Artificial Intelligence and Division of Pharmacovigilance

Narayan Nair, M.D.
Division Director, Division of Pharmacovigilance
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Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate the US FDA.

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Outline

- CBER's management of pharmacovigilance (PV) during COVID-19 Pandemic
- Future Considerations

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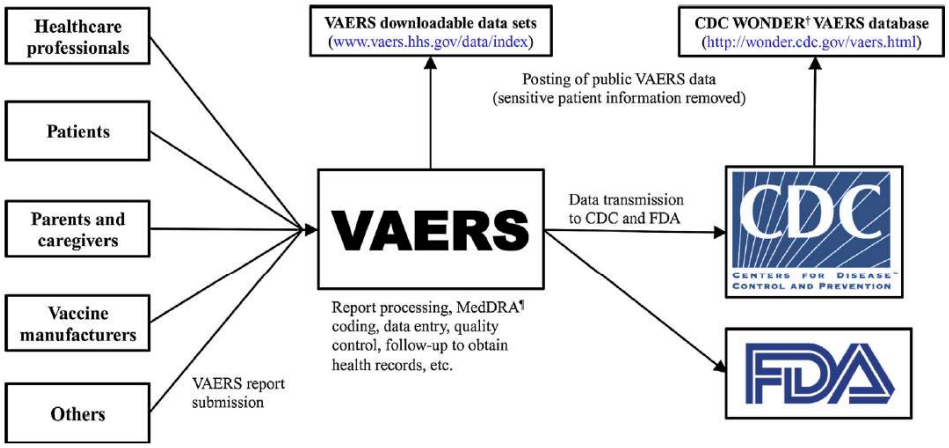
U.S. FOOD & DRUG ADMINISTRATION

CBER Management of PV During COVID-19 Pandemic

VAERS Process

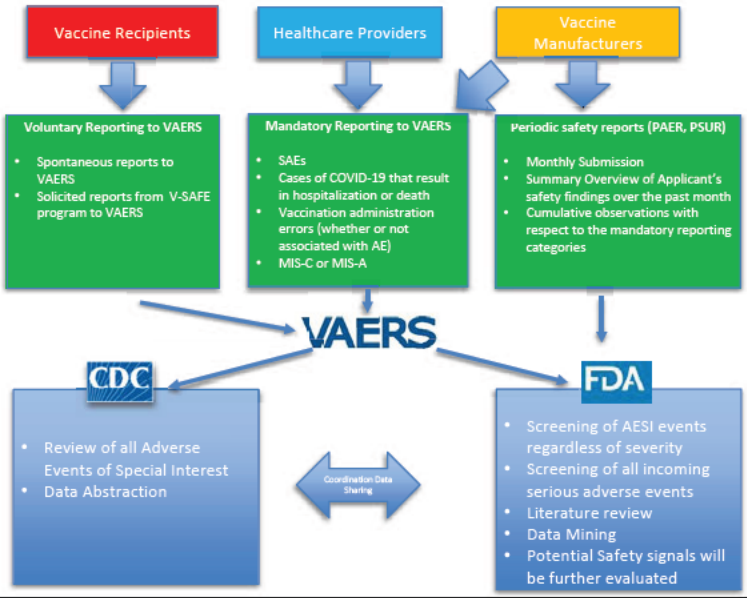


Shimabukuro T, Nguyen M, Martin D, DeStefano F. Safety Monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* doi :10.1016/j.vaccine.2015.07.035.

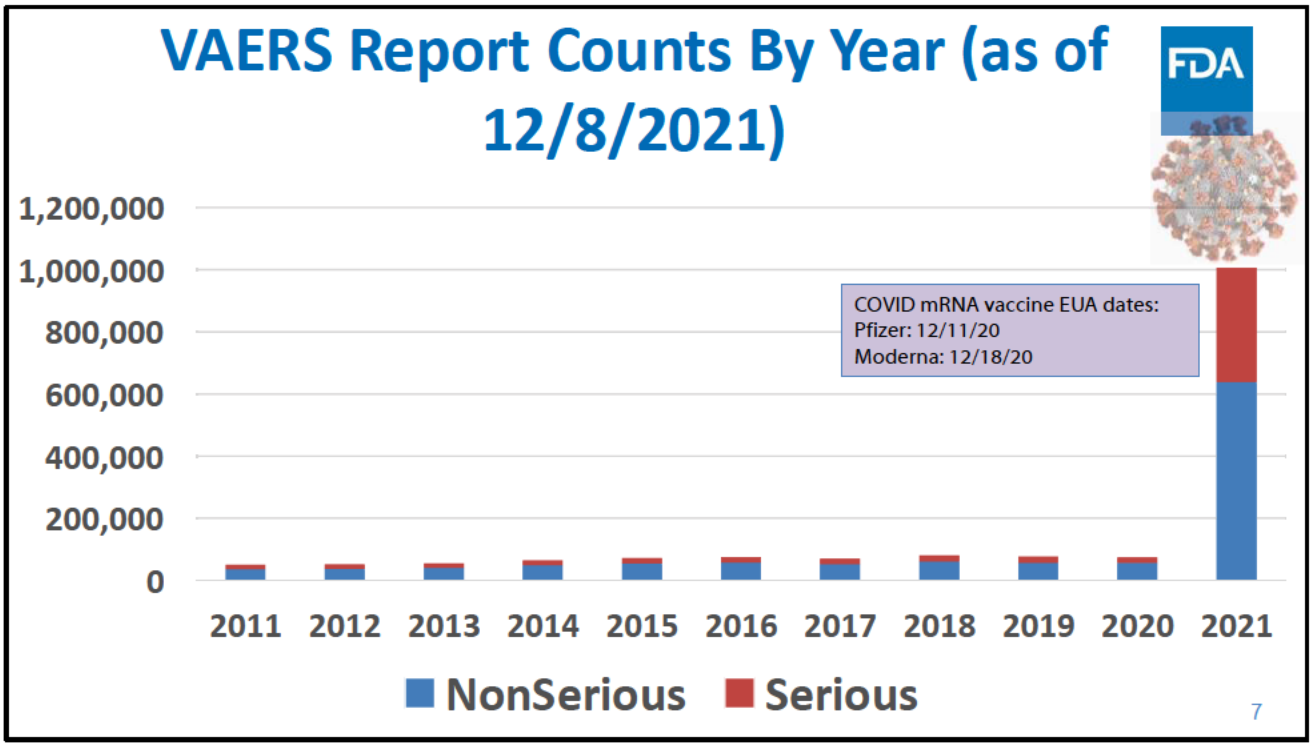
5

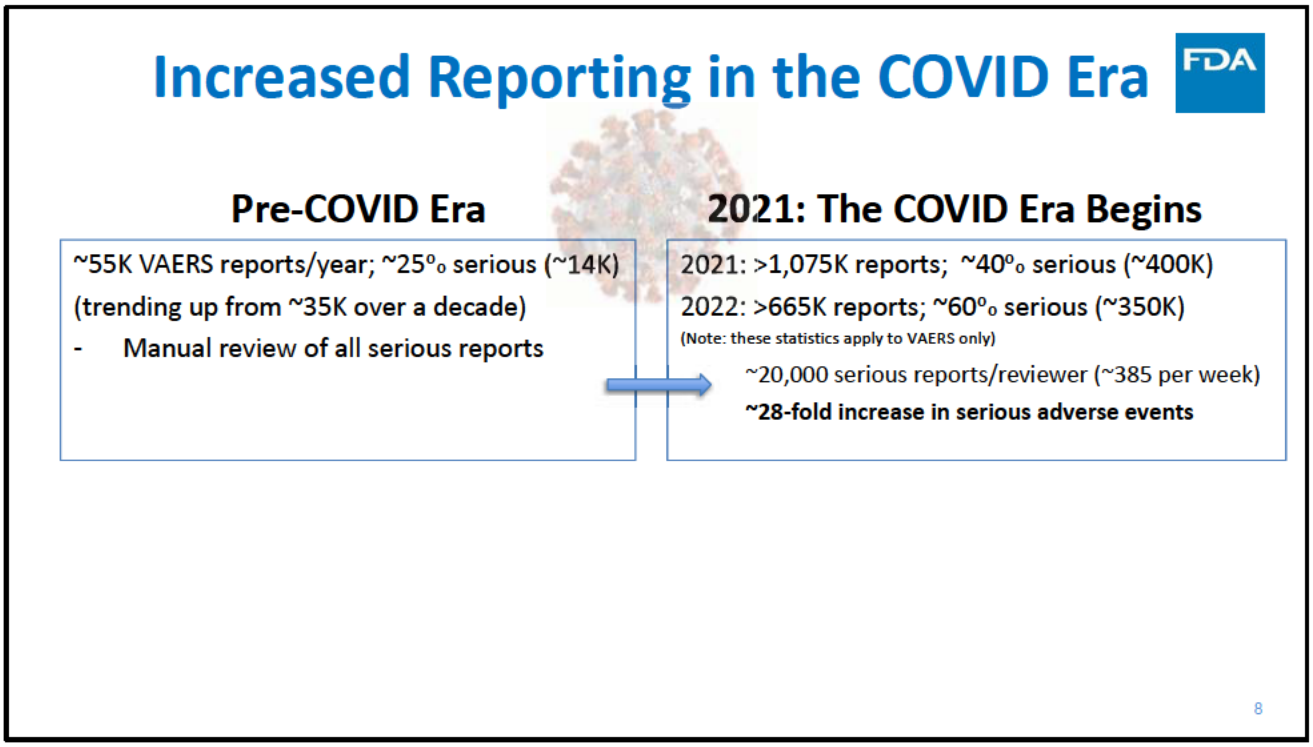
Adverse Event Reporting of COVID-19 Vaccines under Emergency Use Authorization

