, unable to assess further at this time.

January 2023

Notable US Deaths

ID	Age (years)	Sex	Adverse Event	Summary
[redacted]	61	M	DEATH; HYPERVISCOSITY SYNDROME; MULTIPLE ORGAN DYSFUNCTION SYNDROME	Patient presented to ED with acute progressive lethargy and confusion, apparent hyperviscosity syndrome - multisystem organ failure, outcome of death. Onset 5-days post-4th dose. Died 6-days post-vax. Discharge dx: 1. COVID infection; 2. h/o recent COVID-19 vaccination; 3. Probable idiopathic capillary leak syndrome due to #1 or #2; 4. Profound circulatory shock due to #3; 5. Multisystem organ failure including metabolic acidosis, hypoxemic respiratory failure, and stroke due to #3 and #4. *Reviewer comment:* Case confounded by concurrent COVID-19 infection.
[redacted]	unk	M	Myocarditis, thrombosis, death	Clinical course: the patient's father in law died of severe myocarditis and blood clots 1 month after receiving his 2nd Pfizer Covid booster shot. The patient was a "recovered cancer patient who had a perfectly clean bill of health and was just examined prior and had a heart that was in perfect shape." *Reviewer comment:* Limited clinical details available which precludes further assessment at this time.

Notable US Reports

ID	Age (years)	Sex	Adverse Event	Summary
[redacted]	8	F	urticaria and arthralgia/arthritis	8-year-old female with concerns for urticaria and arthralgia/arthritis. No systemic signs of fever. Concern for urticaria multiform or serum sickness-like reaction. Trigger could be COVID-vaccine. Other concerns could be acute rheumatoid arthritis. No other signs of sepsis or other concerns at this time. 12/27/2022: Labs with mild leukocytosis and elevated CRP, normal ESR. Patient developed low-grade fever in ED Rheumatology team consulted, recommended naproxen and PCP f/u. Patient tachycardic and hypotensive in setting of fever, given fluid bolus with improvement in HR but no change in BP. Question post-vaccine hyperinflammatory syndrome vs. serum sickness like reaction vs. urticaria multiforme. D/C summary reports that symptoms ultimately thought to be most likely due to serum sickness like reaction either due to viral illness (pt's brother presented with similar symptoms) or due to COVID booster. Treated with Zyrtec and NSAIDs and one dose dexamethasone. Improving at discharge. *Reviewer comment:* The patient's symptoms might be explained by viral illness given her brother had similar symptoms. Continue routine surveillance.
[redacted]	8	M	TIA/cerebellar and occipital infarct	Patient with PMH of COVID-19 in April 2022 experienced three TIA events (17Dec2022; 20Dec2022; 24Dec2022) + several small

[redacted]				acute infarcts in Lt posterior Cerebellum. Additional acute infarct in occipital subcortical white matter. The patient was hospitalized for transient ischaemic attack (hospitalization duration: 2 days.) Polymerase chain reaction: (23Dec2022) Negative. Onset 2-days post-4th dose. Previously healthy 8 year old boy was diagnosed with four occurrences of transient ischemic attacks (TIAs). MRI revealed three infarctions in the cerebellum and one in the occipital lobe. Symptoms began two days after he received his bivalent booster on 15Dec2022. Primary symptom was weakness on left side and when prolonged occurrence took place on 23Dec2022, parents brought child to emergency room where CT scan and MRI were completed. Head CT, MR Angio WNL. Sars-Cov-2 PCR WNL. PLT, PT, APTT, INR, DDImer, Fibrinogen, Protein C, Protein S, Factor V Leiden - WNL. Family history includes sister with brain cavernous malformation and father with two small benign brain tumors. Pt d/c home on aspirin with f/u appt with neuro, cardiology, peds ID for consult on getting addition COVID-19 vaccines, and peds heme/onc. *Reviewer comment: Pt undergoing hypercoagulable work-up – lab results in VAERS appear normal aside from slightly high AT3. Re-review this report if additional consultant records become available to further assess underlying causes. Ischemic stroke is being evaluated in CDC's VSD and FDA's BEST active surveillance systems. The sponsor was also asked to provide an assessment of thromboembolic events (TEE) following the bivalent vaccine and concluded there is no evidence that TEE, including ischemic stroke, is a safety signal or risk of the bivalent vaccine (STN 125742/245/2).*
[redacted]	38	M	Acute leukemia, thrombocytopenia	A 38-year-old male patient received BNT162b2, BNT162b2 omi ba.4-5 (BNT162B2, BNT162B2 OMI BA.4-5), on 21Oct2022 as dose 4 (booster), single (Lot number: GJ2524) at the age of 38 years intramuscular for COVID-19 immunisation. The patient's relevant medical history included: "Sickle cell anaemia" (unspecified if ongoing), notes: other medical history: sickle cell anemia. The patient took concomitant medications. Vaccination history included: BNT162b2 (Dose Number: 3, Batch/Lot No: FG3527, Route of Administration: Intramuscular), administration date: 05Nov2021, when the patient was 37-year-old, for COVID-19 Immunization; BNT162b2 (Dose Number: 2, Batch/Lot No: ER8732, Route of Administration: Intramuscular), administration date: 25Mar2021, when the patient was 36-year-old, for COVID-19 Immunization; BNT162b2 (Dose Number: 1, Batch/Lot No: EN6198, Route of Administration: Intramuscular), administration date: 04Mar2021, when the patient was 36-year-old, for COVID-19 Immunization. The following information was reported: ACUTE LEUKAEMIA (hospitalization, medically significant) with onset 21Nov2022, outcome "not recovered",

				described as "concern for acute leukemia"; THROMBOCYTOPENIA (hospitalization, medically significant) with onset 21Nov2022, outcome "not recovered", described as "profound thrombocytopenia". The patient was hospitalized for thrombocytopenia, acute leukaemia (hospitalization duration: 5 day(s)). The events "profound thrombocytopenia" and "concern for acute leukemia" required physician office visit and emergency room visit. The patient underwent the following laboratory tests and procedures: SARS-CoV-2 test: Negative. *Reviewer comment:* *Re-review if medical records become available. Confounding due to PMH of sickle cell anemia which could increase risk of leukemia.* (Increased risk of leukemia among sickle cell disease patients in California	Blood	American Society of Hematology (ashpublications.org) Sickle Cell Disease and The Risk for Acute Myeloid Leukemia - New Hope Unlimited (newhopemedicalcenter.com)
[redacted]	8	F	MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE	Patient with PMH ADHD and anxiety experienced severe headache 19-days post-3rd dose. Seizure 3-days later and was diagnosed with Rhino/Entero and Adenovirus. After several weeks of headaches, she was admitted to the hospital on December 26th and underwent testing which diagnosed MOGAD. *Reviewer comment:* *Re-review pending medical records. Confounding due to concurrent viral illness.* Myelin oligodendrocyte glycoprotein antibody-associated disease in children: Are there MRI predictors of relapse? - PubMed (nih.gov) Myelin Oligodendrocyte Glycoprotein Antibody Disease	Children's Hospital of Philadelphia (chop.edu) Myelin-oligodendrocyte glycoprotein antibody-associated disease - The Lancet Neurology MOG Antibody-Associated Disorders Following SARS-CoV-2 Vaccination: A Case Report and Literature Review - PubMed (nih.gov) Matsumoto Y, Ohyama A, Kubota T, Ikeda K, Kaneko K, Takai Y, Warita H, Takahashi T, Misu T, Aoki M. MOG Antibody-Associated Disorders Following SARS-CoV-2 Vaccination: A Case Report and Literature Review. Front Neurol. 2022 Mar 1;13:845755. doi: 10.3389/fneur.2022.845755. PMID: 35299613; PMCID: PMC8922017.
[redacted]	30	M	AMNESIA; BALANCE DISORDER; HYPOAESTHESIA; LUMBAR PUNCTURE ABNORMAL; MAGNETIC RESONANCE	Symptoms of numbness, abnormal balance, loss of memory shortly after receiving vaccine. Onset 2-days post-1st dose. I was admitted to hospital and underwent MRI and Lumbar puncture which determined there were abnormal findings suggestive of nerve

			IMAGING ABNORMAL; NERVE INJURY	damage. I was given IV high dose steroids for 5 days. *Reviewer comment: Limited clinical details preclude further assessment of this report. Re-review if medical records become available.*
[redacted]	37	M	CVA	Patient with hx of influenza-like illness experienced cryptogenic CVA that began at the time listed in form resulting in emergency transport via ambulance to an emergency room where the clot busting drug TNK was administered, and then resulting in a three day ICU admission. Onset 4-days post-vax. Positive bubble study on TEE – dx with patent foramen ovale (PFO), will f/u with interventional cardiologist for PFO closure. *Reviewer comment: This report is confounded by the diagnosis of PFO which is a risk for stroke.*

Thanks,

Deb
Deb Thompson, MD, MSPH, FACPM
Medical Officer

Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance
U.S. Food and Drug Administration
Tel: [redacted]

U.S. FOOD & DRUG ADMINISTRATION

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" <[redacted]
To: "Grohskopf, Lisa A. (CDC/DDID/NCIRD/ID)" <[redacted], "Wallace, Megan (CDC/DDID/NCIRD/CORVD)" [redacted] "Wharton, Melinda (CDC/DDID/NCIRD/OD)" [redacted] "Cardo, Denise M. MD (CDC/DDID/NCEZID/DHQP)" [redacted], "Bell, Michael MD (CDC/DDID/NCEZID/DHQP)" [redacted] "Srinivasan, Arjun (CDC/DDID/NCEZID/DHQP)" [redacted]>, "Helfand, Rita (CDC/DDID/NCEZID/OD)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" <[redacted], "Broder, Karen (CDC/DDID/NCEZID/DHQP)" <[redacted] "Weintraub, Eric (CDC/DDID/NCEZID/DHQP)" <[redacted], "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: Follow-up: Covid bivalent and IIV
Date: Thu, 24 Aug 2023 13:27:27 +0000
Importance: Normal
Attachments: Ischemic_stroke_after_bivalent_COVID-19_vaccination_a_self-controlled_case_series_study_2023-08-23.pptx

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Attached is a presentation describing preliminary data from a post-signal analysis that was conducted by SCK under an NIH grant to develop self-controlled methods. These data are preliminary and predecisional so please treat as confidential. Although this was done under a grant separate from VSD and ISO was not involved, it does use SCK VSD data and includes VSD investigators. Please review in advance if you can. We will go over selected results tomorrow. Thanks.

Tom

-----Original Appointment-----
From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)
Sent: Thursday, August 24, 2023 9:23 AM
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Subject: Follow-up: Covid bivalent and IIV
When: Friday, August 25, 2023 9:00 AM-9:30 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Microsoft Teams Meeting

This is intended to be a scientific discussion on the post-signal analysis. Feel free to fwd the invite to others as necessary. Additional info will follow.

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Ischemic stroke after bivalent COVID-19 vaccination: a self-controlled case series study

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August, 2023

DEPARTMENT OF RESEARCH & EVALUATION

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Outline

- Background
- Objective
- Methods
- Results
- Summary and limitations

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Background

- On August 31, 2022, the U.S. Food and Drug Administration (FDA) granted emergency use authorizations (EUAs) for the Pfizer-BioNTech bivalent COVID-19 vaccine for individuals aged 12 years and older and the Moderna bivalent COVID-19 vaccine for individuals 18 years and older (FDA; Rosenblum, et al., 2022).

- The bivalent vaccines contain mRNA components derived from both the original strain of SARS-CoV-2 and the omicron variant BA.4 and BA.5 sublineages.

- Designed to be administered as a single booster dose, the vaccines were recommended to be given at least ≥60 days after either completing primary vaccination or receiving a monovalent booster dose.

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Background: Safety of bivalent COVID-19 vaccines

- Safety data for bivalent mRNA COVID-19 vaccines were initially limited. Because of the similarities in chemical components and production processes between monovalent and bivalent vaccines, safety data for monovalent vaccines in addition to limited safety data for bivalent vaccines from clinical trials were used in FDA's decision to authorize bivalent vaccines.
- A recent study, which comprehensively assessed potential vaccination-related adverse events using TreeScan, found no increased risk for a broad range of adverse events associated with bivalent vaccines in the Vaccine Safety Datalink (VSD) network (Yih et al., 2023).
- However, based on preliminary results of the VSD COVID-19 RCA, on January 13, 2023, the CDC and FDA announced a possible "safety signal" for ischemic stroke following Pfizer-BioNTech COVID-19 bivalent booster vaccination among those 65 years and older who had received a bivalent booster dose and influenza vaccine on the same day. This safety signal was attenuated as data accumulated.

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Background: Safety of bivalent COVID-19 vaccines

- In a cohort study among adults aged 65 and older, those who received the Pfizer-BioNTech bivalent booster had a similar hazard for ischemic stroke encounters compared to those who received the Moderna bivalent booster vaccine but had a lower hazard than those who received the Pfizer-BioNTech /Moderna monovalent boosters (Gorenflo et al., 2023).

- In a matched cohort study (1:5), compared to monovalent vaccination, bivalent vaccines were not found to be associated with increased risk of ischemic stroke, hemorrhagic stroke, myocardial infarction, and pulmonary embolism (Jabagi et al., 2023).

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Objective

To assess the risk of ischemic stroke after bivalent COVID-19 vaccination among individuals enrolled in Kaiser Permanente Southern California (KPSC) using a modified self-controlled case series (SCCS) design. Subgroup analyses were also conducted by age (<65 years versus ≥65 years), history of SARS-CoV-2 infection, and co-administration of influenza vaccines.

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Methods: Study population, period, and exposure

- **Study Population and study period:** We conducted a SCCS study among members aged ≥12 years from Kaiser Permanente Southern California (KPSC). The SCCS analytic datasets included individuals who experienced ischemic strokes between September 1, 2022 and March 31, 2023, and had completed a primary series and had received their last monovalent dose ≥60 days before September 1, 2022. We required KPSC membership on September 1, 2022.

- **Exposure and observation period:** The exposure was defined as the administration of the Pfizer-BioNTech bivalent COVID-19 vaccine for individuals aged ≥12 years and the Moderna bivalent COVID-19 vaccine for individuals aged ≥18 years during September 1, 2022 - March 31, 2023. The observation period for the recipients of bivalent COVID-19 vaccines started on September 1, 2022, and ended on March 31, 2023, or upon death, or receipt of the second bivalent dose, or disenrollment, whichever came first.

- To adjust for seasonality, we also included ischemic stroke events occurring among individuals who did not receive the bivalent vaccines but had completed a primary series and had received their last monovalent dose ≥60 days before September 1, 2022 (non-bivalent recipients [NBR]). The observation period for these unexposed cases started on September 1, 2022, and ended on March 31, 2023, or upon death or disenrollment, whichever came first.

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Methods: Outcome using VSD RCA ischemic stroke definition

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

We included the first ischemic stroke encounter in the ED/inpatient setting between 9/1/2022-3/31/2023. We also looked back 30 days from September 1, 2022 to ensure the episode was incident.

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Methods: Chart review of automated ischemic stroke events.

- We considered these ischemic stroke events that were identified with ICD-10 codes as automated ischemic stroke events.
- When a safety signal was detected in analyzing automated ischemic stroke events, we conducted chart review to confirm ischemic stroke events among recipients of bivalent COVID-19 vaccines.
- During chart review process, we also determined onset date of ischemic stroke events among recipients of bivalent COVID-19 vaccines. Onset dates were used to determine whether confirmed ischemic stroke events fell in the risk or control interval.
- Confirmation rates were then calculated (number of true cases divided by number of cases being reviewed) and applied to ischemic stroke events among NBR. We did not conduct chart review on ischemic stroke events among NBR due to a large number of events in this group and limited resource.

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Methods: Statistical analyses

- We assessed the risk of ischemic stroke following the administration of the Pfizer-BioNTech and Moderna COVID-19 bivalent vaccines separately.
- Only the first ischemic stroke event in the observation period was included in SCCS analyses (Ghebremichael-Weldeselassie et al., 2022).
- Demographic characteristics of individuals who experienced ischemic stroke events during the study period were described based on the bivalent vaccine product they received.
- The risk intervals were pre-specified as 1-21 days and 1-42 days after administration of bivalent vaccine, with person-time outside of these intervals serving as the control interval. The risk intervals were defined to start on the vaccination date (Day 1).
- Because individuals who had ischemic stroke events might be likely to postpone or avoid bivalent vaccination, we used a SCCS model for event-dependent exposures (Farrington et al., 2009). The modified SCCS used a pseudolikelihood approach in the counter-factual framework to estimate relative incidence (RI) comparing the risk interval to the control interval.

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Methods: Statistical analyses (cont'd)

- In the SCCS analyses, ischemic stroke events occurring among individuals who did not receive the bivalent vaccines were included to account for seasonality, by incorporating calendar months into the model (Ghebremichael-Weldeselassie et al., 2022).

- Additionally, we performed several subgroup analyses based on age (<65 years versus ≥65), administration of bivalent vaccines with or without co-administration of influenza vaccine on the same day, and with or without a history of SARS-CoV-2 infection (confirmed by a positive test or COVID-19 diagnosis) within one year prior to September 1, 2022.

- We only performed chart review on ischemic stroke events among recipients of bivalent COVID-19 vaccines and conducted further analyses only when a potential safety concern was identified.

- In analyzing confirmed ischemic stroke events among recipients of bivalent COVID-19 vaccines, we introduced a randomized allocation of confirmed case status to the NBR group. This allocation was guided by the confirmation rates observed among recipients of bivalent COVID-19 vaccines, as outlined by Xu et al (2018).

- Subsequently, five simulated datasets were generated to replicate this process. Repeated SCCS analyses were conducted on each dataset, and the resulting estimates were aggregated using Rubin's rule (Rubin, 2004), which accounts for both the variability within individual datasets and the variability across the multiple datasets

Results: Characteristics of individuals who had ischemic stroke events

Table 1. Characteristics of individuals who had ischemic stroke events during the period from September 1, 2022, to March 31, 2023.

	Recipients of Pfizer -BioNTech bivalent COVID-19 vaccine, no. (%)	Recipients of Moderna bivalent COVID-19 vaccine, no. (%)	Non-recipients of bivalent vaccines, no. (%)
Overall	1057 (100.0)	827 (100.0)	3049 (100.0)
Age (in years)			
12-17	1 (0.1)	N/A	6 (0.2)
18-44	32 (3.0)	15 (1.8)	261 (8.6)
45-64	245 (23.2)	177 (21.4)	1011 (33.2)
65-74	618 (58.5)	501 (60.6)	1406 (46.1)
75+	161 (15.2)	134 (16.2)	365 (12.0)
Sex			
Female	540 (51.1)	446 (53.9)	1637 (53.7)
Male	517 (48.9)	381 (46.1)	1412(46.3)
Race/ethnicity			
Hispanic	311 (29.4)	259 (31.3)	1186 (38.9)
Non-Hispanic White	470 (44.5)	326 (39.4)	1027 (33.7)
Non-Hispanic Asian	119 (11.3)	99 (12.0)	270 (8.9)
Non-Hispanic Black	139 (13.1)	120 (14.5)	472 (15.5)
Missing	6 (0.6)	9 (1.1)	37 (1.2)
Multiple/Other	12 (1.1)	14 (1.7)	57 (1.9)

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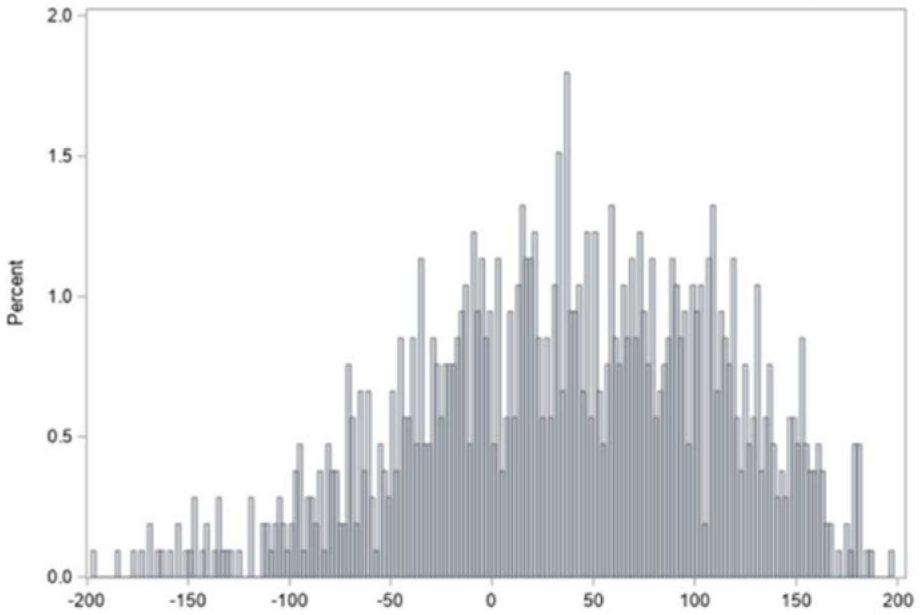
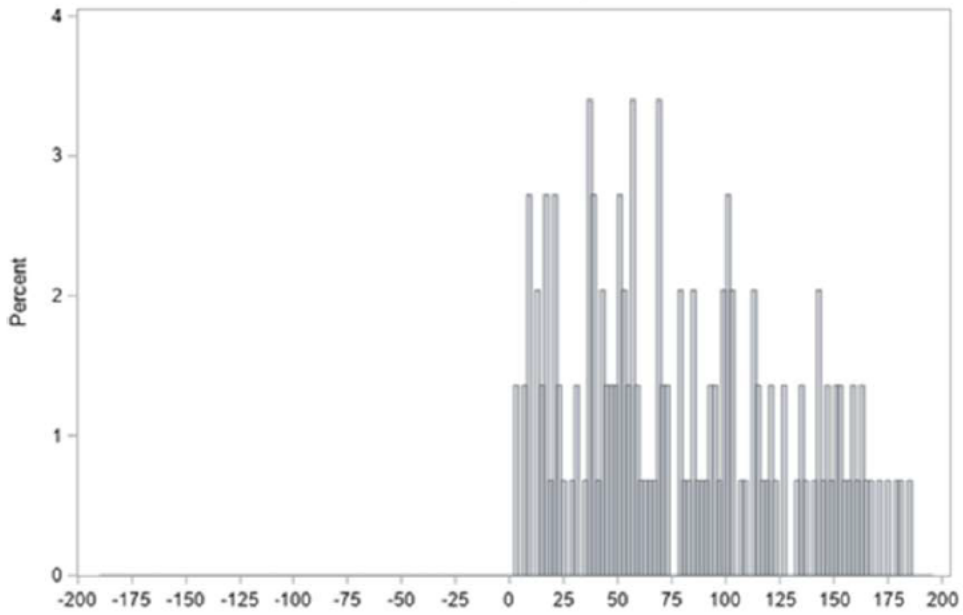
Results: Plot of interval between Pfizer-BioNTech bivalent vaccination and ischemic stroke onset date



Interval between ischemic stroke and Pfizer-BioNTech bivalent vaccination and (n=1057)



Interval between ischemic stroke and Pfizer-BioNTech bivalent vaccination among those with co-administered influenza vaccine (n=147)

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Results: Risk of ischemic stroke following the Pfizer-BioNTech bivalent COVID-19 vaccine

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Results: Analyses of automated ischemic stroke cases with risk interval=21 days after Pfizer-BioNTech bivalent vaccination

Table 2. Numbers of automated ischemic stroke events and relative incidences (RI) in the 21 days after Pfizer-BioNTech bivalent COVID-19 vaccination.

	All ages				<65 years old				≥65 years old			
	Number of events				Number of events				Number of events			
	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)
Overall	103	954	3049	0.90 (0.73–1.12)	19	259	1278	0.68 (0.42–1.12)	84	695	1771	0.98 (0.77–1.25)
With history of SARS-CoV-2[P]	12	162	565	0.68 (0.39–1.19)	2	66	292	0.52 (0.18–1.51)	10	96	273	0.77 (0.40–1.47)
Without history of SARS-CoV-2	91	792	2484	0.96 (0.76–1.21)	17	193	986	0.75 (0.43–1.32)	74	599	1498	1.02 (0.79–1.33)
Co-administration of influenza vaccine, overall	22	125	3049	1.03 (0.65–1.62)	6	25	1278	1.39 (0.60–3.24)	16	100	1771	0.94 (0.55–1.62)
With history of SARS-CoV-2[P]	3	24	565	0.85 (0.31–2.29)	1	9	292	1.35 (0.33–5.52)	2	15	273	0.61 (0.16–2.35)
Without history of SARS-CoV-2	19	101	2484	1.07 (0.65–1.79)	5	16	986	1.41 (0.49–4.02)	14	85	1498	1.02 (0.56–1.83)
No co-administration of influenza vaccine, overall	81	829	3049	0.87 (0.68–1.11)	13	234	1278	0.55 (0.30–1.01)	68	595	1771	0.97 (0.75–1.27)
With history of SARS-CoV-2[P]	9	138	565	0.63 (0.32–1.22)	1	57	292	0.33 (0.07–1.50)	8	81	273	0.78 (0.37–1.62)
Without history of SARS-CoV-2	72	691	2484	0.93 (0.71–1.20)	12	177	986	0.64 (0.33–1.24)	60	514	1498	1.01 (0.76–1.35)

§Non-bivalent recipients (NBR) were eligible individuals who did not receive a bivalent vaccine but had completed a primary series of COVID-19 vaccination and had their last monovalent dose ≥60 days before 9/1/2022. Inclusion of these events helps to adjust for temporal trends (seasonality). The same NBR population was used in overall bivalent analyses as well as bivalent analyses stratified by co-administration of influenza vaccine. ¶Relative incidence. [P] Had SARS-CoV-2 infection (i.e., SARS-CoV-2 positive laboratory test or a COVID-19 diagnosis) during the year prior (08/31/2021-08/31/2022).

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Results: Analyses of automated ischemic stroke cases with risk interval=42 days after Pfizer-BioNTech bivalent vaccination

Table 3. Numbers of automated ischemic stroke events and relative incidences (RI) in the 42 days after Pfizer-BioNTech bivalent COVID-19 vaccination.

	All ages				<65 years old				≥65 years old			
	Number of events				Number of events				Number of events			
	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)
Overall	212	845	3049	0.97 (0.81–1.15)	50	228	1278	0.98 (0.69–1.38)	162	617	1771	0.96 (0.79–1.17)
With history of SARS-CoV-2ᵖ	35	139	565	0.98 (0.66–1.47)	15	53	292	1.22 (0.64–2.33)	20	86	273	0.83 (0.50–1.40)
Without history of SARS-CoV-2	177	706	2484	0.97 (0.80–1.17)	35	175	986	0.91 (0.61–1.38)	142	531	1498	0.99 (0.80–1.22)
Co-administration of influenza vaccine, overall	41	106	3049	0.99 (0.68–1.45)	15	16	1278	2.14 (1.02–4.49)	26	90	1771	0.77 (0.49–1.23)
With history of SARS-CoV-2ᵖ	9	18	565	1.36 (0.61–3.05)	6	4	292	3.94 (1.10–14.16)	3	14	273	0.58 (0.16–2.14)
Without history of SARS-CoV-2	32	88	2484	0.92 (0.60–1.41)	9	12	986	1.58 (0.61–4.09)	23	76	1498	0.81 (0.49–1.33)
No co-administration of influenza vaccine, overall	171	739	3049	0.95 (0.79–1.16)	35	212	1278	0.80 (0.54–1.19)	136	527	1771	1.00 (0.81–1.24)
With history of SARS-CoV-2ᵖ	26	121	565	0.87 (0.55–1.38)	9	49	292	0.82 (0.37–1.80)	17	72	273	0.85 (0.49–1.50)
Without history of SARS-CoV-2	145	618	2484	0.98 (0.80–1.21)	26	163	986	0.81 (0.51–1.28)	119	455	1498	1.03 (0.81–1.30)

§Non-bivalent recipients (NBR) were eligible individuals who did not receive a bivalent vaccine but had completed a primary series of COVID-19 vaccination and had their last monovalent dose ≥60 days before 9/1/2022. Inclusion of these events helps to adjust for temporal trends (seasonality). The same NBR population was used in overall bivalent analyses as well as bivalent analyses stratified by co-administration of influenza vaccine. ¶Relative incidence. ᵖ Had SARS-CoV-2 infection (i.e., SARS-CoV-2 positive laboratory test or a COVID-19 diagnosis) during the year prior (08/31/2021-08/31/2022).

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Chart review of ischemic stroke cases among recipients of the Pfizer-BioNTech bivalent vaccine

- After adjusting for seasonality with the risk interval=42 days, the risk of ischemic stroke was elevated only among those aged <65 years and had bivalent vaccine and influenza vaccine co-administered on the same day. There were 31 cases in this particular subgroup analysis (risk interval=42 days, <65 years, and co-administration of bivalent and influenza vaccines).

- We conducted chart review of these 31 ischemic stroke cases among recipients of Pfizer-BioNTech bivalent vaccine. Among them, 2 were determined to be hemorrhagic strokes, and 8 were subsequently found to not meet the criteria for true ischemic stroke events, yielding a confirmation rate of 68%.

- With the verified 21 ischemic stroke events and ischemic stroke events among NBR (not verified through chart review, but adjusted for using a 68% confirmation rate), we proceeded to re-evaluate this subgroup using the dependent SCCS analysis.

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Results: Analyses of confirmed ischemic stroke cases with risk interval=42 days among recipients of Pfizer-BioNTech bivalent vaccine, aged <65 years

Table 4. Numbers of confirmed ischemic stroke events among recipients of the Pfizer-BioNTech bivalent COVID-19 vaccine aged <65 years, and relative incidences (RI) in the 42 days after co-administration of bivalent and influenza vaccines.

	Number of events			
	Risk interval	Control interval	NBR§	RI¶ (95% CI)
Co-administration of influenza vaccine, overall	10	11	874	2.35 (0.98–5.65)
With history of SARS-CoV-2ᵖ	4	3	197	4.33 (0.98–19.11)
Without history of SARS-CoV-2	6	8	677	1.76 (0.57–5.42)

§Non-bivalent recipients (NBR) were eligible individuals who did not receive a bivalent vaccine but had completed a primary series of COVID-19 vaccination and had their last monovalent dose ≥60 days before 9/1/2022. Inclusion of these events helps to adjust for temporal trends (seasonality). A confirmation rate of 68% was applied to ischemic stroke events among NBR.
¶Relative incidence. ᵖ Had SARS-CoV-2 infection (i.e., SARS-CoV-2 positive laboratory test or a COVID-19 diagnosis) during the year prior (08/31/2021-08/31/2022).

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Characteristics of 10 confirmed ischemic strokes in the 42-day risk interval

- As of 3/31/2023, no deaths occurred.
- Among them, mean age was 58 years, ranging from 48 to 63 years.
- Seven received the single dose, egg-based quadrivalent influenza vaccine, while 3 received an influenza vaccine of unknown formulation.
- Two had history of ischemic stroke: one (TIA) had a stroke 1.5 months ago; the other person (TIA) had a stroke 6 years ago.
- Among the four ischemic stroke cases with a history of SARS-CoV-2 infection, interval between last infection and bivalent vaccination was between 107 days and 386 days.

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Results: Risk of ischemic stroke following the Moderna bivalent COVID-19 vaccine

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Results: Analyses of automated ischemic stroke cases with risk interval=21 days after Moderna bivalent vaccination

Table 5. Numbers of automated ischemic stroke events and relative incidences (RI) in the 21 days after Moderna bivalent COVID-19 vaccination.

	All ages				<65 years old				≥65 years old			
	Number of events				Number of events				Number of events			
	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)
Overall	82	745	3049	0.91 (0.71–1.15)	13	179	1278	0.63 (0.35–1.14)	69	566	1771	0.99 (0.76–1.29)
With history of SARS-CoV-2ᵖ	10	129	565	0.60 (0.32–1.14)	3	33	292	0.87 (0.25–2.97)	7	96	273	0.52 (0.25–1.10)
Without history of SARS-CoV-2	72	616	2484	0.98 (0.75–1.28)	10	146	986	0.58 (0.30–1.13)	62	470	1498	1.11 (0.83–1.47)
Co-administration of influenza vaccine, overall	8	67	3049	0.59 (0.27–1.28)	4	19	1278	1.10 (0.37–3.21)	4	48	1771	0.42 (0.14–1.27)
With history of SARS-CoV-2ᵖ	1	16	565	0.34 (0.04–2.67)	1	6	292	1.03 (0.12–8.79)	0	10	273	-N/A
Without history of SARS-CoV-2	7	51	2484	0.65 (0.28–1.54)	3	13	986	1.07 (0.31–3.63)	4	38	1498	0.52 (0.16–1.67)
No co-administration of influenza vaccine, overall	74	678	3049	0.95 (0.74–1.23)	9	160	1278	0.53 (0.27–1.07)	65	518	1771	1.07 (0.81–1.41)
With history of SARS-CoV-2ᵖ	9	113	565	0.64 (0.33–125)	2	27	292	0.79 (0.18–3.54)	7	86	273	0.59 (0.28–1.24)
Without history of SARS-CoV-2	65	565	2484	1.03 (0.78–1.35)	7	133	986	0.49 (0.22–1.07)	58	432	1498	1.19 (0.89–1.60)

§Non-bivalent recipients (NBR) were eligible individuals who did not receive a bivalent vaccine but had completed a primary series of COVID-19 vaccination and had their last monovalent dose ≥60 days before 9/1/2022. Inclusion of these events helps to adjust for temporal trends (seasonality). The same NBR population was used in overall bivalent analyses as well as bivalent analyses stratified by co-administration of influenza vaccine. ¶Relative incidence. ᵖ Had SARS-CoV-2 infection (i.e., SARS-CoV-2 positive laboratory test or a COVID-19 diagnosis) during the year prior (08/31/2021-08/31/2022).

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Results: Analyses of automated ischemic stroke cases with risk interval=42 days after Moderna bivalent vaccination

Table 6. Numbers of automated ischemic stroke events and relative incidences (RI) in the 42 days after Moderna bivalent COVID-19 vaccination.

	All ages				<65 years old				≥65 years old			
	Number of events				Number of events				Number of events			
	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)	Risk interval	Control interval	NBR§	RI¶ (95% CI)
Overall	161	666	3049	0.92 (0.76–1.12)	34	158	1278	0.99 (0.64–1.53)	127	508	1771	0.90 (0.72–1.13)
With history of SARS-CoV-2Þ	28	111	565	1.02 (0.66–1.59)	10	26	292	2.62 (1.13–6.03)	18	85	273	0.71 (0.42–1.19)
Without history of SARS-CoV-2	133	555	2484	0.90 (0.72–1.12)	24	132	986	0.73 (0.43–1.23)	109	423	1498	0.95 (0.74–1.21)
Co-administration of influenza vaccine, overall	20	55	3049	0.80 (0.45–1.40)	8	15	1278	1.33 (0.56–3.18)	12	40	1771	0.64 (0.31–1.31)
With history of SARS-CoV-2Þ	3	14	565	0.51 (0.14–1.93)	3	4	292	2.43 (0.54–10.87)	0	10	273	NA
Without history of SARS-CoV-2	17	41	2484	0.89 (0.48–1.66)	5	11	986	0.96 (0.33–2.80)	12	30	1498	0.88 (0.41–1.88)
No co-administration of influenza vaccine, overall	141	611	3049	0.93 (0.76–1.15)	26	143	1278	0.90 (0.55–1.49)	115	468	1771	0.94 (0.74–1.18)
With history of SARS-CoV-2Þ	25	97	565	1.14 (0.71–1.82)	7	22	292	2.69 (0.98–7.36)	18	75	273	0.85 (0.49–1.46)
Without history of SARS-CoV-2	116	514	2484	0.90 (0.71–1.14)	19	121	986	0.68 (0.37–1.23)	97	393	1498	0.96 (0.74–1.24)

§Non-bivalent recipients (NBR) were eligible individuals who did not receive a bivalent vaccine but had completed a primary series of COVID-19 vaccination and had their last monovalent dose ≥60 days before 9/1/2022. Inclusion of these events helps to adjust for temporal trends (seasonality). The same NBR population was used in overall bivalent analyses as well as bivalent analyses stratified by co-administration of influenza vaccine. ¶Relative incidence. Þ Had SARS-CoV-2 infection (i.e., SARS-CoV-2 positive laboratory test or a COVID-19 diagnosis) during the year prior (08/31/2021-08/31/2022).

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Chart review of ischemic stroke cases among recipients of the Moderna bivalent vaccine

- After adjusting for seasonality with the risk interval=42 days, the risk of ischemic stroke was elevated among those aged <65 years and had a documented SAS-Cov-2 infection in prior year. There were 36 cases in this particular subgroup analysis (risk interval=42 days, <65 years, and a documented SAS-Cov-2 infection).

- We conducted chart review of these 36 ischemic stroke cases among recipients of Moderna bivalent vaccine. Among them, 1 were determined to be hemorrhagic stroke, and 12 were subsequently found to not meet the criteria for true ischemic stroke events, yielding a confirmation rate of 64%.

- After using a risk interval of 1-42 days following the Moderna bivalent vaccination and applying 64% confirmation rate to ischemic strokes among eligible individuals who did not receive bivalent vaccination, the RI derived from analyzing confirmed ischemic stroke events among those aged <65 years and had a documented SARS-CoV-2 infection was 2.24 (95% CI, 0.78–6.47).

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Summary: Ischemic stroke after Pfizer-BioNTech bivalent vaccination

- The SCCS analyses confirmed the later finding of RCA that the risk of ischemic stroke was not elevated during 1-21 days after coadministration of Pfizer-BioNTech bivalent vaccine and influenza vaccine among those aged ≥65 years.

- After conducting chart review of cases, adjusting for seasonality and with risk interval=42 days, the point estimate for the risk of ischemic stroke was elevated only among those aged <65 years and who had both Pfizer-BioNTech bivalent vaccine and influenza vaccine co-administered on the same day, with relative incidence=2.35 (95% CI, 0.98–5.65) and a p-value of 0.057. The point estimate of the RI increased to 4.33 (95% CI, 0.98–19.11) with a p-value of 0.053 among those who also had SARS-CoV-2 infection within one year prior to 9/1/2022.

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Summary (cont'd): Ischemic stroke after Moderna bivalent vaccination

- The SCCS analyses confirmed the finding of RCA that the risk of ischemic stroke was not elevated during 1-21 days after coadministration of Moderna bivalent vaccine and influenza vaccine among those aged ≥65 years.

- Although there was a safety signal after analyzing automated cases among those aged <65 years who also had a documented history of SARS-Cov-2 infection, the signal disappeared in re-evaluating the risk after conducting chart review of ischemic strokes possibly due to a decreased sample size (RI=2.24; 95% CI, 0.78–6.47).

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Limitations

- Small sample size due to being a single health care system.
- We did not chart review cases among non-bivalent recipients. In addressing this issue, when analyzing chart-review-confirmed ischemic stroke events among recipients of bivalent COVID-19 vaccines, we applied a confirmation rate to these ischemic stroke events.
- We did not chart review cases from those analyses that did not signal.
- While we did exclude ischemic stroke cases occurring within 30 days of SARS-Cov-2 infection, it is possible that some ischemic stroke events included in the analyses involved individuals with asymptomatic or mild COVID-19 disease and did not have a documented SARS-CoV-2 infection.
- The elevated risk of ischemic stroke, while marginally statistically significant, was observed within the 1–42 day period following co-administration of the Pfizer-BioNTech bivalent vaccine and influenza vaccine. This risk interval was longer than the 1–21 days or 1–28 days investigated in earlier research (FDA-RCA, 2023; Jabagi et al., 2023; Ihle-Hansen et al., 2023). However, the biological plausibility for the occurrence of a vaccine-related ischemic stroke beyond 28 days remains uncertain.

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Limitations (cont'd)

- We did not conduct chart review of cases among non-bivalent recipients. In addressing this issue, when analyzing chart-review-confirmed ischemic stroke events among recipients of bivalent COVID-19
- Unknown time-varying confounders may not be adjusted.

- We did not adjust for multiple subgroup analyses by age, the coadministration of bivalent COVID-19 vaccines and influenza vaccines, as well as the history of SARS-Cov-2 infection. These analyses were considered as prior hypotheses due to their potential safety concerns identified in previous studies. The decision not to make multiple comparison adjustments was deliberate, aimed at ensuring that any potential vaccine safety concern could be detected.

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Strengths

- The study addressed the impact of previous ischemic stroke events on the bivalent COVID-19 vaccination by employing an event-dependent SCCS design.
- The study explored effect heterogeneity by conducting subgroup analyses based on factors such as age, documented history of SARS-CoV-2 infection, and coadministration of influenza vaccines
- To adjust for temporal trends, we included ischemic stroke events among eligible individuals who did not receive bivalent COVID-19 vaccines during the study period. This strategic inclusion not only enhanced the accuracy of estimating the baseline rate but also improved the statistical power for identifying potential safety signals.
- We re-analyzed ischemic stroke events that were confirmed through medical chart reviews for those analyses where safety signals were detected.

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Conclusion and future studies

- We found an elevated point estimate for the risk of ischemic stroke with marginal statistical significance within 1–42 days after the co-administration of the Pfizer-BioNTech bivalent vaccine and influenza vaccine among individuals <65 years old, although the sample size was limited.

- Future studies with a large sample size are needed to verify the findings in the current study and to conduct sensitivity analyses such as exclusion of transient ischemic attack (TIA) and exclusion of those who had a history of ischemic stroke.

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From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Weintraub, Eric (CDC/DDID/NCEZID/DHQP)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted], "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: FW: risk of ischemic stroke after bivalent COVID-19 vaccination: SCCS analyses
Date: Thu, 27 Jul 2023 18:19:44 +0000
Importance: High

Let's set up a small group call with Stan and his team for next week – fine to include NCK as well. I need to get a better understanding of what they did and what they found. There is a bit of urgency on this topic as the fall covid vaccination program will likely roll out in the coming months. Thanks.
Tom

From: Stanley Xu [redacted]
Sent: Thursday, July 27, 2023 11:26 AM
To: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] NICOLA P KLEIN <[redacted] Bruce H Fireman <[redacted]
Cc: Kimberly J Holmquist [redacted]; Denison S Ryan [redacted] Bruno J. Lewin <[redacted] Lina Somsouk Sy <[redacted] Lei Qian <[redacted] Xu, Stan [redacted]
Subject: risk of ischemic stroke after bivalent COVID-19 vaccination: SCCS analyses
Importance: High

Hi Eric, Tom, Nicky and Bruce,

I hope this email finds you well. As you know, we have been conducting a SCCS study to assess the risk of ischemic stroke after COVID-19 bivalent vaccination. This is motivated by the findings from the RCA work and is funded by an RO1 (PI: Xu) that involves KPSC investigators Lei, Lina, Bruno, and a couple of non-VSD investigators. Kim Holmquist is our project manager. Thanks to Nicky and Bruce for your approval of the use of chart abstraction tool and agreement to collaborate with us. We have made significant progress and we would like to share some preliminary results with you.