FDA



6


VAERS Report Counts By Year (as of 12/8/2021)
FDA
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
COVID mRNA vaccine EUA dates:
Pfizer: 12/11/20
Moderna: 12/18/20
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
NonSerious
Serious
7



COVID-19 Vaccine Safety Monitoring

- The postmarketing safety review of COVID-19 vaccines includes:
  - Review of all individual serious VAERS reports
  - Case series analysis
  - Aggregate data analysis
  - Review data from other sources (published literature, postmarketing studies)
- In addition to passive surveillance, active surveillance and postmarketing studies play a key role in evaluating and further characterizing the safety of COVID-19 vaccines.

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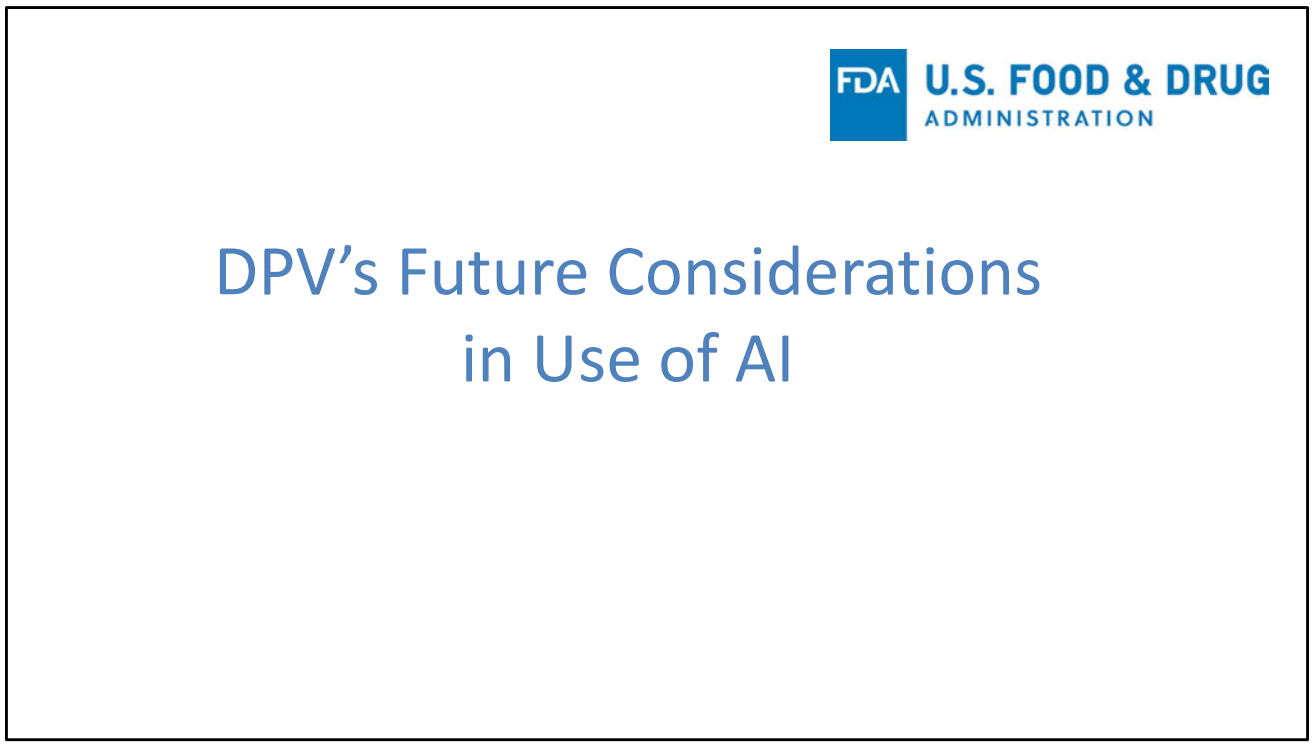
Data Mining

Disproportional Reporting: AEs reported more commonly for one product than others

- Empirical Bayesian Geometric Mean (EBGM):
  - Statistical score ("alert")
  - EB05 ≥2: accepted threshold
- Screening tool for analyzing large databases
- Complements traditional review
- Evaluate Alerts in larger clinical and epidemiologic context.
  - Good for generating hypothesis
  - Does not account for biases, confounding
  - Unexpected and/or unlabeled?
  - Confounding by indication?

(EB05: Lower bound of the 95% confidence interval of EBGM Empirical Bayesian Geometric Mean (EBGM)q

10



Overarching Principles

- Address ethical concerns up front
- Augment Existing Staff
  - Automate tasks and workflow
- Integrate into existing workflow and processes
- Heavy emphasis on user acceptance testing

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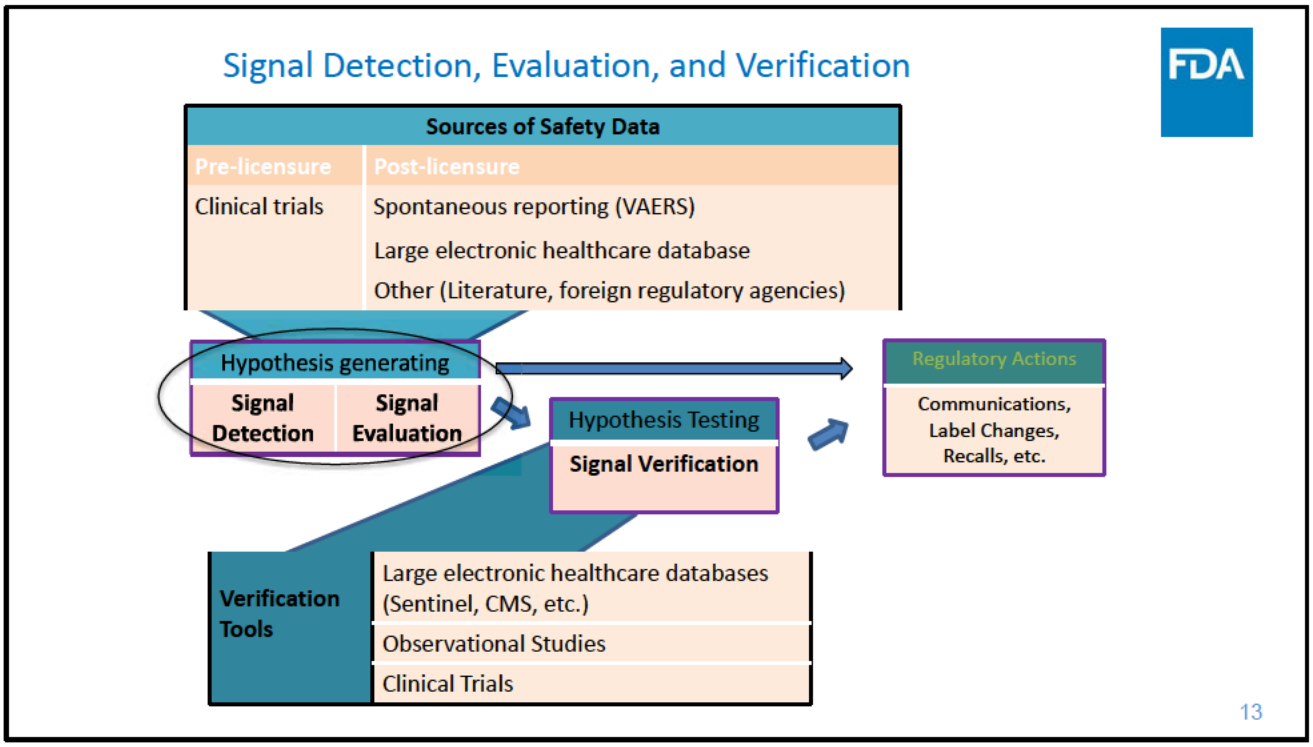

Signal Detection and Evaluation

- Conduct a search in VAERS and in Literature
- Develop a Case Series
  - Establish a Case Definition
  - Remove Duplicate Reports
  - Remove Reports with Missing Information or that do not meet Case Definition
- Conduct an Observed to Expected (O/E) Analysis

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Natural Language Processing

- **Event-based Text-Mining of Health Electronic Records (ETHER)**
- Deconstruction of adverse event descriptions
  - Extracts clinical features (e.g. diagnoses) from safety reports
  - Extracts time information and associates it with the clinical features
- Summarization of adverse event information
  - Creates textual and tabular summaries
  - Visualizes the temporal associations of the extracted features
- Deconstruction supports other tasks
  - Query-based selection of reports
  - Conversion of free text to medical codes

"Decision Support Environment for Medical Product Safety Surveillance." Botsis T, Jankosky C, Arya D, Kreimeyer K, et al. Journal of Biomedical Informatics. 2016 Dec;64:354-362. doi:10.1016/j.jbi.2016.07.023

U.S. FOOD & DRUG ADMINISTRATION

Thank You

From: "Nair, Narayan" [redacted]
To: "Menschik, David" [redacted], "Zinderman, Craig" [redacted], "Baer, Bethany" [redacted]
Subject: RE: Data mining question
Date: Fri, 15 Mar 2024 19:21:26 -0000
Importance: Normal
Inline-Images: image001.png; image002.jpg; image003.jpg; image004.jpg; image005.jpg; image006.jpg

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Ok, thank you for checking.

Narayan

From: Menschik, David [redacted]
Sent: Friday, March 15, 2024 1:30 PM
To: Nair, Narayan [redacted]; Zinderman, Craig [redacted]; Baer, Bethany [redacted]
Subject: RE: Data mining question

I understood we provided CDC language for this limitation for the 6 month safety review of mRNA vaccines (and I could share that language if helpful) but in looking at the published article, it now appears that they took it out before publication. I'm not aware of such language included in another publication.

From: Nair, Narayan [redacted]
Sent: Friday, March 15, 2024 1:04 PM
To: Menschik, David [redacted]; Zinderman, Craig [redacted] Baer, Bethany [redacted]
Subject: Data mining question

Good afternoon,
I know in the past we have discussed one of the possible limitations of data mining currently is the vast number of VAERS reports from the COVID vaccines may limit our ability to detect statistical alerts because disproportionality scores may be driven towards the null. Do you know if there is a public reference that discusses this limitation? I have found some references that discuss general limitations for data mining but not sure if there is one that talks about how a large volume of reports from a single class of products could masks results.

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

Division of Pharmacovigilance
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

From: "Nair, Narayan" [redacted]
To: "Jason, Christopher" [redacted]
Cc: "Thompson, Deborah" [redacted], "Baer, Bethany" [redacted], "Menschik, David" [redacted] "Bazel, Samaneh" [redacted]
Subject: RE: Question regarding Empirica Runs
Date: Tue, 14 Mar 2023 19:52:10 -0000
Importance: Normal
Inline-Images: image003.png; image004.png; image005.png; image006.png; image007.png

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Thanks to everyone for their work on this.

Narayan

From: Jason, Christopher [redacted]
Sent: Tuesday, March 14, 2023 12:23 PM
To: Nair, Narayan [redacted]
Cc: Thompson, Deborah [redacted]; Baer, Bethany [redacted] Menschik, David [redacted]; Bazel, Samaneh [redacted]
Subject: FW: Question regarding Empirica Runs

Hi Narayan

Please find attached the runs (serious and over 65) for the PT, "ischaemic stroke" from Empirica (and the visualized data charts and tables) for the search you requested. Thanks to Bethany and Kusal for making the runs and to Deb for initially identifying the signal. Let me know if you all have questions. The only EB05 >2 is for serious AEs and it does appear to be moderating.

Sincerely
Chris

From: Nguon, Kosal * [redacted]
Sent: Wednesday, March 8, 2023 12:38 PM
To: Jason, Christopher [redacted] Baer, Bethany [redacted]
Cc: Menschik, David [redacted]
Subject: RE: Question regarding Empirica Runs

Hi Chris, Bethany,

Sorry, I have been a bit busy during the last few days, and I have been meaning to respond with an update. I have completed two custom data mining runs, and I have provided a quick summary of each of them below to make sure it is correct.

Also, I know you wanted the two side-by-side graphs of the monovalent and bivalent vaccines similar to the screenshot that was sent earlier. Unfortunately, the graph requires more manipulation and coding to generate from these two custom data mining runs as this is one of the limitations of Signal. I have asked our team to look into the feasibility of this, but it might require more attention and time. I would however suggest that you download the data and make a composite table and use another program (e.g., Excel, R) to graph it out.

Without further ado, here are the custom COVID data mining runs for monovalent and bivalent Pfizer-Biontech vaccines:

Both custom data mining runs are: US only, for the entirety of the VAERS database through March 3, 2023, and cumulative monthly subsets (aka, all the data through October 2022, and then all of the data through November 2022, etc.) with these data restrictions:

1. SP: VAERS Monthly Covid Serious – Only serious events for all ages. The background also only has "Serious" case reports such as the runs in the Signals tab.
2. SP: VAERS Monthly Covid Adult 65Plus – Only age 65 and over for all event types (e.g., serious and non-serious). The background contains only those 65 and over.

You'll have to enter the Pfizer monovalent and bivalent vaccines and the ischaemic stroke event on the "Select Criteria" page (see screenshot #1 for the SP: VAERS Monthly Covid Serious custom data mining run) because in the off-chance you may want to look at other monovalent and/or bivalent covid vaccines (or any other vaccine) and/or events, that data will be available to you. Same applies for the drug and event selection and reasoning for SP: VAERS Monthly Covid Adult 65Plus.

To view the "subsets" (aka, the monthly Signal scores), please select "Columns" in the upper left hand corner of the "Data Mining Results Table" page. A pop-up window appears, tick off the "Show All Columns" box, select "SUBSET" and move it over to the right hand column (double-click or use the single right arrow), then use the "Up/down" arrows for it column placement and finally select "OK" at the bottom (screenshot #2). This will give you the vaccine-event combination of your selection and then the monthly cumulative subsets (screenshot #3; I have ordered it by subset and then vaccine name). You can download the resulting table and then import/open to a software to display a table and/or graph.

Please feel free to reach out if you have any questions with how to display any of this, the analysis or anything else.

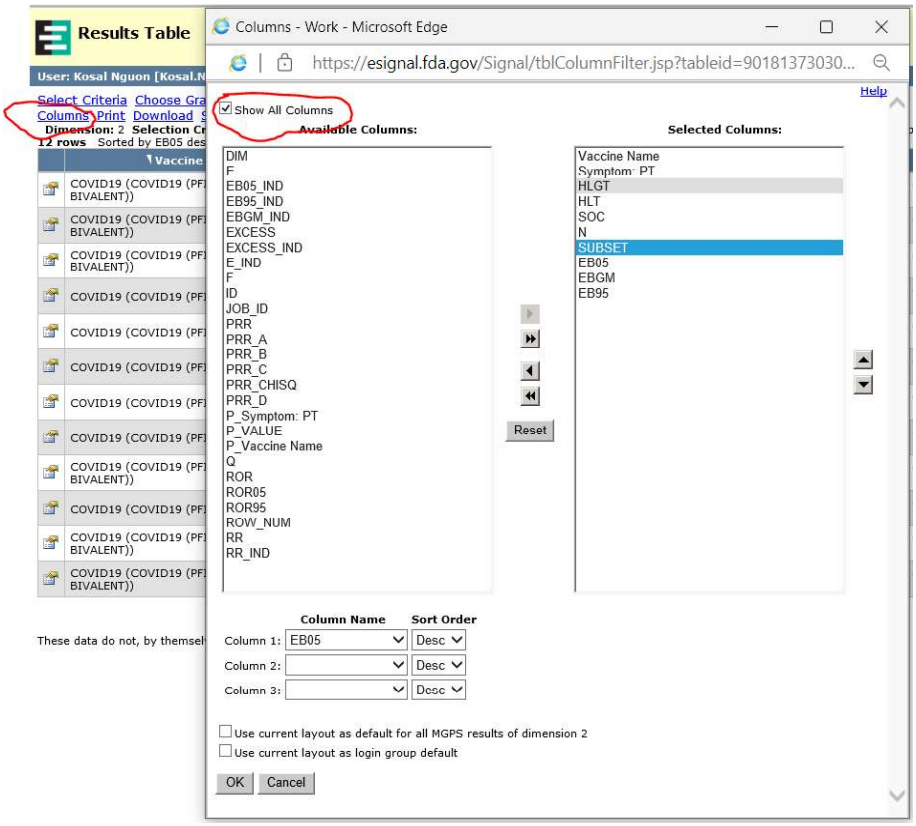
Thanks and have a great day!