Our analysis with SCK data includes both unvaccinated cases and cases prior to vaccination to account for seasonality. Additionally, we employ a dependent SCCS approach to accommodate event-caused delays or cancellations of exposure (i.e., bivalent vaccination). Here are some key details about our approaches and high-level results:

1. we pulled ischemic stroke (IS) and administration of bivalent dose data between 9/1/2022 and 3/31/2023. We divided these cases into three groups based on their exposure: 1) those who received the pfizer bivalent vaccine; 2) those who received the moderna bivalent vaccine; and 3) those who did not receive bivalent vaccine but had completed primary series of COVID-19 vaccines at least 60 days before 9/1/2022.
2. We then applied exclusion criteria as in RCA analyses except that we did not use the incident case definition. Instead, we included the first IS encounter between 9/1/2022-3/1/2023. We also looked back 30 days from September 1, 2022 to ensure the first independent episode.
3. We prespecified two risk intervals (14- and 28-days after bivalent vaccination) and analyzed these electronically identified IS cases overall and by age group (65 and older vs under 65), with and without historical COVID-19, and with and without co-administration of influenza vaccine. **Results**: after adjusting for seasonality

with risk interval= 42 days, risk of IS was elevated **only among those aged <65 years and had both bivalent dose and flu shot on the same day.** There were 31 cases in this particular subgroup analysis (risk interval=42 days, under 65 and coadministration of bivalent and flu vaccines).

4. We chart reviewed these 31 IS cases among recipients of Pfizer bivalent doses. Among these 31 cases, 2 were hemorrhage strokes and 7 were not true cases; they were excluded from further analyses. With the confirmed 22 IS cases and unexposed IS cases (not chart reviewed), we repeated the dependent SCCS analyses for this subgroup. **Results**: the signal remained.

Our next step is to finish moderna analyses and draft the manuscript. Please let us know if you have any questions/suggestions about our approaches and results. We will also be willing to present our findings on a VSD call such as the Wednesday's COVID-19 RCA call or a small group call (for example CDC, NCK and SCK).

Thank you,

Stan

From: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Carter, Christina (CDC/DDID/NCIRD/OD) (CTR)" [redacted]
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: Re: FINAL COPY: Rollout ACIP COVID-19 Session 2/24/23
Date: Fri, 24 Feb 2023 15:14:30 -0000
Importance: Normal

Thanks
Have a nice weekend
Karen

Get Outlook for iOS

From: Carter, Christina (CDC/DDID/NCIRD/OD) (CTR)[redacted]
Sent: Friday, February 24, 2023 10:12:20 AM
To: Broder, Karen (CDC/DDID/NCEZID/DHQP)[redacted]
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: FINAL COPY: Rollout ACIP COVID-19 Session 2/24/23

Karen/Tom,

No problem! I'll update the final version on file, but will not resend to the entire group.

Thank you! Have a great weekend!

Christina Carter, MPH
She/Her (why do pronouns matter?)
Health Communication Specialist
Eagle Global Scientific, LLC
Contractor for Coronavirus & Other Respiratory Viruses Division *(Proposed)*
DDID/NCIRD/OD
[redacted]

From: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Friday, February 24, 2023 9:58 AM
To: Carter, Christina (CDC/DDID/NCIRD/OD) (CTR)[redacted]
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)[redacted]
Subject: FW: FINAL COPY: Rollout ACIP COVID-19 Session 2/24/23
Importance: High

Christina,

Nice work. After reviewing the ACIP slides again, I have one small edit to propose if its not too late. Tom agreed with this edit in green. Can the document be updated?

Thanks,

Karen Broder, MD

Current: Based on the results of the analysis to investigate the ischemic stroke signal, the higher-than-expected rate of ischemic stroke was seen in persons who received the Pfizer-BioNTech bivalent vaccine and high-dose influenza vaccine simultaneously; however, this finding is limited by small numbers.

Proposed edit: Based on the results of the analysis to investigate the ischemic stroke signal, the higher-than-expected rate of ischemic stroke was seen in persons who received the Pfizer-BioNTech bivalent vaccine and high-dose influenza or adjuvanted influenza vaccine simultaneously; however, this finding is limited by small numbers.

From: Carter, Christina (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Sent: Friday, February 24, 2023 9:33 AM
To: Oliver, Sara Elizabeth (CDC/DDID/NCIRD/DVD) [redacted] Twentyman, Evelyn Rebecca Ford (CDC/DDID/NCIRD/DVD) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Britton, Amadea (CDC/DDID/NCIRD/DVD) [redacted] Link-Gelles, Ruth (CDC/DDID/NCIRD/DVD) [redacted] Pearson, Kate L. (CDC/DDID/NCIRD/OD) [redacted] Moorer, Alanna (CDC/DDID/NCEZID/DHQP) [redacted] Broder, Karen (CDC/DDID/NCEZID/DHQP [redacted] Meyer, Sarah (CDC/DDID/NCIRD/ISD) [redacted] Duggar, Christopher (CDC/DDID/NCIRD/ISD [redacted] Hall, Elisha (CDC/DDID/NCIRD/ISD) [redacted] Williams, Paula O. (CDC/DDPHSS/CSELS/OD) [redacted] Thompson, Natarsha (ATSDR/OAD) [redacted] Hall, Aron (CDC/DDID/NCIRD/DVD [redacted] Reott, Erica (CDC/DDNID/NCIPC/OD [redacted] Gallagher, Kathryn M. (CDC/DDNID/NCCDPHP/OSH) [redacted] Mahon, Barbara (CDC/DDID/NCIRD/OD) [redacted] Dowling, Nicole (CDC/DDID/NCIRD/ISD [redacted] Miller, Rebecca (CDC/DDID/NCIRD/ISD) [redacted] Taylor, Melissa (CDC/DDID/NCIRD/ISD) [redacted] Dodge Ramey, Sara (CDC/DDID/NCIRD/ISD) [redacted] Beckett, Geoff (CDC/DDID/NCIRD/OD) (CTR) [redacted] Robertson, Alaina B. (CDC/OD/OADC) [redacted] Bedrosian, Sara (CDC/OD/OADC) [redacted] Boyce, Latifa (CDC/DDPHSIS/CPR/DEO) [redacted] Hansen, Donda L. (CDC/DDPHSIS/CPR/DEO) [redacted] Stamps, Sharleta (CDC/DDID/NCIRD/OD) (CTR) [redacted] Nordlund, Kristen (CDC/OD/OADC) [redacted] Hamburger, Tanya (CDC/DDID/NCEZID/DHQP) [redacted] Fleming-Dutra, Katherine E. (CDC/DDID/NCIRD/DVD) [redacted] Downs, Alycia E. (CDC/DDID/NCIRD/OD) [redacted] Jorgensen, Cynthia (CDC/DDID/NCIRD/OD) [redacted]
Cc: Grusich, Katherina (Kate) (CDC/DDID/NCIRD/OD) [redacted] CORVD Communications (CDC) [redacted]
Subject: FINAL COPY: Rollout ACIP COVID-19 Session 2/24/23
Importance: High

All,

Attached is the final, clean copy of the rollout for today's ACIP COVID-19 session.

Thanks!

Christina Carter, MPH
She/Her (why do pronouns matter?)
Health Communication Specialist
Eagle Global Scientific, LLC
Contractor for Coronavirus & Other Respiratory Viruses Division
DDID/NCIRD/OD
[redacted]

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Hamburger, Tanya (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Nguyen, Lyn (CDC/DDID/NCEZID/DHQP)" [redacted] "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: [For review/clearance] ACIP CoAdmin docs - TPs, media statement, updated web
Date: Fri, 24 Feb 2023 20:20:44 +0000
Importance: Normal
Attachments: ACIP_Updates_2023_02_DHQP.docx; Rollout_Plan_ACIP_COVID-19_2.24.23_FINAL-updated.docx
Inline-Images: image001.png

Tanya,

I just spoke to Lyn b/c Karen and I had been working with her on some ACIP comms documents last week. Also, Karen and I have been working with NCIRD on their rollout plan. Attached are at least 2 of those documents which are pretty late stage drafts. Before I get too far into your reviews, it might make sense to make sure the info in the DHQP TPs are consistent with what's in these documents. If these aren't that time sensitive it might make sense to huddle with policy, comms, and ISO (me, John Su, and Karen) and walk thru some of these products. I get the feeling that in the chaos of ACIP and all the covid presentations, there might be some duplicative work happening. Thanks.

Tom

From: Hamburger, Tanya (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Friday, February 24, 2023 2:22 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: [For review/clearance] ACIP CoAdmin docs - TPs, media statement, updated web

Hi Tom,

Your presentation seems to have gone very well. Hope you're feeling good about it.

I know you're busy today. If you have time, can you review the talking points and media statement created for the VSD signal and Pedro's VAERS paper? Pedro worked with us to fine-tune the content.

DRAFT_ACIP TPs_Coadmin COVID and Flu_CLEAN_02242023_PM_TH_dl_PM.docx

In addition, we propose edits to the web page, CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older | CDC, that also needs your review.

WEB_Prelim Signal Adults 65 and older_02.23.2023.docx

Please let me know if there's anything you'd like to discuss.

Thank you, Tanya

Tanya Hamburger, MPH *(she/her)*
Deputy Associate Director for Communication
Outbreaks & Emerging Issues

Division of Healthcare Quality Promotion (DHQP)
Centers for Disease Control and Prevention (CDC)
[redacted]

CDC Update for Advisory Committee on Immunization Practices (ACIP)
February 22-24, 2023

CDC Agency Updates

COVID-19 Vaccine Implementation Updates

- CDC provides weekly updates on COVID-19 vaccine distribution and administration on the CDC COVID Data Tracker website. As of January 26, 2023, more than 953 million doses have been delivered, and more than 668 million doses have been administered, with more than 229 million individuals being fully vaccinated.
- Since the recommendation of the Pfizer-BioNTech COVID-19 vaccine for children aged 5–11 years more than a year ago, more than 11 million individuals aged 5-11 years old have received at least 1 dose of COVID-19 vaccine, with more than 9 million individuals aged 5-11 being fully vaccinated.
- On October 12, 2022, the CDC director signed a decision memo recommending updated (bivalent) COVID-19 boosters for children 5 years of age and older. This announcement expands on CDC's previous recommendation issued September 1, 2022, for updated COVID-19 boosters for people ages 12 years and older.
    - This action followed the Food and Drug Administration (FDA)'s granting of emergency use authorization for the Pfizer-BioNTech updated COVID-19 booster for children ages 5 through 11 years, and the Moderna updated COVID-19 booster for children and adolescents ages 6 through 17 years.
- Updated COVID-19 boosters protect against the original COVID-19 strain and the most recent Omicron subvariants, BA.4 and BA.5. These subvariants are more transmissible and are more likely to be able to evade antibodies made against earlier subvariants. The FDA advised manufacturers earlier this year to add these subvariant components to their COVID-19 vaccine boosters.
- This new recommendation expands updated booster eligibility to about 9 million children ages 5 through 11 years who have already completed the COVID-19 primary series vaccines in the United States.
- CDC disseminated documents to inform jurisdictional planning of a COVID-19 vaccination program for this age group. This included information on ordering and delivery of this vaccine and At-A-Glance fact sheets on the Moderna and the Pfizer-BioNTech COVID-19 vaccine products with information on storage, preparation, scheduling, administration, and dosage. Communications between CDC, jurisdiction, and partners are ongoing to ensure a smooth and swift rollout. The documents are available at COVID-19 Vaccination for Children | CDC.

COVID-19 Vaccine Safety Updates

- CDC recently published a study in Vaccine titled "A safety study evaluating non-COVID-19 mortality risk following COVID-19 vaccination" which was one of the largest vaccine-safety studies of its kind. CDC found no increased risk of death among people who received the original Pfizer-BioNTech, Moderna, or J&J/Janssen COVID-19 vaccines. The findings support that the safety of COVID-19 vaccines and confirm previous observations and findings that the COVID-19 vaccines are not associated with excess death.
- Following availability and use of updated bivalent mRNA COVID-19 booster vaccines, CDC conducted vaccine safety monitoring for these vaccines in three systems: the Vaccine Adverse Event Reporting System (VAERS) (co-managed by CDC and FDA), v-safe, and Vaccine Safety Datalink (VSD).

Commented [SS(1]: I recommend updating with current numbers. Updates occur every Thursday by 8pm so check on 2/17 for the latest numbers. Right now we are at 956M distributed, 669 administered, and 229 fully vaccinated.

Given the push for bivalent boosters, do you want to mention the # of people that have received an updated booster? It is it at 52M.
Stokley, Shannon (CDC/DDID/NCIRD/ISD)
2023-02-09 09:42:00

Commented [DN(2]: COVID Data Tracker reports as "completed primary series" vs. using "fully vaccinated" terminology. Recommend consistency with language.
Dowling, Nicole (CDC/DDID/NCIRD/ISD)
2023-02-09 10:36:00

Commented [FDKE(3]: This information is correct, but it feels a bit odd not to include the December 9 recommendation to expand use of the updated (bivalent) vaccine in children aged >=6months.
Fleming-Dutra, Katherine E. (CDC/DDID/NCIRD/DVD)
2023-02-09 16:01:00

Commented [DN(4]: Recommend adding numbers for bivalent boosters administered, either here or above.
Dowling, Nicole (CDC/DDID/NCIRD/ISD)
2023-02-09 10:30:00

- CDC published two studies assessing the safety of bivalent COVID-19 vaccines, using data from v-safe and VAERS in the MMWR: Hause AM, Marquez P, Zhang B, et al. Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Children Aged 5–11 Years — United States, October 12–January 1, 2023. MMWR Morb Mortal Wkly Rep 2023;72:39–43. DOI: http://dx.doi.org/10.15585/mmwr.mm7202a5
  - Adverse events reported after a bivalent COVID-19 booster dose in persons aged ≥12 years appeared consistent with those reported after a monovalent booster and were less common and less serious than health impacts associated with COVID-19 illness.
  - Early safety findings for bivalent booster vaccination in children aged 5–11 years were similar to those described for monovalent booster vaccination. Most VAERS reports represented vaccine errors rather than adverse events. Neither myocarditis nor death were reported after bivalent booster vaccination in this age group.

VSD assessed pre-specified health outcomes after bivalent COVID-19 vaccine during weekly sequential monitoring and ~~In the primary analysis risks of pre-specified outcomes 1–21 days following a bivalent vaccination (risk interval) were compared with bivalent-vaccinated individuals who were 22–42 days (comparison interval) following the bivalent dose.~~

- ~~VSD~~ did not identify signals for any pre-specified outcome after Moderna bivalent vaccine in any age group and did not identify any signals after Pfizer-BioNTech bivalent vaccine in persons aged <65 years.
- In November 2022, VSD detected a statistical signal for ischemic stroke after Pfizer-BioNTech bivalent COVID-19 vaccine in persons aged ≥65 years. Through January 7, 2023, approximately 550,000 persons aged ≥65 had received the Pfizer-BioNTech bivalent vaccine in VSD (approximately 290,000 had received Moderna bivalent vaccine in VSD). No signals for other pre-specified outcomes were identified in VSD in this age group. Data describing the signal detection and assessment for ischemic stroke were presented and discussed at the FDA's Vaccines and Related Biological Products Advisory Committee meeting on January 26, 2023.
  - VSD analysis to assess the ischemic stroke signal suggested that the signal was being driven by persons receiving high-dose influenza vaccine simultaneously with the Pfizer bivalent COVID-19 vaccine; however, this finding is limited by small numbers.
  - Unmeasured confounding may be present in the VSD analyses. For example, it is possible that early adopters of bivalent booster (present in the analyses) have different characteristics than later adopters. A secondary analysis in VSD using unboosted comparators did not suggest a risk for ischemic stroke.
  - No other safety systems have shown a similar signal for ischemic stroke after bivalent COVID-19 booster vaccine.
  - At this time, no change in vaccination practice is recommended.
  - CDC and FDA will continue to evaluate additional data on the safety of bivalent COVID-19 vaccines in VSD and other vaccine safety systems.

- On February 3, 2023, at a National Vaccine Advisory Committee (NVAC) meeting, CDC presented preliminary outcome data from enhanced surveillance of myocarditis after mRNA COVID-19 vaccination for individuals aged 12-29 years who had onset of myocarditis symptoms at least one year earlier.
  - These data add to those from a previous assessment that found 81% of patients ages 12–29 years diagnosed with myocarditis after receiving an mRNA COVID-19 vaccine were considered recovered by healthcare providers at least 90 days after myocarditis onset.
  - Combining results from the 90-day and 1-year surveys, 89% of patients were considered to have recovered from myocarditis.

- Entering the third year of COVID-19 vaccine availability, CDC has also prioritized its vaccine safety monitoring efforts to focus on the bivalent COVID-19 vaccine and COVID-19 vaccination in children and pregnant people.

Mpox Vaccine Safety Updates

- CDC's Immunization Safey Office conducted vaccine safety monitoring for JYNNEOS vaccine, used to prevent mpox.
  ~~JYNNEOS is a live vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN), an attenuated, non-replicating orthopoxvirus.~~
  JYNNEOS post-licensure and post-authorization vaccine safety surveillance findings to date are consistent with those observed in clinical trials.
- No new or unexpected safety concerns have been identified.
- Serious adverse events were rare among adults, and none have been identified among persons aged <18 years.
- VAERS and VSD data do not suggest an increased risk for myocarditis or pericarditis following JYNNEOS, but the possibility of a small risk cannot be excluded.

Current Efforts on Maintaining Childhood Vaccination Coverage

- In January, CDC published 2 MMWR articles addressing childhood vaccination coverage:
  - *Vaccination Coverage with Selected Vaccines and Exemption Rates Among Children in Kindergarten — United States, 2021–22 School Year;*
  - *Vaccination Coverage by Age 24 Months Among Children Born in 2018 and 2019— National Immunization Survey–Child, United States, 2019–2021*
- The report on vaccination coverage among children in kindergarten reveals an additional 1~~%~~ percentage point drop in nationwide coverage of measles, mumps and rubella vaccine (MMR), diphtheria, tetanus, and acellular pertussis vaccine (DTaP), poliovirus vaccine (polio) and varicella (chickenpox) vaccines.
- Vaccination coverage has dropped a total of 2~~%~~ percentage points since the start of the pandemic – from 95% reported in the 2019-20 school year to 93% in the 2021-22 school year. This steady decline ~~is significant because it~~ means ~~there are more than~~nearly 275250,000 kindergartners are ~~not completely protected against common, and sometimes very serious, vaccine-preventable diseases~~potentially not protected against measles alone.
- The second report found that while coverage with most childhood vaccines increased by the age of 24 months when comparing children born during 2018–2019 with those born during 2016–2017, the percent of uninsured children ~~without insurance~~ not vaccinated by their second birthday was eight times that of privately insured children ~~were more than eight times as likely to be unvaccinated by age 24 months compared to privately insured children~~. The report also shows differences in vaccination coverage among children living below poverty or in rural areas, with a 4 to 5% decrease in coverage among these groups during the pandemic. ~~The report also found children without insurance were more than eight times as likely to be unvaccinated by age 24 months compared to privately insured children.~~
- These reports add to previous data that highlight the lingering impact of the COVID-19 pandemic on routine childhood vaccinations as well as disparities in coverage that have continued to persist, or even widen, among some groups.
- To help address pandemic-related declines in routine immunizations, CDC is launching Let's RISE, an effort to equip partners and health care providers with actionable strategies, resources, and data to support getting all Americans back on schedule with their routine immunizations. More information about Let's RISE and access to routine immunization resources and data can be found on CDC's website: https://www.cdc.gov/vaccines/partners/routine-immunizations-lets-rise.html

Influenza Updates

Seasonal influenza

Commented [SS(5]: There was a lot of back and forth on this topic when we were developing the comms package for the article. This is the sentence that was cleared so recommend using this instead.
Stokley, Shannon (CDC/DDID/NCIRD/ISD)
2023-02-09 09:57:00

Commented [SS(6]: Similar to the one above, this is the final wording that was cleared for this topic.
Stokley, Shannon (CDC/DDID/NCIRD/ISD)
2023-02-09 10:01:00

Commented [SS(7]: This is a repeat of the above.
Stokley, Shannon (CDC/DDID/NCIRD/ISD)
2023-02-09 10:02:00

- The season is ongoing, but at this time, key indicators used to classify severity indicate a moderately severe flu season. This may change as the season progresses.
- According to the most recent FluView report, seasonal influenza activity continues to decline across the country.
- As of January 14, 2023, 171.52 million doses of influenza vaccine have been distributed in the United States this season.
- A total of ~~91~~ 97 pediatric deaths have been reported during the 2022-2023 season.
- For the 2022-2023 influenza season, there are three influenza vaccines that are preferentially recommended for people 65 years and older: Fluzone High-Dose Quadrivalent vaccine, Flublok Quadrivalent recombinant flu vaccine, and Fluad Quadrivalent adjuvanted flu vaccine.
- For the 2022-23 season, based on claims data for adults 18 and older: approximately 66.7 million flu vaccinations have been administered in pharmacies and physician medical offices this season, compared with an estimated 68.03 million at the same time in January 2022. This is about 1.3 million fewer vaccinations by this measure than at the same time last season, which represents a decrease of approximately 2%.
- CDC has partnered with the AD Council and the American Medical Association (AMA) for their annual Get My Flu Shot campaign. The campaign encourages the American public, with emphasis on Black and Hispanic audiences, to get vaccinated against the flu for the 2022-2023 season.

Polio

- A case of paralytic polio caused by vaccine-derived poliovirus type 2 (VDPV2) was confirmed in an unvaccinated person in Rockland County, New York, on July 21, 2022.
- No new paralytic polio cases have been identified in the U.S. for more than 200~~115~~ days.
- Wastewater samples collected from New York (Rockland, Orange, Sullivan, and Nassau Counties, and New York City) are positive for poliovirus type 2; several of the genome sequences are VDPVs with a genetic linkage to the virus from the case patient and thus meet the World Health Organization (WHO) criteria for circulating vaccine-derived poliovirus (cVDPV).
- New York State Department of Health (NYSDOH) is leading the response to the case of polio and is working with the local health departments, and CDC, to mitigate risks and increase polio vaccine uptake.
- CDC has had staff deployed to NY since August 4th to assist with investigation and vaccination efforts in Rockland and Orange Counties. CDC's actions include:
    - Providing direct assistance in Rockland and Orange Counties, NY to:
        - ~~support enhanced passive surveillance for poliovirus in stool through testing by healthcare provider~~
        - increase vaccination through physician specific reminder-recall for under-vaccinated children
        - support community vaccination for adults and children to catch-up on recommended polio vaccination
        - analyze immunization data and assist with school and daycare vaccination audits
        - conduct qualitative interviews in the community to understand challenges and barriers to vaccination
        - ~~help develop and distribute information to promote safe recreational water use~~
    - Conducting testing for poliovirus in wastewater samples in NY and neighboring states, as well as providing confirmatory testing for clinical specimens.
    - Collaborating with Israel, UK, Canada, and WHO to understand the origins and relatedness of the case patient VDPV2 to those in other countries.
    - Ensuring safe and secure handling and transport of potentially infectious material (PIM) through National Authority for Containment (NAC).
    - Working with State and Local Departments of Health to run and refine syndromic surveillance for paralytic polio.
    - Facilitating the procurement of polio vaccine (single antigen and combination vaccine) for affected areas.

Commented [BHC(8]: Flagging that this will likely change again, with latest data available on 2/17 ahead of the meeting
Boswell, Haley C. (CDC/DDID/NCIRD/ID)
2023-02-07 11:33:00

- Working closely with NYSDOH and county staff on long-term strategies for improving vaccine confidence and demand in areas of low inactivated polio vaccine (IPV) coverage.

- CDC ~~expanded~~ is partnering with an additional 5-6 jurisdictions who have communities at risk for poliovirus transmission to expand wastewater testing ~~for poliovirus in 5–6 additional jurisdictions.~~
- The MMWR on the latest wastewater testing results is available here.

Measles

- On~~As of~~ Sunday, February 5, 2023, Columbus Public Health declared ~~that~~ the measles outbreak ~~is~~ over with 85 total cases in Ohio.
  - A measles outbreak is declared over when two incubation periods (42 days) have passed without another case.
- As of January 27, 2023, provisional data indicate that there have been 2 cases of measles in the United States in 2023 in 2 jurisdictions.
- As of January 19, 2023, provisional data indicate that there were 121 cases of measles in the United States in 2022.
- Jurisdictions at highest risk for measles continue to be those ~~with~~ containing communities with persistently low vaccination coverage and importations from locations with ~~poliovirus circulating~~measles outbreaks.
  - In 2022, ~~100% of~~ confirmed cases ~~were~~as associated with importation by individuals with travel history to Kenya, Somalia, Pakistan, and Tanzania, where measles outbreaks are ongoing.

Respiratory Syncytial Virus

- The COVID-19 pandemic interrupted seasonal circulation of RSV and many other respiratory viruses. Following over a year of limited RSV circulation, the US experienced an intra-seasonal RSV wave that peaked in early August 2021.
- The 2022-2023 RSV season was also atypical and marked by a sharp, early peak in late October concurrent with circulation of other respiratory viruses that rapidly overwhelmed many pediatric hospitals and emergency departments. Current trends in RSV activity suggest a continu~~ed~~ing decline to~~wards~~ typical end-of-winter-season levels.
- The early start to the 2022-2023 RSV season ~~is a reminder for~~underscores the need for continued surveillance of RSV activity throughout the year. The shift from a summer RSV peak in 2021 to a fall peak in 2022 may be an early indicator of movement towards resumption of typical winter seasonality in subsequent years, as has been noted in other countries.
- ~~National trends in RSV activity continue to indicate the peak of seasonal activity has passed in all HHS Regions. RSV activity remains elevated in some regions but is decreasing or stable across all regions.~~
- ~~RSV-associated hospitalizations and emergency department visits among people of all ages have peaked, continue to decrease, and are nearing typical end-of-winter season levels.~~
- ~~As typically seen throughout the year, children ages 4 years and younger, especially those aged <6 months, have the highest RSV-associated hospitalization rates currently. Compared to previous years, there are also more RSV-associated ED visits and hospitalizations among older children.~~
- ~~In preliminary analyses among hospitalized children, there continue to be no indications of increased severity of disease among children who tested positive for RSV this year compared to the 4 pre-pandemic seasons, even when accounting for co-infections.~~
-

Vaccine Preventable Bacterial Diseases

- In 2023, Sanofi Pasteur, Inc. stopped manufacturing the diphtheria and tetanus toxoids absorbed vaccine, commonly known as DT. CDC is currently in discussion to provide updated vaccine recommendations for children aged <7 years with a contraindication to receiving pertussis-containing vaccines.
- On November 15, 2022, the CDC director signed a decision memo with updated recommendations for 20-valent pneumococcal conjugate vaccine (PCV20) use among adults who have previously received a 13-valent pneumococcal conjugate vaccine. This announcement expands on CDC's previous recommendation signed by the CDC director and issued on October 29, 2021, for PCV15 and PCV20 use among adults. The updated adult pneumococcal vaccine recommendations were reflected in the Adult Immunization

Commented [DES9]: The 85 cases in the Ohio outbreak and 1 in KY weren't linked to international travel as we likely missed cases infected from the 10/8 importation or other importations.
Sugerman, David E. (CDC/DDID/NCIRD/DVD)
2023-02-07 13:53:00

Commented [MM(10]: @Hall, Aron (CDC/DDID/NCIRD/DVD) please feel free to edit
McMorrow, Meredith (CDC/DDID/NCIRD/DVD)
2023-02-09 17:23:00

Commented [HA(11R10]: Thanks, looks good. Just a few minor tweaks suggested.
Aron J. Hall
2023-02-09 18:48:00

Scheduled published on February 9, 2023. The CDC website and tools for implementation were updated to reflect the new adult pneumococcal vaccine recommendations. Publication of the MMWR Recommendations and Reports summarizing the adult pneumococcal vaccine recommendations is planned for later this year. Adult Schedule: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2023 | MMWR (cdc.gov)

ACIP MEETING COVID-19 ROLLOUT PLAN – FEB 24, 2023

STEP 1: PRE-CLEARANCE

Group	Name	Date
NCIRD Public Affairs	Kate Grusich	2/15/23
Vaccine Policy Unit	Evelyn Twentyman, Sara Oliver	2/17/23
Updated boosters partners/operations/distribution	Sarah Meyer, Chris Duggar, Andrew Lowndes, Elisha Hall	SM 2/16 EH 2/16
ISO Safety	Alanna Moorer, Tom Shimabukuro, Karen Broder	2/16/23 AM 2/22/23 TS 2/22/23 KB
NCIRD Policy - Congressional	Kate Pearson	2/16/23
CORVD (proposed) Comms	Paula Williams, Natarsha Thompson	2/16/2023 (NT & PW)
NCIRD Partnerships	[redacted] Hilary Eiring and Kathryn Weitzner	2/16/23 (HE & KW)

STEP 2: DIVISION CLEARANCE

Unit	Name	Date
CORVD Comms	Natarsha Thompson	2/17/2023
CORVD ADP	Erica Reott	2/21/2023
CORVD DD Science	Aron Hall	2/17/2023

CORVD DD Strat/M&O	Kathy Gallagher	2/21/2023
CORVD Division Director	Barbara Mahon	2/17/2023
ISD ADS -- R *D for web banners, press releases *I for minor web updates	Nicole Dowling (ncd5)	2/17/23
ISD ADP -- I *D for web banners, press releases, new web pages	Melissa Taylor	2/21/23
ISD ADC -- R *I for minor web updates	Sara Dodge Ramey	2/17/23

R=REQUIRED D=DISCRETIONARY I=INFORMATION COPY D/I=DISCRETIONARY/INFORMATIONAL COPY

STEP 3: CENTER CLEARANCE

Unit	Name	Date
NCIRD ADS -- D *R for significant web updates *I for roll out plans, press releases *N/A for web banners, minor web updates	Alexandre Macedo De Oliveira †will receive from [redacted]	Sent 2/21/23
NCIRD ADP -- D/I *N/A for web banners	Brooke Barry †will receive from [redacted]	Sent 2/21/23
NCIRD ADC -- R *N/A for minor web updates	Geoff Beckett †submit via [redacted]	02/21/23

R=REQUIRED D=DISCRETIONARY I=INFORMATION COPY D/I=DISCRETIONARY/INFORMATIONAL COPY

OVERVIEW

- **Planned Release date:** February 24, 2023
- **Document title:** Meeting of the Advisory Committee on Immunization Practices (ACIP): COVID-19 – February 24, 2023
- **Audience**
  - Primary: vaccine providers; jurisdictions; public
  - Secondary: policymakers, media, federal partners
- **Communication Contact:** Christina Carter, CORVD; Kate Grusich, NCIRD
- **Media Spokesperson:** TBD

BOTTOM LINE UP FRONT (BLUF)

On February 24, 2023, CDC's Advisory Committee on Immunization Practices (ACIP) will meet to review the latest COVID-19 vaccine data, as well as discuss potential updates to future COVID-19 vaccination efforts. No votes will be held, and further discussion will take place in the months ahead.

TICK TOCK

Include all relevant activities planned and notifications needed in the Tick Tock, even those where content associated may not be in the rollout but will also be cleared.

Date /Time (e.g. Day before rollout, day of rollout, etc.)	Activity /Product	POC(s)
February 24 and onward	Reactive media statement	Kate Grusich
February 24, 2023	Email to partners, SHOs, clinicians, awardees, etc.	Hilary Eiring and Kathryn Weitzner and Andrew Lowndes

TOPLINE KEY MESSAGES

COVID-19 vaccines continue to remain a highly effective tool for preventing serious illness, hospitalization and death caused by COVID-19.

- Today, CDC's Advisory Committee on Immunization Practices (ACIP) met to discuss the latest data on COVID-19 vaccine effectiveness, safety, and coverage, as well as potential updates to future COVID-19 vaccination efforts.
- No votes or recommendations were made, but the robust discussion included:
    - an update on vaccine safety,
    - a risk-benefit assessment of updated (bivalent) mRNA COVID-19 vaccination, and
    - anticipated updates to COVID-19 vaccine recommendations later this year.
- Expanding upon some of the discussion at FDA's recent advisory committee meeting, CDC and ACIP members expressed their support for streamlining and simplifying COVID-19 vaccine recommendations this fall.
- What that will specifically entail has yet to be determined, and must follow a rigorous, science-based process that takes into account the latest data, as well as the necessary regulatory approvals by FDA.
- In the meantime, ACIP and CDC continue to emphasize the benefits of staying up to date with COVID-19 vaccination, including the importance of the primary series in protecting people against severe disease, hospitalization, and death.
- We encourage the millions of people in the U.S. who have not yet been vaccinated – or who have not yet completed their COVID-19 vaccine primary series – to do so as soon as possible to protect themselves from more serious illness.
    - Currently only about 5% of children younger than age five have completed the COVID-19 vaccine primary series, while just over 32% of children between the ages of five and 11 years have received their primary series. Among young adults, nearly 34% of people between the ages of 18 and 24 years have yet to receive their primary series.
- Additionally, an updated COVID-19 vaccine is an important option to help restore protection that may have waned since previous vaccination. This is particularly true for older people and those with underlying health conditions who are at higher risk.
    - CDC data show that 41% of people ages 65 years and older have received an updated COVID-19 vaccine dose.

- CDC and ACIP will continue to monitor disease levels and vaccine effectiveness in the months ahead and look forward to further discussions around updated vaccine recommendations this fall.

COVID-19 vaccines are safe and effective, and CDC recommends everyone stay up to date.

- COVID-19 vaccines have undergone—and continue to undergo—the most intense vaccine safety monitoring in U.S. history.
- Clinical research and surveillance support the safety and effectiveness of the recommended COVID-19 primary series vaccines, as well as the recommended updated vaccines.
    - Specifically, new data show that for every million doses given of an mRNA COVID-19 primary series vaccine, an estimated 14,200 hospitalizations were prevented among older adults over a six-month period. Although the benefits are most striking among older age groups, there were nearly 500 hospitalizations prevented among adolescents ages 12 to 17 years.
- The safety of the bivalent mRNA COVID-19 vaccine is monitored using multiple systems including the Vaccine Safety Datalink (VSD), a collaboration between CDC and integrated healthcare organizations. VSD assessed pre-specified health outcomes after bivalent COVID-19 vaccination during weekly monitoring.
- At the ACIP meeting, CDC shared information about bivalent COVID-19 vaccine safety from VSD monitoring.
- In November 2022, VSD detected a signal for ischemic stroke in adults ages 65 years and older following vaccination with the Pfizer-BioNTech bivalent COVID-19 vaccine. As of February 4, 2023, approximately 580,000 people in this age group had received the Pfizer-BioNTech bivalent vaccine in VSD (approximately 300,000 had received Moderna bivalent vaccine in VSD). Based on the results of the analysis to investigate the ischemic stroke signal, the higher-than-expected rate of ischemic stroke was seen in persons who received the Pfizer-BioNTech bivalent vaccine and high-dose or adjuvanted influenza vaccine simultaneously; however, this finding is limited by small numbers. There may also be other factors to explain the signal, such as the possibility that early adopters of the bivalent booster vaccine may have greater risk for stroke. A separate analysis did not detect an increased rate of stroke when the influenza vaccine was administered without the COVID-19 vaccine in this age group.
- The signal for ischemic stroke has not been seen in other safety monitoring systems, and the existing data are insufficient to conclude there is a safety problem. Currently, no change in vaccination practice is recommended. CDC and FDA will continue to evaluate additional data on the safety of bivalent COVID-19 vaccines in VSD and other vaccine safety systems.
- CDC also shared the latest data on the risk of myocarditis following mRNA COVID-19 vaccination. Although there are limited data involving the updated bivalent vaccines, the preliminary findings suggest that myocarditis rates in adolescent males following bivalent booster doses were not higher than what was seen following the first monovalent booster doses. In addition, the risk of adverse cardiac outcomes were approximately 2-6 times higher after SARS-CoV-2 infection than after mRNA COVID-19 vaccination among adolescent males.
- CDC also presented new data on COVID-19 vaccine effectiveness (VE), which support previous evidence on the benefits of COVID-19 vaccination in protecting against severe disease. This includes new research illustrating that the updated vaccines are protecting people against the latest COVID-19 variants.
- Researchers analyzed data collected through the VISION Network that show the updated vaccines cut the risk of being hospitalized by around 50% for most people.
- An evaluation of data through the IVY Network found that adults ages 65 years and older without immunocompromise who received an updated vaccine were:
    - 55% less likely to be hospitalized with COVID-19 than people who were unvaccinated

    - 52% less likely to be hospitalized with COVID-19 compared with people who had previously received two or more doses of a monovalent vaccine alone and are eligible to receive the bivalent COVID-19 booster
    - The overall conclusion – the updated (bivalent) vaccines reduce the risk of hospitalization by around 50%
  - Those who only received the original monovalent doses may have limited immune protection remaining.
- Experts used the national pharmacy program for SARS-CoV-2 testing (known as Increasing Community Access to Testing) to estimate effectiveness of updated (bivalent) mRNA COVID-19 vaccines against symptomatic illness in children ages 5-17 years and adults ages 18 years and older during December 1, 2022 and February 13, 2023.
- They found that updated COVID-19 vaccines help protect against illness with Omicron XBB/XBB.1.5-related variants for at least the first three months after vaccination among people who previously received 2, 3, or 4 doses of the original (monovalent) COVID-19 vaccines.
- These data, combined with previously released data from other vaccine effectiveness systems, reinforce that updated COVID-19 vaccines are working well in real-world conditions.
- In addition, CDC also assessed the vaccine effectiveness of the original (or monovalent) COVID-19 primary series against illness in children ages five years and younger.
- Among the key findings:
    - Complete monovalent Moderna and Pfizer-BioNTech primary series vaccination helped provide protection for children ages 3–5 years against symptomatic SARS-CoV-2 infection for at least the first four months after vaccination.
    - Moderna: A complete primary series (2 doses) was 60% effective against symptomatic infection. The analysis suggests that waning against symptomatic infection may occur (though it was not statistically significant).
    - Pfizer-BioNTech: A complete primary series (3 doses) was 31% effective against symptomatic infection. Waning of monovalent Pfizer-BioNTech VE could not be assessed but is also likely based on analyses in older children and adults.
- CDC will continue to monitor vaccine effectiveness, including against emerging variants, and will update vaccine recommendations as needed.
- It's important for people to stay up to date with recommended COVID-19 vaccines, including an updated booster vaccine when eligible. Most people in the U.S. have not yet received an updated COVID-19 vaccine, with uptake at less than 16 percent. Everyone who has not received a COVID-19 vaccine since September 2022 (when the updated vaccines were authorized) should get the updated vaccine to better protect themselves from severe illness and death. This is particularly important for older people and those with underlying health conditions who are at higher risk.

TOUGH Q&A

Q: Now that both FDA and CDC's advisory committees have met to discuss future COVID-19 vaccination efforts, what happens next?

A: Ongoing discussions are needed, as well as regulatory approvals, before any changes to existing COVID-19 vaccine recommendations are made. FDA's advisory committee is expected to meet in the months ahead to publicly discuss changes to the COVID-19 vaccine strain composition for the 2023 fall and winter, as well as the immunization schedules moving forward. Manufacturers must then meet the recommendations issued by FDA for any updated vaccines, and submit their applications to FDA, who will then decide whether to

authorize the updated vaccines. Following FDA authorization, CDC's Advisory Committee on Immunization Practices (ACIP) will meet to review the data submitted and make recommendations based on a thorough review of the available evidence. If the CDC Director agrees with those recommendations, they become policy.

Q: What is the main takeaway from today's presentations and discussion?
A: CDC and ACIP support efforts to simplify and streamline COVID-19 vaccination efforts and look forward to further discussion about what this might entail. Overall, today's updates on vaccine safety and effectiveness show that COVID-19 vaccines are safe and are helping to protect people from severe COVID-19 in the real world, including against the latest variants. Bottom line, the many people who haven't gotten a COVID-19 vaccine since the fall, when the updated vaccines were released, should do so now to better protect themselves from severe illness and death. This is particularly true for older people and those with underlying health conditions who are at higher risk.

Q: What was the rationale for keeping the vaccine recommendations as-is right now?
A: COVID-19 cases, hospitalizations, and deaths have continued to go down in recent weeks, and much of the country has protection against circulating strains either through vaccination, previous infection, or a combination of both. CDC continues to recommend that everyone stay up to date on their COVID-19 vaccines, especially those who are older or at high risk for severe disease because of underlying health conditions. CDC and FDA are currently reviewing the most recent data to support future COVID-19 vaccine recommendations.

Q: When do you expect that the primary series will transition to bivalent vaccines?
A: CDC and ACIP support the use of the updated COVID-19 vaccine for the primary series. The updated COVID-19 vaccines protect against the original COVID-19 strain, and recent Omicron subvariants. In January 2023, FDA's advisors unanimously endorsed replacing the original vaccine with the updated vaccine. The proposed change would only affect people who have not yet received their primary vaccination series. FDA must make the necessary regulatory approvals authorizing this change before CDC could make a recommendation.

Q: How many cases of myocarditis have been reported following a bivalent booster in adolescents?
A: Preliminary findings indicate that myocarditis rates in adolescent males following updated bivalent booster doses are not higher than what was seen following the monovalent booster doses, although the data are limited. Specifically, CDC's Vaccine Safety Datalink (VSD) shows only one myocarditis case reported among anyone who received bivalent boosters between the ages of 18 and 29 years, however, this is based on limited data due to the low number of doses given in this age group. When CDC analyzed both the potential benefits and harms for adolescents together, using recent hospitalization rates, we would expect to prevent between 31 and 136 hospitalizations, 9 to 40 ICU admissions, and 1 death per every million bivalent booster doses given. Based on the preliminary data on myocarditis following a bivalent booster in VSD, we have seen zero myocarditis cases in nearly 50,000 adolescent males that have received a bivalent booster dose, and no cases in females with a similar number of doses.

Q: How will the government's recent announcement about ending the public health emergency impact the COVID-19 vaccine program?
A: The U.S. government is committed to ensuring that COVID-19 vaccines and treatments will be widely accessible to all who need them, including after the public health emergency phase ends on May 11. When the transition to traditional health care coverage occurs later this year, many Americans will continue to pay nothing out-of-pocket for the COVID-19 vaccine. CDC has also entered into Data Use Agreements with most jurisdictions to ensure they continue reporting of vaccine administration data referenced under the PHE.

Q: What does the latest data show about a potential stroke risk among older adults who received the bivalent booster?
A: In November 2022, The Vaccine Safety Datalink (VSD) detected a safety signal for ischemic stroke after Pfizer-BioNTech bivalent COVID-19 vaccination in persons aged 65 years and older. Based on the results of the analysis to investigate the ischemic stroke signal, the higher-than-expected rate of ischemic stroke was seen in persons who received the Pfizer-BioNTech bivalent vaccine and high-dose or adjuvanted influenza vaccine simultaneously; however, this finding is limited by small numbers. There may also be other factors to explain the signal, such as the possibility that early adopters of the bivalent booster vaccine may have greater risk for stroke. No other safety systems have shown a similar signal for ischemic stroke after bivalent COVID-19 booster vaccine. At this time, no change in vaccination practice is recommended. CDC and FDA will continue to evaluate additional data on the safety of bivalent COVID-19 vaccines in VSD and other vaccine safety systems.