Best,

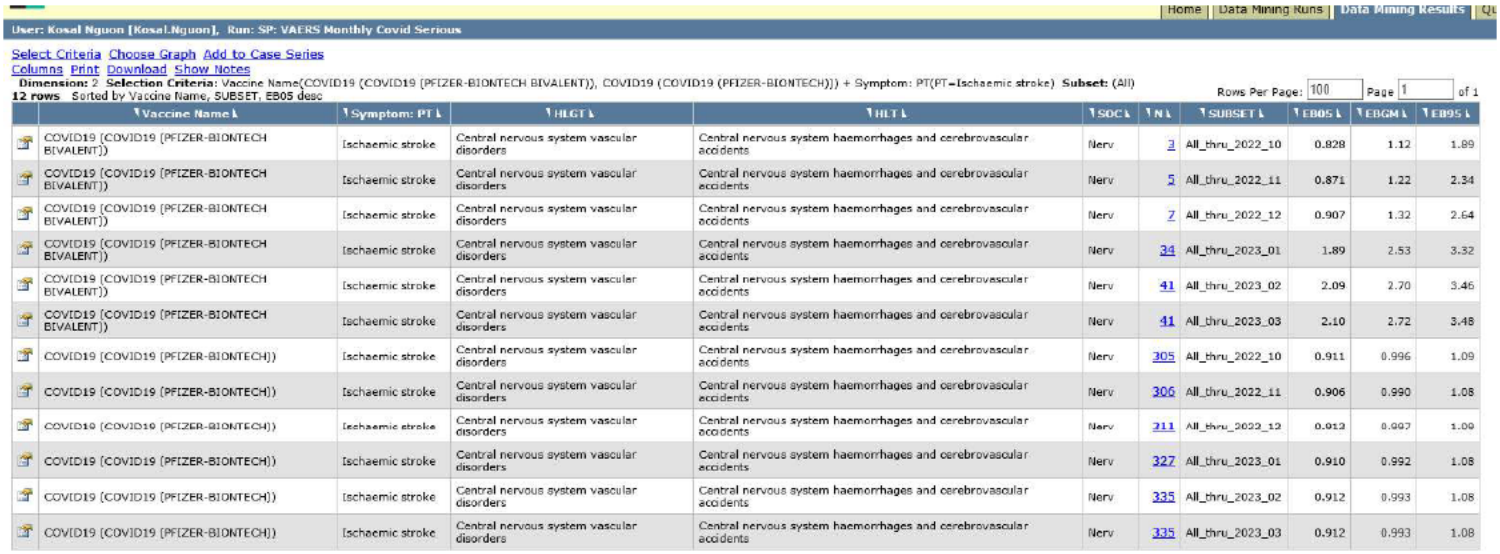
Kosal

Screenshot #1: Vaccine and Event Selection

Screenshot #2: Show Subsets Steps



Screenshot #3: Results Table by Covid Vaccine Name and Subset



Home | Data Mining Runs | Data Mining Results | QI

User: Kosal Nguon [Kosal.Nguon], Run: SP: VAERS Monthly Covid Serious

Select Criteria Choose Graph Add to Case Series
Columns Print Download Show Notes
Dimension: 2 Selection Criteria: Vaccine Name(COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT)), COVID19 (COVID19 (PFIZER-BIONTECH))) + Symptom: PT(PT=Ischaemic stroke) Subset: (All)
12 rows Sorted by Vaccine Name, SUBSET, EB05 desc

Rows Per Page: 100 Page 1 of 1

Vaccine Name	Symptom: PT	HLGT	HLT	SOC	N	SUBSET	EB05	EBGM	EB95
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	3	All_thru_2022_10	0.828	1.12	1.89
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	5	All_thru_2022_11	0.871	1.22	2.34
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	7	All_thru_2022_12	0.907	1.32	2.64
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	34	All_thru_2023_01	1.89	2.53	3.32
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	41	All_thru_2023_02	2.09	2.70	3.46
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	41	All_thru_2023_03	2.10	2.72	3.48
COVID19 (COVID19 (PFIZER-BIONTECH))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	305	All_thru_2022_10	0.911	0.996	1.09
COVID19 (COVID19 (PFIZER-BIONTECH))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	306	All_thru_2022_11	0.906	0.990	1.08
COVID19 (COVID19 (PFIZER-BIONTECH))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	311	All_thru_2022_12	0.913	0.997	1.09
COVID19 (COVID19 (PFIZER-BIONTECH))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	327	All_thru_2023_01	0.910	0.992	1.08
COVID19 (COVID19 (PFIZER-BIONTECH))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	335	All_thru_2023_02	0.912	0.993	1.08
COVID19 (COVID19 (PFIZER-BIONTECH))	Ischaemic stroke	Central nervous system vascular disorders	Central nervous system haemorrhages and cerebrovascular accidents	Nerv	335	All_thru_2023_03	0.912	0.993	1.08

Kosal Nguon, MPH (contractor)
Commonwealth Informatics, Inc.
Empirica Signal Support Team

Office of Translational Sciences
FDA/CDER/OTS
[redacted]
FDA U.S. FOOD & DRUG ADMINISTRATION

From: Jason, Christopher [redacted]
Sent: Friday, March 3, 2023 7:49 PM
To: Nguon, Kosal * [redacted]
Subject: RE: Question regarding Empirica Runs

Sure that works

From: Nguon, Kosal * [redacted]
Sent: Friday, March 3, 2023 5:09 PM
To: Jason, Christopher [redacted]; Baer, Bethany [redacted]
Cc: Menschik, David [redacted]
Subject: RE: Question regarding Empirica Runs

Hi Chris and Bethany,

Many thanks for all the clarifications and answers; these will set the parameters and criteria for our custom run.

Lastly, as I mentioned previously, the server storage space gets critically low when we do our weekly ETL jobs for Signal on Sunday to early Monday morning. As such, I would like to ensure the normal data mining runs are completed, so I probably can get the custom data mining run to you on Tuesday (March 7th) morning. Does that time frame work for you?

Thanks and have a great weekend.

Best,

Kosal

Kosal Nguon, MPH (contractor)
Commonwealth Informatics, Inc.
Empirica Signal Support Team

Office of Translational Sciences
FDA/CDER/OTS
[redacted]
FDA U.S. FOOD & DRUG ADMINISTRATION

From: Jason, Christopher [redacted]
Sent: Friday, March 3, 2023 2:28 PM
To: Baer, Bethany [redacted]; Nguon, Kosal * [redacted]

Cc: Menschik, David [redacted]
Subject: RE: Question regarding Empirica Runs

I would do 65 and older and serious separately if possible. Almost all the reports were serious though so an all reports search may give us falsely low EB05s compared to serious reports only. If 2 runs are too difficult I would do 1 run with both serious and over 65.

Sincerely,
Chris

From: Baer, Bethany [redacted]
Sent: Friday, March 3, 2023 2:14 PM
To: Jason, Christopher [redacted] Nguon, Kosal * [redacted]
Cc: Menschik, David [redacted]
Subject: RE: Question regarding Empirica Runs

Hi Chris and Kosal,
I agree with Chris' responses and the effort to keep things as close to our usual runs as possible. So, for question 1, I would use all the vaccines in the database. And Q4 – the whole time frame, with history showing the EB05 changes by month for end of 2022.
For 2 -3 - Chris, do you want a single combined result looking at the group that is both >65 years old and serious? That's what I thought you were going for so it would combine those two. Please clarify if I misunderstood. I think we can get the single result for "ischaemic stroke" for just >65 or just serious from the individual signals runs in the data mining results tab (although I don't see how to show the history for the EB05). Don't let me confuse things, Chris, if you have a better understanding of what Narayan was aiming for.
Bethany

From: Jason, Christopher [redacted]
Sent: Friday, March 3, 2023 1:53 PM
To: Nguon, Kosal * [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: Question regarding Empirica Runs

His Kosal
Regarding your questions answers in blue. Bethany feel free to jump in as I am not sure of some of the inputs

1. For the background, do you want to compare to all vaccines or the other covid vaccines (e.g., Moderna, Janssen, etc.)? Or maybe only the Pfizer vaccines?
   Whatever you compare for the signals tab I would do that. Unfortunately I am not sure what the inputs are for the various tabs in Empirica
2. Also for the background, do you only want serious case reports to be used (not recommended based the forwarded email thread)?
   Yes do 2 runs 1 serious (like the signals tab)
3. Same question for the 65 years and older—do you want the background/comparator to be only 65 years and older?
   And 1 65 and older
4. For the time frame, do you want to compare for the entirety of the VAERS database or from a specific time period moving forward (i.e., this is important if you only want to compare against the other covid vaccines, so you can set the date as November 1, 2019 or some other point)? I think we can start with the entire VAERS database and timeframe and then limit if further analyses are needed.
   I agree. I think it is difficult to know exactly what I want because I am not sure of the inputs. I think our boss wanted the chart in my initial email to you but 2 runs and limited to serious reports for one and 65 and older for the other
5. Also, please confirm the name of the two vaccines as:
   Monovalent: COVID19 (COVID19 (PFIZER-BIONTECH))
   Bivalent: COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))
   yes

From: Nguon, Kosal * [redacted]
Sent: Friday, March 3, 2023 1:16 PM
To: Jason, Christopher [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: Question regarding Empirica Runs

Hi Chris,

Thanks for reaching out, and thanks to Bethany for the referral; I always enjoy working with Bethany and the great folks from CBER!

Regarding your request, I did some research, I believe we can finagle Empirica Signal to produce results for which you are seeking. I do have a few follow-up questions, so I can create the correct custom data mining run. Please find them below:

1. For the background, do you want to compare to all vaccines or the other covid vaccines (e.g., Moderna, Janssen, etc.)? Or maybe only the Pfizer vaccines?
2. Also for the background, do you only want serious case reports to be used (not recommended based the forwarded email thread)?
3. Same question for the 65 years and older—do you want the background/comparator to be only 65 years and older?
4. For the time frame, do you want to compare for the entirety of the VAERS database or from a specific time period moving forward (i.e., this is important if you only want to compare against the other covid vaccines, so you can set the date as November 1, 2019 or some other point)? I think we can start with the entire VAERS database and timeframe and then limit if further analyses are needed.
5. Also, please confirm the name of the two vaccines as:
   Monovalent: COVID19 (COVID19 (PFIZER-BIONTECH))
   Bivalent: COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))

And one last question: when do you need the results by? We've, unfortunately, have been running close to our allotted server space, and this has flagged us and delayed some things. I want to be mindful of this for our technical team, and also ensure that we can deliver for you.

Please feel free to reach out with any comments/questions. Thanks and looking forward to this very tangible and interesting analysis!

Best,

Kosal

Kosal Nguon, MPH (contractor)
Commonwealth Informatics, Inc.
Empirica Signal Support Team

Office of Translational Sciences
FDA/CDER/OTS
[redacted]
U.S. FOOD & DRUG ADMINISTRATION

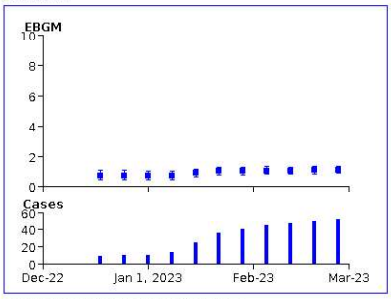
From: Jason, Christopher [redacted]
Sent: Friday, March 3, 2023 7:55 AM
To: Nguon, Kosal * [redacted]
Cc: Baer, Bethany <Bethany.Baer@fda.hhs.gov>
Subject: Question regarding Empirica Runs

Dear Kosal

I am one of the reviewers in DPV and management recently wanted some information on the Pfizer COVID Vaccine disproportionality that the standard runs will not be able to get. I attached the email with Bethany Baer who suggested contacting you. In short we are looking for a Empirica runs with Pfizer Bivalent and Pfizer Monovalent, US only, for the PT "Ischaemic stroke" for ages 65 and older and serious? We are looking to get monthly Eb05s starting in October similar to the "signals history" view. Any help would be appreciated

Sincerely,
Chris

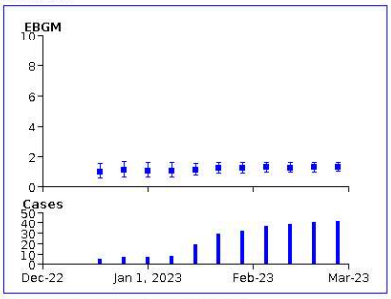
Signal set
All
Attributes:



Period start: 12/18/2022 **End:** 02/26/2023

02/26/2023	PT	HLT	SOC
N	53	275	4611
EB05	0.893	0.77	0.898
EBGM	1.114	0.851	0.92
EB95	1.377	0.938	0.943

Signal set
US
Attributes:



Period start: 12/18/2022 **End:** 02/26/2023

02/26/2023	PT	HLT	SOC
N	41	167	3249
EB05	1.01	0.808	0.951
EBGM	1.293	0.917	0.979
EB95	1.635	1.038	1.007

Comments:

From: "Nair, Narayan" [redacted]
To: "Menschik, David" [redacted]
Subject: RE: Data mining limitations
Date: Thu, 26 Oct 2023 18:57:32 -0000
Importance: Normal

Thanks for this info

Narayan

From: Menschik, David [redacted]
Sent: Thursday, October 26, 2023 2:29 PM
To: Nair, Narayan <Narayan.Nair@fda.hhs.gov>
Subject: Data mining limitations

Here's the slide deck I presented to CDC shortly after the first EUAs for COVID vaccines…

From: "Nair, Narayan" [redacted]
To: "Menschik, David" [redacted], "Alimchandani, Meghna" [redacted], "Zinderman, Craig E" [redacted]
Cc: "Baer, Bethany" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Fri, 10 Sep 2021 16:01:32 -0000
Importance: Normal

Good idea to add this language.

Narayan

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 7:58 AM
To: Nair, Narayan [redacted]; Alimchandani, Meghna [redacted]; Zinderman, Craig E [redacted]
Cc: Baer, Bethany [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

FYI
(expanded data mining limitation section to address potential concern regarding year-stratification and potential masking of class effects, etc.)

From: Menschik, David
Sent: Friday, September 10, 2021 7:53 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi Hannah,

Bethany and I have edits for the data mining limitations section on page 13 of the attached draft manuscript. Please see attached and glad to discuss if any questions.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, September 09, 2021 3:44 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Sounds like a plan!

Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 9, 2021 3:41 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Thanks – working with Bethany now on new data mining limitation language and will share with you in near future.
I'll wait to run changes by my leadership for clearance until you advise me that no further substantive edits are forthcoming prior to submission.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, September 09, 2021 3:33 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Definitely
Here's the latest version – the discussion has gotten a little messy so if you can excuse some of the part that is clearly still in revision.

Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 9, 2021 3:01 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Thanks Hannah!
Given the current stage of the manuscript, would we be able to add an additional data mining limitation to the manuscript?
Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, September 09, 2021 2:20 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Dear David,
Thanks so much for writing. The manuscript has moved through CDC clearance rather quickly but we've decided to revise some of the analysis about reported deaths to make it more meaningful/interpretable.
Will definitely send you an updated version of the manuscript as this evolves.

Thanks so very much for your continued engagement on this,

Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 9, 2021 1:32 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi Hannah,

Hope all well on your end. Wondering if there is any status update for this manuscript?

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, August 05, 2021 2:48 PM
To: Baer, Bethany [redacted]
Cc: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Excellent!! I hope you had a nice leave. On my end, we're ***almost*** through the CDC clearance process – will keep you posted!

Hannah

From: Baer, Bethany [redacted]
Sent: Thursday, August 5, 2021 2:44 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Menschik, David (FDA/CBER) [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi Hannah,
I was on leave for several weeks, so I realize my response is a little delayed. I have caught up on the email exchanges between you and David. I have reviewed the manuscript you sent on July 21st and the minor changes you mentioned in the email below. I, Bethany Baer, approve submission of the manuscript titled 'Reactogenicity and Adverse Events during the First Six Months of mRNA COVID-19 Vaccination in the United States: A Prospective Observational Study of Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe ' to clearance and to journal publication."

Thank you for all of your hard work on this!
Bethany

From: Menschik, David [redacted]
Sent: Thursday, July 29, 2021 3:37 PM
To: Rosenblum, Hannah (CDC) [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi Hannah,

I agree that these are not substantive changes and will send you the authorship agreement statement shortly.

Thanks so much to you and other teammates for all the amazing work on this very impressive paper!

Congratulations on this key milestone!
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, July 29, 2021 3:33 PM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks for asking and sorry I didn't write to you about this earlier.
Several small changes were made since you saw the draft (and I'm not sure what you consider substantive so I'll just list them all here):

1. A previously supplemental table about impressions of deaths was moved to a main table (Table 4)
2. The previous table 9 had duplicate data as Figure 2 so that table was moved to supplemental
3. We split 'serious reports' and 'non serious reports' by meddra PT code in Table 2 to more accurately reflect the breakdown.
4. A sentence was added in the discussion stating that the serious /nonserious report distribution is similar to other adult vaccines (since there was concern that we didn't include enough about adverse events in the discussion).

Thank you so so much for all of your responses, feedback and work on this.
Warm regards,
Hannah

From: Menschik, David [redacted]
Sent: Thursday, July 29, 2021 3:26 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Baer, Bethany (FDA/CBER) [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Thanks Hannah! Can you please confirm that there were no substantive edits since the version cleared at FDA (or else share these edits)?

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, July 29, 2021 3:22 PM
To: Gee, Julianne M (CDC) [redacted]; Liu, Ruiling (CDC) [redacted]; Marquez, Paige L (CDC) [redacted]; Zhang, Bi C (CDC) [redacted]; Strid, Penelope (CDC) [redacted]; Abara, Winston E (CDC) [redacted]; Mcneil, Michael M (CDC) [redacted]; Myers, Tanya R (CDC) [redacted]; Hause, Anne M (CDC) [redacted]; Menschik, David [redacted]; Baer, Bethany [redacted] Su, John (CDC) [redacted]; Shimabukuro, Tom (CDC) [redacted]; Shay, David K (CDC) [redacted]
Subject: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Importance: High

Dear co-authors,

Thank you so much for all of your hard work and feedback on the 6 month safety review manuscript. The manuscript has been revised based on all of your feedback, and we're in a good position to submit to CDC clearance.