Q: How effective are the updated vaccines at protecting against the XBB variants that are currently circulating?
A: Previous studies have shown that during the period of Omicron variant dominance, the updated COVID-19 vaccine cut the risk of visiting an emergency department (ED) or urgent care (UC) or being hospitalized with COVID-19 by around half for most people. Our latest data suggest that updated COVID-19 vaccines continue to provide protection against symptomatic infection with XBB-related variants for at least the first 3 months after vaccination, which supports current recommendations for updated vaccines. People who have not received an updated vaccine after Sept 1, 2022, should do so as soon as possible.

Q: For those who got their updated vaccine in September 2022, when it was authorized, has their protection worn off? How long does protection last?
A: It's too early to know how or when protection from the updated vaccine may wane, as it was authorized in the U.S. only a few months ago. Only three months of data have been collected, but we'll continue to monitor vaccine effectiveness to better understand this in the months ahead. We do know, from the original (monovalent) vaccine, that protection decreases over time, especially against symptomatic infection. But we also know that protection lasts longer against more serious illness. So, it's likely that people who have received the updated vaccine in recent months will remain protected against severe COVID-19 for a longer period of time.

Q: Does CDC research support a need for another booster any time soon?
A: It's hard to tell if another booster is needed especially since 85% of people who are eligible for an updated vaccine have not yet received one. However, the data presented today confirm that updated COVID-19 vaccines are helping to protect people from serious COVID-19 illness, including against the latest variants.

Q: Does CDC research reveal whether the updated vaccine works better than the monovalent vaccine did against protecting against symptomatic infection, as well as severe disease?
A: In the U.S., we're not able to do a head-to-head comparison of monovalent vs. bivalent vaccine performance because they weren't authorized at the same time, and we do see variation in protection based on when people were vaccinated, how many doses they received, and other factors. However, our data do reveal that people who received the updated vaccine were better protected than people who had received the original (monovalent) vaccine but had not yet received the updated (bivalent) vaccine.

Q: How long do we expect VE to stay at this level?
A: We are still assessing vaccine effectiveness for the updated (bivalent) vaccine, as it was authorized relatively recently. However, we know from the original (monovalent) vaccine that protection against infection can wane over time. Generally, protection against more severe disease lasts longer than protection against infection. And we know that the updated vaccine can restore protection that has waned over time from previous vaccines.

Q: Do we know how well these vaccines work for people who are immunocompromised?
A: These studies aimed to determine how well updated COVID-19 vaccines work for people who are not immunocompromised and do not provide data on how well they work for people who are immunocompromised. It's important to remember COVID-19 vaccines are effective at protecting people from getting seriously ill, being hospitalized, and even dying. People who are moderately or severely immunocompromised may significantly lower their risk of severe COVID-19 illness and death when they stay up to date with COVID-19 vaccines and take multiple prevention steps including masking in crowded indoor places and having a plan with their doctor for what to do if they do get infected.

Q: Given that the vast majority of the U.S. population appears to have some form of immunity against COVID-19, why should people continue to stay up to date on COVID-19 vaccines or get the updated vaccine if they haven't already?
A: It's important to remember that new variants continue to emerge – and even if you had COVID-19 before, reinfection is possible, and can cause serious illness. We also know that protection from infection-related immunity wanes, just like it does from vaccination. So, for people who were infected last spring or summer, and who have delayed getting an updated vaccine, they may not have as much protection currently as someone who is up to date on their COVID-19 vaccination. The updated vaccine can help provide added protection, which is important to protect yourself – as well as loved ones – against severe COVID-19. People who recently had COVID-19 infection may consider delaying a COVID-19 vaccine for 3 months from symptom onset or positive test (if infection was asymptomatic).

REACTIVE MEDIA STATEMENT

Today, CDC's Advisory Committee on Immunization Practices (ACIP) met to review the latest data on COVID-19 vaccine effectiveness, safety and coverage, as well as discuss potential updates to future COVID-19 vaccination efforts. Although no changes to existing COVID-19 vaccination recommendations were made, CDC and ACIP members echoed recent discussions – previously outlined at FDA's recent advisory committee meeting – to streamline and simplify COVID-19 vaccine recommendations this fall. Any changes to COVID-19 vaccine composition and immunization schedules must follow a rigorous, science-based process that factors in the most recent data on the epidemiology of the COVID-19 pandemic and SARS-CoV-2 variants, as well as on the safety and effectiveness of COVID-19 vaccines.

Millions of people in the U.S. have not yet been vaccinated or have not yet completed their COVID-19 vaccine primary series. CDC data continue to show that COVID-19 vaccines are effective at preventing severe disease, hospitalization, and death. And for those who have already received their primary series, an updated (bivalent) COVID-19 vaccine is an important option to help restore protection that may have waned since previous vaccination. This is particularly true for older people and those with underlying conditions who are at higher risk.

CDC and ACIP will continue to monitor COVID-19 disease levels and vaccine effectiveness in the months ahead and look forward to future discussion around potential updates this fall.

PARTNER OUTREACH EMAIL

Dear Partners,

Today, CDC's Advisory Committee on Immunization Practices (ACIP) met to review the latest data on COVID-19 vaccine effectiveness, safety, and coverage, as well as discuss potential updates to future COVID-19 vaccination efforts.

Although no changes to existing COVID-19 vaccination recommendations were made, CDC and ACIP members upheld plans to streamline and simplify COVID-19 vaccine recommendations this fall. It's important to note that any changes to COVID-19 vaccine composition and immunization schedules will follow a rigorous, science-based process that factors in the most recent data on the epidemiology of the COVID-19 pandemic and SARS-CoV-2 variants, as well as on the safety and effectiveness of COVID-19 vaccines.

Millions of people in the U.S. have not yet been vaccinated or completed their COVID-19 vaccine primary series, nonetheless CDC data continue to show the currently recommended COVID-19 vaccines are effective at preventing severe disease, hospitalization, and death. For those who have already received their primary series, an updated (bivalent) COVID-19 vaccine is an important option to help restore protection that may have waned since previous vaccination, especially for older people and those with underlying conditions who are at higher risk.

CDC and ACIP will continue to monitor COVID-19 disease levels and vaccine effectiveness in the months ahead and look forward to future discussions around potential updates this fall.

Please see the attached topline key messages to help you communicate this important update to your various audiences. We thank you for your continued support and all that you are doing to promote the health and well-being of the communities you serve.

From: "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted] "Shay, David (CDC/DDID/NCEZID/DHQP)" [redacted] "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: VaST Planning Call
Date: Wed, 11 Jan 2023 12:59:40 +0000
Importance: Normal
Attachments: Closed_session_report__Jan_9_2023draftv4-GMLke.docx

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Comments coming in from VaST members; wanted you to see those from Grace and Kathy. Will compile all and update report later today Just wanted you to see this. Let me know if you disagree with any in the first sections.

Lauri

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Tuesday, January 10, 2023 11:03 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted] Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Woo, Jared (CDC/DDID/NCEZID/DHQP) [redacted] 'Hopkins jr., Robert H' <HopkinsRobertH [redacted] Shay, David (CDC/DDID/NCEZID/DHQP) [redacted] 'Broder, Karen (CDC/OID/NCEZID)' [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: VaST Planning Call

Thank you all for a good call. Attached is the clean version I will send to VaST members now for review.
Lauri

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Tuesday, January 10, 2023 8:11 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Wharton, Melinda (CDC/DDID/NCIRD/OD) [redacted] Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Woo, Jared (CDC/DDID/NCEZID/DHQP) [redacted] 'Hopkins jr., Robert H' [redacted] Shay, David (CDC/DDID/NCEZID/DHQP) [redacted] 'Broder, Karen (CDC/OID/NCEZID)' [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: VaST Planning Call

Dear all,
Attached is the draft closed session report from yesterday – for review on our morning call today.
Lauri

-----Original Appointment-----
From: Young, Mardia (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Sent: Tuesday, August 31, 2021 10:58 AM
To: Young, Mardia (CDC/DDID/NCEZID/DHQP) (CTR); Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP); Wharton, Melinda (CDC/DDID/NCIRD/OD); MacNeil, Jessica R. (CDC/DDID/NCIRD/OD); [redacted] Gee, Julianne (CDC/DDID/NCEZID/DHQP); [redacted] Su, John (CDC/DDID/NCEZID/DHQP); Shanley, Edwin (CDC/DDID/NCIRD/OD); Woo, Jared (CDC/DDID/NCEZID/DHQP)

Cc: CDC IMS 2019 NCOV Response VCU Operations; Hopkins jr., Robert H; Markowitz, Lauri (CDC/DDID/NCIRD/DVD); Shay, David (CDC/DDID/NCEZID/DHQP); Moorer, Alanna (CDC/DDID/NCEZID/DHQP); Broder, Karen (CDC/OID/NCEZID); Avery, Lacey (CDC/DDID/NCEZID/DHQP); McNeil, Michael (CDC/DDID/NCEZID/DHQP)
Subject: VaST Planning Call
When: Tuesday, January 10, 2023 10:00 AM-11:00 AM (UTC-05:00) Eastern Time (US & Canada).
Where: Microsoft Teams Meeting

Microsoft Teams meeting

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COVID-19 VaST Work Group Report – January 9, 2023
DRAFT

The Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Safety Technical (VaST) Work Group has reviewed post-authorization COVID-19 vaccine safety data on a regular basis since the start of the U.S. COVID-19 vaccination program. Updates of VaST activities and VaST assessments of safety data have been presented at ACIP meetings and are available at ACIP Meetings Information | CDC; ACIP meetings are open to the public. When an ACIP meeting is not scheduled, a summary of VaST comments is posted to an ACIP webpage.

The VaST session on January 9, 2023, included review of data on signal detection/signal assessment for bivalent COVID-19 booster vaccination in active surveillance. There was one presentation from the Vaccine Safety Datalink (VSD) and two verbal updates, one from FDA on analysis of the Centers for Medicare & Medicaid Services (CMS) data and one from the Department of Veterans Affairs (VA) on their active surveillance data.

VSD findings:

- ≥ ~~65 year~~65-year age group
  - In the rapid cycle analysis, ~~for the past 6 weeks,~~ there ~~has been a~~is a statistical signal for ischemic stroke/transient ischemic attack (TIA) after bivalent Pfizer-BioNTech COVID-19 booster vaccination during the period 1-21 days after vaccination vs. a comparison period of 22-42 days after vaccination, with a rate ratio that range~~d~~ from 1.5 to 2.0.
    - There was ~~significant~~ temporal clustering of ischemic stroke/TIA codes in days 11-22 following receipt of the bivalent Pfizer-BioNTech COVID-19 booster vaccine.
    - 22/24 cases available for chart review were confirmed as incident cases
  - There is no statistical signal for ischemic stroke/TIA after bivalent Moderna COVID-19 booster vaccination
  - Previous surveillance found no evidence of increased risk of ischemic stroke/TIA after the primary series or monovalent COVID-19 booster ~~vaccination~~vaccines for either Pfizer-BioNTech or Moderna products.
  - During chart review, it was noted that many adults ≥ 65 years had received same day co-administration of bivalent Pfizer-BioNTech COVID-19 booster vaccine and influenza vaccine (most received high dose).
  - ~~Previous surveillance found no evidence of increased risk of ischemic stroke/TIA after the primary series or monovalent COVID-19 booster vaccination.~~
  - ~~On chart review, 22/24 cases reviewed were confirmed; most reviewed cases had received same day co-administration of bivalent Pfizer-BioNTech COVID-19 booster vaccine and influenza vaccine (most received high dose).~~
- 18–~~64 year~~64-year age group
  - In the rapid cycle analysis, there ~~has been~~is no statistical signal for the bivalent Pfizer-BioNTech COVID-19 booster vaccine or for the bivalent Moderna COVID-19 booster vaccine.. ~~The rate ratio after bivalent Pfizer-BioNTech COVID-19 booster vaccination ranged from 1.1 to 2.1.~~
  - ~~The rate ratio attenuated in the most recent weekly analysis.~~
- ~~There has been no elevated risk of ischemic stroke/TIA after bivalent Moderna COVID-19 booster vaccination.~~
- ~~The comparison group in the VSD's rapid cycle analysis is drawn from vaccinated persons 22-42 days following receipt of the bivalent booster vaccination.~~ In a secondary analysis, when the comparison group was drawn from persons eligible to receive a booster but had not received it, no increased risk of ischemic stroke/TIA was seen.

CMS and VA findings:

Commented [LG1]: I forgot to ask - did this confirm onset of timing, or was this based on coding?
Lee, Grace
2023-01-10 09:25:00

Commented [LG2R1]: And assuming that is incident of course, not follow-up.
Lee, Grace
2023-01-10 09:26:00

Commented [LG3R1]: I made some suggested edits but take or leave
Lee, Grace
2023-01-10 09:27:00

Commented [LG4]: (during the risk period, or also during the comparison period?)
Lee, Grace
2023-01-10 09:28:00

Commented [LG5]: I might just delete this text. If there's no signal no reason to comment on rate ratios. We have so many events where the rate ratios exceed one or fall below one, but we don't comment if there's not a signal.
Lee, Grace
2023-01-10 09:32:00

Commented [LG6]: Is this only for the 65+ years? Might insert above for the analysis it's relevant to. And I think it's not clear what the message is. You might either need to simplify and drop this, or you'll have to explain more why this is relevant (i.e. that the risk might actually be lower in the comparison window chosen based on what we know about the protctive effects of vaccines....hence the team used an alternative comparison group....
Lee, Grace
2023-01-10 09:41:00

- In the CMS rapid cycle analysis, there was no statistical signal for ischemic stroke after Pfizer-BioNTech or Moderna COVID-19 booster vaccination.
- In the VA rapid cycle analysis, there was no statistical signal for ischemic stroke/TIA after Pfizer-BioNTech or Moderna COVID-19 booster vaccination.
- Both the CMS and VA rapid cycle analyses use historical comparison groups.

VaST concluded that:

- The statistical signal among persons aged ≥ 65 years for ischemic stroke/TIA following bivalent Pfizer-BioNTech COVID-19 booster vaccination in VSD is based on limited data and ~~was~~ has not been observed ~~replicated~~ in two other active vaccine safety monitoring systems in the United States. ~~These two systems used different comparison groups in their analytic methods.~~
- VaST highlighted several areas for further exploration:~~VaST~~
  - Investigate the ~~Understand~~ impact of concomitant/recent respiratory viral infections (e.g., COVID-19, influenza) on risk of ischemic stroke/TIA
  - Consider protective efforts of bivalent COVID vaccine on the reducing risk of complications due to disease with COVID-19 or influenza during the comparison window (i.e. 22 to 42 days post-vaccination)
  - Estimate risk of same day vs. separate day vaccination
- ~~was encouraged to know that additional analyses from VSD would be available soon. Importantly, the additional data include analyses of potential interaction with co-administered vaccines. VaST would like to be updated as more data become available.~~
- VaST will continue to review data from the additional analyses planned from VSD, CMS and the VA.

- VaST noted there was no signal after bivalent Moderna COVID-19 booster vaccination; in VSD there were fewer bivalent Moderna COVID-19 booster doses administered compared with bivalent Pfizer-BioNTech booster doses. Bivalent Moderna COVID-19 booster doses were administered later in the calendar year and fewer were co-administered with influenza vaccine.
- ~~VaST was encouraged to know that additional analyses from VSD would be available soon. Importantly, the additional data include analyses of potential interaction with co-administered vaccines. VaST would like to be updated as more data become available.~~
- ~~VaST will continue to review data from the additional analyses planned from VSD, CMS and the VA.~~
- ~~VaST members commented that COVID-19 can be thrombogenic and that vaccination prevents COVID-19 disease.~~

Commented [LG7]: I wonder if we can comment on the pros and cons of the various comparison groups and why it's helpful to have the multiple systems and different approaches to help us understand whether or not a signal is robust
Lee, Grace
2023-01-10 09:44:00

Commented [LG8]: Suggest moving this to the above and keep the conclusions simpler.
Lee, Grace
2023-01-10 09:45:00

Commented [LG9]: Might move this to the data section, and focus on conclusions here.
Lee, Grace
2023-01-10 09:45:00

Commented [LG10]: Might make this more in lay terms.
Lee, Grace
2023-01-10 09:56:00

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: CISA Flu-COVID study update - human subjects
Date: Tue, 31 Jan 2023 20:36:50 +0000
Importance: Normal
Inline-Images: image001.jpg

Not really. I was just wondering about the origins and use of the term UPIRTSO. The letter implies that there is an actual risk to patients but we don't know that.

From: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Tuesday, January 31, 2023 3:34 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: CISA Flu-COVID study update - human subjects

The call about this is 430 -530. Do you want an invite?
Karen

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Tuesday, January 31, 2023 11:13 AM
To: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted] McNeil, Michael (CDC/DDID/NCEZID/DHQP) [redacted] Cortese, Margaret (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Museru, Oidda I. (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: CISA Flu-COVID study update - human subjects

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

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

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

Karen

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

Hi Oidda,

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

Thank you,
Anne

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

Upcoming OOO: 2/13/2023 – 2/17/2023

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

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

As you are aware, CDC and FDA are evaluating a vaccine safety signal for ischemic stroke in people ages 65 years and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. More information is available here: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older | CDC and summarized below. Today (January 18, 2023) CDC study staff met with CISA Principal investigators to discuss human subjects considerations regarding the CISA Simultaneous mRNA COVID-19 and IIV4 Vaccination Study - Full Text View - ClinicalTrials.gov. We agreed that each of the 3 CISA sites will notify their IRB about this signal and follow local policies as they pertain to this study. In addition, out of an abundance of caution, the PIs agreed to pause enrollment of persons age 65 years and older in this CISA study, until after the FDA VRBPAC meeting on 1/26/23; the situation will be reassessed after that meeting.

Additional information about the signal is below.

- "Following the availability and use of the updated (bivalent) COVID-19 vaccines, CDC's Vaccine Safety Datalink (VSD), a near real-time surveillance system, met the statistical criteria to prompt additional investigation into whether there was a safety concern for ischemic stroke in people ages 65 and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Rapid-response investigation of the signal in the VSD raised a question of

whether people 65 and older who have received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22-42 following vaccination"

- "Although the totality of the data currently suggests that it is very unlikely that the signal in VSD represents a true clinical risk, we believe it is important to share this information with the public"
- "No change in vaccination practice is recommended. CDC continues to recommend that everyone ages 6 months of age and older stay up-to-date with COVID-19 vaccination; this includes individuals who are currently eligible to receive an updated (bivalent) vaccine."
- "CDC and FDA will continue to evaluate additional data from these and other vaccine safety systems. These data and additional analyses will be discussed at the upcoming January 26 meeting of the FDA's Vaccines and Related Biological Products Advisory Committee." Vaccines and Related Biological Products Advisory Committee January 26, 2023 Meeting Announcement - 01/26/2023 | FDA
- The EUA factsheets and package inserts for COVID-19 vaccines have not changes for mRNA COVID-19 vaccines. COVID-19 Vaccines | FDA

Sincerely,

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

From: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted] "Weintraub, Eric (CDC/DDID/NCEZID/DHQP)" [redacted] "Shay, David (CDC/DDID/NCEZID/DHQP)" [redacted] "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: FW: BV booster monitoring
Date: Mon, 23 Jan 2023 13:10:24 +0000
Importance: Normal
Inline-Images: image001.png

From: Anders Peter Hviid [redacted]
Sent: Monday, January 23, 2023 5:00 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Niklas Andersson [redacted]
Subject: SV: BV booster monitoring

Tom, just to let you know that our safety evaluation is now public on medRxiv:

https://www.medrxiv.org/content/10.1101/2023.01.21.23284855v1

Anders Hviid
Head of Department,
Professor of Pharmacoepidemiology,
M.Sc.,Dr.Med.Sci.
Department of Epidemiology Research
Statens Serum Institut
[redacted]
Address: Artillerivej 5 | DK-2300 Copenhagen S

STATENS SERUM INSTITUT

Fra: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sendt: 18. januar 2023 14:19
Til: Anders Peter Hviid [redacted]
Cc: Niklas Andersson [redacted]
Emne: RE: BV booster monitoring

Thanks. This is very helpful.

From: Anders Peter Hviid [redacted]
Sent: Wednesday, January 18, 2023 3:32 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Niklas Andersson [redacted]
Subject: SV: BV booster monitoring

Dear Tom,

Happy new year! Yes, we have conducted an analysis. I have appended a confidential summary of our analysis for your information.

Br
Anders

Anders Hviid
Head of Department,
Professor of Pharmacoepidemiology,
M.Sc.,Dr.Med.Sci.
Department of Epidemiology Research
Statens Serum Institut
[redacted]
Address: Artillerivej 5 | DK-2300 Copenhagen S

Fra: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sendt: 17. januar 2023 20:50
Til: Anders Peter Hviid[redacted]
Emne: BV booster monitoring

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

Dear Anders,

Happy New Year and I hope you are well. Re: the recent CDC-FDA statement above, are you by any chance monitoring for ischemic stroke in your mRNA COVID-19 bivalent booster vaccination surveillance? Thanks.

Regards,

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, MS H16-3, Atlanta, GA 30329
[redacted]

STATENS SERUM INSTITUT
[redacted]

Denne e-mail, inklusiv vedhæftede filer er tiltænkt den eller de personer, der er angivet ovenfor, og kan indeholde fortrolige oplysninger. Uautoriseret læsning, videregivelse, kopiering, distribution eller anden brug af disse oplysninger kan krænke rettighederne til beskyttede oplysninger. Hvis du ikke er en tiltænkt modtager, bedes du returnere denne e-mail til afsenderen og slette din kopi. Tak skal du have.

Læs mere om hvordan SSI behandler personoplysninger (DA)

From: "Cortese, Margaret (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: question
Date: Thu, 4 May 2023 17:09:01 +0000
Importance: Normal

Can you add something like this? If not ..seems fine as it is..

Sincerely,

Margaret

From: Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Thursday, May 4, 2023 1:05 PM
To: Cortese, Margaret (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: question

This is one of the questions I was trying to answer
There is a question in the Q&A that could use your response: I am confused by the last speakers presentation. Is there an increased risk of ischemic stroke with the Pfizer bivalent vaccination even without also concomitant influenza vaccination being given?

See what you think? (mix of Tom's TP)

The data are insufficient to conclude that a risk exists for ischemic stroke following bivalent COVID-19 vaccination **or** following simultaneous bivalent COVID-19 and high-dose or adjuvanted flu vaccination. The ischemic stroke signal after bivalent Pfizer-BioNTech COVID-19 vaccine was detected in one system, the Vaccine Safety datalink..DURING THE FIRST WEEKS...; THE (cumulative?) RISK RATIO NOT ELEVATED IN THAT SYSTEM BEGINNING XX MONTH and later... This signal has not been detected in other surveillance systems.
Statistical signals do not necessarily equate to increased risks or causal association for adverse events. CDC and FDA are engaged in epidemiologic analyses regarding simultaneous vaccination with bivalent mRNA COVID-19 vaccine and influenza vaccine

Answer

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

From: "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]

To: "Anderson, Steven (FDA/CBER)" [redacted] "Beresnev, Tatiana (NIH) [C]" [redacted] "Bridges, Carolyn (CDC/DDID/NCIRD/OD) (CTR)" [redacted] "Broder, Karen (CDC/DDID/NCEZID/DHQP)" [redacted] "Clark, Matthew (IHS/AKA/AO)" [redacted] "Cunningham, Fran" [redacted] "Daley, Matt" [redacted] "Edwards, Kathy" [redacted] "Farizo, Karen (FDA/CBER)" [redacted] "Forshee, Richard (FDA/CBER)" [redacted] "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted] "Godfrey, Monica (CDC/DDID/NCIRD/DVD)" [redacted] "Hamburger, Tanya (CDC/DDID/NCEZID/DHQP)" [redacted] "Hause, Anne M. (CDC/DDID/NCEZID/DHQP)" <VOE5[redacted] "Helfand, Rita (CDC/DDID/NCEZID/OD)" [redacted] "Hopkins, Bob" [redacted] "Jackson, Lisa" <[redacted] Jennifer Nelson [redacted], Joseline Zafack [redacted] "Kelman, Jeffrey (CMS/CM)" [redacted] "Lee, Grace" [redacted], "Lu, Yun (CBER) (FDA/CBER)" [redacted] "MacNeil, Jessica R. (CDC/DDID/NCIRD/OD)" [redacted] Margaret Ryan [redacted], Margaret Ryan [redacted] "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted] "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted] "Marshall, Valerie (HHS/OASH)" [redacted] "McNally, Veronica" [redacted] "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted], "Meyer, Sarah (CDC/DDID/NCIRD/ISD)" [redacted] "Moorer, Alanna (CDC/DDID/NCEZID/DHQP)" [redacted] "Moro, Pedro (CDC/DDID/NCEZID/DHQP)" [redacted], "Myers, Tanya R. (CDC/DDID/NCEZID/DHQP)" [redacted] "Nair, Narayan (FDA/CBER)" [redacted] "Oliver, Sara Elizabeth (CDC/DDID/NCIRD/DVD)" [redacted] "Oster, Matt (CDC/DDNID/NCBDDD/DBDID) (CTR)" [redacted] "Patricia Whitley-Williams [redacted] "Riley, Laura" [redacted] "Scarbrough, Sierra (CDC/DDID/NCIRD/OD) (CTR)" [redacted] "Schechter, Robert" [redacted] "Sharan, Martha (CDC/DDID/NCEZID/DHQP)" [redacted] "Shay, David (CDC/DDID/NCEZID/DHQP)" [redacted] "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted] "Shoaibi, Azadeh (FDA/CBER)" [redacted], "Styles, Timothy (HRSA)" [redacted] "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted] "Talbot, Keipp" <keipp.talbot[redacted] "Weintraub, Eric (CDC/DDID/NCEZID/DHQP)" [redacted] "Wharton, Melinda (CDC/DDID/NCIRD/OD)" [redacted] "Whittaker, Christine (CDC/NIOSH/DSI)" [redacted] "Wong, Hui-Lee (FDA/CBER)" [redacted] "Woo, Jared (CDC/DDID/NCEZID/DHQP)" [redacted] "Young, Mardia (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted]

Subject: FW: VaST call: March 27, 2023 agenda and presentations - Confidential

Date: Mon, 27 Mar 2023 16:32:19 +0000

Importance: Normal

Attachments: 2023-03-27_-_VaST_agenda_draft_confidential.docx; VaST_CISA_Research_Update.3.27.23_draft_confidential.pdf; VAMedSAFECOVID-19RCA_and_Safety_Surveillance_Summary___March2023_Update_draft_confidential.pdf; VaST_VSD_RCA_COVID-19_Safety_Surveillance.03.24.23_draft_confidential.pdf

---

There have been a few changes, so I am resending.
Lauri

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Monday, March 27, 2023 12:16 PM
Subject: VaST call: March 27, 2023 agenda and presentations - Confidential

Dear VaST members and call participants,

The call today includes a comprehensive summary presentation from the Vaccine Safety Datalink and an update from CISA. The agenda and presentations are attached.
Also attached is a brief update from the VA – these slides will not be reviewed during the call.

The VaST call information for today at 1:30 should be on your calendars.
Reminder - all VaST documents and communications are confidential.

Regards,
Lauri Markowitz and Melinda Wharton

Lauri Markowitz, MD
VaST Co-Lead
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

VaST Agenda

March 27, 2023
Confidential

1:30 – 3:00 pm

Introduction and announcements	Chairs and WG leads
VSD RCA transition presentation	Dr. Nicola Klein, KNC
CISA: Clinical Research Study Update	Dr. Karen Broder, CDC

National Center for Emerging and Zoonotic Infectious Diseases

Clinical Immunization Safety Assessment (CISA) Project: Clinical Research Study Update

COVID-19 Vaccine Safety Technical (VaST) Subgroup
March 27, 2023

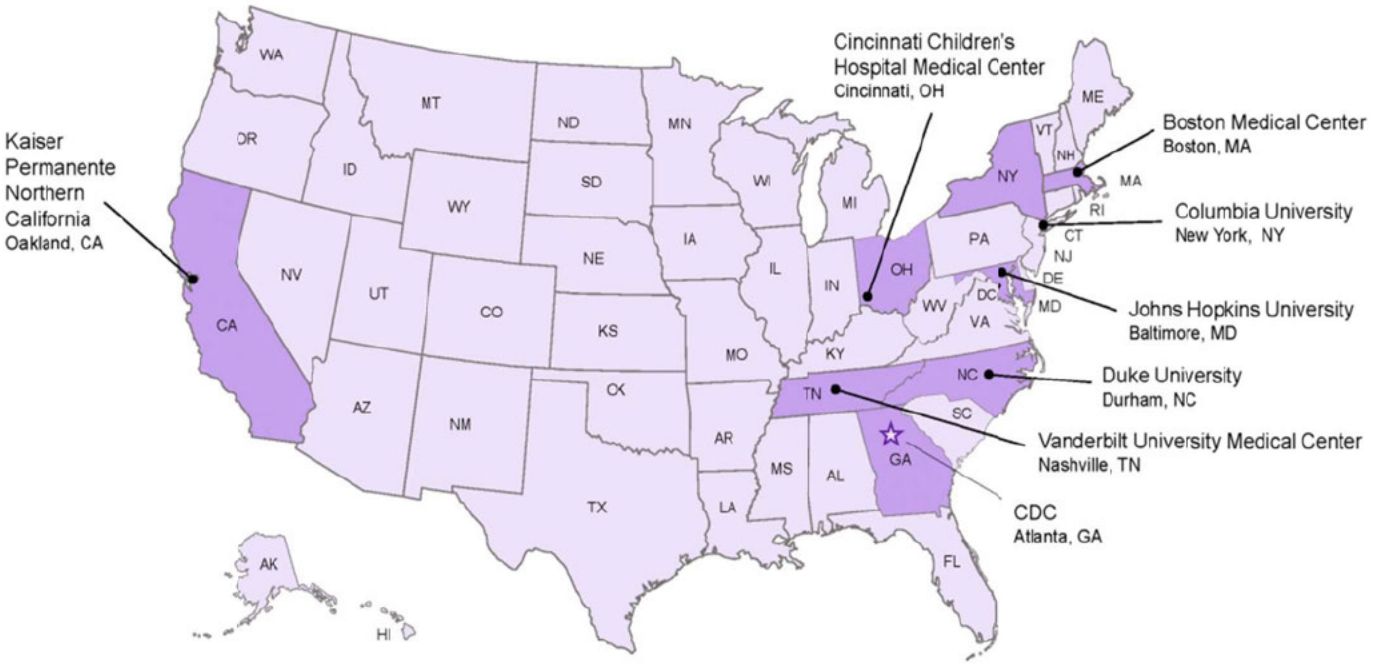
Karen Broder, MD
Captain, U.S. Public Health Service
Chief Medical Officer
Immunization Safety Office, Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention (CDC)

Disclaimer

- The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the CDC
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC

CISA

Clinical Immunization Safety Assessment (CISA) Project



7 participating medical research centers with vaccine safety experts

- clinical consult services†
- clinical research

†More information about clinical consults available at http://www.cdc.gov/vaccinesafety/Activities/CISA.html

CISA prospective clinical research studies

- Designed to address real world public health needs
- May use randomized clinical trial (RCT) design
  - evaluate vaccine safety questions that may not be amenable to retrospective study
- Allow for clinical data and laboratory specimen collection
- CISA developed and implemented clinical research studies to complement other vaccine safety monitoring efforts for COVID-19 vaccines, across the life stages

Study 1: Simultaneous mRNA COVID-19 vaccine and IIV4 study (NCT05028361)

- CISA Sites:*
  - Duke University (Lead), Johns Hopkins University, Cincinnati Children's Hospital Medical Center
- Design:
  - Randomized clinical trial (RCT) in nonpregnant persons aged ≥5 years to evaluate the safety of simultaneous vs. sequential vaccination with mRNA COVID-19 vaccine and IIV4;** randomized 1:1 to:
    - Simultaneous group: mRNA COVID-19 vaccine and IIV4 at visit 1, placebo injection at visit 2 (1–2 weeks later)
    - Sequential group: mRNA COVID-19 vaccine and placebo injection at visit 1, IIV4 at visit 2 (1–2 weeks later)

*Study Principal Investigators (PIs): Emmanuel B. Walter, MD, MPH (Duke); Kawsar Talaat, MD (JHU); Elizabeth P. Schlaudecker, MD, MPH (Cincinnati); Karen R. Broder, MD (CDC)

**COVID-19 vaccine first dose or booster (monovalent or bivalent); IIV4 standard dose aged <65 and high-dose for ≥65 years

Study 1: Main safety outcomes (NCT05028361)*

- Local and systemic reactogenicity
  - Primary research hypothesis: The proportion of participants with moderate or more severe fever, chills, myalgia or arthralgia will be noninferior (not higher) in the Simultaneous group versus the Sequential group (1-7 days following visit 1 and visit 2)**
- Serious adverse events (SAE) and adverse events of special interest (AESI) (through 4 months after visit 1)
- Health-related quality of life (HRQOL) changes before and after vaccination (first visit)
- Safety profiles by baseline SARS-CoV-2 antibody status (positive versus negative)

*Study will also assess immunogenicity for influenza and COVID-19 vaccine antigens
**Day 1 is the day of vaccination

Study 1: Timeline and milestones (NCT05028361)

- October 2021: First participant enrolled
- April 2022: Safety panel assessed no safety concerns after first season
- February 2023: Last participant enrolled
  - Enrolled 349 (78%) of target goal 450
- March 2023: Enrollment completed; collecting safety data from participants
  - Anticipate that all participants will complete study visits by third quarter 2023
- Fourth quarter 2023: Preliminary safety results are anticipated to be available (ClinicalTrials.gov safety results to be submitted by February 2024)
- Public information available: study protocol and informed consent form posted at ClinicalTrials.gov; safety panel assessment presented at June 2022 ACIP meeting in influenza session*

*Influenza Work Group: Summary and Proposed Recommendations for the 2022-23 Influenza Season (cdc.gov)

Study 2: Safety of pediatric COVID-19 vaccination study (NCT05157191)

- CISA Sites:*
  - Duke University (Lead), Cincinnati Children's Hospital Medical Center, Kaiser Permanente Northern California, Columbia University
- Design:
  - Prospective observational study to evaluate the safety of mRNA COVID-19 vaccine in children and adolescents aged 5–15 years
  - Children enroll at time of receipt of the first mRNA COVD-19 primary series dose or a booster dose

*Study PIs: Michael J. Smith, MD (Duke); Elizabeth P. Schlaudecker, MD, MPH (Cincinnati); Nicola Klein, MD, PhD (Kaiser); Melissa Stockwell, MD, MPH (Columbia); Karen R. Broder, MD (CDC)

Study 2: Main safety outcomes (NCT05157191)*

- Local and systemic reactogenicity (Days 1–7 after vaccination)**
- SAE and AESI (through 6 months after visit 1)
- Safety profiles by simultaneous vaccination vs. COVID-19 vaccination alone status
- Safety profiles by baseline SARS-CoV-2 antibody status (positive vs. negative)
- Adolescent and parent perceptions about COVID-19 vaccines (separate surveys)

*Study will also assess immunogenicity for COVID-19 vaccine antigens; blood draws are optional

**Day 1 is the day of vaccination

Study 2: Timeline and milestones (NCT05157191)

- April 2022: First participants enrolled
- September 2022: Safety panel assessed no safety concerns
- March 2023: Enrolling participants
  - Enrolled 280 (88%) of target goal 320 (as of 3/23/23)
- Second quarter 2024: Preliminary safety results are anticipated to be available
- Public information currently available: study protocol posted at ClinicalTrials.gov

Study 3: Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children*

- CISA Sites: same sites and PIs as study 2
- Design: RCT in children aged 6 months–4 years to evaluate the safety of simultaneous vs. sequential vaccination;** randomized 1:1 to:
  - Simultaneous group: mRNA COVID-19 vaccine (any dose) and non-COVID-19 vaccines at visit 1, health education (no vaccinations) at visit 2 (1–2 weeks later)
  - Sequential group: non-COVID-19 vaccines at visit 1, mRNA COVID-19 vaccine and health education at visit 2 (1–2 weeks later)
- Timeline goals:
  - Third quarter 2023: Begin enrollment (target goal 600 children)
  - Fourth quarter 2024: Preliminary safety results are anticipated to be available

*Protocol in development and subject to change; study will be registered at ClinicalTrials.gov before first enrollment

**Study design similar to prior CISA study: Fever After Influenza, Diphtheria-Tetanus-Acellular Pertussis, and Pneumococcal Vaccinations | Pediatrics | American Academy of Pediatrics (aap.org)

Study 3: Main Safety Outcomes (proposed)

- Fever*
  - Primary research hypothesis: The proportion of children with fever will be noninferior (not higher) in the simultaneous group vs. the sequential group (fever is present if temperature ≥ 38.0°C on day 1 and/or day 2 following visit 1 and/or visit 2)
- Systemic reactogenicity events, antipyretic use, medical care utilization (days 1–7 after each visit)
- SAE and AESI, including seizures (through ~3 months after visit 1)
- Parent perceptions of their child receiving COVID-19 vaccine and other vaccines at the same visit or receiving the vaccines at separate visits

*Day 1 is the day of vaccination for visit 1 and the day of vaccination or health education (no vaccination) for visit 2

Study 4: Observational maternal COVID-19 vaccination study (NCT04826640)

- CISA Sites:*
  - Duke University (Lead), Cincinnati Children's Hospital Medical Center, Boston Medical Center
- Design:
  - Prospective observational study to evaluate the safety of COVID-19 vaccine in pregnancy
  - Pregnant participants enroll at time of receipt of the first COVID-19 vaccine primary series dose or a booster dose
    - Aged 18–45 years and <34 weeks gestational age

*Study PIs: Geeta K. Swamy, MD (Duke); Elizabeth P. Schlaudecker, MD, MPH (Cincinnati); Stephen I. Pelton, MD; Karen R. Broder, MD (CDC)

Study 4: Main safety outcomes (NCT04826640)*

- Pregnancy outcomes
  - Composite adverse pregnancy outcome:** preterm birth, spontaneous abortion, fetal death, neonatal death
- Local and systemic reactogenicity (days 1–7 after vaccination)***
- Maternal SAEs
- Infant health outcomes through 3 months of life
- Safety profile by baseline SARS-CoV-2 antibody status (positive vs. negative)

*Study will also assess immunogenicity for COVID-19 vaccine antigens and antibodies in infant umbilical cord blood
**This outcome was the primary outcome in a separate CISA influenza pregnancy RCT conducted at the same sites: Safety of RIV4 Versus IIV4 in Pregnant Women - Full Text View - ClinicalTrials.gov
***Day 1 is the day of vaccination

Study 4: Timeline and milestones (NCT04826640)

- July 2021: First participant enrolled
- November 2022: Safety panel assessed no safety concerns
- March 2023: Enrolling participants
  - Enrolled 149 (43%) of target goal 350 (as of 3/22/23)
- Second quarter 2024: preliminary safety results are anticipated to be available
- Public information currently available: protocol posted at ClinicalTrials.gov

Study 5: Simultaneous mRNA COVID-19 and IIV4 vaccination in pregnancy study (concept)*

- Design: RCT in pregnant persons to evaluate the safety of simultaneous vs. sequential vaccination; randomized 1:1 to:
  - Simultaneous group: mRNA COVID-19 vaccine and IIV4 at visit 1, no vaccine at visit 2 (1–2 weeks later)
  - Sequential group: mRNA COVID-19 vaccine at visit 1, IIV4 at visit 2 (1–2 weeks later)
- Main outcomes: maternal reactogenicity and maternal and infant health outcomes**
- Draft timeline:
  - Implement study during third quarter 2023; develop protocol and enroll participants during 2024-25 influenza season; preliminary results are anticipated to be available during fourth quarter 2026

*Proposal, not yet implemented; study design is subject to change; study will incorporate elements of CISA COVID-19 studies 1 and 4 and an earlier CISA influenza study: Safety of RIV4 Versus IIV4 in Pregnant Women - Full Text View - ClinicalTrials.gov

**May also assess immunogenicity for influenza and COVID-19 vaccine antigens and cord blood antibodies

Summary: CISA COVID-19 vaccine safety clinical studies

1. Simultaneous mRNA COVID-19 vaccine and quadrivalent inactivated influenza vaccine (IIV4) study (NCT05028361)*
2. Safety of pediatric COVID-19 vaccination study (NCT05157191)*
3. Safety of simultaneous mRNA COVID-19 vaccine with other childhood vaccines in young children (protocol in development)
4. Observational maternal COVID-19 vaccination study (NCT04826640)*
5. Simultaneous mRNA COVID-19 and IIV4 vaccination in pregnancy study (*study concept, not yet implemented*)

*Registered at ClinicalTrials.gov

Acknowledgements

- CISA sites
  - Boston Medical Center
  - Columbia University
  - Cincinnati Children's Hospital Medical Center
  - Duke University
  - Johns Hopkins University
  - Kaiser Permanente Northern California
  - Vanderbilt University Medical Center
- CDC Immunization Safety Office
- CDC COVID-19 Response
- CDC Influenza Division
- **We thank individuals (and their parents/guardians) for participating in CISA clinical studies!**

U.S. Department of Veterans Affairs

VA COVID-19 Vaccine Safety Updates – Ongoing Evaluations

VAMEDSAFE

MARCH 27, 2023

Overview

- Monovalent vaccine summary presented 11/2022
  - Manuscripts submitted
- Bivalent Vaccine
  - Brief Overview of Rapid Cycle Analysis
  - RCA Results
  - List of Full Evaluations Underway

Rapid Cycle Analysis (RCA)