Please double check your names/degrees to make sure I haven't made any mistakes and that you are listed appropriately.

If you agree with submission of the draft in its current form, please reply with "I, **NAME**, approve submission of the manuscript titled 'Reactogenicity and Adverse Events during the First Six Months of mRNA COVID-19 Vaccination in the United States: A Prospective Observational Study of Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe ' to clearance and to journal publication."

We are planning to submit to the journal *Lancet ID* and the formatting of the draft matches their requirements.

All the very best,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

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

From: "Nair, Narayan" [redacted]
To: "Su, John (CDC/NCEZID/DHQP)" [redacted], "Bazel, Samaneh" [redacted]
Cc: "Shimabukuro, Tom (CDC)" [redacted]
Subject: RE: [EXTERNAL] RE: FDA coauthor for tinnitus paper
Date: Fri, 27 Oct 2023 19:03:47 -0000
Importance: Normal

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

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

Narayan

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

Hi folks,

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

- John

From: Su, John (CDC/NCEZID/DHQP)
Sent: Thursday, October 26, 2023 9:10 AM

To: Maro, Judy [redacted]; Yih, Katherine [redacted]
Cc: Shimabukuro, Tom (CDC/NCEZID/DHQP) [redacted] Moro, Pedro (CDC/NCEZID/DHQP) [redacted]; Nair, Narayan (FDA/CBER) [redacted]
Subject: RE: FDA coauthor for tinnitus paper

Hi Judy,

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

- John

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

Hi Judy,

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

- John

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

Hi John –

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

So, one would need

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

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

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

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

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

Best
Judy

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

Hi Judy,

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

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

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

- John

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

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

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

Happy to help in any way I can,

Best
Judy

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

Sounds great – thanks!

- John

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

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

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

Hi Katherine,

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

- John

SMR1.Point32Health.org made the following annotations

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From: "Nair, Narayan" [redacted]
To: "Woo, Jane" [redacted], "Baumblatt, Jane" [redacted], "Alimchandani, Meghna" [redacted], "Niu, Manette" [redacted], "Thompson, Deborah" [redacted], "Blanc, Phillip" [redacted], "Mba-Jonas, Adamma (CBER)" [redacted], "Zinderman, Craig E" [redacted]
Subject: RE: FDA-CDC Coordination Call 10-28-21
Date: Fri, 29 Oct 2021 12:01:01 -0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-update_92121_forclearance_clean.docx

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This is the last version I saw.

Narayan

From: Woo, Jane [redacted]
Sent: Friday, October 29, 2021 7:57 AM
To: Baumblatt, Jane [redacted]; Nair, Narayan [redacted]; Alimchandani, Meghna [redacted]; Niu, Manette [redacted]; Thompson, Deborah [redacted]; Blanc, Phillip [redacted]; Mba-Jonas, Adamma (CBER) [redacted]; Zinderman, Craig E [redacted]
Subject: RE: FDA-CDC Coordination Call 10-28-21

Thank you! Will someone please send me a copy of the 6-month summary of mRNA vaccines? We're preparing to write one for Janssen, and it would be helpful to see the scope and methods.

I hope everybody has a good weekend!

From: Baumblatt, Jane [redacted]
Sent: Thursday, October 28, 2021 5:39 PM
To: Nair, Narayan [redacted]; Alimchandani, Meghna [redacted]; Niu, Manette [redacted]; Thompson, Deborah [redacted]; Blanc, Phillip [redacted]; Mba-Jonas, Adamma (CBER) [redacted]; Woo, Jane [redacted]; Zinderman, Craig E [redacted]
Subject: FDA-CDC Coordination Call 10-28-21

All,
meeting notes from tonight

-Tom gave an update on his ACIP presentation, includes info on VAERS, myocarditis analysis,
-VSD analytic strategy for ages 5-11, reference slide on prespecified outcomes being studied, including chart review for myo/pericarditis.
-CISA's role, BEST role
-Matt Oster is going to present his presentation on myocarditis at ACIP
- Surveillance review of 6 months of mRNA vaccines paper submitted to Lancet ID (David M. and Bethany B. are coauthors)
-Myocarditis post mRNA paper being finalized for resubmission to JAMA
-No VaST meeting on Monday, next meeting Nov 8

-Narayan explained that authorization for ages 5-11 for Pfizer is imminent. Our plan for surveillance is to do daily reviews for all serious reports for kids initially.
-CDC will be focusing on myo/pericarditis using their case definition, and also look at other AESIs
-FDA may run some of the J&J myo/pericarditis cases by CDC which are uncertain as to meeting case definitions
-J&J myo/pericarditis dose 1 cases were 121 cases total as of 10/21/21, 57 verified, 44 met case definition

-To end on a crazy note, Steve Kirsch wrote an editorial saying John Su should be fired…. smh

Thanks!
Jane

Jane

From: "Nair, Narayan" [redacted]
To: "Thompson, Deborah" [redacted] "Alimchandani, Meghna" [redacted] "Welsh, Kerry" [redacted] "Jason, Christopher" [redacted], "Bazel, Samaneh" [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke
Date: Tue, 28 Feb 2023 16:12:18 -0000
Importance: Normal
Attachments: VAST_20230227_Forshee_Slides_draft_confidential.pdf
Inline-Images: image007.png; image008.png; image009.jpg; image010.jpg; image011.jpg; image012.jpg; image013.jpg

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Thanks Deb for sharing this. I will let leadership know. The last update I had from the VSD was that the signal had been attenuating. For BEST, there has been intense interest in this potential safety issue. I have attached some slides that provide detailed data. There has been no signal found in multiple data bases for non-hemorrhagic stroke. In addition, to BEST, the VA and Foreign active surveillance databases have not found anything related to stroke. However, they are planning a dedicated epi study to evaluate this.

Please don't share the slides.

Narayan

From: Thompson, Deborah [redacted]
Sent: Tuesday, February 28, 2023 10:55 AM
To: Nair, Narayan [redacted]; Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted]
Subject: Data Mining for Pfizer Bivalent: Ischemic Stroke

Hi Narayan, Meghna, Kerry, Chris, and Sam,

While doing my weekly surveillance review for the Pfizer bivalent COVID-19 vaccine, ischemic stroke appeared as a new data mining finding with an EB05>2 for US serious, although the EB05=1.01 for overall US:

Drug	Event	US EB05 20230224	US Serious EB05 20230224	US Fatal EB05 20230224	US Infant EB05 20230224	US Child EB05 20230224	US Teen EB05 20230224	US Adult1 EB05 20230224	US Adult2 EB05 20230224	US Adult3 EB05 20230224	US Female EB05 20230224	US Male EB05 20230224
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Incorrect product formulation	1.965			6.099	3.335	2.815	2.022	1.232	0.909	1.849	1.969
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	1.01	2.056	0.855				0.707	0.53	1.029	0.807	0.98
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Off label use	2.773	0.977	0.86		0.62	0.654	1.275	1.788	3.074	2.609	1.969
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Product preparation error	1.91			0.564	1.227	1.063	5.39	1.103	1.525	1.36	2.205
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Product use issue	2.844	1.047	0.854		0.53	0.743	1.381	2.534	2.384	2.569	1.964

The QQ-LL report for Pfizer bivalent for ischemic stroke shows a total of 53 reports (41 US and 12 foreign).

Among the 41 US reports:

- 39 (95.1%) non-fatal serious/OMIC reports and 2 (4.9%) death reports
- 19 (46.3%) females and 22 (53.7%) males
- Median age=69 years (range=20-90 years)
- Median onset=21 days post-vax (range=0-128 days)
- US reporting rate=1.19 reports per million doses administered (CDC COVID Data Tracker: Vaccinations in the US)

I've also attached the recent IR response from Pfizer, which evaluated thromboembolic events (TEE) following the Pfizer bivalent vaccine and concluded that there is no evidence that TEE, including ischemic stroke, are a safety signal or risk of the bivalent vaccine.

I'm wondering if you are aware of any updates from CDC VSD or BEST on the monitoring/assessment of ischemic stroke following the Pfizer bivalent vaccine?

Please let me know if you have any questions or need any additional information.

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
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Update on Original COVID-19 Vaccine and COVID-19 Vaccine, Bivalent Safety

Richard Forshee
Deputy Director, FDA/CBER/OBPV

VaST
February 27, 2023

PSI-HHS-000001160423

Outline

- **CBER Active Surveillance Program (BEST Initiative)**
- Bivalent COVID-19 mRNA Vaccines Safety Surveillance
- Conclusion

BEST Initiative Data Sources

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

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

Rapid Cycle Analysis (RCA) Data Sources

Claims Data Source	Age (years)	Population Enrolled (million)
CMS Medicare	65+	36
DP 1	0-4 5-17 18-64	1.2 3.1 14.8
DP 2	0-4 5-17 18-64	1.0 2.6 11.6
DP 3	0-4 5-17 18-64	1.4 3.7 17.1

Immunization Information Systems (IIS)

- Confidential, population-based, computerized databases that record immunization doses administered by participating providers to persons in U.S. public health jurisdictions
- Supplements claims-based COVID-19 vaccine administration data
- Undercapture of COVID-19 vaccines in claims databases due to vaccines administered without insurance reimbursement

Phases of Vaccine Active Surveillance

Descriptive Monitoring provides descriptive statistics of vaccine doses and selected adverse events.