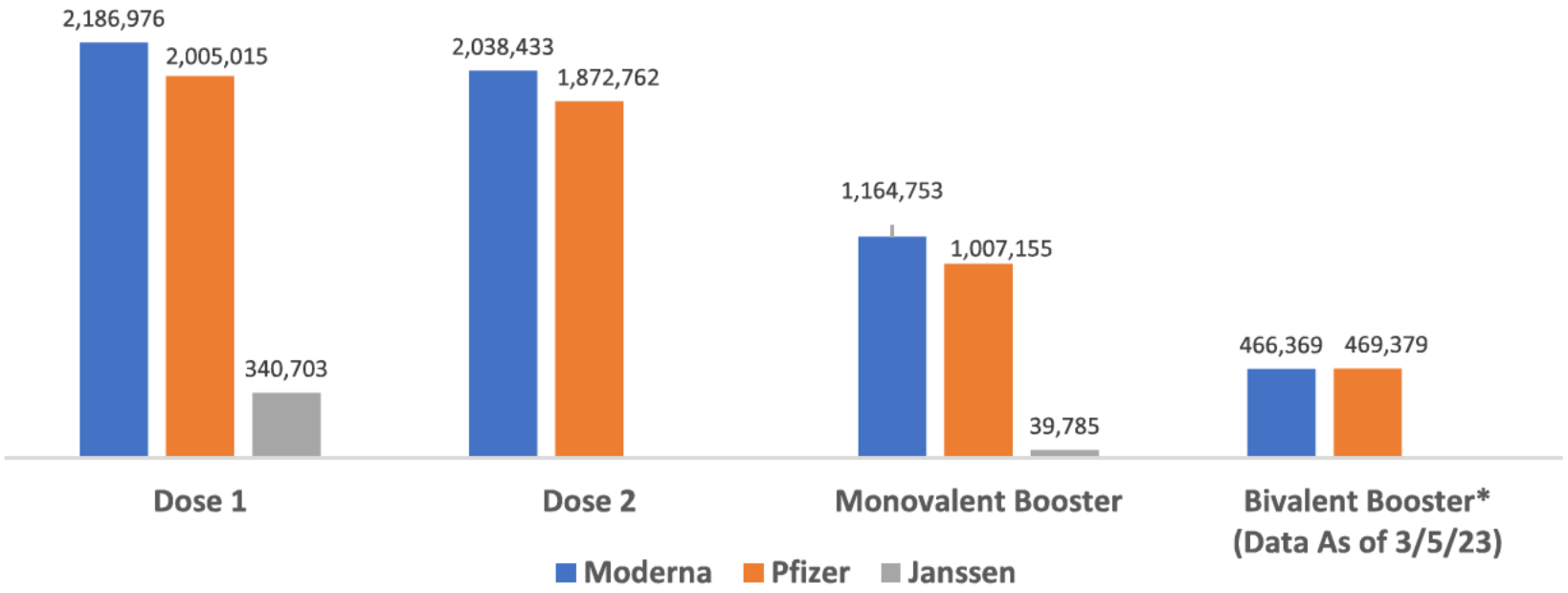
- Compare observed to expected number of AESIs from historical rates
  - Historical comparators (all vaccines - fiscal year 2016-2020)
  - *Target trial RCA pilot*
- Risk windows: 0-1 day for anaphylaxis and 1-21d for all other AESIs
- Weekly analysis – using sequential tests
  - Bivalent Booster
- Full analysis to assess signals
  - Cohort
  - Self Controlled Case Series
  - Target Trial Emulation

Prespecified Adverse Events of Special Interest (AESIs)

Acute disseminated encephalomyelitis (ADEM)
Acute myocardial infarction (AMI)
Anaphylaxis (0-1 day)
Convulsions/seizures
Disseminated intravascular coagulation (DIC)
Encephalitis/myelitis/encephalomyelitis (Non-ADEM)
Guillain-Barre syndrome (GBS)
Immune thrombocytopenic purpura (ITP)
Myocarditis/pericarditis
Narcolepsy and cataplexy
Hemorrhagic Stroke
Ischemic Stroke
Transverse myelitis (TM)
Venous thromboembolism (VTE)
Bell's Palsy
Appendicitis
Pulmonary Embolism (PE)
Thrombotic thrombocytopenic purpura (TTP)
Cerebral Venous Thrombosis (CVST)

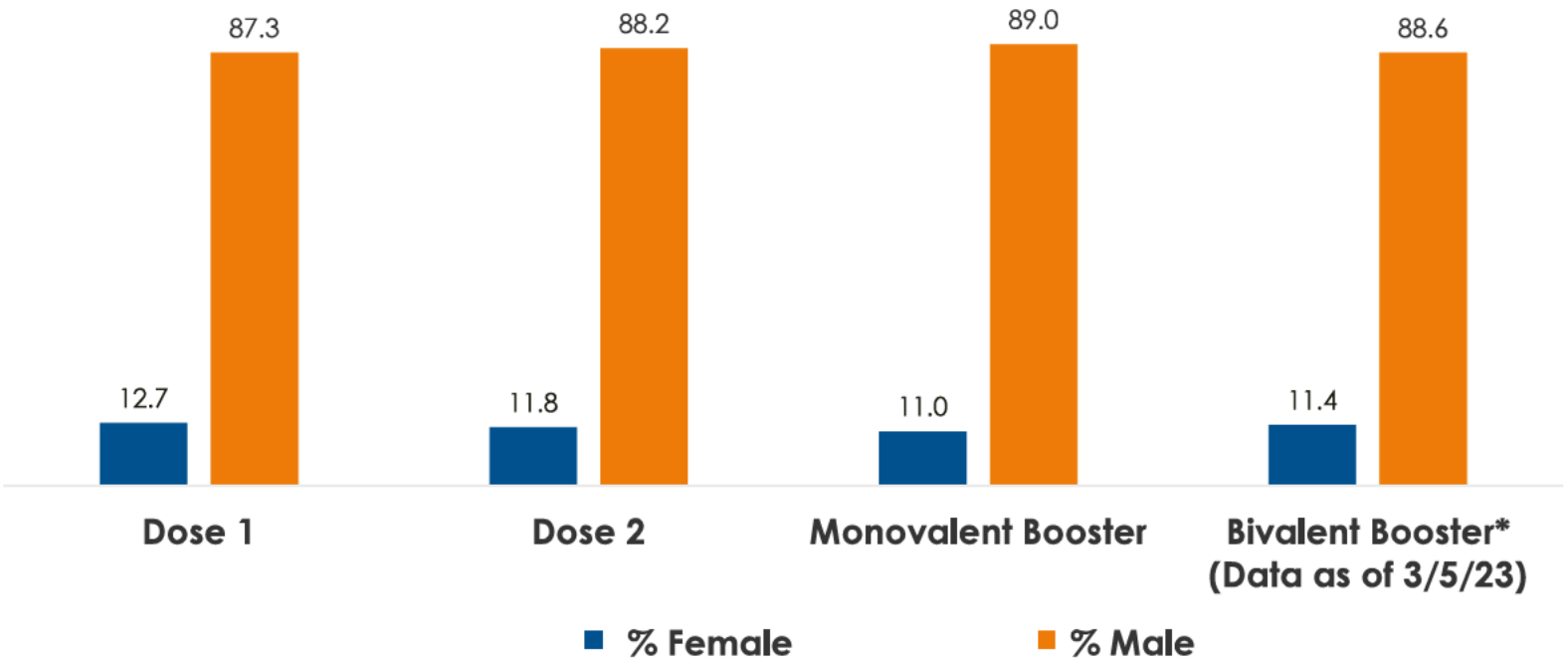
COVID-19 Vaccine Administration by Vaccine Dose

As of 12/31/22



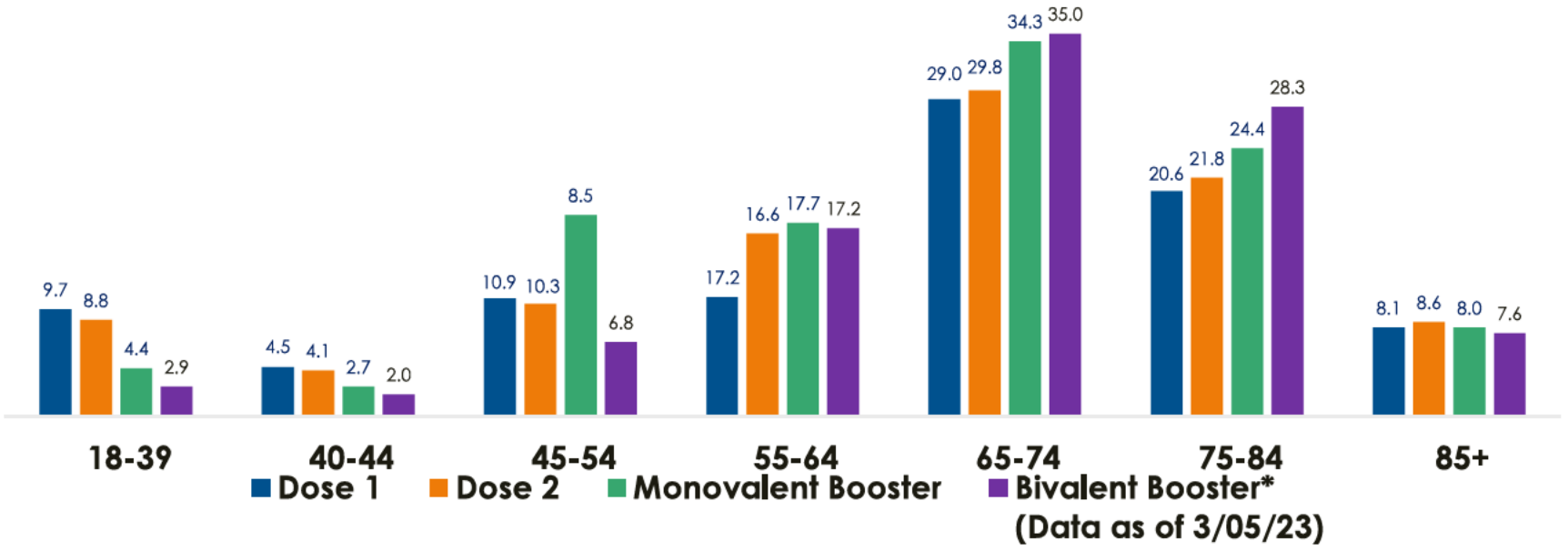
COVID-19 Vaccine Administration By Gender

As of 12/31/22



COVID-19 Vaccine Administration By Age Group

As of 12/31/22



Bivalent RCA - Moderna

Number of vaccinations thru 03/05/2023 = 466,369 21 days				
AESIs	# of Observed AEs	# of Expected AEs	Risk Ratio	Signal
Acute disseminated encephalomyelitis (ADEM)	0	0.07	0	N
Acute myocardial infarction	110	119.81	0.92	N
Anaphylaxis 0-1 day	1	0.64	1.571	N
Convulsions/seizures	82	110.72	0.74	N
Disseminated intravascular coagulation (DIC)	2	2.52	0.79	N
Encephalitis/myelitis/encephalomyelitis/meningoencephalitis	0	2.37	0	N
Guillain-Barre Syndrome (GBS)	0	1.01	0	N
Immune thrombocytopenic purpura (ITP)	4	16.95	0.24	N
Myocarditis/pericarditis	2	3.33	0.60	N
Narcolepsy and cataplexy	9	18.39	0.49	N
Hemorrhagic Stroke	10	15.23	0.66	N
Ischemic Stroke	44	105.29	0.41	N
Transverse myelitis (TM)	0	0.99	0	N
Venous thromboembolism (VTE)	197	298.09	0.66	N
Bell's Palsy	30	29.44	1.02	N
Appendicitis	8	9.03	0.88	N
Pulmonary Embolism (PE)	81	129.47	0.62	N
Thrombotic thrombocytopenic purpura (TTP)	0	0.21	0	N
Cerebral Venous Thrombosis (CVST)	0	0.54	0	N
Myocarditis/pericarditis OP	7	7.35	0.95	N

Bivalent RCA Moderna >/=65 years

Number of vaccinations thru 03/05/2023 = 338,826 21 days				
AESI	# of Observed AEs	# of Expected AEs	Risk Ratio	Signal
Acute disseminated encephalomyelitis (ADEM)	0	0	.	N
Acute myocardial infarction	95	100.67	0.94	N
Anaphylaxis 0-1 day	0	0.33	0	N
Convulsions/seizures	52	67.75	0.77	N
Disseminated intravascular coagulation (DIC)	1	1.93	0.51	N
Encephalitis/myelitis/encephalomyelitis/meningoencephalitis	0	1.64	0	N
Guillain-Barre Syndrome (GBS)	0	0.87	0	N
Immune thrombocytopenic purpura (ITP)	2	13.46	0.15	N
Myocarditis/pericarditis	1	2.26	0.43	N
Narcolepsy and cataplexy	2	9.47	0.21	N
Hemorrhagic Stroke	9	12.95	0.69	N
Ischemic Stroke	36	85.69	0.42	N
Transverse myelitis (TM)	0	0.62	0	N
Venous thromboembolism (VTE)	168	224.47	0.75	N
Bell's Palsy	22	19.15	1.15	N
Appendicitis	6	5.31	1.13	N
Pulmonary Embolism (PE)	71	99.8	0.71	N
Thrombotic thrombocytopenic purpura (TTP)	0	0.06	0	N
Cerebral Venous Thrombosis (CVST)	0	0.43	0	N
Myocarditis/pericarditis OP	6	4.32	1.39	N

Bivalent RCA Pfizer

Number of vaccinations thru 03/05/2023 = 469,364 21 days				
AESI	# of Observed AEs	# of Expected AEs	Risk Ratio	Signal
Acute disseminated encephalomyelitis (ADEM)	0	0.08	0	N
Acute myocardial infarction	115	116.08	0.99	N
Anaphylaxis 0-1 day	0	0.67	0	N
Convulsions/seizures	69	113.48	0.61	N
Disseminated intravascular coagulation (DIC)	2	2.47	0.81	N
Encephalitis/myelitis/encephalomyelitis/meningoencephalitis	0	2.36	0	N
Guillain-Barre Syndrome (GBS)	1	1	1.01	N
Immune thrombocytopenic purpura (ITP)	6	16.87	0.36	N
Myocarditis/pericarditis	6	3.4	1.77	N
Narcolepsy and cataplexy	2	19.67	0.10	N
Hemorrhagic Stroke	13	14.69	0.89	N
Ischemic Stroke	75	102.75	0.73	N
Transverse myelitis (TM)	1	1.02	0.98	N
Venous thromboembolism (VTE)	233	295.7	0.79	N
Bell's Palsy	15	29.83	0.50	N
Appendicitis	5	9.51	0.53	N
Pulmonary Embolism (PE)	105	128.27	0.82	N
Thrombotic thrombocytopenic purpura (TTP)	0	0.22	0	N
Cerebral Venous Thrombosis (CVST)	0	0.55	0	N
Myocarditis/pericarditis OP	11	7.61	1.45	N

Bivalent Pfizer >/= 65 years

Number of vaccinations thru 03/05/2023 = 325,001 21 days				
AESIs	# of Observed AEs	# of Expected AEs	Risk Ratio	Signal
Acute disseminated encephalomyelitis (ADEM)	0	0	.	N
Acute myocardial infarction	99	95.4	1.04	N
Anaphylaxis 0-1 day	0	0.33	0	N
Convulsions/seizures	49	64.81	0.76	N
Disseminated intravascular coagulation (DIC)	1	1.84	0.54	N
Encephalitis/myelitis/encephalomyelitis/meningoencephalitis	0	1.57	0	N
Guillain-Barre Syndrome (GBS)	0	0.84	0	N
Immune thrombocytopenic purpura (ITP)	4	12.97	0.31	N
Myocarditis/pericarditis	5	2.2	2.27	N
Narcolepsy and cataplexy	1	9.13	0.11	N
Hemorrhagic Stroke	13	12.22	1.06	N
Ischemic Stroke	65	81.52	0.80	N
Transverse myelitis (TM)	1	0.6	1.67	N
Venous thromboembolism (VTE)	189	214.61	0.88	N
Bell's Palsy	12	18.41	0.65	N
Appendicitis	3	5.16	0.58	N
Myocarditis/pericarditis OP	9	4.18	2.16	N

Summary

- RCA
  - Bivalent Booster dose:
    - Heterologous evaluation
    - No signals for Pfizer or Moderna Bivalent booster doses to date
  - Full evaluations underway to assess ischemic stroke
    - Continuous users of the VA system
      - Cohort Study
      - SCCS
    - Target Trial Emulation (under development)

COVID-19 Vaccine Safety Surveillance: Summary from VSD RCA

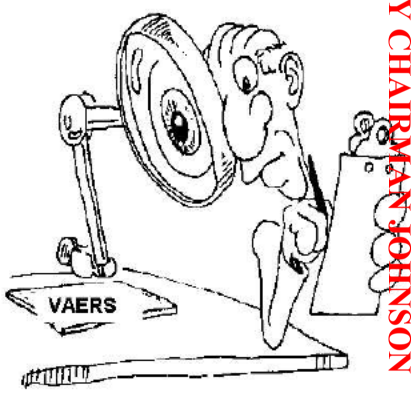
Nicola Klein, MD, PhD
Director, Kaiser Permanente Vaccine Study Center
Kaiser Permanente Northern California

ACIP Vaccine Safety Technical (VaST) Workgroup
March 27, 2023

KAISER PERMANENTE®
VACCINE STUDY CENTER

Vaccine Safety Datalink

- Active surveillance: newly licensed vaccines
  - Rapid Cycle Analysis (RCA)
- Evaluate vaccine safety:
  - of new recommendations for existing vaccines
  - for vaccines in high-risk populations, particularly pregnant women (+ other groups)
- Develop new methods for vaccine safety assessment
- Test hypotheses that emerge from elsewhere (e.g., VAERS, clinical trials, other platforms).



Strengths of VSD Rapid Cycle Analysis (RCA)

- **Population**
  - ~12.5 million people (equal to ~4% of the U.S. population) across VSD data sites are geographically and racially/ethnically diverse
- **Data**
  - Near real-time data, with analyses updated weekly
  - Access to comprehensive medical records, including exposures (vaccination) and outcomes, allowing rapid chart reviews to obtain additional clinical information as needed
- **Innovative Methods**
  - *Vaccinated concurrent comparators:* Recent vaccinees who are beyond their risk interval are expected to be similar to current vaccinees who are within their risk interval. They serve as better comparators than unvaccinated individuals, historical controls or non-concurrent self controls because they permit:
    - Careful adjustment for potential biases associated with calendar time, site, and demographic factors
    - Analyses that can begin sooner than alternative methods
  - *Supplemental analyses conducted weekly:* Unvaccinated/un-boosted comparators would also be available to provide context in real time

VSD COVID-19 Vaccine RCA

Aims:

1. To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

2. To describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity.

Surveillance began in December 2020 and was ready when the first doses of COVID-19 vaccines were given.

COVID Vaccine Safety RCA Surveillance: Monitoring 23 Serious Outcomes

Inclusion in prior vaccine safety studies

- Acute disseminated encephalomyelitis
- Anaphylaxis*
- Encephalitis / myelitis
- Guillain-Barré syndrome
- Immune thrombocytopenia
- Kawasaki disease
- Narcolepsy and cataplexy*
- Seizures
- Transverse myelitis

Outcomes added/enhanced due to emerging concerns

- Cerebral venous sinus thrombosis
- Myocarditis / pericarditis
- Thrombosis with thrombocytopenia syndrome

Hypothetical concerns regarding an association with COVID-19 disease

- Acute myocardial infarction
- Acute respiratory distress syndrome*
- Disseminated intravascular coagulation
- Multisystem Inflammatory Syndrome*
- Pulmonary embolism
- Stroke, hemorrhagic
- Stroke, ischemic
- Thrombotic thrombocytopenic purpura
- Venous thromboembolism

Imbalances in phase 3 COVID-19 vaccine clinical trials

- Appendicitis
- Bell's palsy

COVID Vaccine Safety RCA Surveillance: Monitoring 23 Serious Outcomes

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*monitored with [illegible]

COVID Vaccine Safety RCA Surveillance: Monitoring 23 Serious Outcomes

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- Acute disseminated encephalomyelitis ✓
- Anaphylaxis* ✓
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- Myocarditis / pericarditis ✓
- Thrombosis with thrombocytopenia syndrome

Imbalances in phase 3 COVID-19 vaccine clinical trials

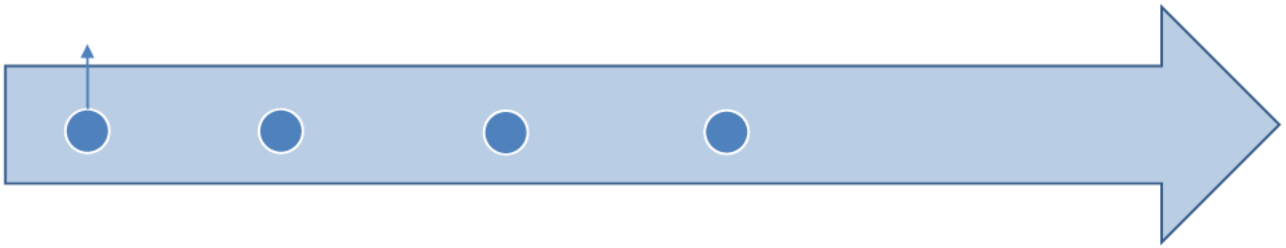
- Appendicitis
- Bell's palsy

✓ Only chart confirmed cases

*monitored with [illegible]

Chart Review and Adjudication Process

Case identified within appropriate interval following a COVID-19 vaccination.



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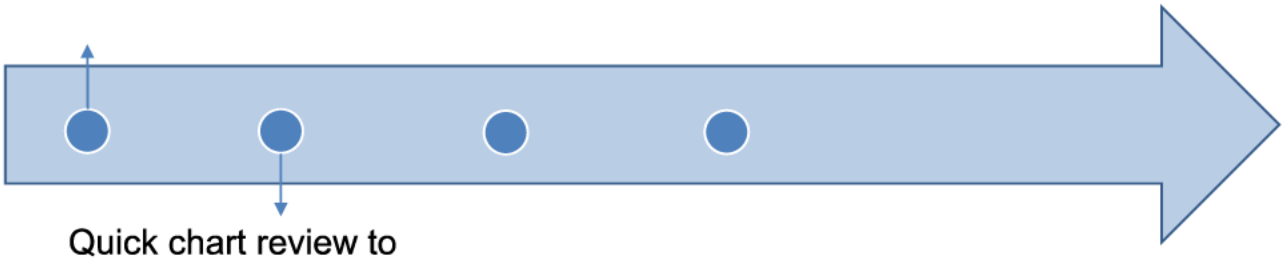

Quick chart review to determine if the case appears to be incident with symptom onset after COVID-19 vaccination. "Quick reviews" generally occur within one week.

Chart Review and Adjudication Process

Case identified within appropriate interval following a COVID-19 vaccination.

✔ If the case meets the VSD incident definition, then it is included in the weekly analyses.

✖ If the case does not meet the VSD incident definition, then it is excluded from all future analyses.

Quick chart review to determine if the case appears to be incident with symptom onset after COVID-19 vaccination. "Quick reviews" generally occur within one week.

Chart Review and Adjudication Process

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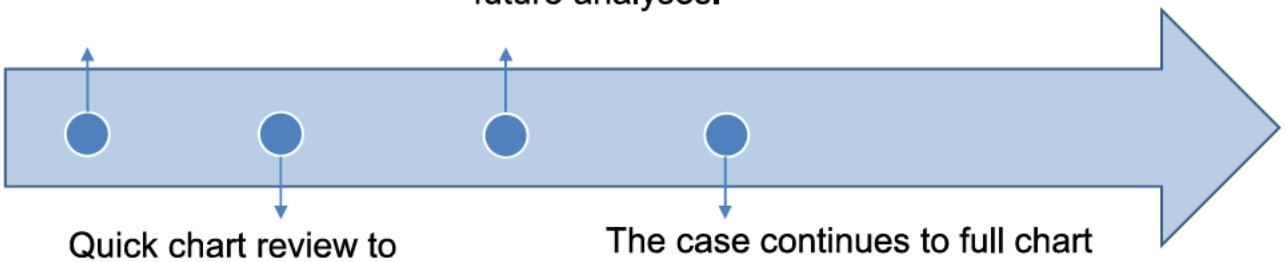

Quick chart review to determine if the case appears to be incident with symptom onset after COVID-19 vaccination. "Quick reviews" generally occur within one week.

The case continues to full chart abstraction/adjudication after the appropriate time has passed from the initial date of the diagnosis (varies by outcome) – this allows time for diagnostic information and follow-up visits to accumulate in the medical record.

Chart Review and Adjudication Process

Case identified within appropriate interval following a COVID-19 vaccination.

✔ If the case meets the VSD incident definition, then it is included in the weekly analyses.

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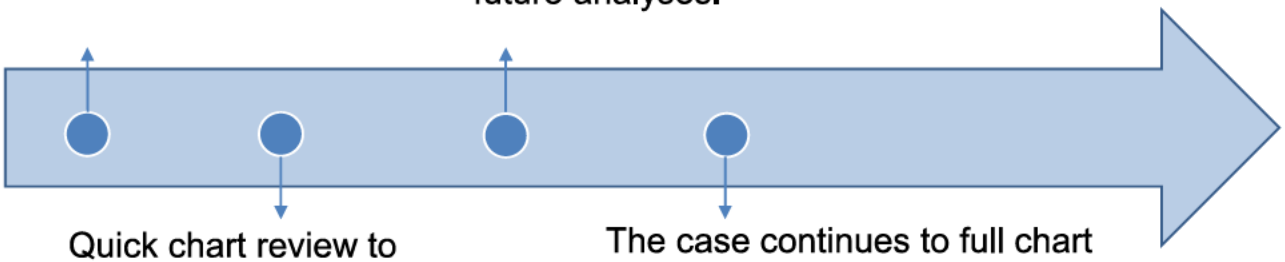


Quick chart review to determine if the case appears to be incident with symptom onset after COVID-19 vaccination. "Quick reviews" generally occur within one week.

The case continues to full chart abstraction/adjudication after the appropriate time has passed from the initial date of the diagnosis (varies by outcome) – this allows time for diagnostic information and follow-up visits to accumulate in the medical record.

For each week's analyses, VSD RCA results included a mix of:
1) all cases confirmed after full chart abstraction and adjudication
2) all quick-reviewed cases pending full chart abstraction

This allowed for a balance between analyzing quick chart-confirmed data (i.e., timely but still higher quality) while ultimately only including cases with complete follow-up.

It also meant that case counts could change across analytic weeks.

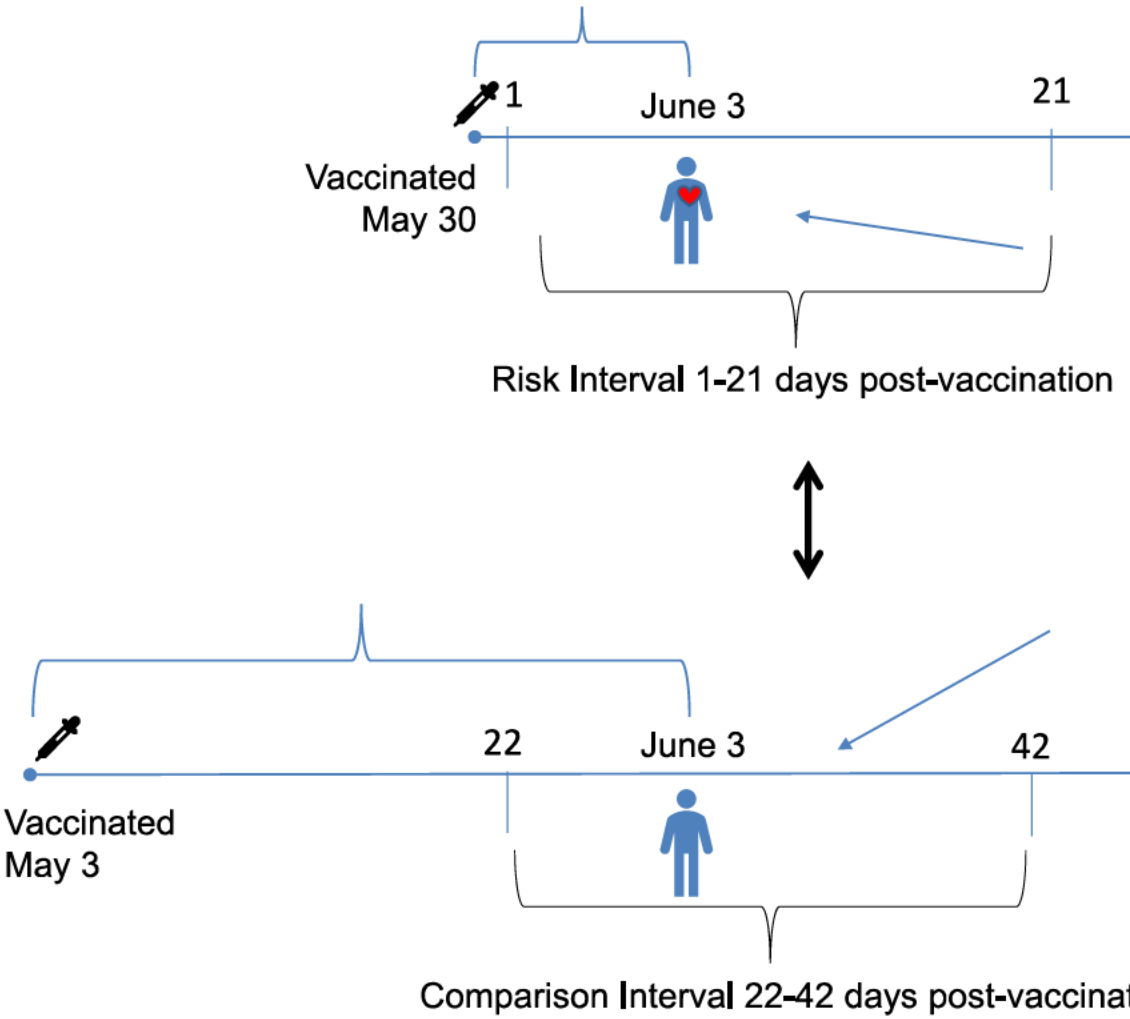
COVID Vaccine Safety RCA Surveillance: Analytic Strategy

- For the primary analysis, the number of outcomes observed in the risk interval (1-21 days) after COVID-19 vaccination were compared to the number expected.

- The expected was derived from "vaccinated concurrent comparators" who were in a comparison interval (days 22-42) after COVID-19 vaccination.

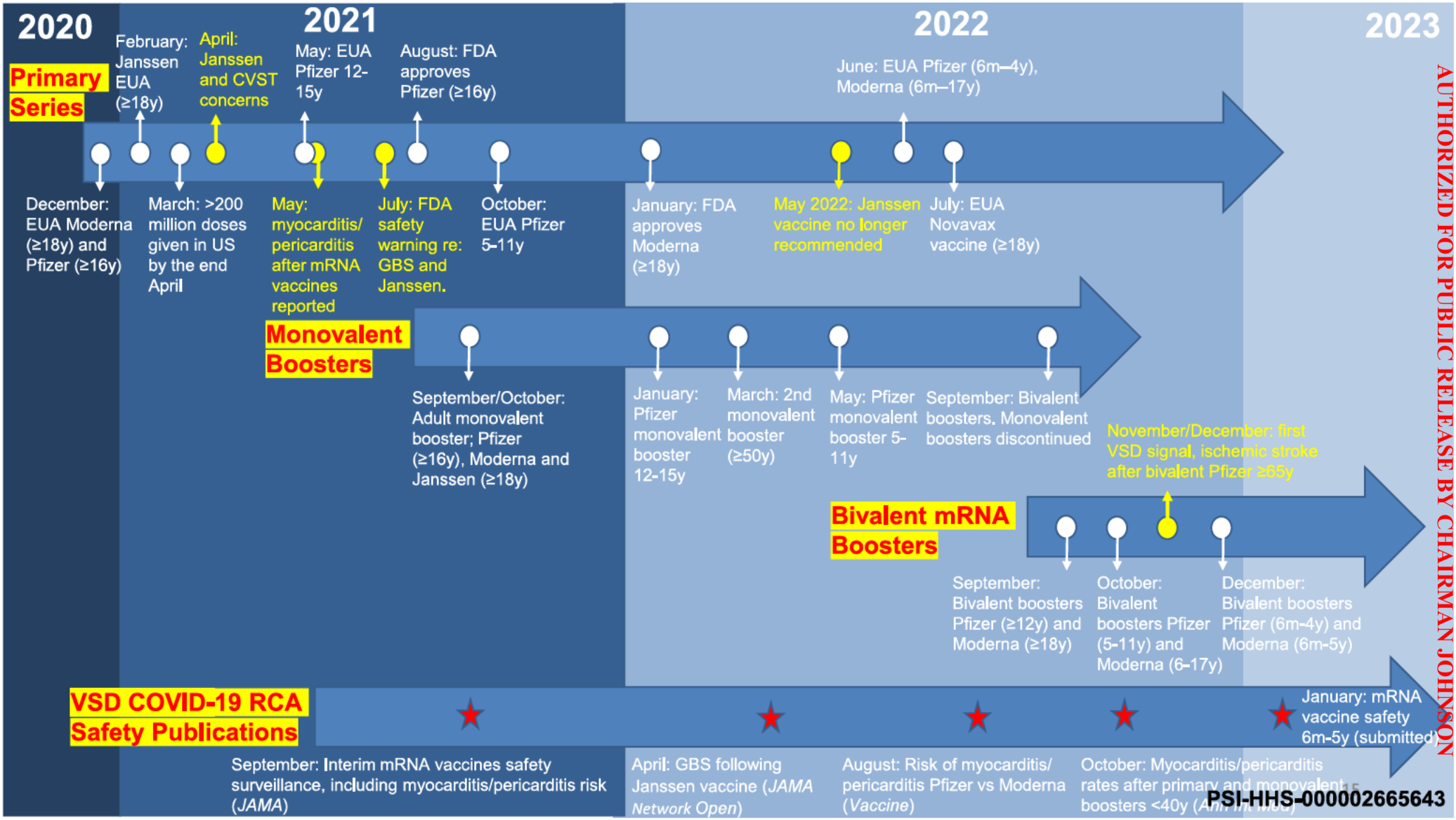
- On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval.
  - Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, as well as calendar date.

Vaccinee with Myocarditis in Risk Interval and a Concurrent Comparator



On each calendar day that an outcome occurred in a vaccinee (e.g., June 3), we compared vaccinees in their risk interval (day 1-21) with similar vaccinees in their comparison interval (day 22-42).

By similar, we mean they were in the same age group and of the same sex, race, and at the same VSD site.



JAMA | Original Investigation

Surveillance for Adverse Events After COVID-19 mRNA Vaccination

Nicola P. Klein, MD, PhD; Ned Lewis, MPH; Kristin Goddard, MPH; Bruce Fireman, MA; Ousseny Zerbo, PhD; Kayla E. Hanson, MPH; James G. Donahue, DVM, PhD; Elyse O. Kharbanda, MD, MPH; Allison Naleway, PhD; Jennifer Clark Nelson, PhD; Stan Xu, PhD; W. Katherine Yih, PhD, MPH; Jason M. Glanz, PhD; Joshua T. B. Williams, MD; Simon J. Hambidge, MD, PhD; Bruno J. Lewin, MD; Tom T. Shimabukuro, MD, MPH, MBA; Frank DeStefano, MD, MPH; Eric S. Weintraub, MPH

JAMA. doi:10.1001/jama.2021.15072
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Results using vaccinated concurrent comparators

Table 3. Outcome Events in the 21-Day Risk Interval After Either Vaccine Dose Compared, on the Same Calendar Day, With Outcome Events in Individuals 22-42 Days After Their Most Recent Dose, December 14, 2020-June 26, 2021

Outcome	Events in risk interval (events/million person-years)[a]	Events in comparison interval (events/million person-years)[a,b]	Adjusted rate ratio[c] (95% CI)[d]	*P* value		Signal, 1-sided *P* < .0048[e]	Excess cases in risk interval per million doses (95% CI)[f]
				2-Sided[d]	1-Sided		
Thrombotic thrombocytopenic purpura	6 (9.1)	2 (5.5)	2.60 (0.47-20.66)	.29	.23	No	0.3 (-0.6 to 0.5)
Cerebral venous sinus thrombosis[g]	7 (10.6)	3 (8.2)	1.55 (0.37-8.17)	.59	.41	No	0.2 (-1.1 to 0.5)
Transverse myelitis[g]	2 (3.0)	1 (2.7)	1.45 (0.10-47.73)	.82	.64	No	0.1 (-1.6 to 0.2)
Encephalitis/myelitis/ encephalomyelitis	16 (25.7)	5 (13.7)	1.27 (0.45-4.10)	.69	.44	No	0.3 (-1.8 to 1.1)
Myocarditis/pericarditis	87 (131.7)	39 (106.9)	1.18 (0.79-1.79)	.44	.25	No	1.2 (-2.1 to 3.3)
Venous thromboembolism	626 (951.9)	327 (895.9)	1.16 (1.00-1.34)	.05	.03	No	7.5 (-0.1 to 14.0)
Immune thrombocytopenia	48 (72.6)	23 (63.0)	1.12 (0.65-1.97)	.70	.40	No	0.4 (-2.2 to 2.1)
Convulsions/seizures	285 (431.3)	150 (411.0)	1.04 (0.84-1.29)	.74	.39	No	0.9 (-4.8 to 5.6)
Acute myocardial infarction	613 (935.3)	375 (1030.2)	1.02 (0.89-1.18)	.75	.39	No	1.2 (-6.9 to 8.3)
Pulmonary embolism	503 (762.8)	290 (794.6)	1.01 (0.86-1.19)	.92	.48	No	0.4 (-7.2 to 6.9)
Bell palsy	535 (821.8)	301 (824.7)	1.00 (0.86-1.17)	.99	.52	No	0.0 (-7.9 to 6.7)
Stroke, ischemic	1059 (1611.8)	650 (1780.9)	0.97 (0.87-1.08)	.61	.70	No	-2.7 (-13.8 to 7.2)
Stroke, hemorrhagic	240 (364.7)	149 (408.2)	0.90 (0.72-1.13)	.37	.83	No	-2.3 (-8.3 to 2.5)
Thrombosis with thrombocytopenia syndrome	73 (112.0)	53 (145)	0.86 (0.58-1.27)	.45	.81	No	-1.0 (-4.6 to 1.4)
Appendicitis	762 (1178.9)	491 (1345.2)	0.82 (0.73-0.93)	.002	>.99	No	-14.8 (-25.5 to -5.3)
Guillain-Barré syndrome[g]	10 (15.1)	6 (16.4)	0.70 (0.22-2.31)	.53	.83	No	-0.4 (-3.0 to 0.5)
Disseminated intravascular coagulation	30 (45.4)	25 (68.5)	0.70 (0.39-1.28)	.25	.91	No	-1.1 (-4.1 to 0.6)
Kawasaki disease	0	2 (5.5)	0.00 (0.00-2.52)	.16	.16	No	-0.3 (-0.3 to 0.0)
Acute disseminated encephalomyelitis[g]	2 (3.0)	0	NE (0.07-NE)	.66	.66	No	0.2 (-2.5 to NE)

Abbreviation: NE, not estimable.

[a] There were 660 766 person-years of follow-up in the risk interval and 364 988 person-years in the comparison interval.

[b] Comparison interval was 22 to 42 days after either dose 1 or 2. The smaller case counts were due to the reduced available person-time of follow-up in the comparison interval. Most comparator follow-up was 22 to 42 days after dose 2 but some was 22 to 42 days after dose 1 in individuals who had not received dose 2.

[c] Overall estimate from Poisson regression stratified by site, 5-year age group, sex, race and ethnicity, and calendar date.

[d] CIs and *P* values do not account for the multiple chances for a false-positive signal during surveillance.

[e] One-sided *P* < .0048 required for a signal. This keeps the probability of a false-positive signal (owing to chance alone) below .05 in 2 years of surveillance.

[f] CIs for the excess risk estimates were based on the CIs of the corresponding adjusted rate ratios.

[g] Only medical record-confirmed cases are included in the analysis.

PSI-HHS-000002665646

Klein NP, Lewis N, et. al. *JAMA*. Published online September 03, 2021. doi:10.1001/jama.2021.15072

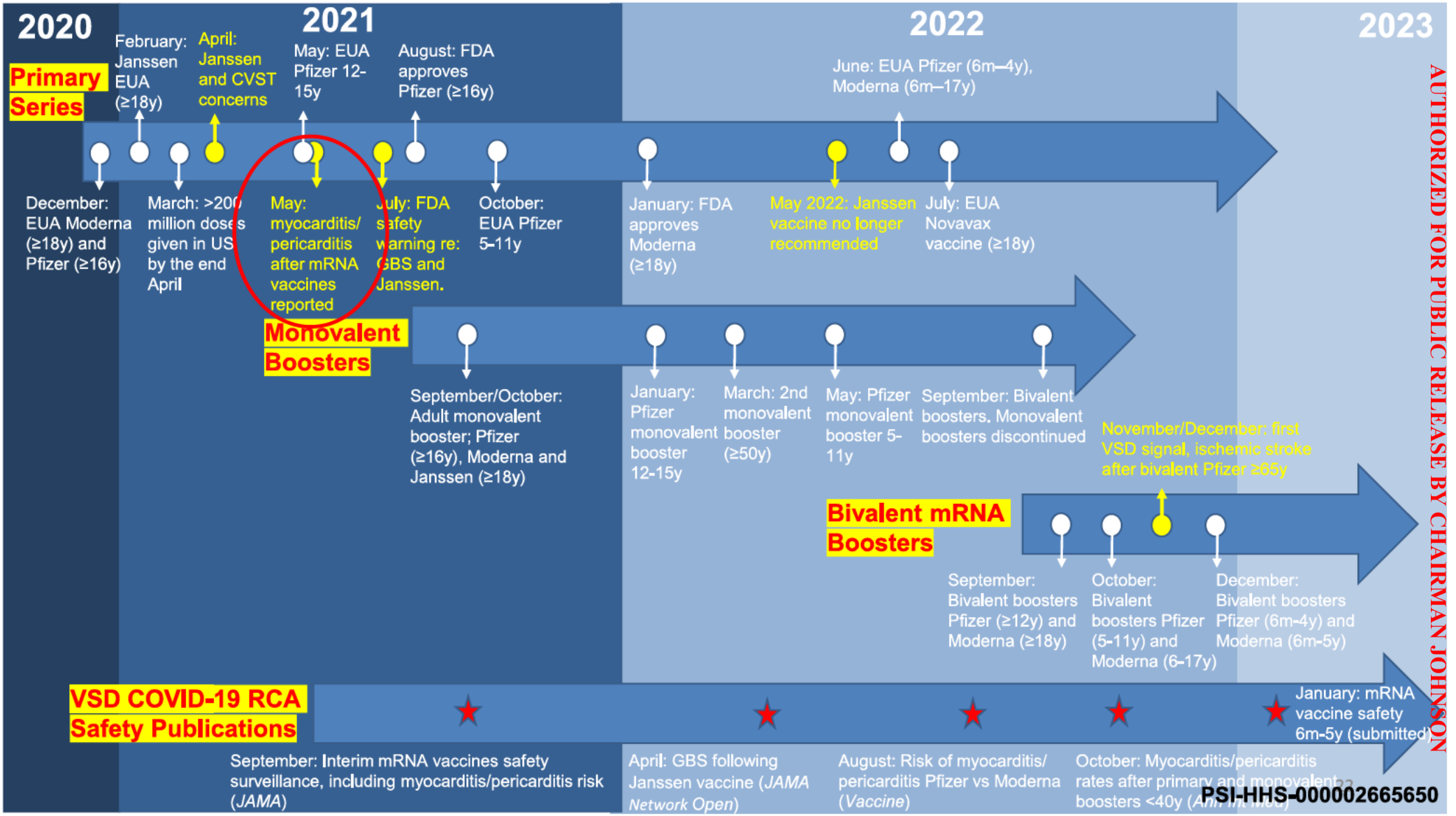
Outcomes Monitored Without Comparators

Table 5. Confirmed Anaphylaxis Cases After Medical Record Review Through May 29, 2021[a]

	No. (%)	
	BNT162b2 (n = 30)	mRNA-1273 (n = 25)
Age, mean (SD), y	42.8 (14.5)	45.7 (15.5)
Female sex	30 (100)	22 (88)
Time from vaccination to symptom onset, median (IQR) [N], min[b]	10.0 (5.0-20.0) [21]	10.0 (5.0-20.5) [20]
Time to symptom onset, min		
≤15[b]	19 (63)	17 (68)
≤30[b]	26 (87)	22 (88)
History		
Allergies[c]	24 (80)	19 (76)
Anaphylaxis[d]	15 (50)	5 (20)
Dose		
1	25 (83)	20 (80)
2	5 (17)	5 (20)
Brighton Collaboration case definition level[e]		
1, High certainty	13 (43)	6 (24)
2, Moderate certainty	17 (57)	18 (72)
3, Low certainty	0	1 (4)
Confirmed anaphylaxis cases per million doses (95% CI)[f]	4.8 (3.2-6.9)	5.1 (3.3-7.6)
Confirmed anaphylaxis cases per million doses among female individuals (95% CI)[f]	8.9 (6.0-12.7)	8.6 (5.2-12.5)

JAMA. Published online September 03, 2021. doi:10.1001/jama.2021.15072

VSD COVID-19 RCA Surveillance: Outcomes Monitored Due to Emerging Concerns



Myocarditis and Pericarditis Following mRNA Vaccines

World Health Organization

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Home / News / COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviews cases of mild myocarditis reported with COVID-19 mRNA vaccines

COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviews cases of mild myocarditis reported with COVID-19 mRNA vaccines

26 May 2021 | Statement | Reading time: 2 min (429 words)

The COVID-19 subcommittee of the WHO Globa Advisory Committee on Vaccine Safety (GACVS) is reviewing reports of a small number of cases of myocarditis reported in individuals vaccinated with the COVID-19 mRNA vaccines. The subcommittee noted that in most of the reported cases, the individuals have recovered. The subcommittee is soliciting and monitoring for additional information to assess for any relationship to COVID-19

Related

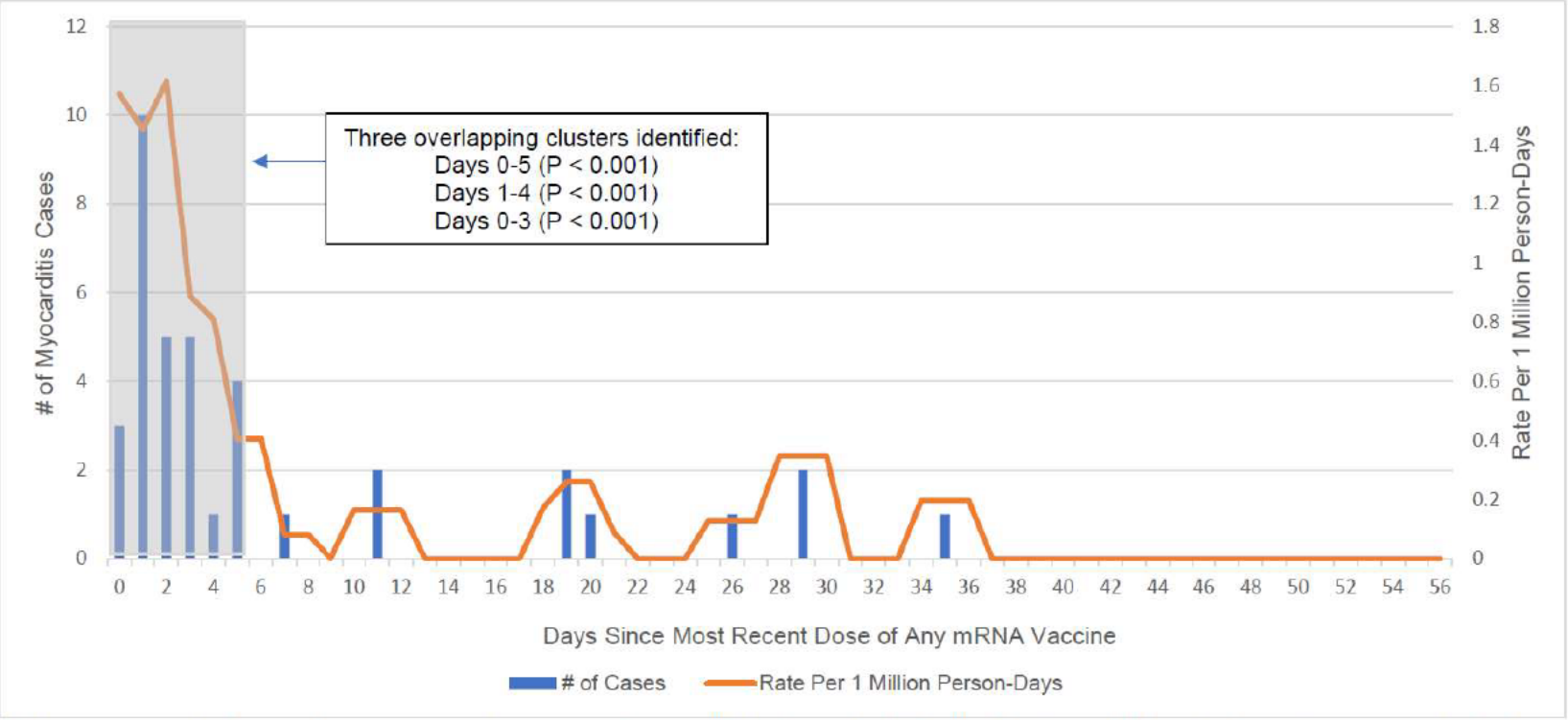
COVID-19 vaccine safety surveillance manual

Myocarditis / Pericarditis Among Subgroup <40 Years of Age

- **Chart reviews began May 2021**

- **All identified cases of myocarditis/pericarditis during the 98 days after vaccination were chart reviewed, followed by infectious disease clinician and/or a cardiologist adjudication to:**
  - Confirm case was incident following vaccination
  - Met CDC case definition (myocarditis, pericarditis, or myopericarditis)
  - Evaluated level of certainty for myocarditis

Clustering of Confirmed Myocarditis/pericarditis by Days Since Most Recent Dose of any mRNA Vaccine Among 12-39 Year-Olds



Blue bars denote number of cases of medical-record confirmed myocarditis/pericarditis during days 0-56 after either dose of an mRNA vaccine. Orange line represents the rate of confirmed myocarditis/pericarditis per 1 million person-days. The rate is a moving 3 day mean. Clusters were identified using Kulldorff's scan statistic [17].

PSI-HHS-000002665654
JAMA. Published online September 03, 2021. doi:10.1001/jama.2021.15072

Table 4. Confirmed Myocarditis/Pericarditis After Receipt of mRNA Vaccines Compared With Vaccinated Comparators Among Individuals Aged 12-39 Years by Dose and Risk Interval, December 14, 2020-June 26, 2021

Risk interval, d[a]	Dose	Events in risk interval (events/million person-years)[b]	Events in 21-d comparison interval[b,c] (events/million person-years)[b,c]	Adjusted rate ratio (95% CI)[d]	2-Sided *P* value	Excess cases in risk interval per million doses (95% CI)[e]
0-21	Both	34 (141.2)	4 (35.0)	3.75 (1.38 to 12.84)	.007	6.2 (2.3 to 7.8)
	1	9 (70.4)	4 (35.0)	3.67 (0.92 to 17.35)	.07	3.1 (-0.4 to 4.0)
	2	24 (221.3)	4 (44.6)	4.07 (1.45 to 14.18)	.005	10.1 (4.1 to 12.4)
0-7	Both	29 (320.8)	4 (35.0)	9.83 (3.35 to 35.77)	<.001	6.3 (4.9 to 6.8)
	1	5 (104.2)	3 (35.0)	7.27 (1.29 to 50.15)	.02	2.0 (0.5 to 2.2)
	2	23 (565.9)	4 (44.6)	10.4 (3.54 to 37.76)	<.001	11.2 (8.9 to 12.1)
8-14	Both	2 (25.7)	4 (35.0)	1.22 (0.14 to 7.74)	.82	0.1 (-3.0 to 0.4)
	1	2 (48.0)	3 (35.0)	3.25 (0.31 to 29.64)	.30	0.6 (-2.0 to 0.9)
	2	0	4 (44.6)	0 (0 to 3.22)	.28	-0.9 (-0.9 to 0)
15-21	Both	3 (41.3)	4 (35.0)	1.55 (0.28 to 7.78)	.58	0.3 (-2.0 to 0.7)
	1	2 (52.3)	4 (35.0)	2.58 (0.27 to 18.62)	.37	0.6 (-2.7 to 0.9)
	2	1 (29.1)	4 (44.6)	0.67 (0.03 to 5.64)	.79	-0.3 (-21.2 to 0.5)

Klein NP, Lewis N, et. al. *JAMA*. Published online September 03, 2021. doi:10.1001/jama.2021.15072

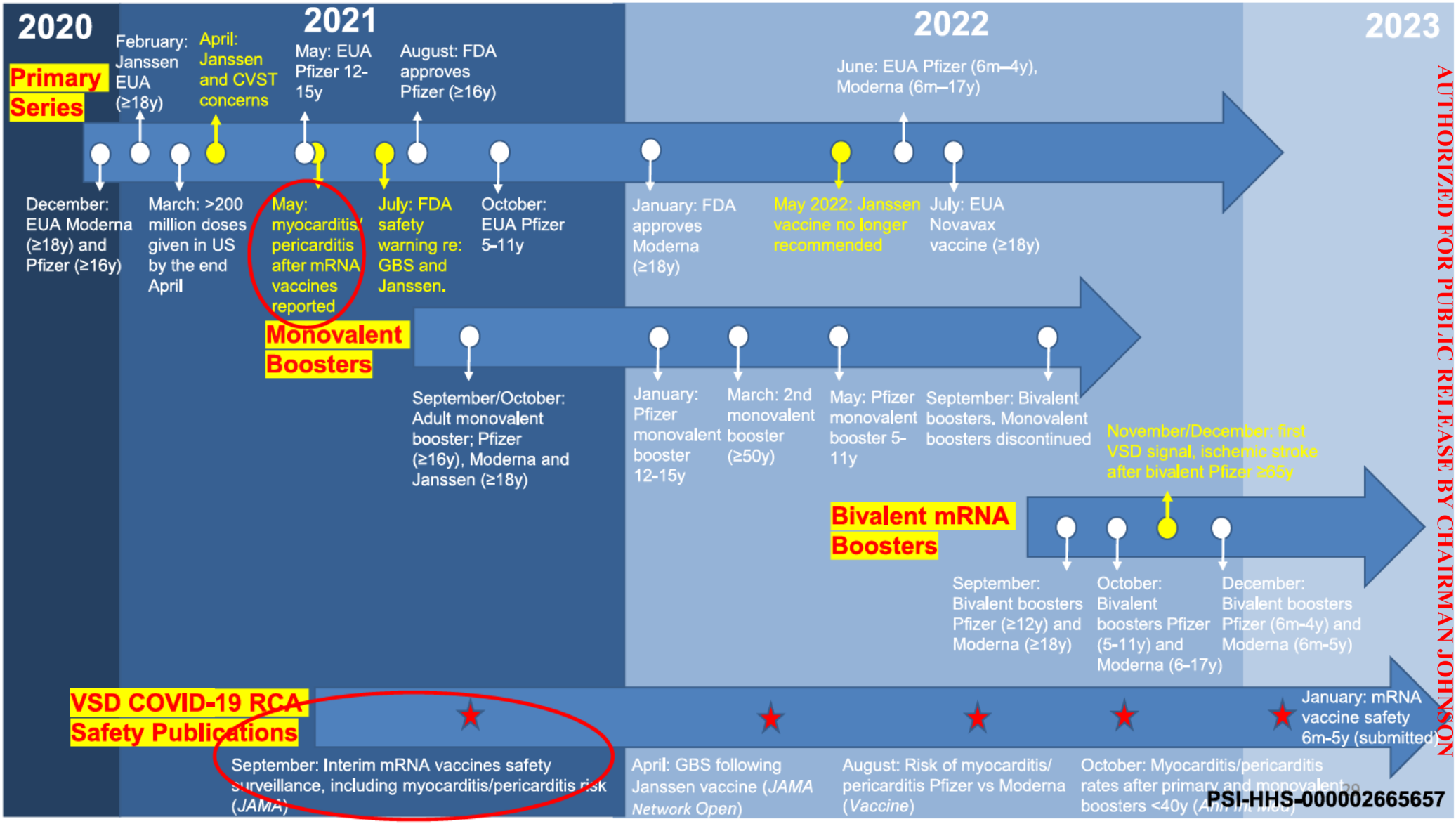
Interim Analyses Summary (data through June 2021)

- No safety signals for any outcome in the 21 days after both mRNA doses in the overall VSD population, including all ages ≥12 years.

- In the subgroup aged 12–39 years, the rate ratio for myocarditis/pericarditis was elevated after both Pfizer and Moderna during days 0-21 after vaccination, and especially during days 0-7.
  - In subgroup analyses, both mRNA vaccines were associated with myocarditis/pericarditis in persons aged 12-39 years.

- In the VSD, rate of anaphylaxis after mRNA vaccines was ~ 5 cases / million doses.

- VSD surveillance was ongoing.



RCA Signal* for Myocarditis/Pericarditis in the 1-21 Day Risk Interval, all VSD population >12 years

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

			Sequential Test[1]	
Outcome	Event in Risk Interval	Adjusted Rate Ratio (95% CI)[2]	1-sided P-value	'Signal' 1-sided p <0.0048?
Myocarditis / pericarditis	138	1.72	<0.001	Yes

[1]Sequential test requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. Comparison interval is 22–42 days after either dose.

*signal as of August 2021

Contents lists available at ScienceDirect

Vaccine

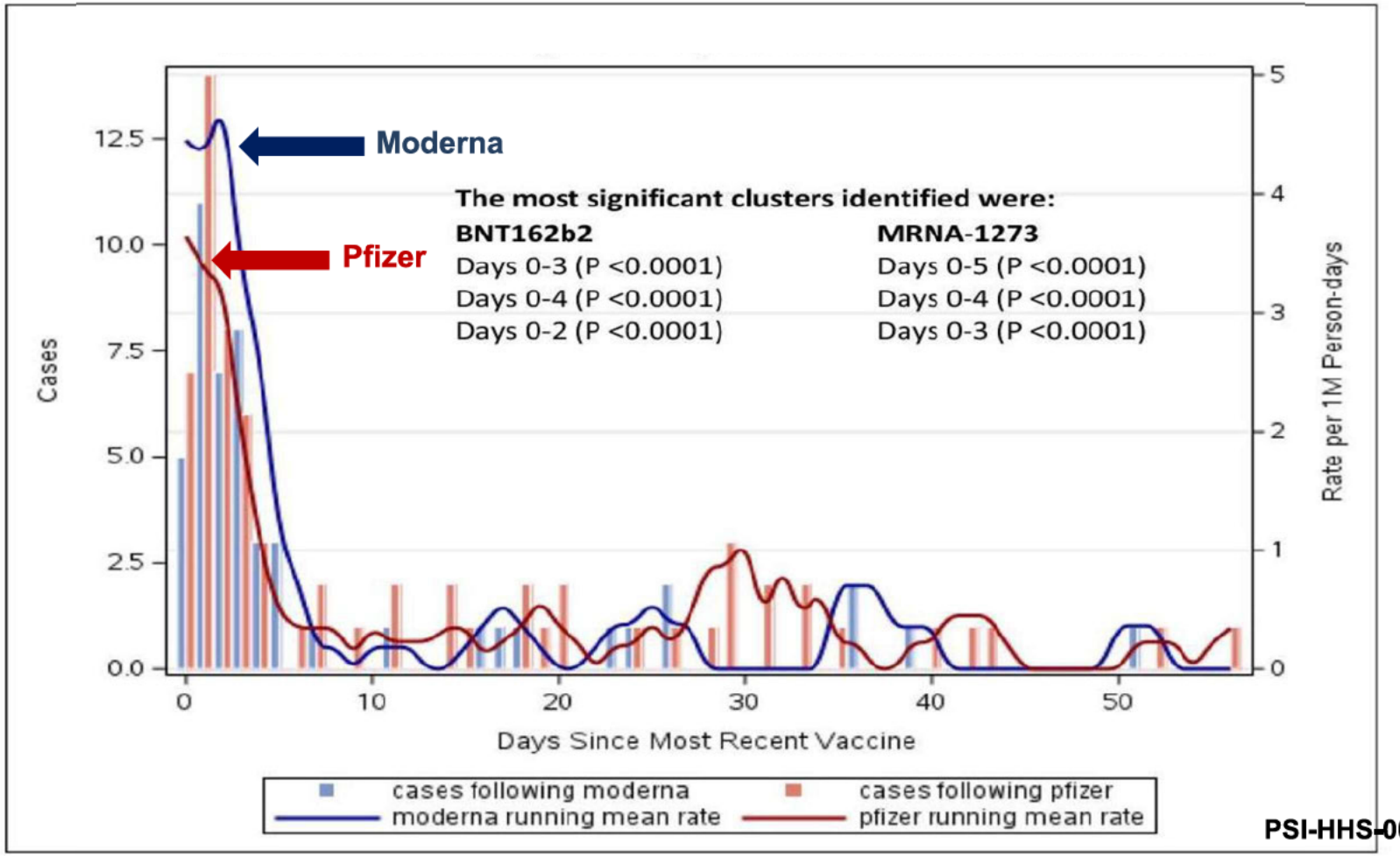
journal homepage: www.elsevier.com/locate/vaccine

Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination

Kristin Goddard [a], Ned Lewis [a], Bruce Fireman [a], Eric Weintraub [c], Tom Shimabukuro [c], Ousseny Zerbo [a], Thomas G. Boyce [b], Matthew E. Oster [c,d], Kayla E. Hanson [b], James G. Donahue [b], Pat Ross [a], Allison Naleway [e], Jennifer C. Nelson [f], Bruno Lewin [g], Jason M. Glanz [h], Joshua T.B. Williams [i], Elyse O. Kharbanda [j], W. Katherine Yih [k], Nicola P. Klein [a,*]

- This study assessed whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer
- We conducted both indirect and direct head-to-head comparisons among 18–39-year-olds

Symptom Onset of 79 Verified Myocarditis and Pericarditis among 18–39-Year-Olds by Vaccine Product



PSI-HHS-000002665660

Verified Myocarditis and Pericarditis in the 0-7 Day Risk Interval, among 18–39-Year-Olds by Product and Dose, December 14, 2020-January 14, 2022

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

Vaccine	Dose	Cases in 0–7 day risk interval (Rate of cases /million person years)	Cases in 22–42-day comparison interval (Rate of cases/million person years)	Adjusted rate ratio[2] (95% confidence interval)	2-Sided P-value	Cases in risk period per million doses	Excess cases in risk period per million doses[4]
Both mRNA	Either Dose[1]	79 (768.2)	20 (125.2)	7.55 (4.52–13.04)	<0.001	16.8	14.6
	Dose 1[1]	16 (303.9)	20 (125.2)	3.29 (1.52–7.07)	0.003	6.7	4.6
	Dose 2	63 (1255.2)	13 (99.4)	13.63 (7.39–26.55)	<0.001	27.5	25.5
BNT162b2	Either Dose[1]	41 (647.2)	13 (143.9)	6.94 (3.57–14.13)	<0.001	14.2	12.1
	Dose 1[1]	7 (216.0)	13 (144.2)	3.02 (1.03–8.33)	0.044	4.7	3.2
	Dose 2	34 (1099.1)	8[3] (111.5)	14.34 (6.45–34.85)	<0.001	24.1	22.4
mRNA-1273	Either Dose[1]	38 (962.4)	7 (100.2)	9.18 (4.12–22.89)	<0.001	21.1	18.8
	Dose 1[1]	9 (444.9)	7 (100.5)	3.46 (1.12–11.07)	0.031	9.7	6.9
	Dose 2	29 (1506.1)	4 (80.0)	18.75 (6.73–64.94)	<0.001	33.0	31.2

[1] Comparison interval is 22–42 days after either dose.

[2] Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

[3] One case was non-informative in the BNT162b2, Dose 2 comparator interval.

[4] Excess cases are in addition to an estimated background rate of 2 cases/per million doses.

Goddard, et al. *Vaccine*.

PSI-HHS-000002665661

Head-to-Head Comparison of Moderna versus Pfizer Regarding Myocarditis and Pericarditis During Days 0-7 Day Post-Vaccination in 18–39-Year-Olds

Dose	Sex	Myocarditis, myopericarditis, and pericarditis			Myocarditis and myopericarditis (pericarditis excluded)		
		Adjusted rate ratio[1] (95% CI)	2-sided p-value	Excess cases in risk period per 1 M doses of mRNA-1273 vs BNT162b2 [2]	Adjusted rate ratio[1] (95% CI)	2-sided p-value	Excess cases in risk period per 1 M doses of mRNA-1273 vs BNT162b2 [2]
Either Dose	All	1.61 (1.02–2.54)	0.041	8.0	1.35 (0.82–2.19)	0.237	4.3
	Male	1.52 (0.93–2.48)	0.097	13.4	1.32 (0.78–2.22)	0.288	8.1
	Female	2.34 (0.65–8.71)	0.188	3.5	1.57 (0.27–8.12)	0.585	1.1
Dose 2	All	1.48 (0.88–2.50)	0.141	10.7	1.24 (0.70–2.14)	0.454	5.2
	Male	1.50 (0.86–2.61)	0.152	21.9	1.31 (0.73–2.31)	0.361	13.6
	Female	1.35 (0.23–7.15)	0.714	1.6	0.53 (0.02–5.81)	0.658	–1.8

Abbreviation: CI = confidence interval.

[1] Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the mRNA-1273 rate divided by the BNT162b2 rate.

[2] Excess cases is an estimate of the mRNA-1273 rate minus the BNT162b2 rate. Excess cases per million doses were estimated by dividing the mRNA-1273 incidence rate by the rate ratio estimate and subtracting the result from the mRNA-1273 rate.

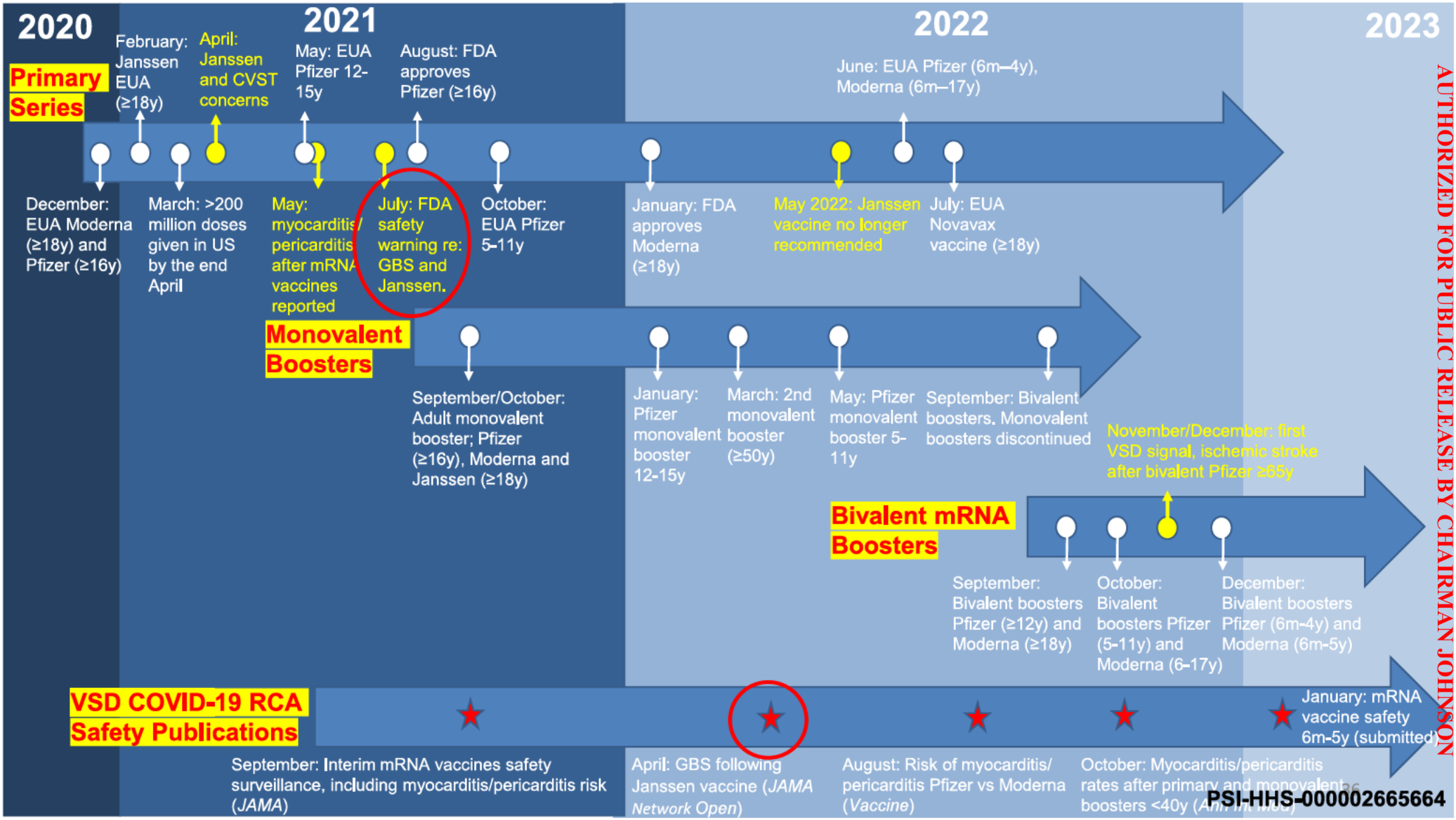
Annals of Internal Medicine

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after mRNA vaccination in 5–39-year-olds, by product, age groups, sex and dose number*

Product and Patient Group	Dose 1		Dose 2		First Booster	
	Cases/Doses Administered†	Incidence Rate/ Million Doses (95% CI)	Cases/Doses Administered†	Incidence Rate/ Million Doses (95% CI)	Cases/Doses Administered†	Incidence Rate/ Million Doses (95% CI)
Pfizer‡						
Male, *age*						
5–11 y	0/221 975	0.0 (0.0–13.5)	3/207 958	14.4 (3.0–42.2)	0/50 415	0.0 (0.0–59.4)
12–15 y§	2/212 977	9.39 (1.1–33.9)	31/205 955	150.5 (102.3–213.6)	5/81 613	61.3 (19.9–143.0)
16–17 y	1/105 147	9.51 (0.2–53.0)	14/102 091	137.1 (75.0–230.1)	9/47 874	188.0 (86.0–356.9)
18–29 y	4/348 080	11.5 (3.1–29.4)	27/331 889	81.4 (53.6–118.4)	7/166 973	41.9 (16.9–86.4)
30–39 y	1/352 403	2.8 (0.1–15.8)	5/341 527	14.6 (4.8–34.2)	3/197 554	15.2 (3.1–44.4)
Female, *age*						
5–11 y	0/215 986	0.0 (0.0–13.9)	0/202 596	0.0 (0.0–14.8)	0/49 261	0.0 (0.0–60.8)
12–15 y	0/210 741	0.0 (0.0–14.2)	5/204 074	24.5 (8.0–57.2)	0/84 114	0.0 (0.0–35.6)
16–17 y	1/110 066	9.1 (0.2–50.6)	1/107 173	9.3 (0.2–52.0)	2/55 004	36.4 (4.4–131.3)
18–29 y	1/414 730	2.4 (0.1–13.4)	2/400 321	5.0 (0.6–18.0)	1/240 226	4.2 (0.1–23.2)
30–39 y	0/420 934	0.0 (0.0–7.1)	3/410 713	7.3 (1.5–21.3)	1/268 412	3.7 (0.1–20.8)
Moderna‖¶						
Male, *age*						
18–29 y	5/207 073	24.2 (7.8–56.3)	19/195 809	97.0 (58.4–151.5)	7/109 337	64.0 (25.7–131.9)
30–39 y	1/223 064	4.5 (0.1–25.0)	8/216 583	36.9 (15.9–72.8)	1/149 468	6.7 (0.2–37.3)
Female, *age*						
18–29 y	1/253 773	3.9 (0.1–22.0)	0/243 560	0.0 (0.0–12.3)	1/156 707	6.4 (0.2–35.6)
30–39 y	1/265 362	3.8 (0.1–21.0)	1/259 780	3.9 (0.1–21.4)	2/191 765	10.4 (1.3–37.7)

* Data through August 20, 2022

Goddard K, et al. . *Ann Intern Med*. 2022;175:1169-1771



Guillain-Barre Syndrome Following Janssen Vaccine

Morbidity and Mortality Weekly Report

Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices — United States, July 2021

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JAMA | Original Investigation

Association of Receipt of the Ad26.COV2.S COVID-19 Vaccine With Presumptive Guillain-Barré Syndrome, February-July 2021

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Original Investigation | Infectious Diseases

Incidence of Guillain-Barré Syndrome After COVID-19 Vaccination in the Vaccine Safety Datalink

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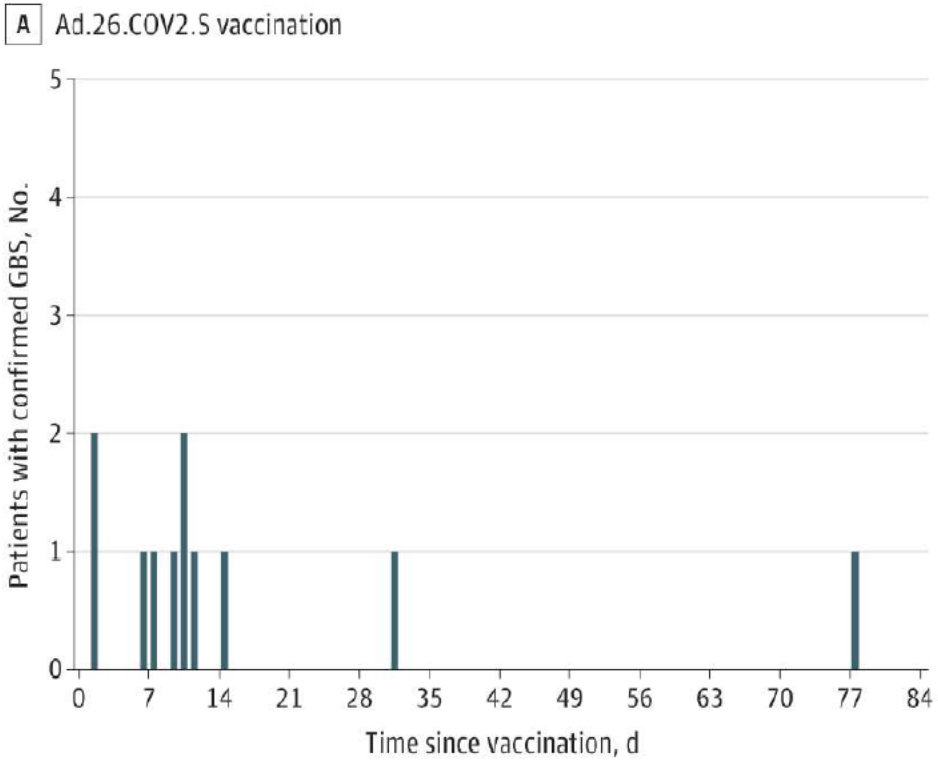
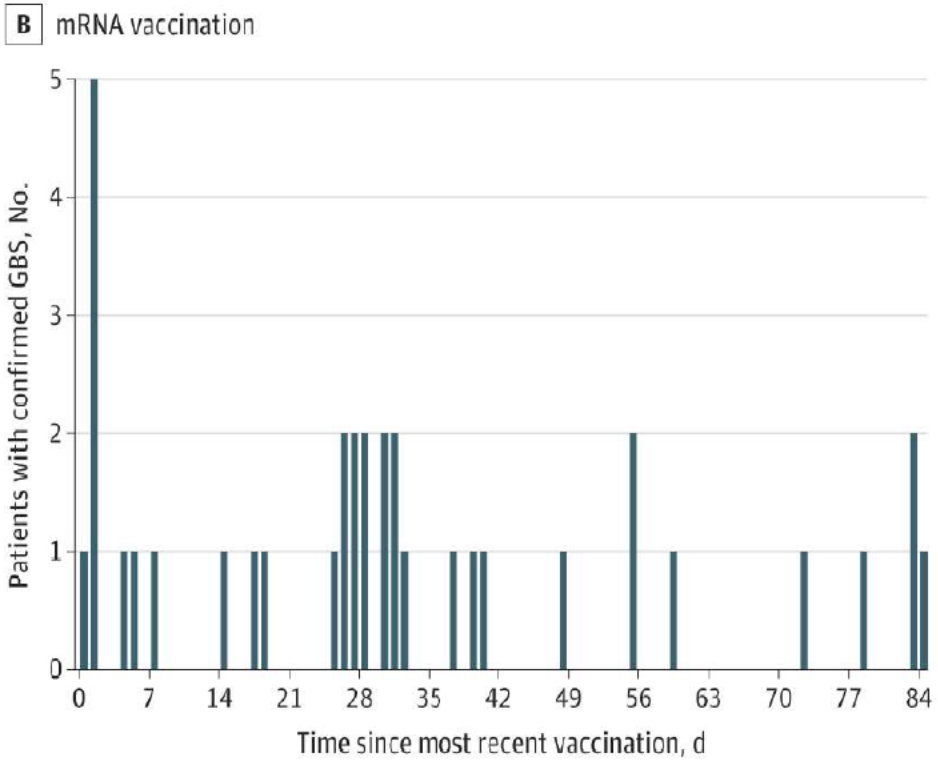
JAMA Netw Open. 2022;5(4):e228879.https://doi.org/10.1001/jamanetworkopen.2022.8879

- Describe GBS cases and incidence following COVID-19 vaccine primary series
- Assess the risk of GBS after vaccination with Janssen and mRNA vaccines

Timing of GBS Symptom Onset after COVID-19 Vaccination, December 13, 2020-November 14, 2021



- 11/22 (50%) GBS cases confirmed after review and adjudication
  - 9/11 (82%) cases had symptom onset within 1-21 days
- Cases temporally clustered days 1-14 (*P*=0.003)



- 36/78 (50%) cases confirmed after review and adjudication
  - 11/36 (31%) cases had symptom onset within 1-21 days
  - 15/36 (42%) cases had symptom onset within 22-42 days
  - 9/36 (25%) cases had symptom onset within 43-84 days

PSI-HHS-000002665668
Hanson, K, et al. JAMA Netw Open. 2022;5(4):e228879. doi:10.1001/jamanetworkopen.2022.8879

Table 3. Incidence Rate of Confirmed GBS in the 1 to 21 Days and 1 to 42 Days After COVID-19 Vaccination

Vaccine type	Risk window, d	Including BL 4 cases[a]	No.			Unadjusted incidence rate (95% CI)		P value, 2-sided[c]
			GBS cases	Vaccine doses	Person-years[b]	Per million doses	Per 100 000 person-years	
Ad.26.COV2.S	1-21	Yes	9	483 053	27 773	18.6 (8.5-35.4)	32.4 (14.8-61.5)	<.001
		No	8	483 053	27 773	16.6 (7.2-32.6)	28.8 (12.4-56.8)	<.001
	1-42	Yes	10	483 053	55 546	20.7 (9.9-38.1)	18.0 (8.6-33.1)	<.001
		No	9	483 053	55 546	18.6 (8.5-35.4)	16.2 (7.4-30.8)	<.001
mRNA vaccine	1-21	Yes	11	14 637 020	831 790	0.8 (0.4-1.3)	1.3 (0.7-2.4)	.20
		No	9	14 637 020	831 790	0.6 (0.3-1.2)	1.1 (0.5-2.1)	.06
	1-42	Yes	26	14 637 020	1 329 815	1.8 (1.2-2.6)	2.0 (1.3-2.9)	.99
		No	23	14 637 020	1 329 815	1.6 (1.0-2.4)	1.7 (1.1-2.6)	.56

Abbreviations: BL, Brighton level; GBS, Guillain-Barré syndrome.

[a] Sensitivity analyses were conducted excluding Brighton level 4 cases (suspected cases).

[b] Follow-up time after dose 1 of either mRNA vaccine was censored after receipt of dose 2.

[c] The background rate of GBS is 1 to 2 per 100 000 person-years.[14,15] Exact Poisson regression was used to compare the observed number of GBS cases with the expected number of cases, which was derived from a background rate of 2 per 100 000 person-years and the observed number of person-years.

Hanson, K, et al. JAMA Netw Open. 2022;5(4):e228879. doi:10.1001/jamanetworkopen.2022.8879

- Unadjusted incidence rates of confirmed GBS per 100,000 person-years after Janssen vaccination were significantly higher than background rate of 2 per 100,000 person-years.*

*Sejvar, et. al. *Neuroepidemiology*. 2011;36(2):123-133. https://doi.org/10.1159/000324710

Table 4. Head-to-Head Comparisons of Confirmed GBS Incidence After Ad.26.COV2.S vs mRNA Vaccination

Risk window, d	No. GBS cases after Ad.26.COV2.S	No. GBS cases after mRNA vaccination[a]	Adjusted RR (95% CI)[b]	*P* value, 2-sided	Excess cases in risk interval per million doses
1-21	9	8	20.56 (6.94-64.66)	<.001	15.5
1-42	10	21	11.46 (4.83-26.16)	<.001	17.5

Abbreviations: GBS, Guillain-Barré syndrome; RR, rate ratio.

[a] Not all confirmed cases of GBS after mRNA vaccination are included in this analysis, such as cases that occurred prior to the authorization of Ad.26.COV2.S.

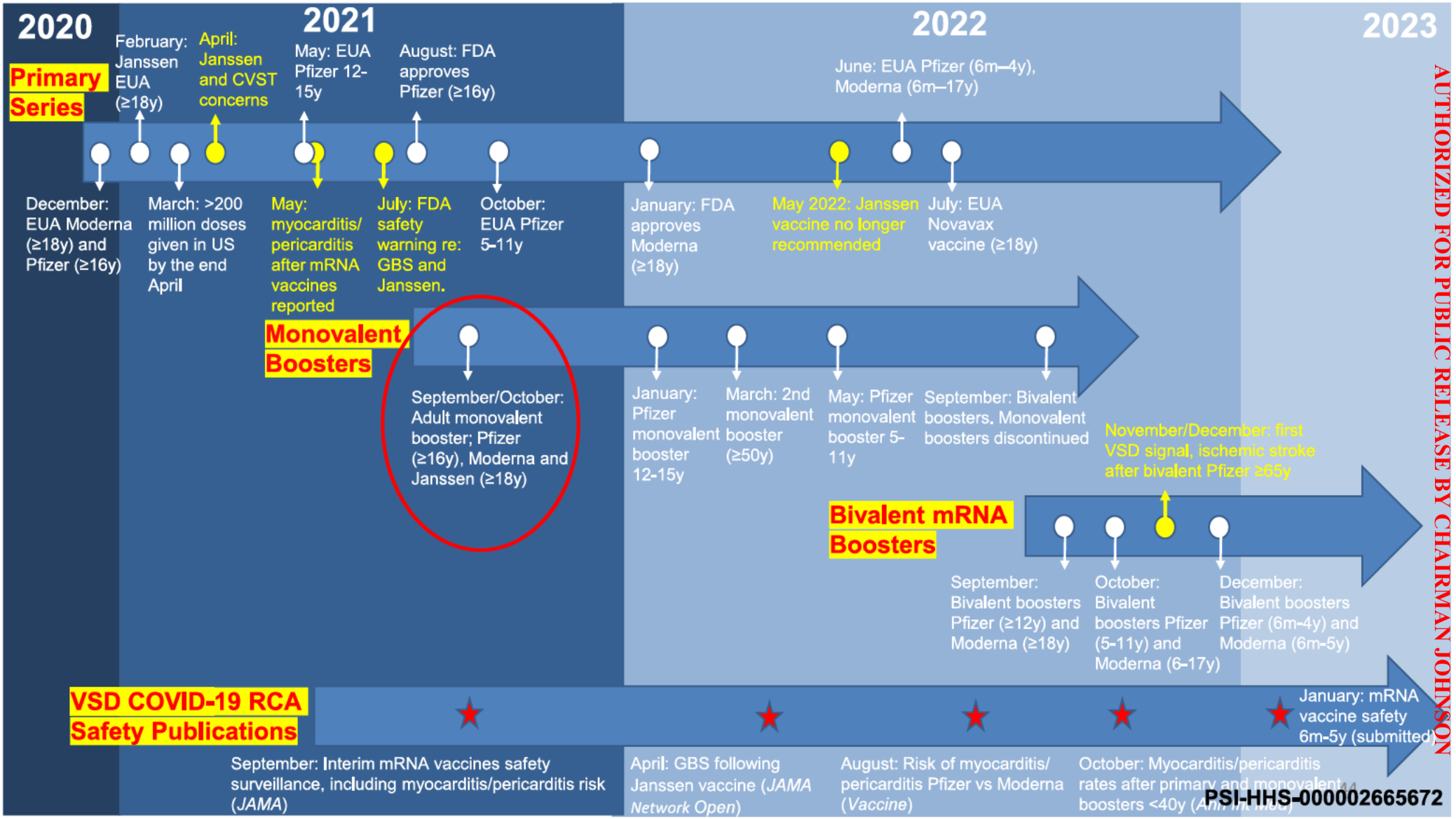
[b] Adjusted for 5-year age group, sex, race and ethnicity, site, and calendar day.

- When directly compared with mRNA vaccines, the risk of GBS after Janssen vaccine was significantly higher.