Signal Detection performs sequential testing, while vaccine doses accumulate, to identify potential safety risks early; does not prove causal relationship.

Signal Evaluation uses more robust study designs to evaluate potential safety signals.

Outline

- CBER Active Surveillance Program (BEST Initiative)
- **Bivalent COVID-19 mRNA Vaccines Safety Surveillance**
- Conclusion

COVID-19 Bivalent mRNA Vaccines Rapid Cycle Analyses

Administered Doses By Age Group

Age Groups (years)	BNT162b2 (# vaccinations)	mRNA-1273 (# vaccinations)	Total (# vaccinations)
5/6-17[1]	196,992	13,016	210,008
18-35[1]	442,870	211,694	654,564
36-64[1]	1,248,430	654,220	1,902,650
65+[2]	4,265,244	3,042,074	7,307,318

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

COVID-19 Bivalent mRNA Vaccines Safety Monitoring

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

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

FDA Adverse Events Monitored

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

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

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

Signals Detected

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

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

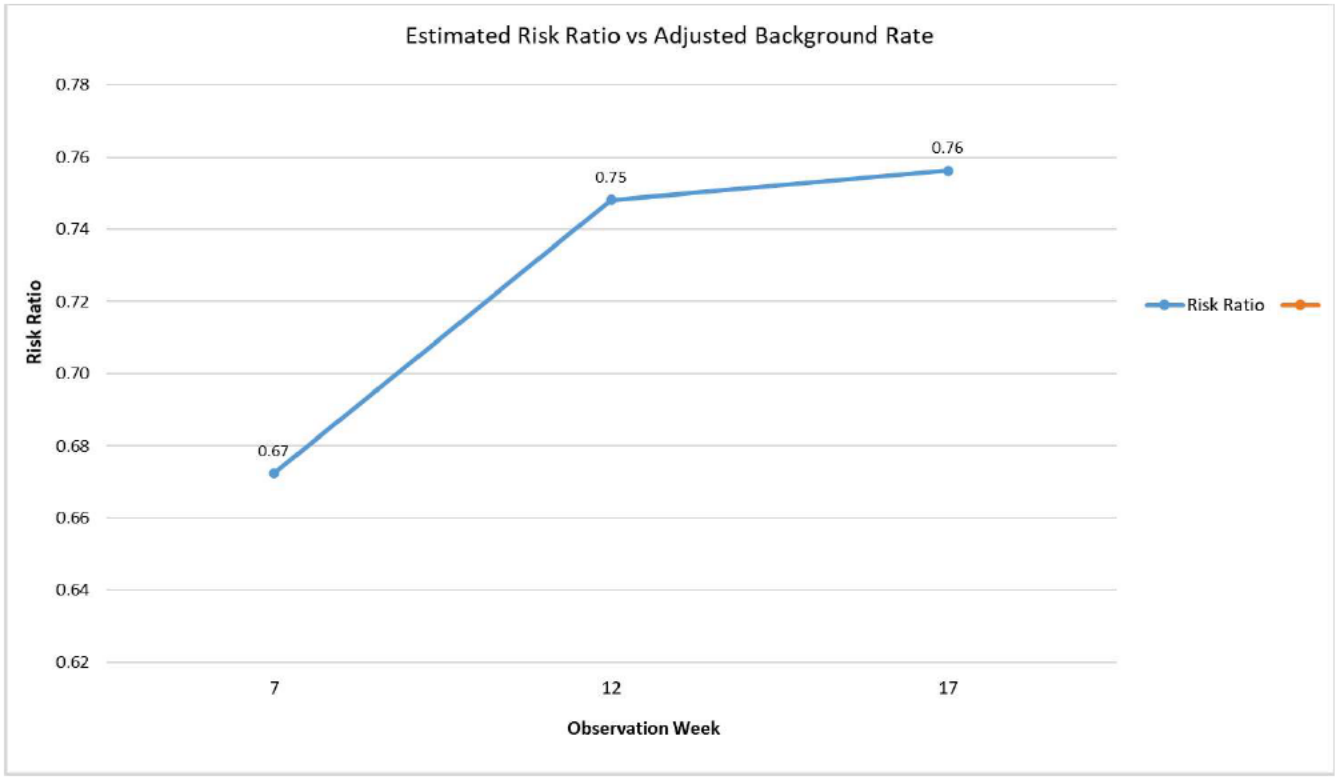
AEs and the associated vaccine brand with a safety signal are noted.

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

Adverse Events that Completed Surveillance Period

Adverse Event (AE)	Ages 65+ years
Acute Myocardial Infarction	BNT162b2, mRNA-1273
Deep Vein Thrombosis	BNT162b2, mRNA-1273
Bell's Palsy	BNT162b2
Common Site Thrombosis with Thrombocytopenia	BNT162b2
Non-Hemorrhagic Stroke	BNT162b2, mRNA-1273
Pulmonary Embolism	BNT162b2

Risk Ratio Non-hemorrhagic Stroke for Pfizer Bivalent Compared to Historical Rates (2019)



We reached the maximum length of surveillance without a signal

Concomitant Influenza Vaccination

- Approximately 4.25 million doses of the Pfizer-BioNTech bivalent vaccine have been administered in the CMS database in individuals 65 years and older
- 38% of the Medicare recipients who received a Pfizer bivalent COVID-19 booster received a seasonal influenza vaccination on the same day
- 78% received a seasonal influenza vaccination within +/- 42 days
- Further work to be done to segment out the different influenza vaccine types administered with the COVID-19 vaccines
- No signal seen at this time for non-hemorrhagic stroke

COVID-19 Bivalent mRNA Vaccines RCA

Summary

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

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

1) No excess reports of stroke from VAERS
2) CMS database with about 4.25 million doses shows no increase in stroke
3) VA database run shows no increase in stroke on preliminary query
4) Various countries in Europe as well as Israel indicate no increased risk of stroke in their surveillance systems
5) Pfizer notes no increase in signal in their global safety database or when comparing the monovalent to bivalent vaccines

In any case, a formal epidemiologic study is being initiated by FDA to prepare for potential vaccine coadministration in 2023-2024

U.S. FOOD & DRUG ADMINISTRATION

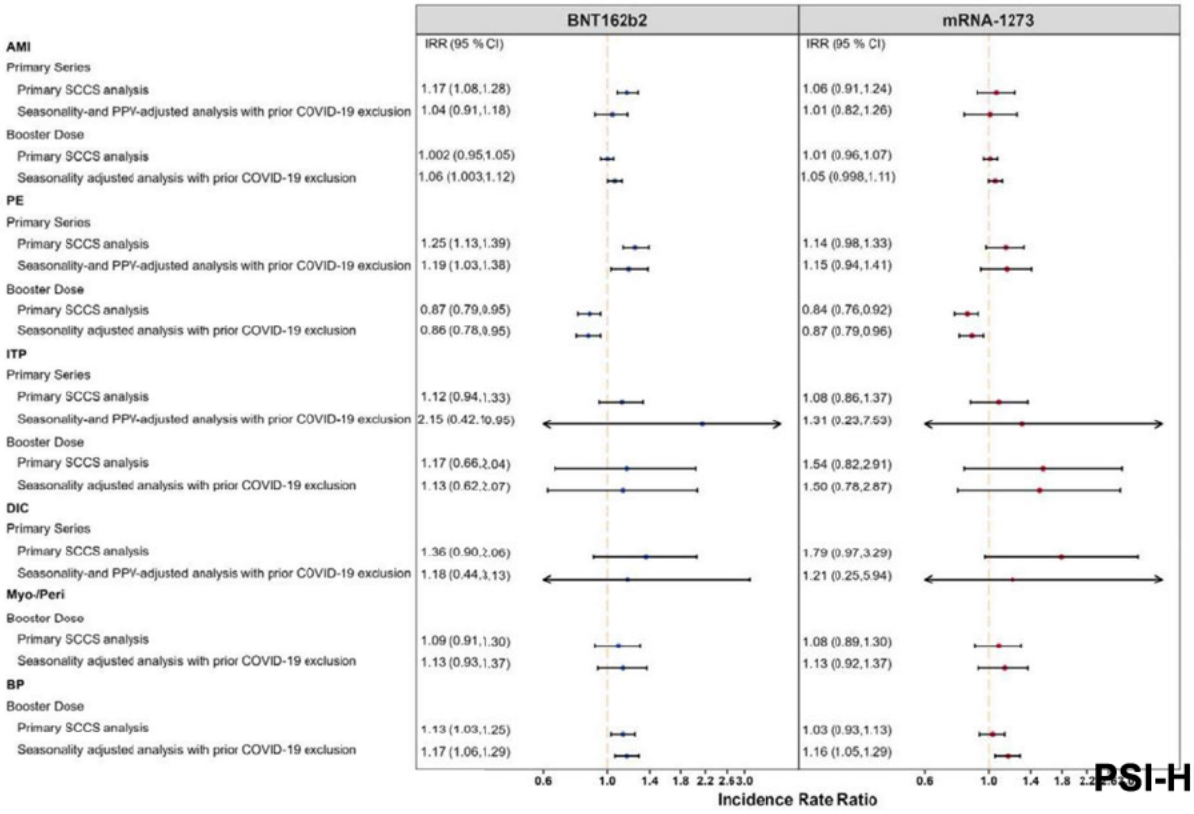
Self-Controlled Analysis of Potential Adverse Events