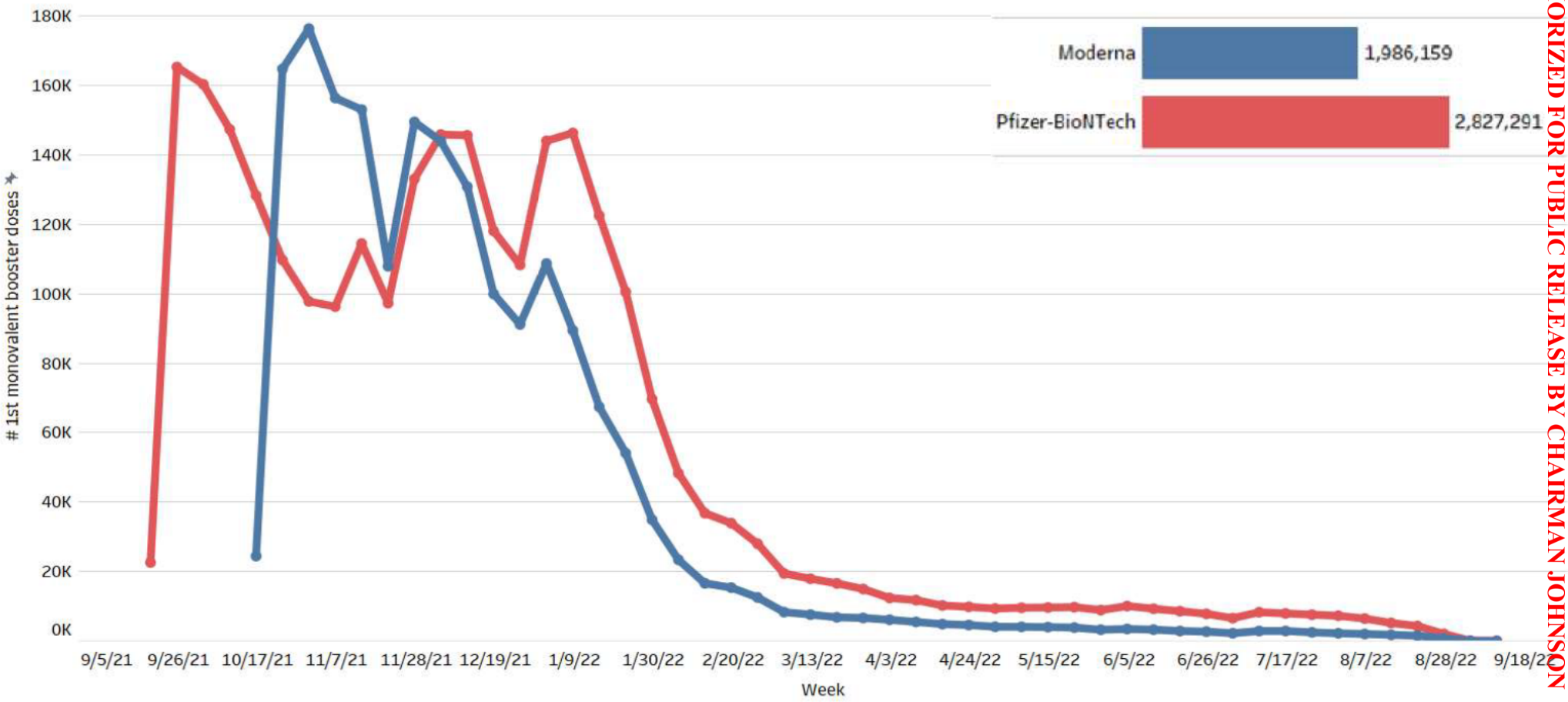
Hanson, K, et al. JAMA Netw Open. 2022;5(4):e228879. doi:10.1001/jamanetworkopen.2022.8879

Summary: Guillain-Barre After COVID-19 Vaccination in the VSD

- Findings were consistent with an association between increased risk of GBS and Janssen COVID-19 vaccine.
  - Incidence after Janssen vaccine was 21 times higher than after mRNA vaccines.
- No evidence of association between GBS and mRNA-based COVID-19 vaccines
  - Incidence of GBS in the 21 days after mRNA vaccines was similar to the expected background rate
  - No statistical signals in weekly surveillance with vaccinated concurrent comparators
- ACIP preferentially recommended mRNA-based COVID-19 vaccines over Janssen vaccine in December 2021.
  - As of May 2022, Janssen vaccine is no longer recommended.
- Since this publication VSD monitoring through February 2023 has identified 4 additional confirmed cases of GBS after mRNA vaccines and 1 additional confirmed case after Janssen.
  - 2 in the 1-21 risk interval (1 mRNA and 1 Janssen), 1 in the 22-42 day window, and 2 in the 43-84 day window.
  - All new cases were among males aged 55-65 years, except one case which was in a 4-year-old male.



Monovalent Booster Uptake Among Persons Aged ≥12 Years in the VSD, Over Time*



* Data through September 10, 2022 when monovalent booster were discontinued in favor of bivalent boosters.

Summary of RCA Findings in the 1-21 Day Risk Interval After Monovalent Boosters ≥12 Years

Compared with Outcome Events 22-42 Days After in Vaccinated Comparators*

		Either mRNA	Pfizer	Moderna	Janssen		
Risk Period Days	Outcome Event	Either mRNA Signal?**	Pfizer Signal?**	Moderna Signal?**	Pfizer Signal?**	Moderna Signal?**	Janssen Signal?**
1-21	Acute disseminated encephalomyelitis	No	No	-	-	-	-
	Acute myocardial infarction	No	No	No	No	No	No
	Appendicitis	No	No	No	No	No	No
	Bell's palsy	No	No	No	Yes	No	No
	Cerebral venous sinus thrombosis	No	No	No	-	-	No
	Disseminated intravascular coagulation	No	No	No	No	-	-
	Encephalitis / myelitis / encephalomyelitis	No	No	No	-	-	-
	Guillain-Barre syndrome	No	No	No	No	-	No
	Stroke, hemorrhagic	No	No	No	No	No	No
	Stroke, ischemic	No	No	No	No	No	No
	Immune thrombocytopenia	No	No	No	No	No	-
	Myocarditis / pericarditis	Yes	No	No	No	No	No
	Seizures	No	No	No	No	No	No
	Transverse myelitis	No	No	No	-	-	-
	Thrombotic thrombocytopenic purpura	No	No	No	-	-	No
	Thrombosis with thrombocytopenia syndrome	No	No	No	-	No	-
	Venous thromboembolism	No	No	No	No	No	No
	Pulmonary embolism (subset of VTE)	No	No	No	No	No	No

- **Following <u>mRNA primary series and monovalent booster</u>, only myocarditis/pericarditis met the signaling criteria in the 21 days among ages ≥12 years in the VSD population.**

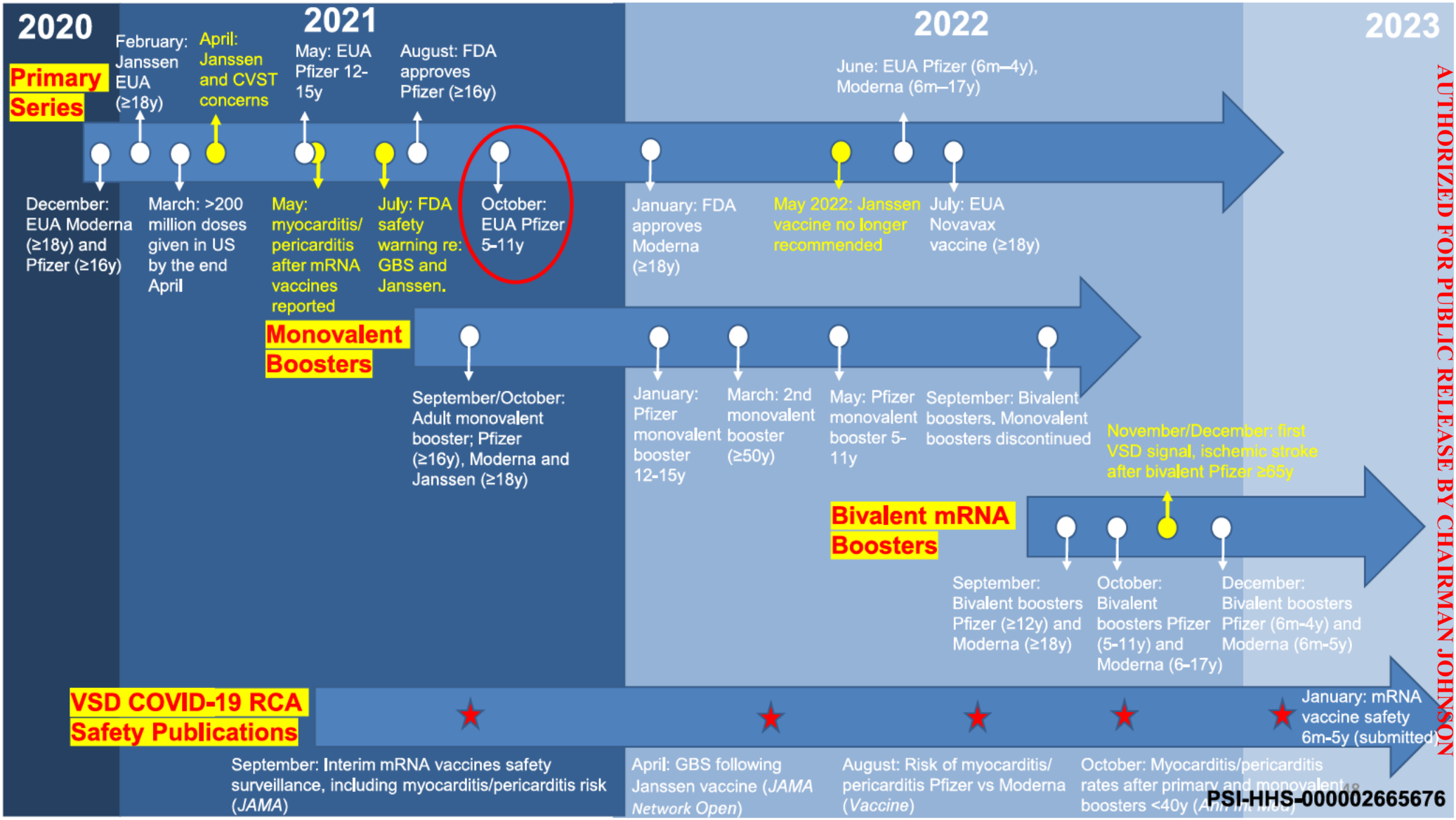
*Final analyses through September 2022
**Signaling threshold PRR=0.01 (one-sided)

Verified Myocarditis and Pericarditis in 0–7 Days Following Monovalent Booster in 12–39-Year-Olds

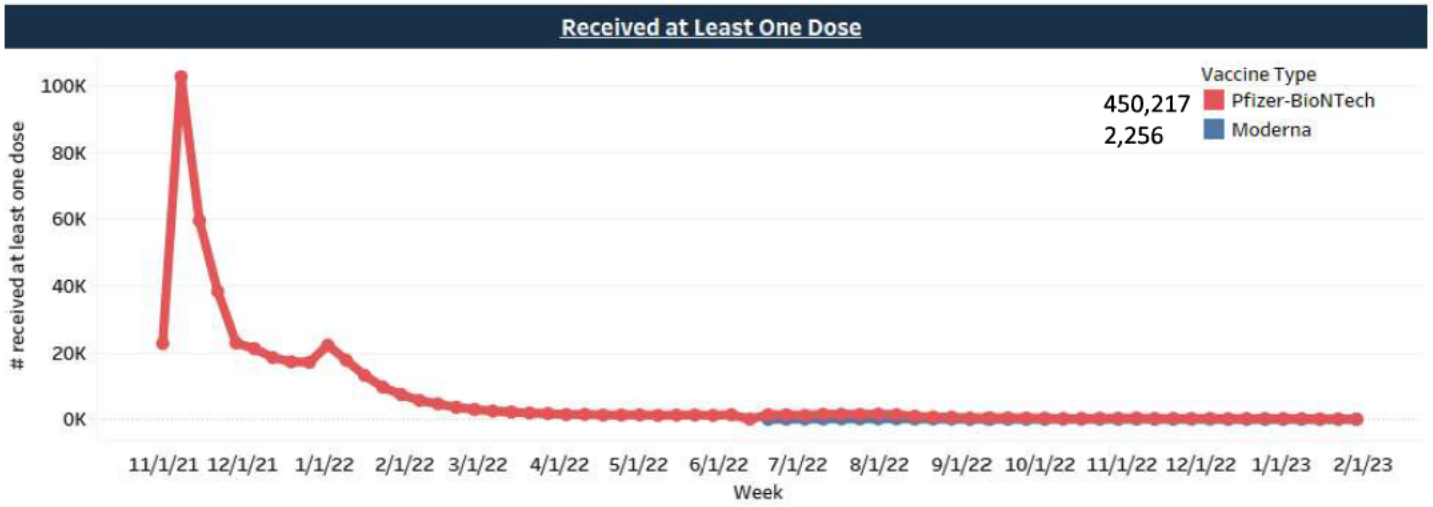
Compared with Events on the Same Calendar Days among Boosted Comparators

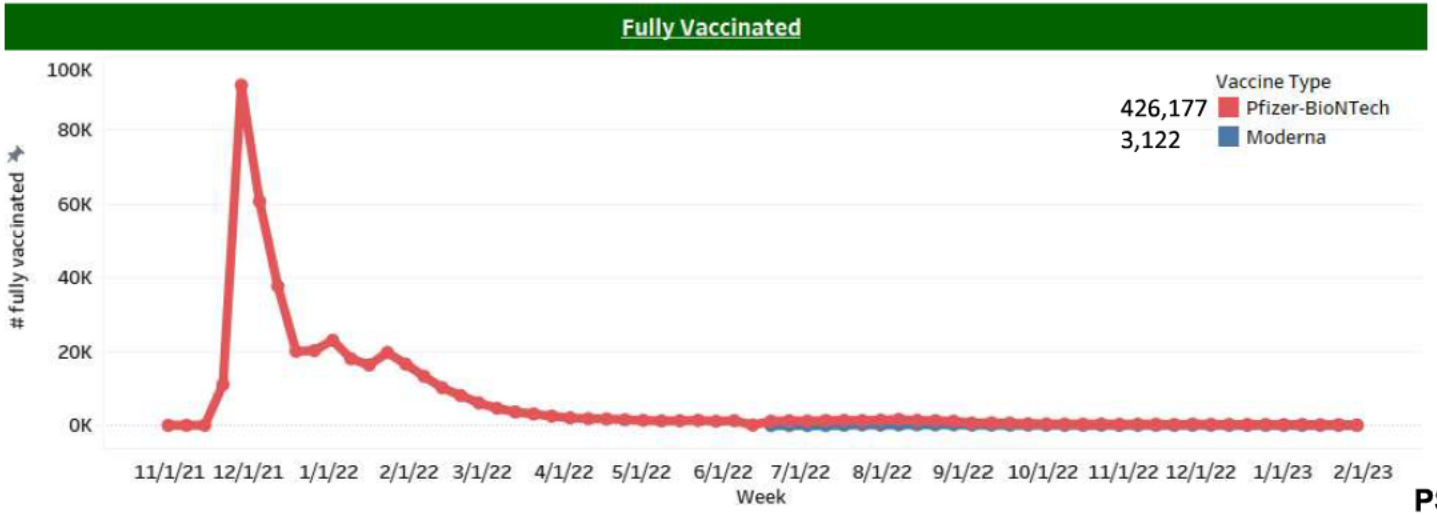
					Analysis			
	Ages	Vaccine	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Events/Million Doses
Monovalent Booster[3]	12 - 17	Pfizer[4]	15	4	**7.21**	**2.04 – 29.66**	**0.002**	59.9 (34.3 – 97.3)
	18–39	Either	22	10	**4.46**	**2.02 – 10.37**	**<0.001**	15.8 (9.9 – 23.9)
	18–39	Pfizer	11	5	**4.81**	**1.55 – 16.81**	**0.006**	14.3 (7.1 – 25.5)
	18–39	Moderna[5]	6	4	3.27	0.82 – 14.23	0.093	16.8 (7.3 – 33.1)

[1]Comparison interval is 22–42 days after booster dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, calendar date, and time since primary series.
[3]"Either" includes heterologous and homologous primary -> booster doses. Product specific analyses include only homologous primary->booster doses.
[4]One additional case was in the risk interval but not included because there were no appropriate comparators. This case is included in the events/million dose calculation.
[5]Two additional cases were in the risk interval but were not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.



Primary Series uptake among persons aged 5-11 years in the VSD, over time*





* Data through February 4, 2023

Summary of RCA Findings in the 1-21 Day Risk Interval, 5–11-year-olds

Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

		Pfizer		
Risk Interval	Outcome Event	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses
1 -21	Appendicitis	No	No	No
	Bell's palsy	No	No	No
	Encephalitis / myelitis / encephalomyelitis	No	No	No
	Stroke, hemorrhagic	No	No	No
	Stroke, ischemic	No	-	No
	Immune thrombocytopenia	No	No	No
	Kawasaki disease	No	No	No
	Myocarditis / pericarditis	No	No	No
	Seizures	No	No	No
	Thrombotic thrombocytopenic purpura	No	-	No

- **Among children aged 5-11 years in the VSD, no outcome met the signaling criteria in the 21 days after primary series vaccination.**

*Final analyses through January 2023
**Signaling threshold P<0.061 (one-sided)

PSI-HHS-000002665678

Safety of COVID-19 Vaccination in United States Children Ages 5 to 11 Years

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Affiliations + expand

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www.pediatrics.org/cgi/doi/10.1542/peds.2022-057313

Abstract

Background and objectives: Limited postauthorization safety data for the Pfizer-BioNTech coronavirus disease 2019 vaccination among children ages 5 to 11 years are available, particularly for the adverse event myocarditis, which has been detected in adolescents and young adults. We describe adverse events observed during the first 4 months of the United States coronavirus disease 2019 vaccination program in this age group.

Methods: We analyzed data from 3 United States safety monitoring systems: v-safe, a voluntary smartphone-based system that monitors reactions and health effects; the Vaccine Adverse Events Reporting System (VAERS), the national spontaneous reporting system comanaged by the Centers for Disease Control and Prevention and Food and Drug Administration; and the Vaccine Safety Datalink, an active surveillance system that monitors electronic health records for prespecified events, including myocarditis.

Results: Among 48 795 children ages 5 to 11 years enrolled in v-safe, most reported reactions were mild-to-moderate, most frequently reported the day after vaccination, and were more common after dose 2. VAERS received 7578 adverse event reports; 97% were nonserious. On review of 194 serious VAERS reports, 15 myocarditis cases were verified; 8 occurred in boys after dose 2 (reporting rate 2.2 per million doses). In the Vaccine Safety Datalink, no safety signals were detected in weekly sequential monitoring after administration of 726 820 doses.

Conclusions: Safety findings for Pfizer-BioNTech vaccine from 3 United States monitoring systems in children ages 5 to 11 years show that most reported adverse events were mild and no safety signals were observed in active surveillance. VAERS reporting rates of myocarditis after dose 2 in this age group were substantially lower than those observed among adolescents ages 12 to 15 years.

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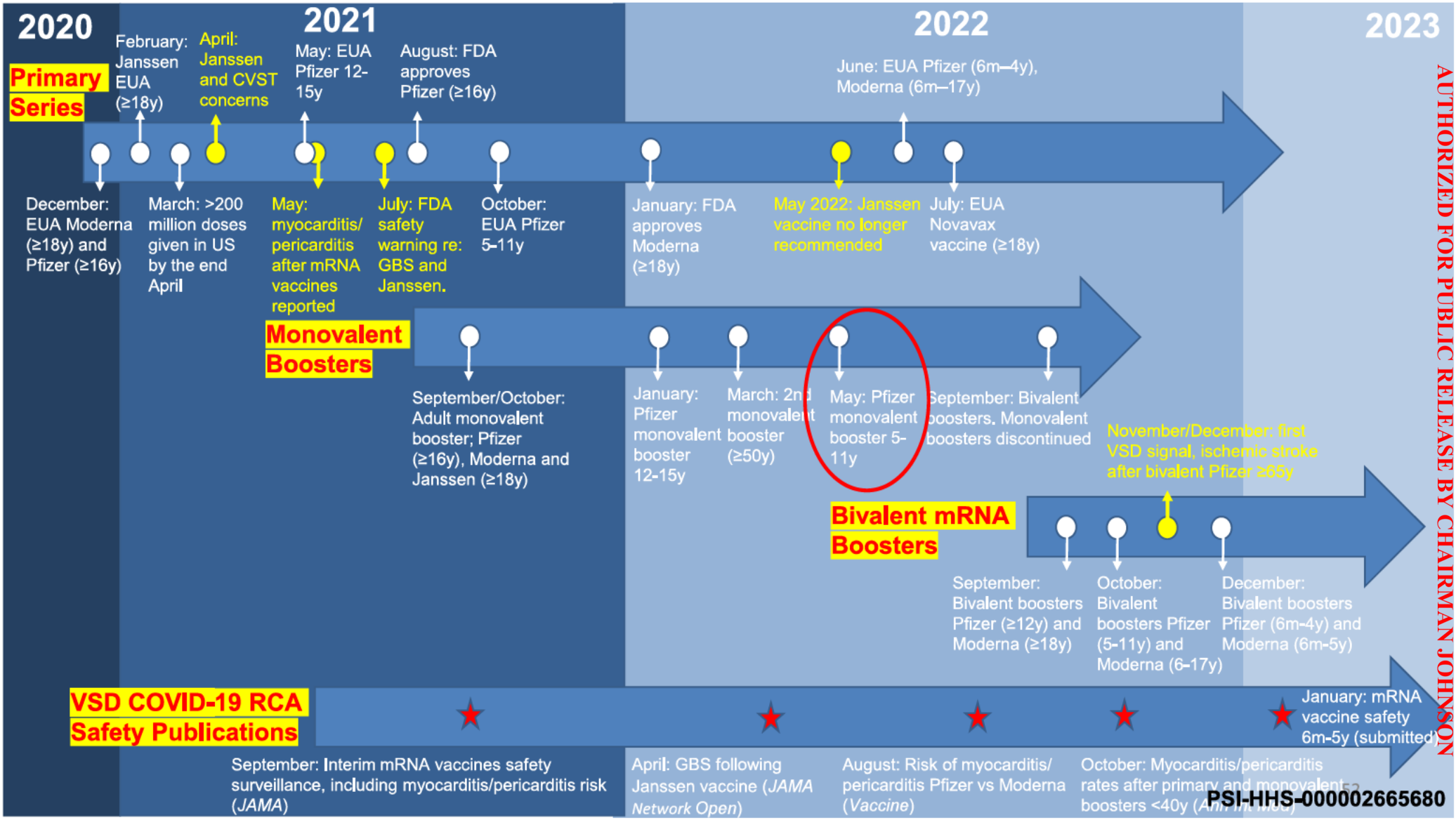
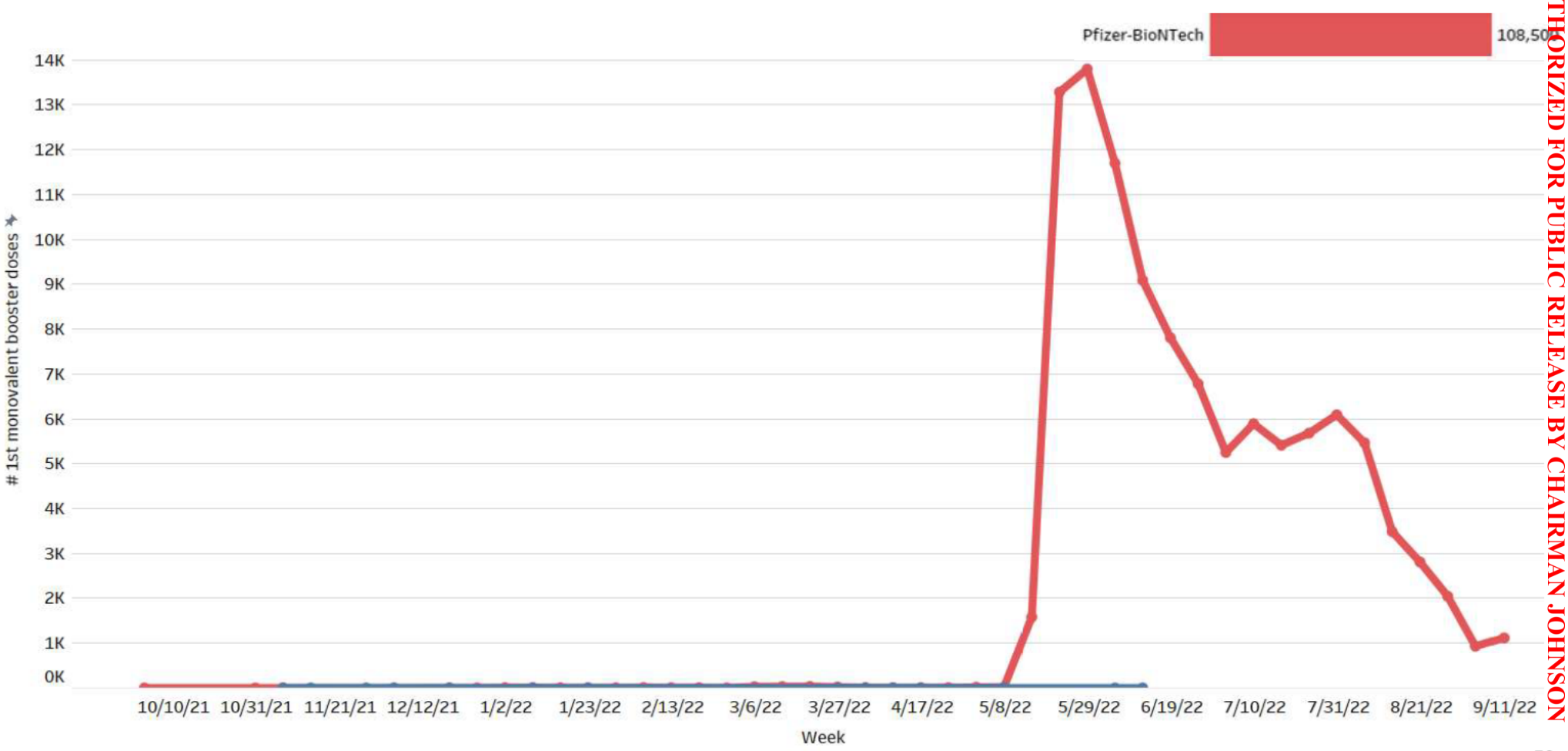


Monovalent Booster Uptake Among Persons Aged 5-11 Years in the VSD, Over Time*



* Data through September 10, 2022

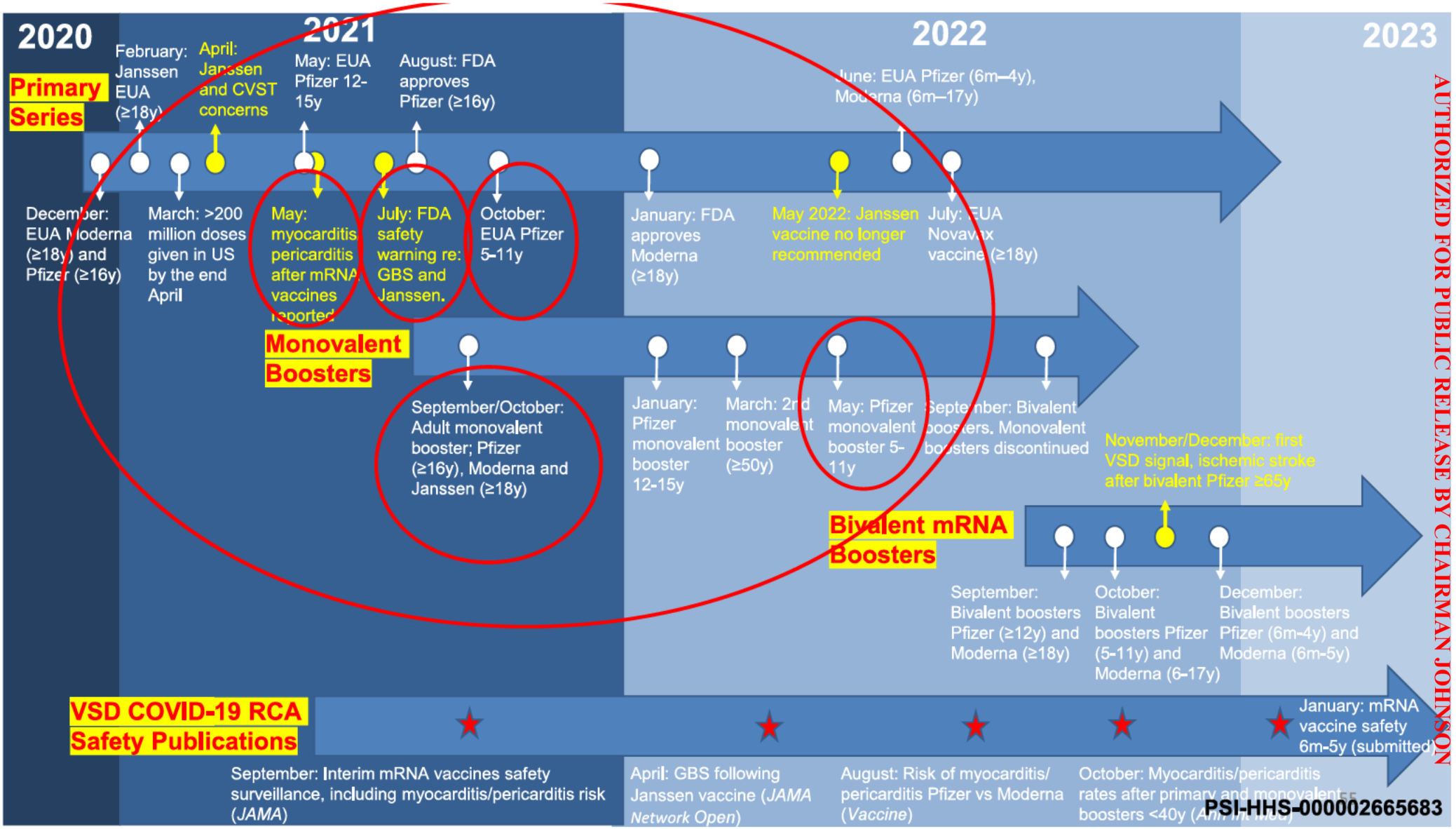
Summary of RCA Findings in the 1-21 Day Risk Interval after Monovalent Booster, 5–11-year-olds Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

		Either mRNA	Pfizer	Moderna	Janssen		
Risk Period Days	Outcome Event	Either mRNA	Pfizer Signal?**	Moderna	Pfizer	Moderna	Janssen
1-21	Appendicitis	-	No	-	-	-	-
	Bell's palsy	-	No	-	-	-	-
	Immune thrombocytopenia	-	No	-	-	-	-
	Seizures	-	No	-	-	-	-

- = analyses not yet possible

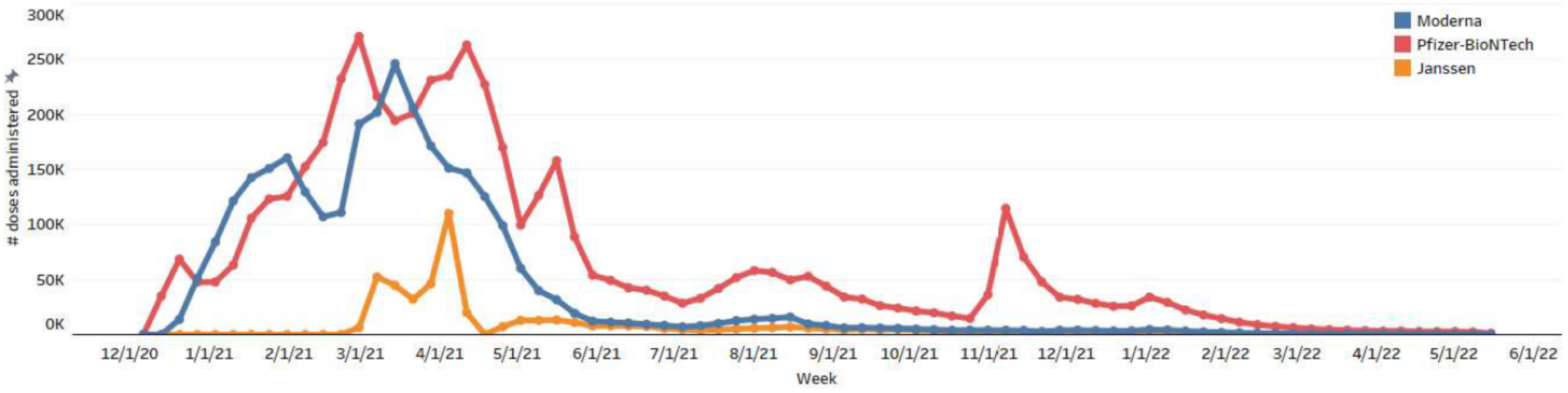
- **Among children aged 5-11 years in the VSD, no outcome met the signaling criteria in the 21 days after monovalent booster vaccination. However, vaccine uptake was low.**

*Final analyses through January 2023
**Signaling threshold P<0.011 (one-sided)

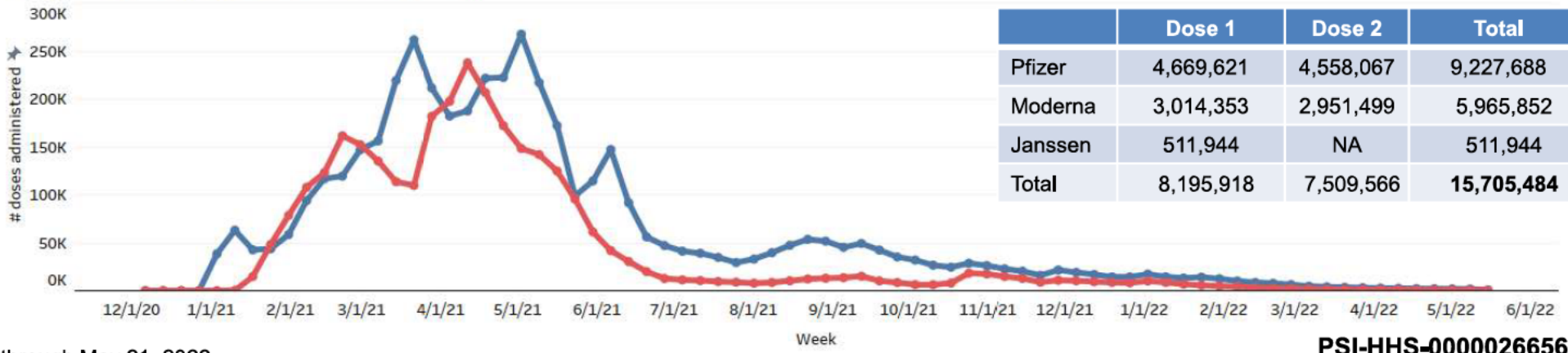


Primary Series Uptake Among Persons Aged ≥12 Years in the VSD, Over Time*

Number of people who received at least one dose



Number of people fully vaccinated over time



	Dose 1	Dose 2	Total
Pfizer	4,669,621	4,558,067	9,227,688
Moderna	3,014,353	2,951,499	5,965,852
Janssen	511,944	NA	511,944
Total	8,195,918	7,509,566	**15,705,484**

* Data through May 21, 2022

Final RCA Findings in the 1-21 Day Risk Interval After Primary Series ≥12 Years

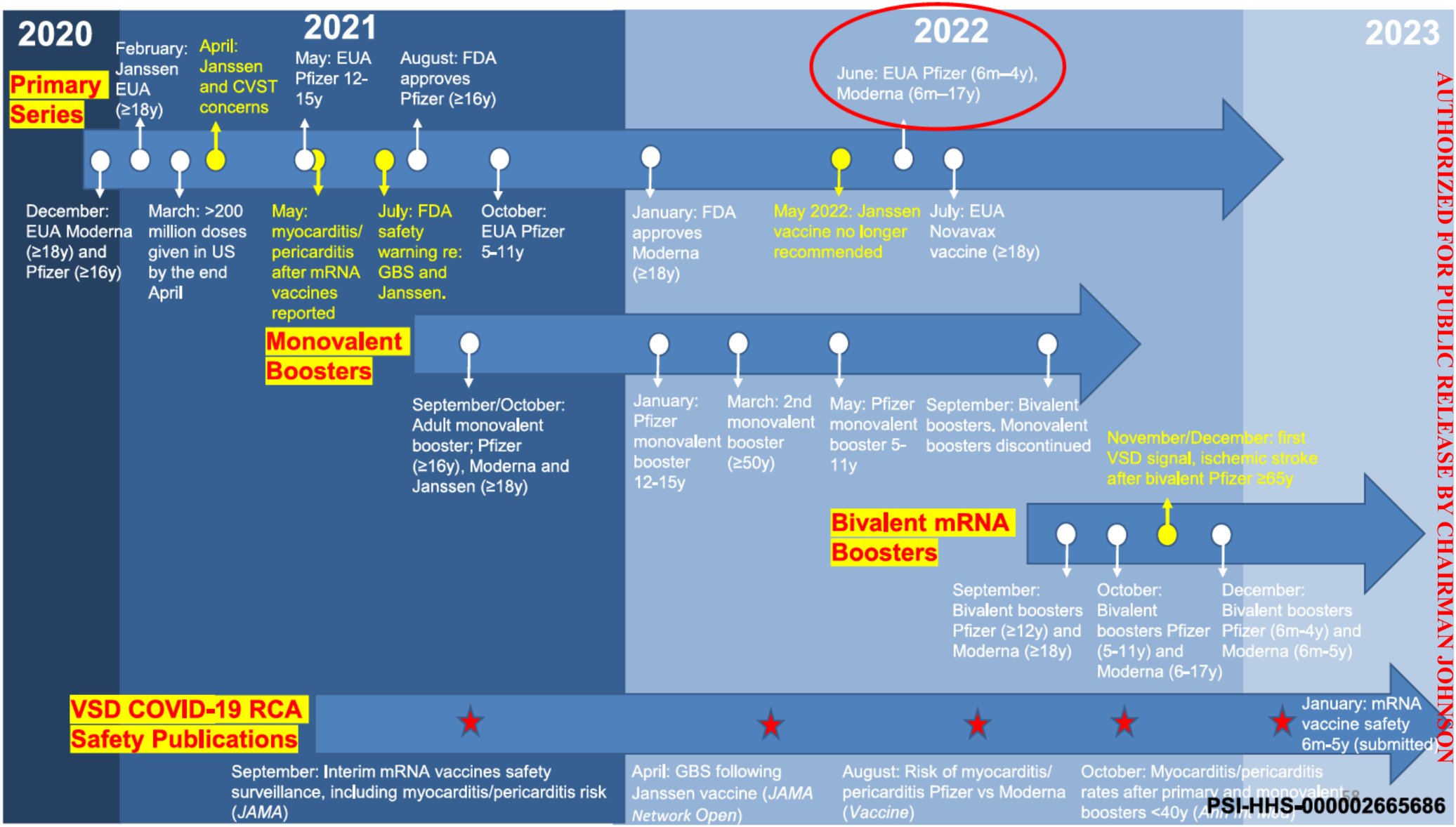
Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

		Moderna			Pfizer			Both mRNA Vaccines			Janssen
Risk Period Days	Outcome Event	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses	Dose 1 Signal?**
1-21	Acute disseminated encephalomyelitis	-	No	No	No	-	No	No	No	No	-
	Acute myocardial infarction	No	No	No	No	Yes	No	No	Yes	No	No
	Appendicitis	No	No	No	No	No	No	No	No	No	No
	Bell's palsy	No	No	No	No	No	No	No	No	No	No
	Cerebral venous sinus thrombosis	No	No	No	No	No	No	No	No	No	-
	Disseminated intravascular coagulation	No	No	No	No	No	No	No	No	No	No
	Encephalitis / myelitis / encephalomyelitis	No	No	No	No	No	No	No	No	No	-
	Guillain-Barre syndrome	No	No	No	No	No	No	No	No	No	No
	Stroke, hemorrhagic	No	No	No	No	No	No	No	No	No	No
	Stroke, ischemic	No	No	No	No	No	No	No	No	No	No
	Immune thrombocytopenia	No	No	No	No	No	No	No	No	No	No
	Kawasaki disease	No	No	No	-	-	-	No	No	No	-
	Myocarditis / pericarditis	No	No	No	No	Yes	Yes	No	Yes	Yes	No
	Seizures	No	No	No	No	No	No	No	No	No	No
	Transverse myelitis	No	No	No	No	No	No	No	No	No	No
	Thrombotic thrombocytopenic purpura	No	No	No	No	No	No	No	No	No	No
	Thrombosis with thrombocytopenia syndrome	No	No	No	No	No	No	No	No	No	No
	Venous thromboembolism	No	No	No	No	Yes	Yes	No	Yes	Yes	No
	Pulmonary embolism (subset of VTE)	No	No	No	No	No	No	No	No	No	No

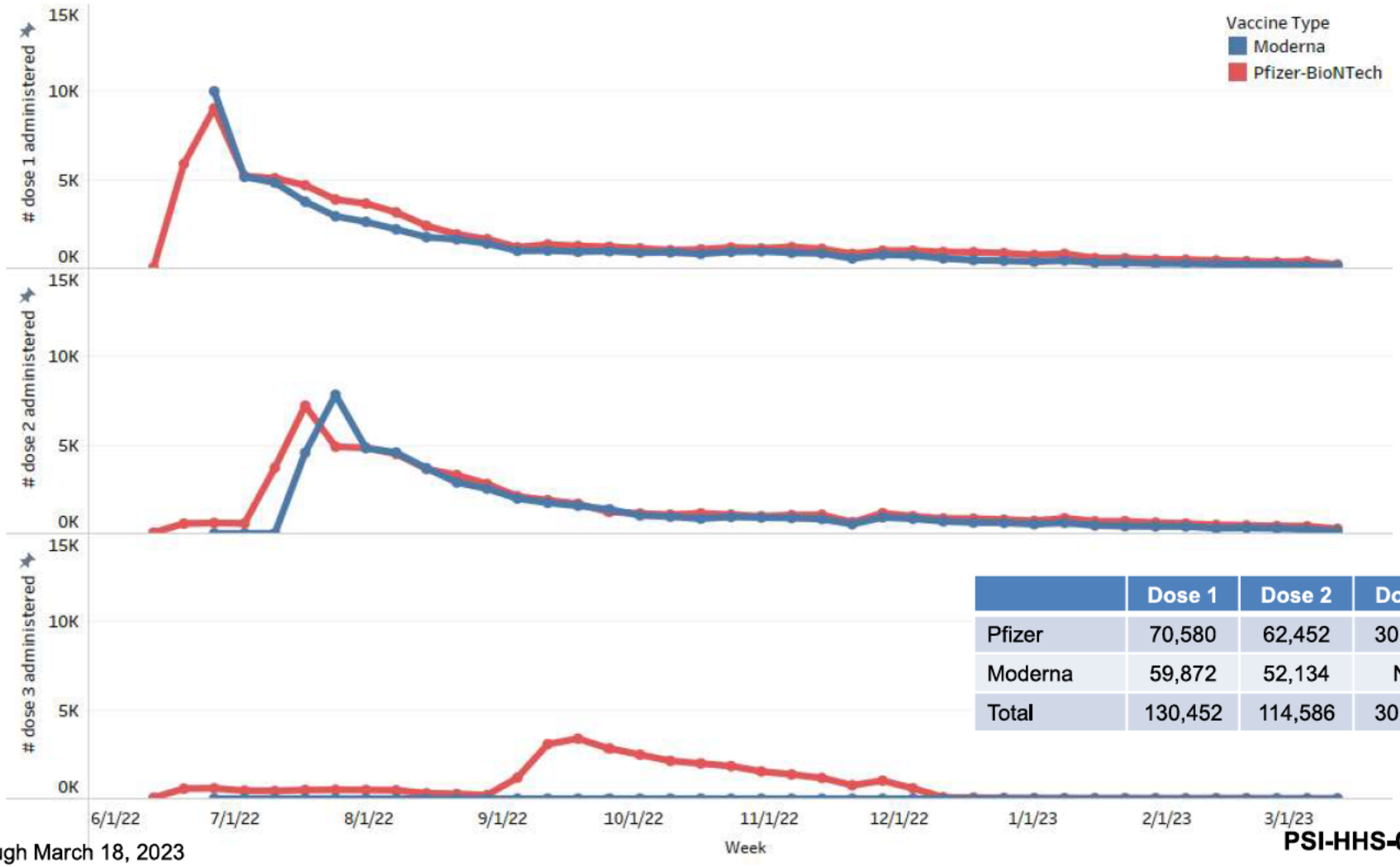
- = analyses not yet possible

*Final analyses through May 2022

**Signaling threshold PRR=3.01 (one sided)



Primary Series Uptake Among Persons Aged 6 Months- 5 Years in the VSD, Over Time*



	Dose 1	Dose 2	Dose 3	Total
Pfizer	70,580	62,452	30,641	163,673
Moderna	59,872	52,134	NA	112,006
Total	130,452	114,586	30,641	**275,679**

* Data through March 18, 2023

RCA in the 1-21 Day Risk Interval, 6 months-4/5-year-olds

Compared with Outcome Events 22-42 days after in Vaccinated Comparators on the Same Calendar Days, June 18, 2022 - Feb 25, 2023

Outcome*	Risk interval (days)	Vaccine type	Events in risk interval	Events in comparison interval (22-42 days)	Adjusted rate ratio (95% CI)**	1-sided p-value	Signal? P<0.011
Appendicitis	1 – 21	Pfizer-BioNTech	1	1	0.48 (0.01 – 26.31)	0.91	No
		Moderna	0	1	0.00 (0.00 – 12.67)	0.40	No
Bell's Palsy	1 – 21	Pfizer-BioNTech	0	1	0.00 (0.00 – 38.00)	0.67	No
		Moderna	1	0	NE (0.06 - ∞)	0.49	No
Encephalitis/myelitis/ encephalomyelitis	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	1	0	NE (0.02 - ∞)	0.74	No
Guillain-Barre Syndrome	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 26.56)	0.58	No
Immune thrombocytopenia	1 – 21	Pfizer-BioNTech	0	1	0.00 (0.00 – 19.00)	0.50	No
		Moderna	1	1	1.13 (0.03 – 44.21)	0.72	No
Kawasaki disease	1 – 21	Pfizer-BioNTech	2	1	2.05 (0.15 – 60.78)	0.49	No
		Moderna	0	3	0.00 (0.00 – 1.10)	0.06	No
Pulmonary embolism	1 – 21	Pfizer-BioNTech	1	0	NE (0.08 – ∞)	0.41	No
		Moderna	-	-	-	-	-
Seizures	0-7	Pfizer-BioNTech	9	23	0.68 (0.26 – 1.60)	0.86	No
		Moderna	5	19	0.85 (0.17 – 2.31)	0.71	No
	0-21	Pfizer-BioNTech	38	23	1.02 (0.58 – 1.80)	0.53	No
		Moderna	23	19	1.09 (0.57 – 2.11)	0.46	No
Stroke, hemorrhagic	1 – 21	Pfizer-BioNTech	1	1	1.12 (0.03 – 44.64)	0.72	No
		Moderna	-	-	-	-	-
Transverse Myelitis	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 38.00)	0.67	No
Venous thromboembolism	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 38.00)	0.67	No

CI=confidence intervals; NE=not estimable. -: analysis not yet possible

*Outcomes were only included in this table if there were events in either the risk or comparison interval for either vaccine type, making analyses possible.

**Stratified by Vaccine Safety Datalink site, age (year), sex, race/ethnicity, and calendar date

RCA in the 1-21 Day Risk Interval, 6 months-4/5-year-olds

Compared with Outcome Events 22-42 days after in Vaccinated Comparators on the Same Calendar Days, June 18, 2022 - Feb 25, 2023

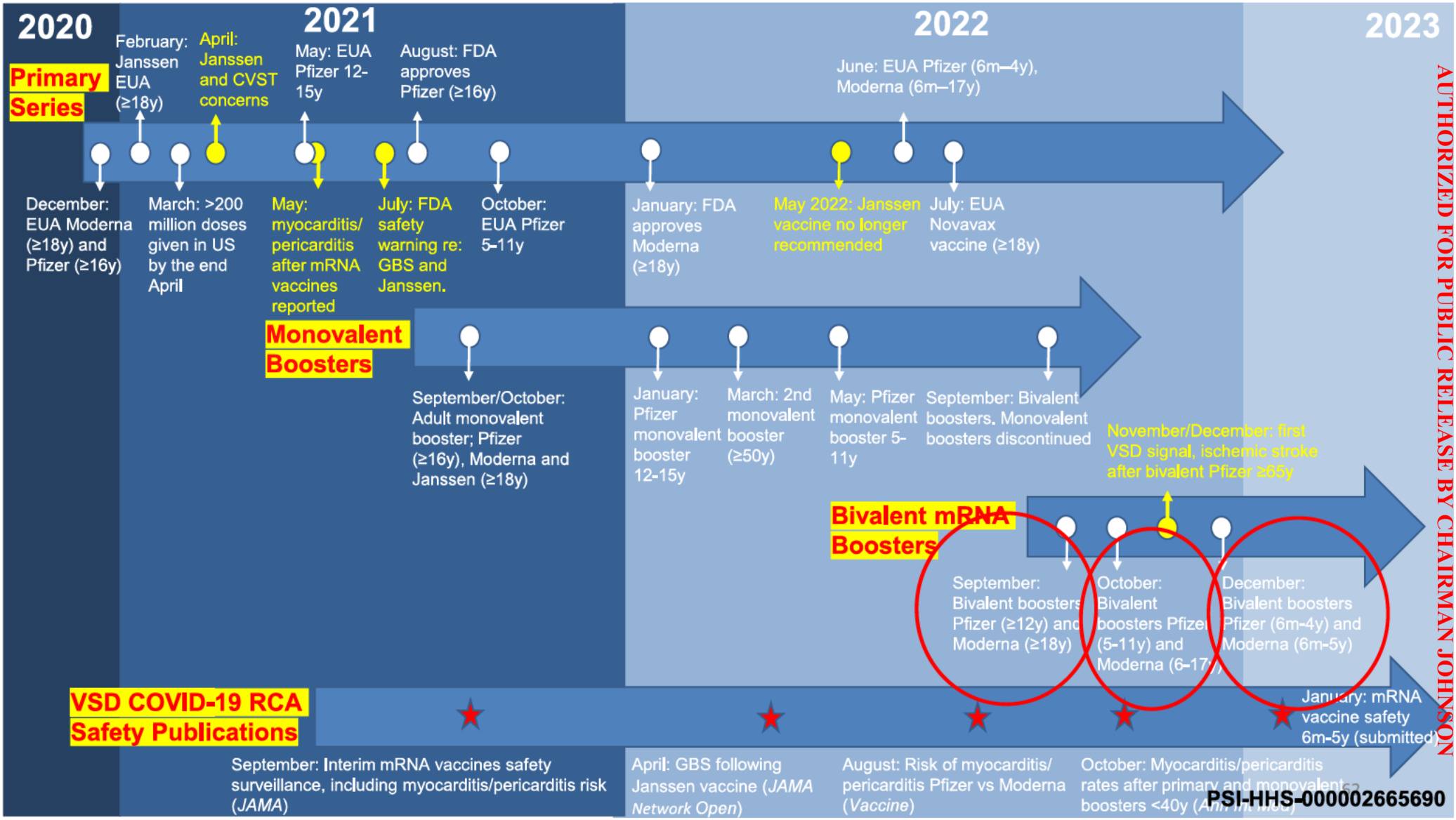
Outcome*	Risk interval (days)	Vaccine type	Events in risk interval	Events in comparison interval (22-42 days)	Adjusted rate ratio (95% CI)**	1-sided p-value	Signal? P<0.011
Appendicitis	1 – 21	Pfizer-BioNTech	1	1	0.48 (0.01 – 26.31)	0.91	No
		Moderna	0	1	0.00 (0.00 – 12.67)	0.40	No
Bell's Palsy	1 – 21	Pfizer-BioNTech	0	1	0.00 (0.00 – 38.00)	0.67	No
		Moderna	1	0	NE (0.06 – ∞)	0.49	No
Encephaliti encephalor							
Guillain-Ba							
Immune thr							
Kawasaki d							
Pulmonary							
Seizures	0-21	Pfizer-BioNTech	38	23	1.02 (0.58 – 1.80)	0.53	No
		Moderna	23	19	1.09 (0.57 – 2.11)	0.46	No
Stroke, hemorrhagic	1 – 21	Pfizer-BioNTech	1	1	1.12 (0.03 – 44.64)	0.72	No
		Moderna	-	-	-	-	-
Transverse Myelitis	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 38.00)	0.67	No
Venous thromboembolism	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 38.00)	0.67	No

- Among children 6 month-4/5 years, no outcome met the signaling criteria in the 21 days after primary series.
- No cases of myocarditis or pericarditis within the risk interval
- However, vaccine uptake has been low

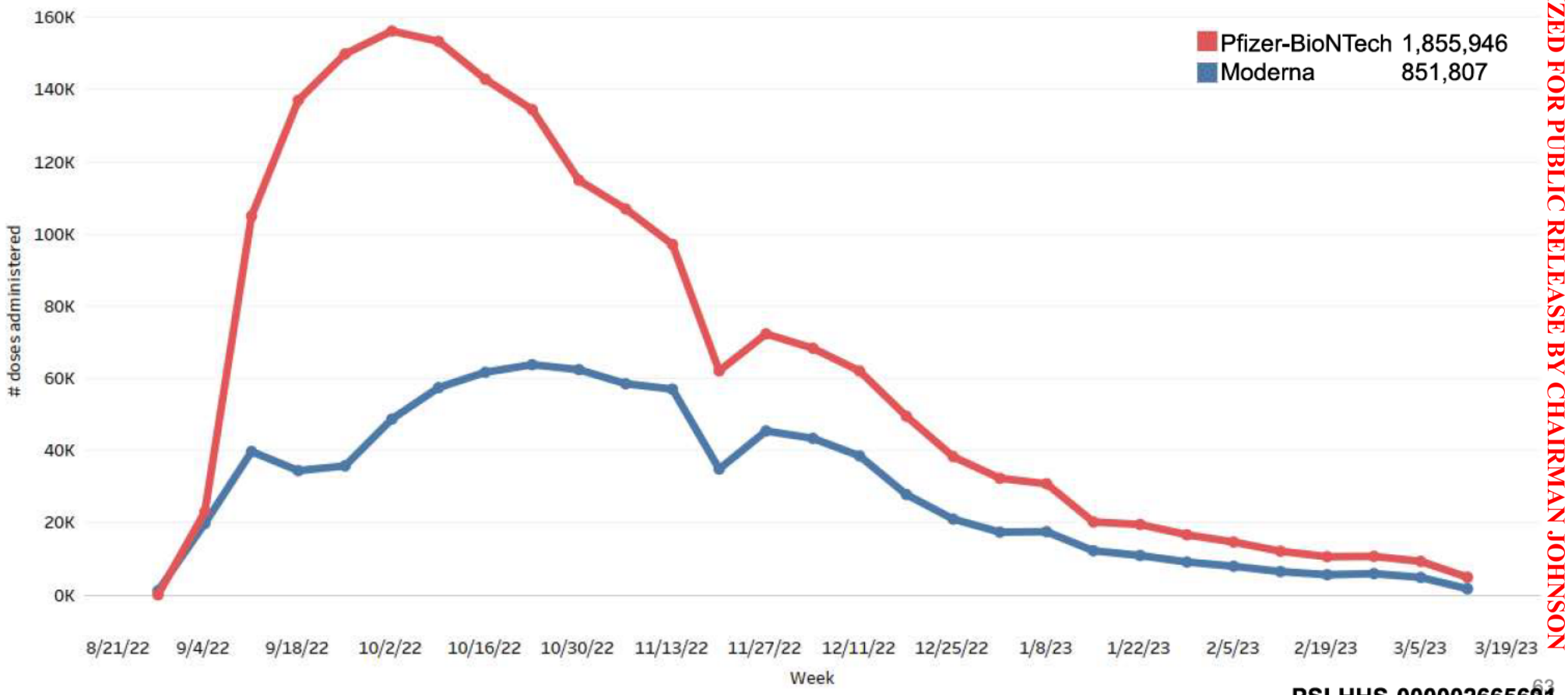
CI=confidence intervals; NE=not estimable. -: analysis not yet possible

*Outcomes were only included in this table if there were events in either the risk or comparison interval for either vaccine type, making analyses possible.

**Stratified by Vaccine Safety Datalink site, age (year), sex, race/ethnicity, and calendar date



Bivalent Booster Uptake Among Persons Aged ≥12 Years, Over Time*



* Data through March 18, 2023

Summary RCA Findings in the 1-21 Day Risk Interval after Bivalent Booster 6 months - 64 years

Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

Risk Interval Days	Age Group	Outcome Event	Either mRNA	Pfizer Signal?**	Moderna Signal?**
1 -21	0-4y	Kawasaki disease	No	No	-
	5-11y	Appendicitis	No	No	-
		Bell's palsy	No	No	-
		Stroke, hemorrhagic	No	No	-
		Immune thrombocytopenia	No	No	-
		Seizures	No	No	-
	12-17y	Appendicitis	No	No	No
		Bell's palsy	No	No	-
		Encephalitis / myelitis / encephalomyelitis	No	No	-
		Immune thrombocytopenia	No	No	-
		Seizures	No	No	-
		Venous thromboembolism	No	No	-
	18-64y	Acute disseminated encephalomyelitis	No	No	-
		Acute myocardial infarction	No	No	No
		Appendicitis	No	No	No
		Bell's palsy	No	No	No
		Cerebral venous sinus thrombosis	No	No	No
		Disseminated intravascular coagulation	No	-	No
		Encephalitis / myelitis / encephalomyelitis	No	No	No
		Guillain-Barre syndrome	No	No	-
		Stroke, hemorrhagic	No	No	No
		Stroke, ischemic	No	No	No
		Immune thrombocytopenia	No	No	No
		Myocarditis / pericarditis	No	No	No
		Seizures	No	No	No
		Transverse myelitis	No	No	-
		Thrombotic thrombocytopenic purpura	No	No	No
		Thrombosis with thrombocytopenia syndrome	No	No	No
		Venous thromboembolism	No	No	No
		Pulmonary embolism (subset of VTE)	No	No	No

- Among ages 5 - 64 years in the VSD, no outcomes have met the signaling criteria in the 21 days after bivalent booster vaccine. Surveillance is ongoing.

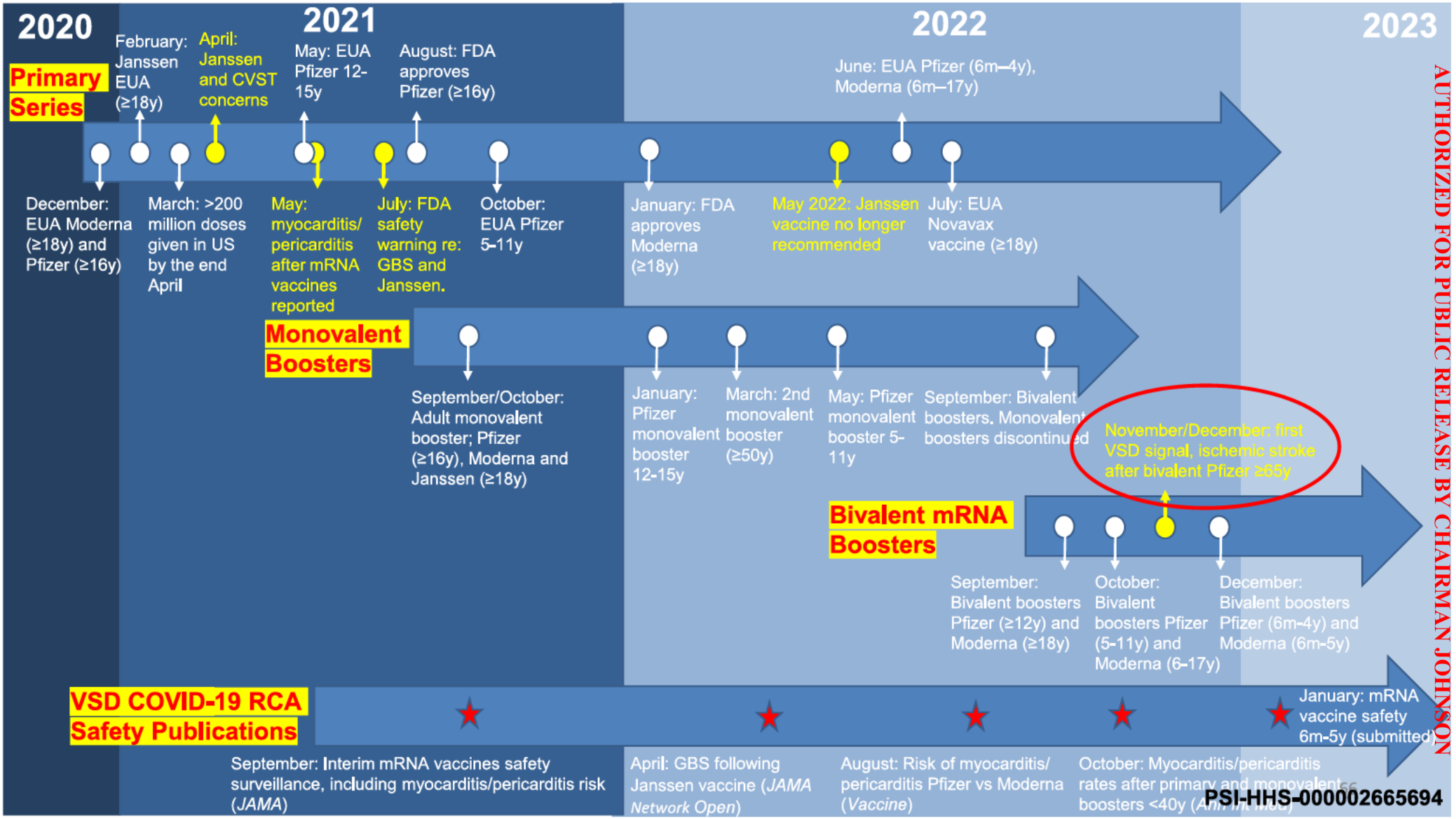
*Analyses through March 2023

**Signaling threshold PRR=3.01 (one sided)

VSD Incidence Rates of Verified Myocarditis or Pericarditis in the 0–7 Days After Bivalent Booster in Ages 12–39 years*

	Dose 2 primary series Pfizer-BioNTech			Monovalent booster dose Pfizer-BioNTech			Bivalent Booster Doses		
Age Group (yrs)	Cases	Total Dose 2 (N)	Incidence rate/ million doses (95% CI)	Cases	Total Doses (N)	Incidence rate/ million doses (95% CI)	Cases	Total Doses (N)	Incidence rate/ million doses (95% CI)
Pfizer									
12–17									
Males	45	308,046	146.1 (106.6–195.5)	14	129,487	108.1 (59.1–181.4)	0	55,649	0.0 (0.0–53.8)
Females	6	311,247	19.3 (7.1–42.0)	2	139,118	14.4 (1.7–51.9)	0	57,776	0.0 (0.0–51.9)
18–29									
Males	27	331,889	81.4 (53.6–118.4)	7	166,973	41.9 (16.9–86.4)	1	60,338	16.6 (0.4 – 92.3)
Females	2	400,321	5.0 (0.6–18.0)	1	240,226	4.2 (0.1–23.2)	0	95,162	0.0 (0.0–31.5)
30–39									
Males	5	341,527	14.6 (4.8–34.2)	3	197,554	15.2 (3.1–44.4)	0	97,171	0.0 (0.0–30.8)
Females	3	410,713	7.3 (1.5–21.3)	1	268,412	3.7 (0.1–20.8)	0	133,305	0.0 (0.0–22.5)
Moderna									
18–29									
Males	19	195,809	97.0 (58.4 – 151.5)	7	109,337	64.0 (25.7 – 131.9)	0	22,247	0.0 (0.0–134.7)
Females	0	243,560	0.0 (0.0 – 12.3)	1	156,707	6.4 (0.2 – 35.6)	0	35,393	0.0 (0.0–84.6)
30–39									
Males	8	216,583	36.9 (15.9 – 72.8)	1	149,468	6.7 (0.2 – 37.3)	1	41,820	23.9 (0.6–133.2)
Females	1	259,780	3.9 (0.1 – 21.4)	2	191,765	10.4 (1.3 – 37.7)	0	55,816	0.0 (0.0–53.7)

* Primary series and monovalent booster data through August 20, 2022:; source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccin... Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771. **Bivalent booster data through March 11, 2023**



Summary RCA Findings in the 1-21 Day Risk Interval After Bivalent Booster ≥65 years

Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

Risk Interval Days	Age Group	Outcome Event	Either mRNA Signal?**	Pfizer Signal?**	Moderna Signal?**
1 -21	65+	Acute myocardial infarction	No	No	No
		Appendicitis	No	No	No
		Bell's palsy	No	No	No
		Cerebral venous sinus thrombosis	No	No	-
		Disseminated intravascular coagulation	No	No	No
		Guillain-Barre syndrome	No	No	No
		Stroke, hemorrhagic	No	No	No
		Stroke, ischemic	Yes	Yes	No
		Immune thrombocytopenia	No	No	No
		Myocarditis / pericarditis	No	No	No
		Seizures	No	No	No
		Thrombotic thrombocytopenic purpura	No	No	No
		Thrombosis with thrombocytopenia syndrome	No	No	No
		Venous thromboembolism	No	No	No
		Pulmonary embolism (subset of VTE)	No	No	No

- Ischemic stroke signaled in the 21 days after bivalent booster vaccine among ≥65 years in the VSD.

*Analyses through March 2023

**Signaling threshold [illegible]

Ischemic Stroke Following Pfizer Bivalent Booster Vaccination in 65+ Years of Age

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

Updated Jan. 13, 2023 Español | Other Languages Print

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.

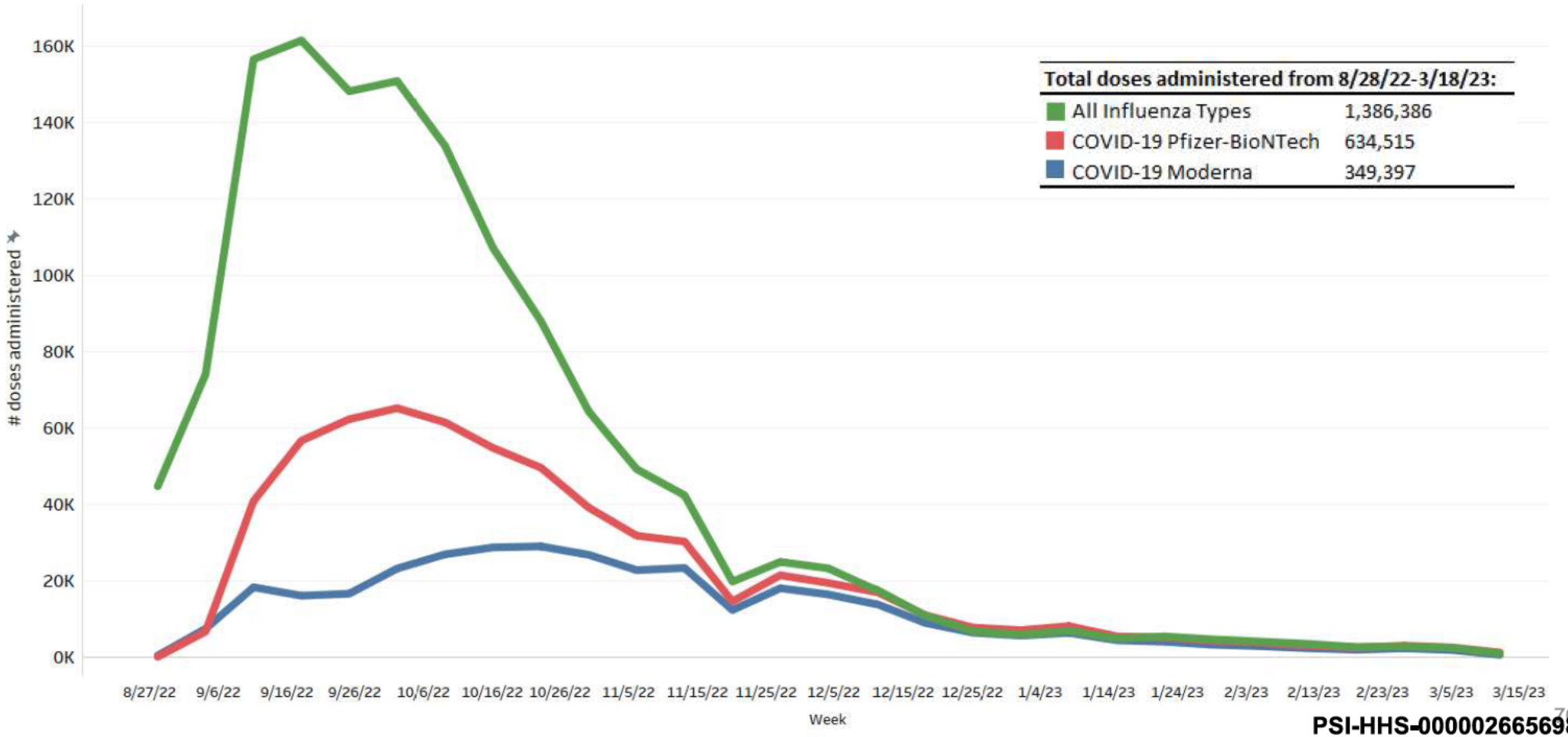
All signals require further investigation and confirmation from formal epidemiologic studies. When one system detects a signal, the other safety monitoring systems are checked to validate whether the signal represents an actual concern with the vaccine or if it can be determined to be of no clinical 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 22-42 following vaccination.

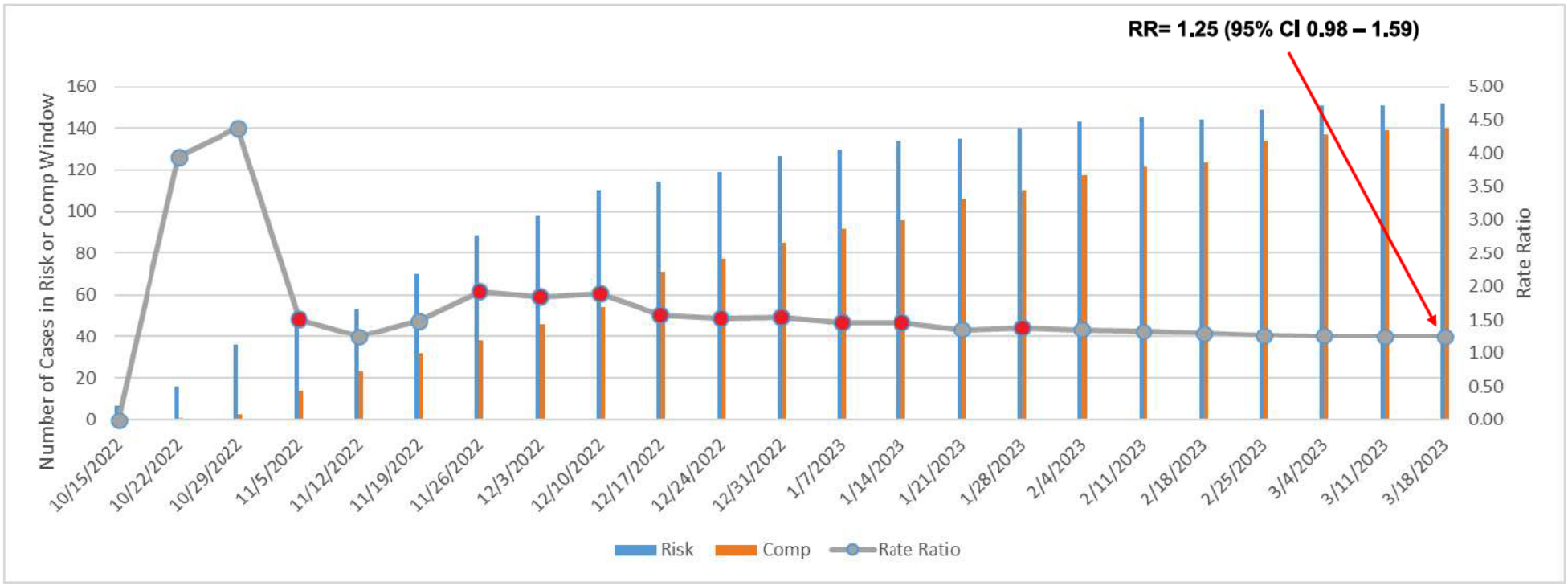
This preliminary signal has not been identified with the Moderna COVID-19 Vaccine, Bivalent. There also may be other confounding factors contributing to the signal identified in the VSD that merit further investigation. Furthermore, it is important to note that, to date, no other safety systems have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

Number of COVID-19 Bivalent Booster Doses and Influenza Vaccine Doses Administered Over Time Among Persons Aged ≥65 years, by Vaccine Type

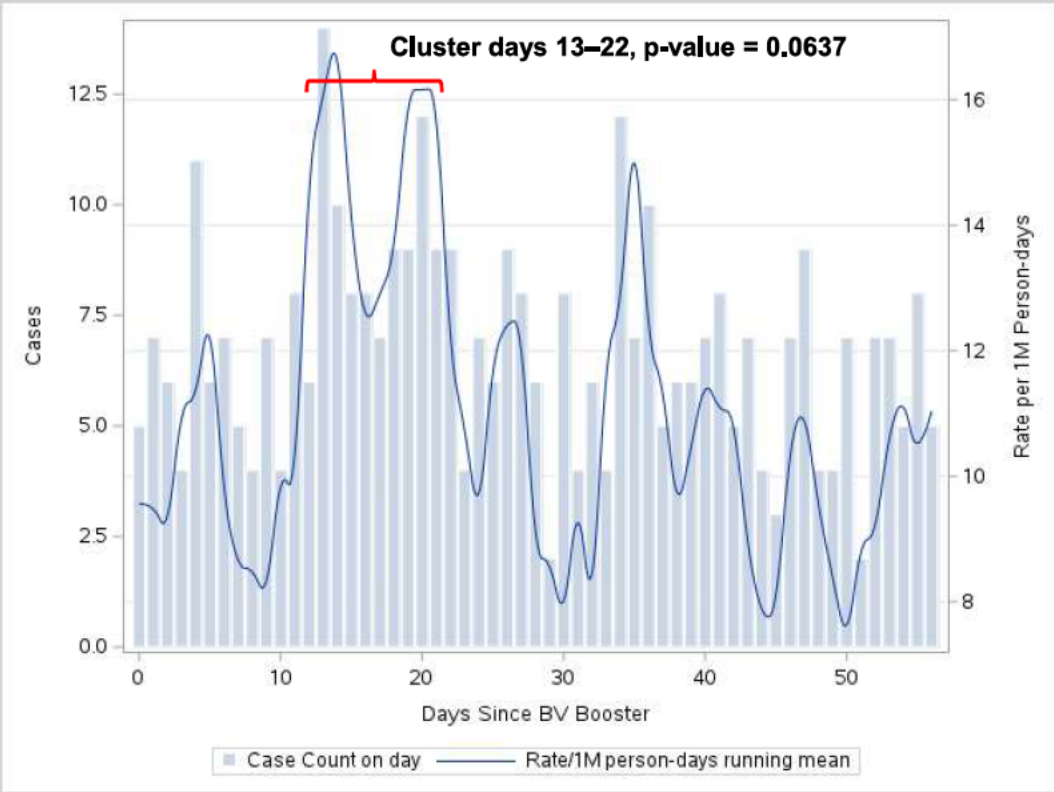


Ischemic Stroke After Pfizer-BioNTech Bivalent Booster, Age ≥65 years, Counts and Adjusted Rate Ratios (Oct 15, 2022 – March 18, 2023)



- Red dot represents sequential signal: p-value <0.01 (1-sided)

Ischemic Stroke by Day after Pfizer-BioNTech Bivalent Booster, People Aged ≥65 Years*



* Data cutoff 2/28/2023

Post-Signal analyses*: Ischemic Stroke Incidence During Days 1–21 Compared with Days 22–42, Among ≥65 Years With and Without Simultaneous Influenza Vaccination

Analytic population	Cases in 1–21-day Risk Interval (N=139)	Cases in 22–42-day Comparison Interval (N=108)	Adjusted Rate Ratio** (95% CI)	P-value
Bivalent Pfizer + same-day high-dose or adjuvanted flu vaccine	43	27	1.59 (0.99 – 2.61)	0.06
Bivalent Pfizer + same day standard dose flu vaccine	8	11	0.73 (0.28 - 1.83)	0.50
Bivalent Pfizer without any same day flu vaccine	107	99	1.08 (0.82 – 1.42)	0.58

* Analyses only include vaccination data through January 14, 2023, and stroke outcome data through February 25, 2023
** Adjusted by 5-year age groups

Additional Considerations for Stroke Outcome

- **Small numbers of strokes and imprecise rate ratios limit some analyses**
  - Uptake of Moderna booster was delayed and reduced due to distribution delays
  - Follow-up of individuals concurrently given bivalent booster + hi-dose flu was limited by small numbers
- **Difficult to interpret temporal clustering which attenuated as rate ratio attenuated**
- **Possible unmeasured confounding**
  - Results may be influenced by confounders that vary over time
  - Do early adopters of bivalent booster vaccine have greater risk of near-term cardiovascular events?
    - Same trend has not been observed for acute myocardial infarctions
    - Potential impact of differential vaccine availability after EUA (Pfizer-BioNTech > Moderna)
- **Possible role of SARS-CoV-2 infection before booster?**
  - Background incidence of SARS-CoV-2 infection was rapidly changing during bivalent booster uptake
    - Analysis excluded cases with COVID-19 diagnosis or positive test in prior 30 days, although asymptomatic infections and home antigen tests are not consistently documented in EHR; however, KPNC chart reviews did not find recent SARS-CoV-2 infection or exposure

Incidence of Confirmed Anaphylaxis Cases Following COVID-19 Vaccination in the Vaccine Safety Datalink by Vaccine Type and Dose

	Confirmed Cases (N)	Total Doses (N)	Incidence per Million Doses (95% CI)
Primary Series (6m+)	*89*	--	--
Pfizer-BioNTech	49	10,199,998	4.8 (3.6-6.4)
Dose 1	39	5,085,188	7.7 (5.5-10.5)
Dose 2	10	5,114,810	2.0 (0.9-3.6)
Moderna	33	6,212,227	5.3 (3.7-7.5)
Dose 1	25	3,088,454	8.1 (5.2-11.9)
Dose 2	8	3,123,773	2.6 (1.1-5.0)
Janssen	7	511,707	13.7 (5.5-28.2)
Monovalent Booster (5yrs+)	*5*	--	--
Pfizer-BioNTech	0	3,160,912	0.0 (0.0-0.9)
Moderna	4	2,234,583	1.8 (0.5-4.6)
Janssen	1	77,179	13.0 (0.3-72.2)
Bivalent Booster (6m+)	*2*	--	--
Pfizer-BioNTech	2	1,926,149	1.0 (0.1-3.8)
Moderna	0	845,342	0.0 (0.0-3.5)

Summary of Safety Findings after COVID-19 Vaccines in the VSD

Anaphylaxis

- The rate of anaphylaxis was ~ 5 cases/million doses for the mRNA primary series.
  - The rate of anaphylaxis was <5 cases/million doses for mRNA booster doses.

Myocarditis/Pericarditis after mRNA vaccines

- During days 0-7 post vaccination, both mRNA vaccines were associated with increased risk of myocarditis/pericarditis in 12–39-year-olds.
- Risk estimates of myocarditis/pericarditis in 18–39-year-olds during days 0-7 after 2 doses were modestly higher after Moderna than after Pfizer.
- For persons ages 12–39 years, rates of myocarditis/pericarditis 0–7 days after primary and monovalent boosters were highest among male 12-15 and 16–17-year-olds.
  - Evidence suggests an increased risk for myocarditis/pericarditis following monovalent booster dose for some age groups.
  - No current evidence for an increased rate of myocarditis/pericarditis following bivalent boosters. Uptake is low in age groups expected to be at highest risk.

Summary of Safety Findings After COVID-19 Vaccines in the VSD

Ischemic stroke after Pfizer bivalent booster

- Rate ratio met signaling criteria consistently for 8 weeks but slowly attenuated and now does not meet signaling criteria
- Temporal clustering 13–22 days after vaccination (significant at time of initial signal but attenuated as the rate ratio estimate attenuated)
- Supplemental analyses using un-boosted concurrent comparators showed a rate ratio RR=1.07 (95% CI 0.89–1.28) (data not shown)
- Analyses evaluating simultaneous high-dose or adjuvanted flu vaccine showed a rate ratio RR=1.59 (95% CI 0.99 – 2.61)
  - Separate analyses did not detect an elevated RR for stroke after flu vaccine alone (data not shown)

GBS after Janssen vaccine

- Findings were consistent with an association between increased risk of GBS and Janssen COVID-19 vaccine.

Continued Work and Future Considerations

- Continued work - VSD RCA surveillance is ongoing, including in children aged < 5 years and bivalent booster doses.

- Future Studies - VSD may consider further investigating:
  - mRNA vaccine primary series signals of VTE and AMI
  - Bell's palsy after Janssen primary and mRNA monovalent booster (limited data since neither vaccine is currently available or used)
  - Ischemic stroke after concomitant bivalent boosters and flu vaccines in >65-year-olds in future season

Challenges and Lessons in Rapidly Generating Vaccine Safety Evidence During the Pandemic

Challenges in Rapidly Generating Vaccine Safety Evidence During the Pandemic

1. Vaccine uptake was early & unpredictable.
   - One rationale for using vaccinated concurrent comparators
   - Most RCA findings from the primary series in adults came early and have been mostly unchanged since fall 2021.

2. The VSD COVID-19 RCA analytic methods have been hard to understand.
   - Important features of this RCA differed from traditional sequential analyses, and from how we have framed past RCAs.

3. Our vaccine safety research questions have frequently changed and expanded, requiring us to rapidly adapt our surveillance to include new outcomes and age groups
   - Focus switched from primary series in adults to boosters to younger ages, etc.
   - Flexibility in routinely accommodating (sometime substantial) changes has been critical.

4. Challenging to digest and interpret the large amounts of potentially relevant data and results that we put "on the shelf" weekly (e.g., comparisons with unvaccinated people).
   - Supplementary analyses were (are) available should a safety concern arise from VSD or elsewhere

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#2. Our methods have been hard to understand.

- Vaccinated concurrent comparators is an unfamiliar approach and difficult to explain how the follow up in the comparison interval is concurrent (i.e., on the same calendar day) with the follow up in the risk interval

- Vaccinated concurrent comparators are advantageous because they adjust for potential biases associated with calendar time, site, and demographic factors.

- For this reason, we believe that vaccinated concurrent comparators are less vulnerable to bias.

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- For this reason, we believe that vaccinated concurrent comparators are less vulnerable to bias.

- However, our publications and talks have been occasioned by intense public/media focus on COVID vaccine safety (rather than by safety signals or pre-specified endpoints) and were mainly driven by the need to communicate
  - with the ACIP (both WG and public meetings) and other government stakeholders
  - about emerging safety concerns
- Thus, since we were frequently communicating preliminary results on short notice, methods that are hard to concisely explain and understand posed substantial challenges.

#3. Our research questions frequently expanded…

Vaccinees

➢Changing age groups

- Primary series: adults → to adolescent 12-15 years → to children 5-11 years → to youngest children < 5 years.

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Vaccines

- Changing number of doses
  - 1st monovalent boosters → 2nd monovalent boosters (but only in >50-year-olds and immune-compromised)
  - Now Omicron-specific bivalent boosters
- Vaccines that use different technology (e.g., Janssen, Novavax)

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  - Now Omicron-specific bivalent boosters (but only >12-year-olds)
- Vaccines that use different technology (e.g., Janssen)

Outcomes

- Originally pre-specified 21 outcomes → 23 outcomes
  - Revised ICD codes and adding new age subgroups for specific outcomes (e.g., myocarditis/pericarditis).
  - Expanded outcomes to add emerging concerns (i.e., cerebral venus sinus thrombosis, thrombosis with thrombocytopenia syndrome).

Lessons Learned

- VSD is very well-situated to respond to vaccine safety needs in a pandemic and features:
  - Analyses that are updated weekly, are population based and are geographically diverse.
  - Flexible structure with access to comprehensive medical record data, including charts to conduct rapid case confirmation when needed.
  - Ability to rapidly add new outcomes in response to emerging concerns.
  - Ability to compare observed outcome incidence with the incidence expected from several kinds of comparators, including vaccinated and unvaccinated concurrent comparators.
- VSD RCA surveillance complements other vaccine safety monitoring systems.
- During a pandemic, an RCA protocol is a living document and may rapidly evolve as surveillance needs change.
  - Surveillance we plan today will not necessarily be the same population or vaccines we monitor in several months.
  - Surveillance has to focus on doing work that adds value.

Acknowledgements

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  - Ned Lewis, Kristin Goddard, Bruce Fireman, Ousseny Zerbo, Karen Nunley, Pat Ross, Nandini Bahkshi, Laurie Aukes, Berwick Chan, Arnold Yee
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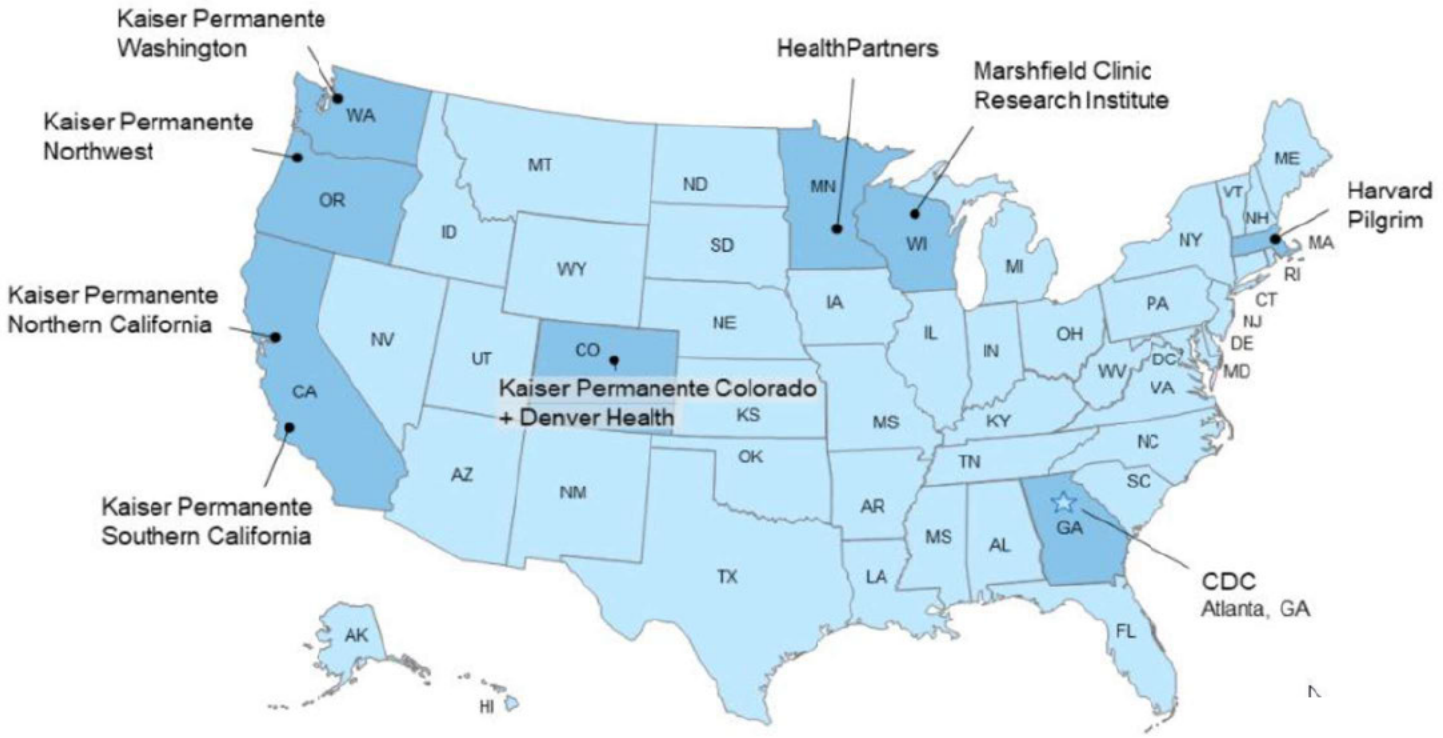
- CDC Immunization Safety Office:
  - Eric Weintraub, Tom Shimabukuro, Matt Oster, Tat'Yana Kenigsberg, Jonathan Duffy, Frank Destefano, Tanya Myers
- VSD Sites
  - HealthPartners Institute, Minneapolis, Minnesota
  - Kaiser Permanente Colorado, Denver, Colorado
  - Kaiser Permanente Northwest, Portland, Oregon
  - Kaiser Permanente Southern California, Los Angeles, California
  - Kaiser Permanente Washington, Seattle, Washington
  - Denver Health, Denver, Colorado

Backup Slides

The Vaccine Safety Datalink (VSD)



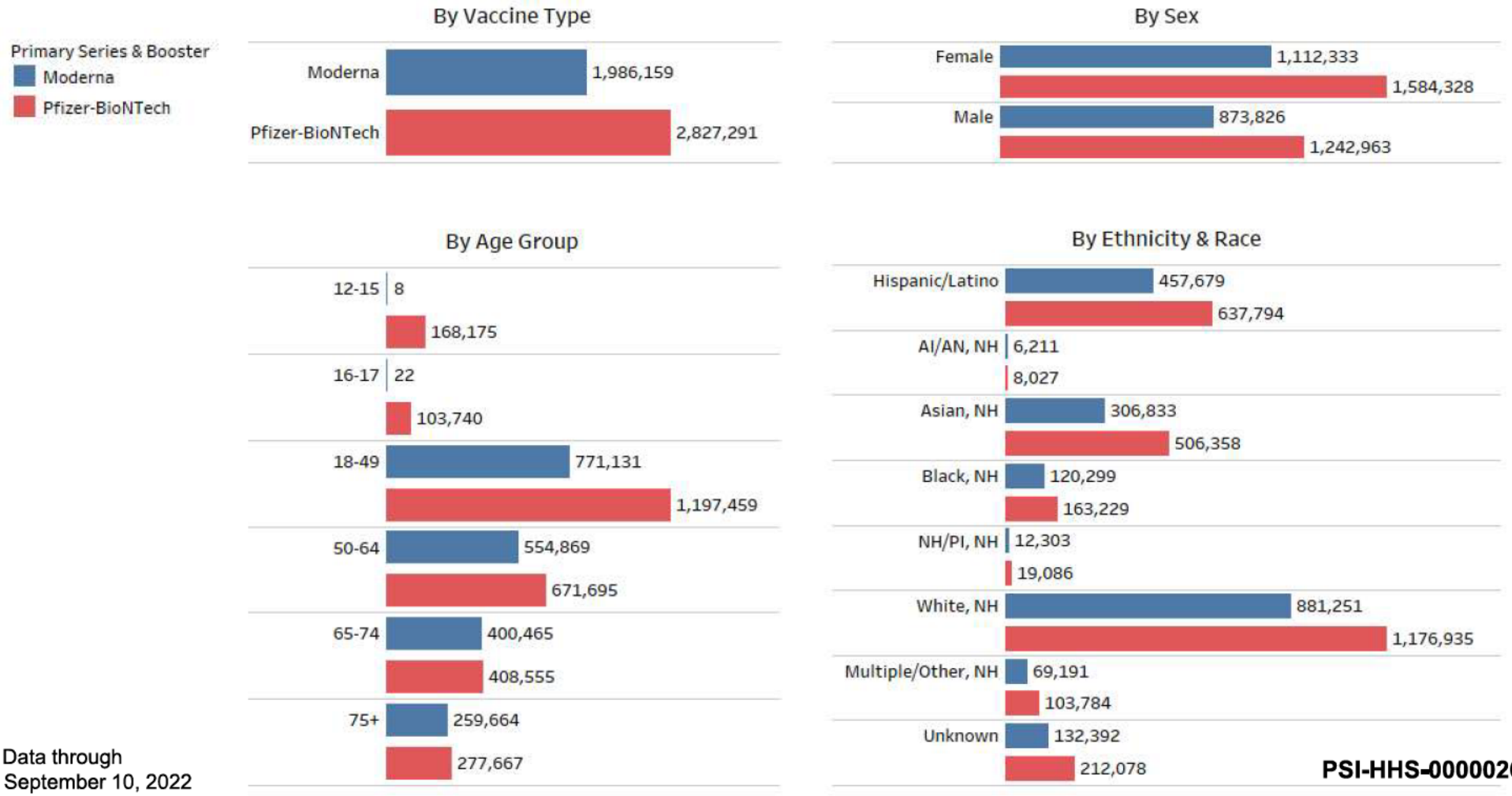
- Established in 1990
- Collaborative project between CDC and 9 integrated healthcare organizations

VSD has Monitored the Safety of Many New Vaccines: Prior Rapid Cycle Analyses

- RCA: VSD updates the data and the sequential analyses.
  - Meningococcal Conjugate (Menactra®)
  - H1N1 Influenza Vaccines
  - Influenza Vaccines
  - DTaP-IPV (Kinrix®)
  - DTaP-IPV/Hib (Pentacel®)
  - COVID-19 Vaccines
  - HPV 4 & 9 (Gardasil®)
  - PCV13
  - Shingrix
  - Rotavirus (Rotateq® and Rotarix®)
  - Measles, Mumps, Rubella, and Varicella (MMRV) (Proquad®)
  - Tdap (Adacel® and Boostrix®)

- VSD's rapid cycle analyses are best suited for outcomes that are:
  - Clinically well-defined and coded in the electronic medical records
  - Acute-onset (i.e., within a few days or weeks) of vaccination
  - Serious

Monovalent booster uptake among persons aged ≥12 years in the VSD*

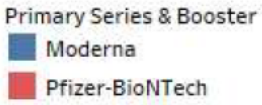


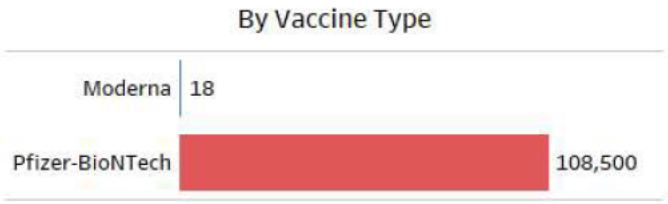
* Data through September 10, 2022

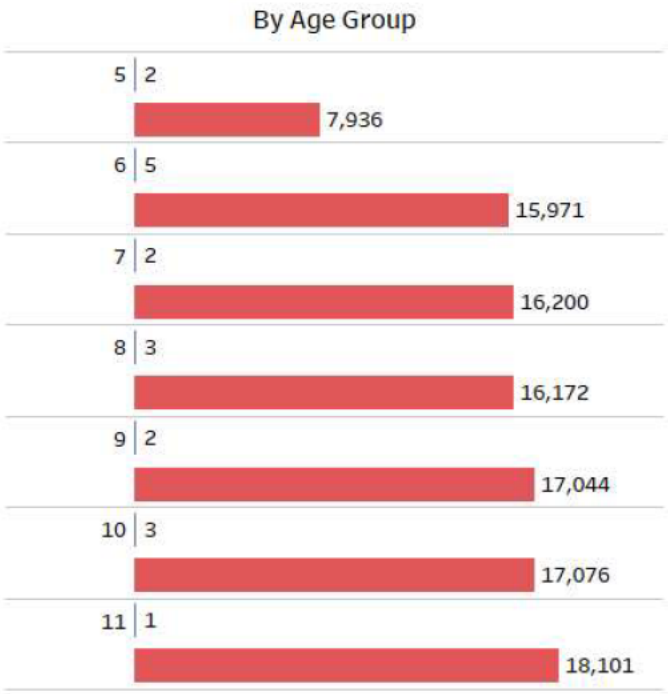
Primary Series uptake among persons aged 5-11 years in the VSD*

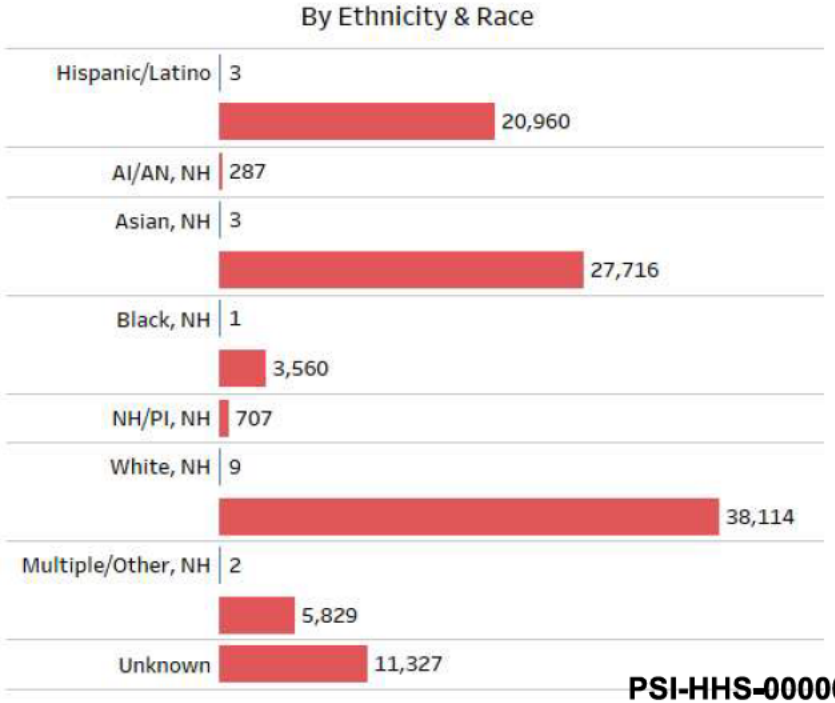
* Data through February 4, 2023

Monovalent booster uptake among persons aged 5-11 years in the VSD*





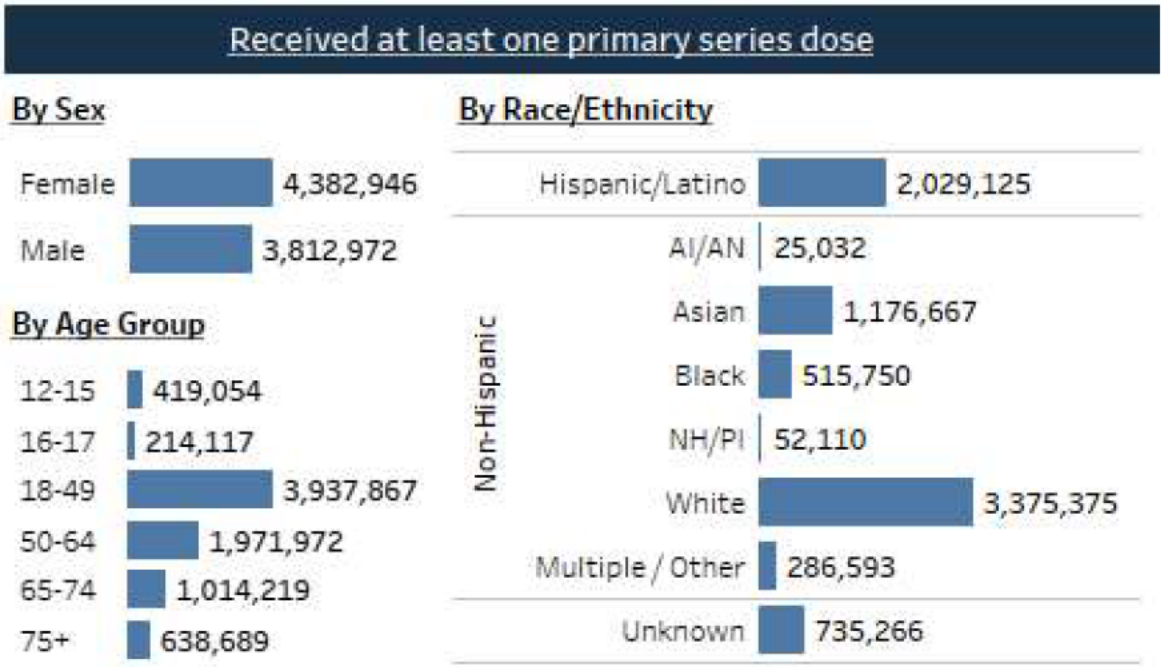




* Data through September 10, 2022

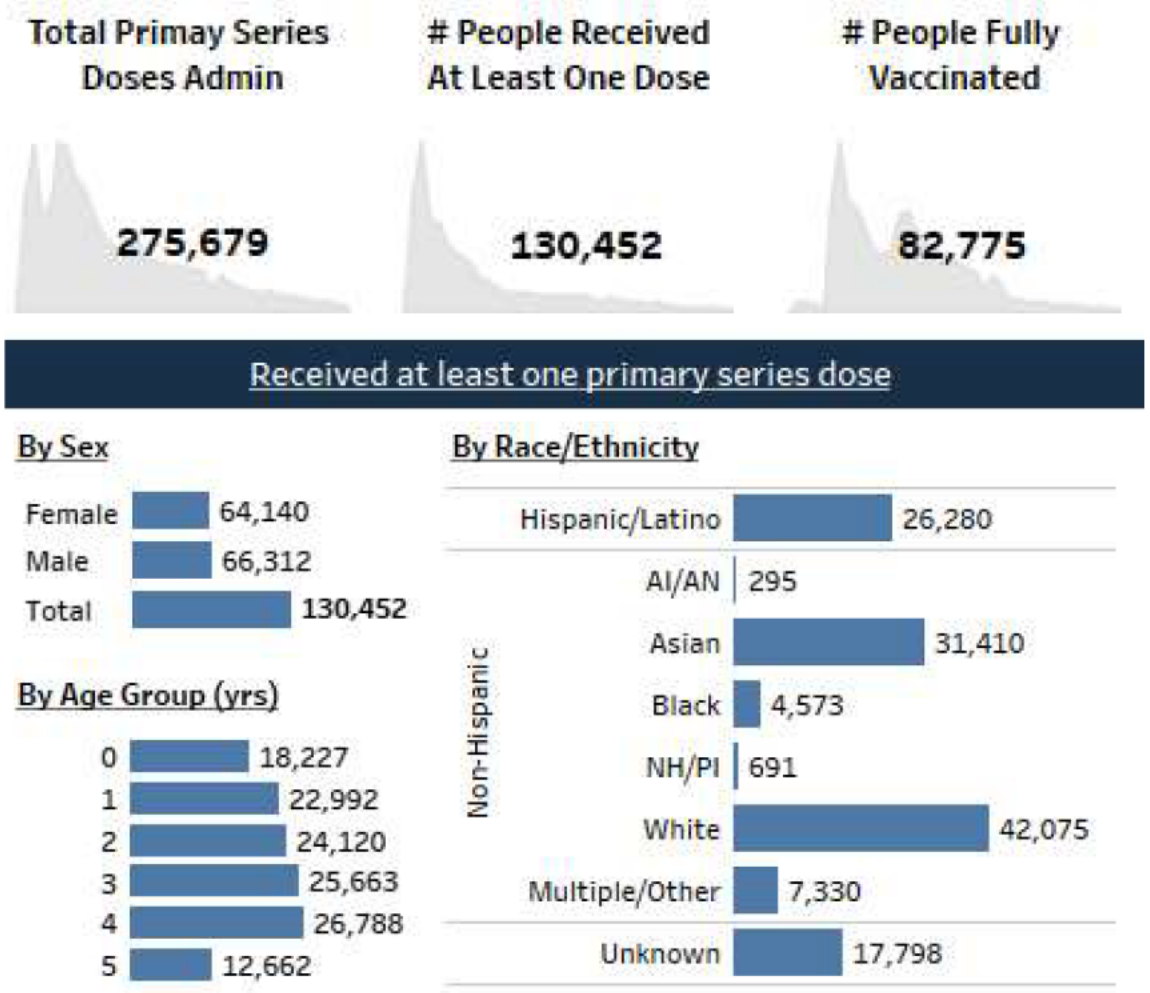
Primary Series uptake among persons aged ≥12 years in the VSD*

Total Doses Administered	Total Doses Admin per 100K	# People Received At Least One Dose	# People Fully Vaccinated
15,913,829	149,902	8,195,918	8,021,510



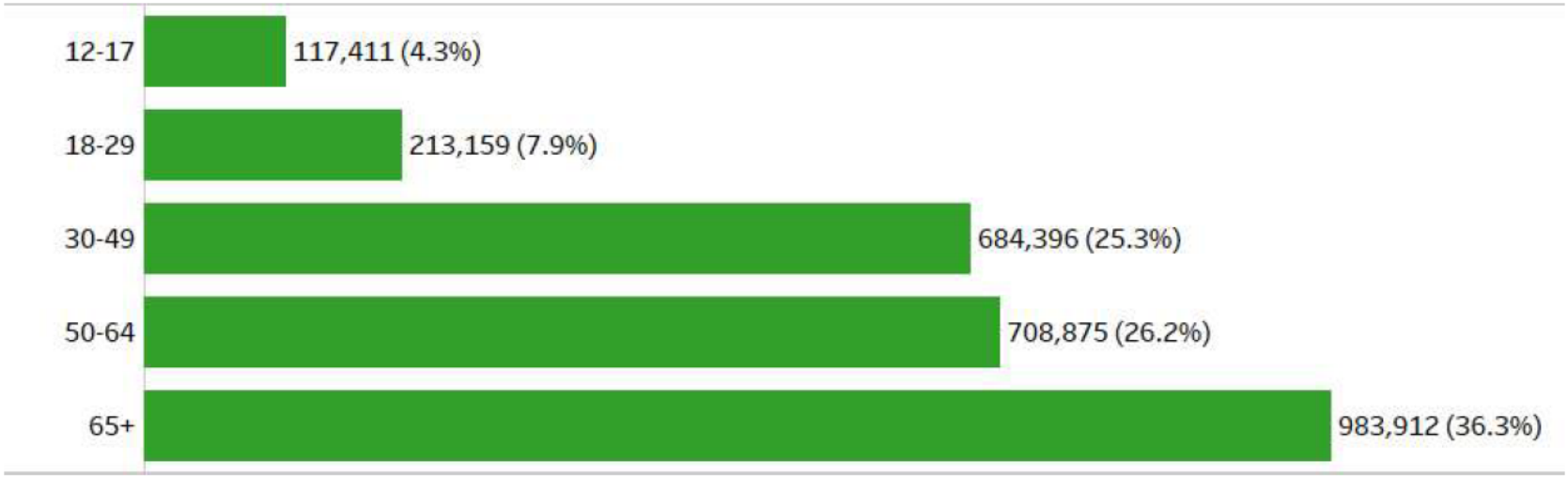
* Data through May 21, 2022

Primary Series uptake among persons aged 6 months-5 years in the VSD*



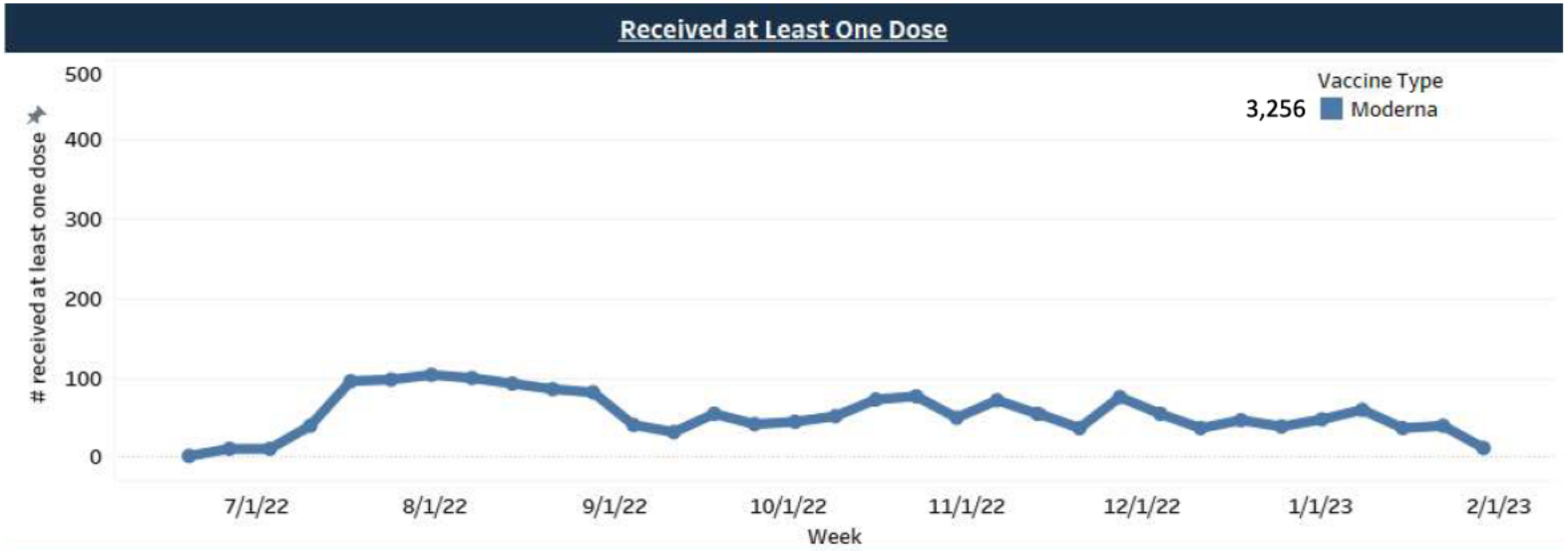
* Data through March 18, 2023

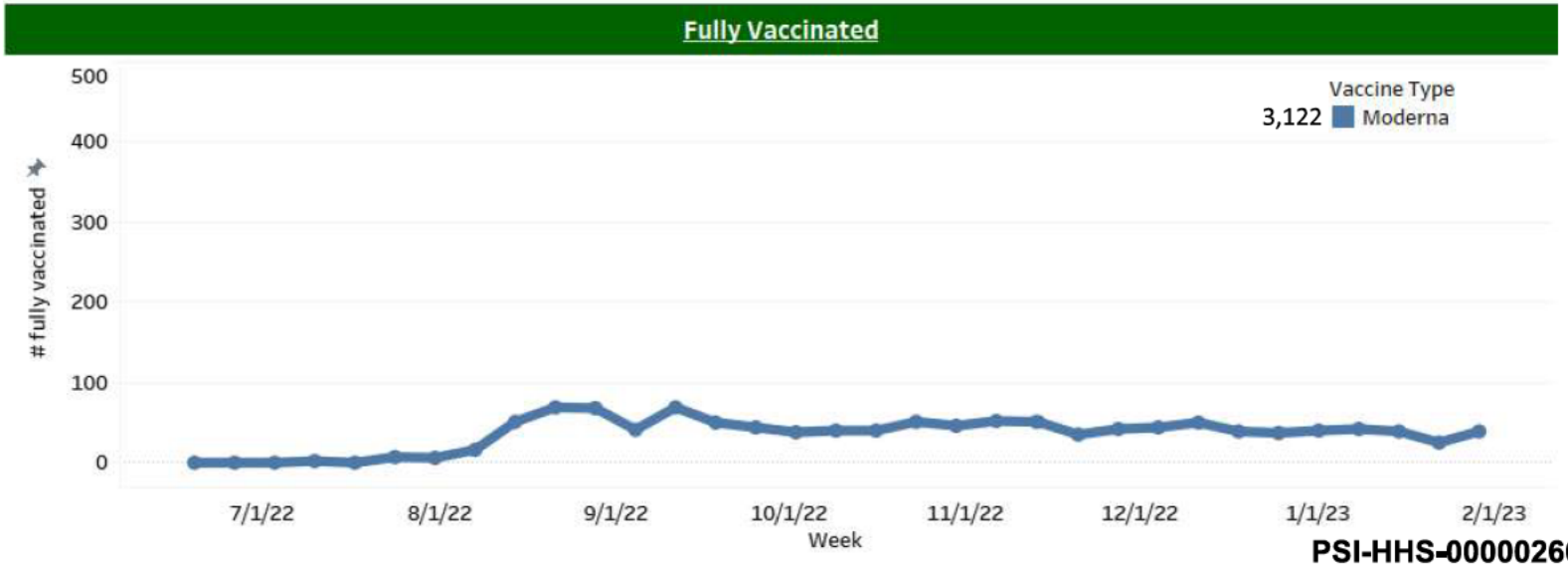
Bivalent booster uptake among persons aged ≥12 years in the VSD by age group*



* Data through March 18, 2023

Moderna Primary Series uptake among persons aged 5-11 years in the VSD, over time*





* Data through February 4, 2023

Summary of MIS cases occurring after vaccination

A total of 32 potential MIS cases were identified post vaccination, with 18 (56%) confirmed following chart review.

- Of these 18 confirmed cases 4 (22%) were in adults and 14 (78%) were in children (<18)
- For the 14 cases occurring in the <18 population
  - All following Pfizer-BioNTech
  - Age ranged from <1 to 18 YOA, median age at onset was 7.5 years
  - 11/14 (79%) male
  - Highest level of care: ICU (57%)

Brighton Level

- 11 (79%) Level 1
- 2 (14%) Level 2a
- 1 (7%) Level 4

Timing of MIS relative to COVID-19 vaccination

- 5 (36%) COVID-19 infection -> COVID-19 vaccination -> MIS
- 3 (21%) COVID-19 vaccination -> COVID-19 infection -> MIS
- 3 (21%) COVID vaccine -> known COVID exposure -> MIS
- 1 (7%) COVID-19 vaccination -> MIS
- 1 (7%) Unclear timeline, but have both COVID infection and COVID vaccine prior to MIS
- 1 (7%) Unclear history of COVID as no testing results available in the medical record

Total Uptake for Novavax in VSD: 3,779 doses

Myocarditis and Pericarditis: Electronic Case Identification using ICD-10 Codes

Code List[+] (based on cardiologist and VSD feedback)
• B33.22 Viral myocarditis
• B33.23 Viral pericarditis
• I30.* Acute pericarditis
• I40.* Acute myocarditis
• I51.4 Myocarditis, unspecified
• I31.9 Disease of the pericardium, unspecified

[+]Individuals with COVID-19 diagnosis or positive PCR 30 days prior to myocarditis/pericarditis were excluded. Those with COVID diagnosis or positive PCR >30 days prior were included.

- All identified cases 98 days after vaccination were chart reviewed, followed by infectious disease clinician and/or a cardiologist adjudication to:
  - Confirm case was incident following vaccination
  - Met CDC case definition (myocarditis, pericarditis, or myopericarditis)
  - Evaluated level of certainty for myocarditis

Moderna vs Pfizer "Head-to-Head" Comparison

- **Moderna** and **Pfizer** vaccinees were directly compared during the risk interval within groups
- The groups are comprised of:
  - Individuals inside the risk interval (days 0-7 post-vaccination)
  - Individuals of the same age group, sex, and race/ethnicity and from the same VSD site
  - On a calendar day when an mRNA vaccinee had myocarditis/pericarditis
- We estimated rate ratios with 95% confidence intervals (rate post-Moderna / rate post-Pfizer)
- We tested the null hypothesis that the rate of myocarditis and pericarditis after vaccination does not differ between Moderna and Pfizer

Myocarditis and Pericarditis after an mRNA Vaccine Among 18-39 year olds: Chart Review Summary

- 95 potential cases were identified during days 0-7 after mRNA vaccination
- Chart review and adjudication verified 79/95 (83%) myocarditis and pericarditis cases
  - 16 cases were after dose 1 of either vaccine
  - 63 cases were after dose 2 of either vaccine
- 41/79 (51.9%) verified cases were after either dose of Pfizer
- 38/79 (48.1%) verified cases were after either dose of Moderna

eTable 4. Medical record review of 34 confirmed myocarditis/pericarditis cases 0-21 days after mRNA vaccines among individuals aged 12-39 years, December 14, 2021 - June 19, 2021.

	Confirmed Myocarditis/Pericarditis N=34 (%)
Age, median (range)	24 years (13 – 39 years)
12-15 years	1 (3)
16-19 years	7 (21)
20-24 years	10 (29)
25-29 years	3 (9)
30-34 years	7 (21)
35-39 years	6 (18)
Male sex	29 (85)
Race/Ethnicity	
Hispanic/Latino	7 (21)
White, Non-Hispanic	17 (50)
Black, Non-Hispanic	0 (0)
Asian, Non-Hispanic	5 (15)
Native Hawaiian/Pacific Islander, Non-Hispanic	0 (0)
American Indian/Alaskan Native, Non-Hispanic	0 (0)
Multiple/Other	2 (6)
Unknown	3 (9)
History of COVID-19 infection	3 (9)
History of myocarditis/pericarditis	3 (9)
Time from vaccination to symptom onset, median (range)	2 days (0 – 20 days)
Signs and symptoms	
Chest pain/pressure/discomfort	34 (100)
Dyspnea/Shortness of breath	15 (44)
Palpitations	4 (12)
Pericardial rub	1 (3)
Other (fever, fatigue, chills, numbness, tingling nausea, etc)	20 (59)
Diagnostic testing	
Troponin level obtained	34 (100)
Abnormal troponin Level	28 (82)
ECG obtained	34 (100)
Abnormal ECG	30 (88)
Echocardiogram obtained	30/34 (88)
Abnormal echocardiogram	15/30 (50)
Cardiac MRI obtained	9/34 (26)
Abnormal cardiac MRI	8/9 (89)
Diagnosis after adjudication	
Acute myocarditis	7 (21)
Acute pericarditis	6 (18)
Myopericarditis	21 (62)
Highest level of care	
Outpatient	1 (3)
Emergency department	5 (14)
Admitted to hospital	26 (76)
Admitted to ICU	2 (6)
Length of hospital stay, median (range)	1 day (0 – 13 days)
Status at time of medical record review	
Discharged to home	34 (100)
Follow-up visit[1]	31 (91)

[1]Nearly all follow-up notes indicated resolution of symptoms time of follow-up visit. Of those that had follow-up ECG/echo or lab testing, most had returned to normal or baseline. Most patients were noted to be tapering off some medications (nonsteroidal anti-inflammatory drug, prednisone, etc). Follow-up Notes also indicated use of colchicine maintenance and recommendations for reduced activity for 3-6 months.

RCA Analyses AMI after Pfizer mRNA Vaccine

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

Vaccine	Age group	Risk Interval	Events in Risk Interval	Events in Comparison Interval	Adjusted Rate Ratio (95% CI)2	1-sided P-value	'Signal' 1-sided
Primary series, Dose 2	12+ YOA	1-21 days	224	190	1.26 (1.02 – 1.56)	0.019	Yes
Monovalent Booster (following Pfizer primary series)	12+ YOA	1-21 days	123	160	0.97 (0.76 – 1.24)	0.619	No
Bivalent Booster	18-64 YOA	1-21 days	31	30	1.10 (0.65 – 1.85)	0.413	No
	65+ YOA	1-21 days	114	123	1.17 (0.90 – 1.40)	0.236	No

RCA Analyses VTE after Pfizer mRNA Vaccine

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

Vaccine	Age group	Risk Interval	Events in Risk Interval	Events in Comparison Interval	Adjusted Rate Ratio (95% CI)2	1-sided P-value	'Signal' 1-sided
Primary series, Dose 2	12+ YOA	1-21 days	238	177	1.50 (1.21 – 1.85)	<0.001	Yes
Monovalent Booster (following Pfizer primary series)	12+ YOA	1-21 days	86	125	0.83 (0.62 – 1.10)	0.914	No
Bivalent Booster	18-64 YOA	1-21 days	34	44	0.77 (0.47 – 1.25)	0.882	No
	65+ YOA	1-21 days	65	66	1.05 (0.72 – 1.52)	0.432	No

Assessing GBS in the VSD COVID-19 RCA

- Potential cases of GBS in the emergency department or inpatient setting in the 1-98 days after COVID-19 vaccination
  - Potential cases were identified using ICD-10 codes
  - Individuals with a history of GBS (G61.0) since 10/1/2015 excluded

- All potential cases of GBS underwent medical record review and adjudication according to the Brighton Collaboration criteria*
  - Analyses include Brighton level 1-4 cases

- Cases of GBS identified among unvaccinated individuals did not undergo medical record review

*Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre Syndrome and Fisher Syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. *Vaccine*. 2011;29(3):599-612. https://doi.org/10.1016/j.vaccine.2010.06.003

RCA Analyses Verified GBS after mRNA Vaccines, December 13, 2020-Novemer 16, 2021

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

Comparators	Risk Interval	Comparison Interval	Adjusted Rate Ratio (95% CI)[a]	2-sided P-value	1-sided P-value[b]	Signal?[c]
Vaccinated	1-21 days	22-42 days	0.56 (0.21-1.48)	0.25	0.93	No
Unvaccinated[d]	1-21 days	22-42 days	0.83 (0.50-1.33)	0.45	N/A	N/A
Unvaccinated[d]	1-42 days	43-84 days	0.85 (0.57-1.27)	0.44	N/A	N/A

[a]Adjusted for 5-year age group, sex, race/ethnicity, site, and calendar day.
[b]1-sided sequential testing was only conducted for primary weekly analyses with vaccinated concurrent comparators.
[c]Signal threshold is 1-sided *P*-value<0.0048.
[d]Unvaccinated concurrent comparator analyses are conducted using unverified electronic data.

- Rate ratios not elevated; no statistical signals

RCA Analyses Verified GBS after Janssen Vaccine, December 13, 2020-Novemer 16, 2021

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

Comparators	Risk Interval	Comparison Interval	Adjusted Rate Ratio (95% CI)[a]	2-sided P-value	1-sided P-value[b]	Signal?[c]
Vaccinated	1-21 days	22-42 days	6.03 (0.79-147.79)	0.09	0.08	No
Vaccinated	1-42 days	43-84 days	8.64 (1.18-207.32)	0.03	0.03	No
Unvaccinated[d]	1-21 days	22-42 days	10.57 (5.15-20.16)	<0.001	N/A	N/A
Unvaccinated[d]	1-42 days	43-84 days	10.05 (5.75-16.96)	<0.001	N/A	N/A

[a]Adjusted for 5-year age group, sex, race/ethnicity, site, and calendar day.
[b]1-sided sequential testing was only conducted for primary weekly analyses with vaccinated concurrent comparators.
[c]Signal threshold is 1-sided *P*-value<0.0048.
[d]Unvaccinated concurrent comparator analyses are conducted using unverified electronic data.

- Vaccinated concurrent comparator analyses did not signal, though rate ratios were elevated compared with unvaccinated comparators

VSD RCA Safety Surveillance

Final signaling table for primary series in the 6 months – 4 or 5 years of age population (early March 2023)

Signaling threshold was 0.01.

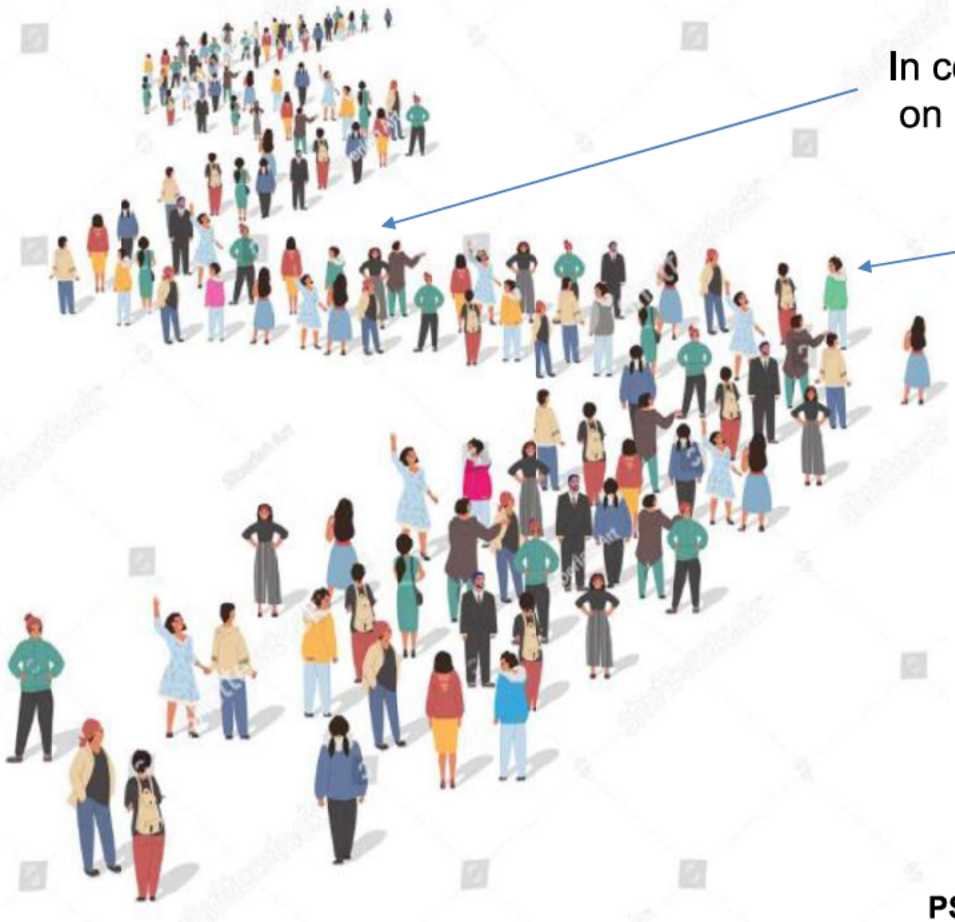
No monitored outcomes after either mRNA vaccine met the signaling criteria in the 21 days after primary series vaccination among children aged 6 months – 4 or 5 years in the VSD population. Notably, no cases of myocarditis or pericarditis within the risk interval.

		Pfizer				Moderna		
Risk Period Days	Outcome Event	Dose 1	Dose 2	Dose 3	All Doses	Dose 1	Dose 2	All Doses
1-21	Appendicitis	-	No	-	No	No	-	No
	Bell's palsy	No	-	-	No	No	-	No
	Encephalitis / myelitis / encephalomyelitis	-	-	-	-	-	-	No
	Guillain-Barre syndrome	-	-	-	-	-	No	No
	Stroke, hemorrhagic	No	No	-	No	-	-	-
	Immune thrombocytopenia	-	No	-	No	-	No	No
	Kawasaki disease	-	No	No	No	No	No	No
	Transverse myelitis	-	-	-	-	No	-	No
	Venous thromboembolism	-	-	-	-	-	-	No
	Pulmonary embolism (subset of VTE)	-	No	-	No	-	-	-

- = analyses not yet possible

People early in line for a jab may differ in AE risk from those later in line, or not in line, but this source of bias is less with vaccinated controls than with unvaccinated controls

Hesitant



Incidence per Million Doses of Confirmed Anaphylaxis Cases following COVID-19 Vaccination in the Vaccine Safety Datalink, Overall and by Sex

	Overall			Female			Male		
	No. Confirmed Cases	No. Doses	Incidence per Million Doses (95% CI)	No. Confirmed Cases	No. Doses	Incidence per Million Doses (95% CI)	No. Confirmed Cases	No. Doses	Incidence per Million Doses (95% CI)
Primary Series (6m +)	89	--	--	81	--	--	8	--	--
Pfizer-BioNTech	49	10,199,998	4.8 (3.6-6.4)	47	5,449,527	8.6 (6.3-11.5)	2	4,750,471	0.4 (0.1-1.5)
Dose 1	39	5,085,188	7.7 (5.5-10.5)	37	2,716,034	13.6 (9.6-18.8)	2	2,369,154	0.8 (0.1-3.0)
Dose 2	10	5,114,810	2.0 (0.9-3.6)	10	2,733,493	3.7 (1.8-6.7)	0	2,381,317	0.0 (0.0-1.3)
Moderna	33	6,212,227	5.3 (3.7-7.5)	28	3,362,853	8.3 (5.5-12.0)	5	2,849,374	1.8 (0.6-4.1)
Dose 1	25	3,088,454	8.1 (5.2-11.9)	21	1,671,816	12.6 (7.8-19.2)	4	1,416,638	2.8 (0.8-7.2)
Dose 2	8	3,123,773	2.6 (1.1-5.0)	7	1,691,037	4.1 (1.7-8.5)	1	1,432,736	0.7 (0.0-3.9)
Janssen	7	511,707	13.7 (5.5-28.2)	6	235,194	25.5 (9.4-55.5)	1	276,513	3.6 (0.1-20.1)
Monovalent Booster (5 YOA +)	5	--	--	5	--	--	0	--	--
Pfizer-BioNTech	0	3,160,912	0.0 (0.0-0.9)	0	1,759,834	0.0 (0.0-1.7)	0	1,401,078	0.0 (0.0-2.1)
Moderna	4	2,234,583	1.8 (0.5-4.6)	4	1,237,255	3.2 (0.9-8.3)	0	997,328	0.0 (0.0-3.0)
Janssen	1	77,179	13.0 (0.3-72.2)	1	37,401	26.7 (0.7-149.0)	0	39,778	0.0 (0.0-75.3)
Bivalent Booster (6m +)	2	--	--	1	--	--	1	--	--
Pfizer-BioNTech	2	1,926,149	1.0 (0.1-3.8)	1	1,066,727	0.9 (0.0-5.2)	1	859,422	1.2 (0.0-6.5)
Moderna	0	845,342	0.0 (0.0-3.5)	0	469,239	0.0 (0.0-6.4)	0	376,103	0.0 (0.0-8.0)