PSI-HHS-000001160439

Self-Controlled Analysis of AEs Identified in Sequential Analysis

- "Evaluation of Potential Adverse Events Following COVID-19 mRNA Vaccination Among Adults Aged 65 Years and Older: A Self-Controlled Study in the U.S"
- Available at: https://doi.org/10.1101/2023.01.19.23284803

Forest Plot of Results



Conclusion

- We did not find an increased risk for AMI, ITP, DIC, and Myo/Peri;
- The results were not consistent for PE;
- There was a small elevated risk of BP after exposure to COVID-19 mRNA vaccines.
- These results support the favorable safety profile of COVID-19 mRNA vaccines administered in the elderly.

Acknowledgements

- Steven A. Anderson
- CBER Surveillance Team: Azadeh Shoaibi, Hui-Lee Wong, Tainya C. Clarke, Joyce Obidi, Joann F. Gruber, Patricia C. Lloyd, Sylvia Cho
- CBER OBPV
- Federal Partners: CMS, VA, CDC
- FDA Partners: Acumen, Blue Health Intelligence, CVS Health, HealthCore, IBM, IQVIA, OHDSI, Optum, RTI Health Solutions

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Subject: [EXTERNAL] VaST - Draft minutes and report from February 13, 2023 (CONFIDENTIAL)

Date: Fri, 17 Feb 2023 13:01:47 +0000

Importance: Normal

Attachments: 2023-02-13_-_VaST_minutes_draft_confidential.docx; 2023-02-13_-_VaST_Report_and_Data_Table_draft_confidential.docx

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sender and know the content is safe.

Dear VaST members and participants,

Attached are the draft minutes and report from the VaST call this week. Please let us know if there are any corrections or edits.

Reminder - there is an ACIP meeting next week. The COVID-19 vaccine session is February 24.
The specific talks in the COVID-19 session are not included in the posted agenda, but vaccine safety data will be presented and there will be a short VaST assessment.

Regards and many thanks to all,
Lauri Markowitz and Melinda Wharton

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

VaST meeting notes
February 13, 2023
Confidential - DRAFT

Presentations and verbal updates are briefly summarized in meeting notes. Chat notes not answered verbally on the call are available and some have been incorporated into the minutes.

Participants
Workgroup members: Matt Daley, Kathy Edwards, Grace Lee, Bob Hopkins (NVAC-chair), Lisa Jackson, Veronica McNally, Jennifer Nelson, Laura Riley, Rob Schechter, Keipp Talbot (VaST chair), Pat Whitley-Williams

Ex officio and liaison participants: Tatiana Beresnev (NIH), Matthew Clark (IHS), Karen Farizo (FDA), Jeff Kelman (CMS), Valerie Marshall (HHS), Timothy Styles (HRSA)

Federal Partners: Margaret Ryan (DoD)

CDC: Karen Broder, Monica Godfrey, Rita Helfand, Jessica MacNeil, Lauri Markowitz (CDC Co-lead), Paige Marquez, Pedro Moro, Sara Oliver, Sierra Scarbrough, Martha Sharan, David Shay, Tom Shimabukuro, John Su, Evelyn Twentyman, Eric Weintraub, Melinda Wharton (CDC Co-lead), Jared Woo

Technical SMEs: Steve Anderson (FDA), James Donahue (VSD), Rich Forschee (FDA), Kristin Goddard (VSD), Kayla Hanson (VSD), Nicky Klein (VSD), Ned Lewis (VSD), Yun Lu (FDA), Azadeh Shoaibi (FDA), Ousseny Zerbo (VSD)

Agenda
COVID 19 mRNA bivalent booster vaccine safety, Dr. Tom Shimabukuro and Dr. Nicky Klein

Administrative issues and announcements - Co-chairs and Co-leads
- Reminders about COI and confidentiality
- ACIP meeting February 22-24 – COVID-19 session on Friday, February 24
- Doses distributed: 958,658,535; Doses administered: 670,306,507 (last updated: February 9)
  - Doses distributed: Pfizer-BioNTech: 578,036,915; Pfizer-BioNTech(bivalent): 77,808,240; Moderna: 348,034,020; Moderna (bivalent): 36,978,000; Janssen/J&J: 31,502,000; Novavax: 1,085,600; Other: N/A
  - Doses administered: Pfizer-BioNTech: 399,620,284; Pfizer-BioNTech(bivalent): 33,740,344; Moderna: 250,820,655; Moderna (bivalent): 19,131,358 Janssen/J&J: 18,971,123; Novavax: 77,551; Other: 816,894
  - At least one dose: 269,208,743; Primary series: 229,820,324; Bivalent booster dose: 52,499,720
  - These data are posted on the CDC website and are updated regularly (https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total).

COVID 19 mRNA bivalent booster vaccine safety – Dr. Tom Shimabukuro (CDC) and Dr. Nicky Klein (VSD)
Dr. Klein presented an updated analysis of the signal for ischemic stroke/transient ischemic attack (TIA) following bivalent Pfizer-BioNTech booster vaccination in VSD for the ACIP presentation on February 24. The RCA signal was first detected in November 2022 (rate ratio >4) and the rate ratio has slowly attenuated, reaching 1.36 recently, and only intermittently meeting signal criteria. The supplemental

analysis comparing bivalent boosted to un-boosted concurrent comparators showed a rate ratio of 1.07 (95% CI: 0.89–1.28). Post-signal analysis evaluating concomitant high-dose or adjuvanted flu vaccine showed a rate ratio of 1.65 (95% CI 1.02–2.72; p-value 0.04). Bivalent Pfizer-BioNTech booster vaccination without concomitant flu vaccine showed a rate ratio of 1.19 (95% CI 0.87 – 1.62). Supplemental analyses suggested comparison interval (22–42 days) rates were lower than expected. The conclusions and discussion noted possible unmeasured confounding that could be contributing to these findings.

Discussion and questions

1. In the chart reviewed cases, was co-administration with high dose or adjuvanted flu vaccine?
   - Nearly all of the confirmed cases that had co-administration were co-administered with high dose.
2. Why were the risk intervals defined as 1-21 days and 22-42 days when cases cluster 11-22 days after vaccination?
   - The risk interval of 1-21 days and 22-42 days have been the standard risk intervals for VSD. The clustering/graphs are done after the signal was identified. The RCA is not designed to be a definitive study; further work to address this can be done in a follow-up study.
   - The temporal analysis has never crossed day 21.
3. Are there data on race/ethnicity, realizing that the absolute numbers are small.
   - There are race/ethnicity data on the cases in the back-up slides.
4. Were chart reviews done on all patients with a stroke outcome?
   - No, only the cases identified in December in the clustering interval in KPNC. VSD is planning to review a random sample of chart reviews across sites (~100 patients).
5. VaST members discussed providing context around the VSD signal for presentation to ACIP. It was suggested to include data from other surveillance systems and that FDA presentation will immediately follow the VSD presentation at ACIP.
   - It needs to be noted that VSD definition of stroke includes TIA and FDA does not.
6. Are there any proposed hypotheses for non-causal association?
   - There are additional considerations regarding non-causal association on slide 25.
7. What are the vaccination coverage rates for CMS data?
   - In VSD coverage is ~47% and in the FDA analysis CMS coverage appears to be much lower. FDA will have coverage numbers for FFS Medicare ready for ACIP.

Combined Systems Safety Monitoring Report
February 13, 2023
Confidential – DRAFT

The VaST session on February 13, 2023 included an update of the Vaccine Safety Datalink (VSD) ischemic stroke/transient ischemic attack (TIA) signal assessment and a preview of findings for the February ACIP meeting next week.

Background: VaST first reviewed VSD data on the ischemic stroke/TIA signal at the January 9, 2023 VaST call. Those data were through December 31, 2022. At that call, VaST also heard a verbal report that in the CMS rapid cycle analysis there was no statistical signal for ischemic stroke after bivalent Pfizer-BioNTech or Moderna COVID-19 booster vaccination. Also, in a verbal report from the VA rapid cycle analysis, there was no statistical signal for ischemic stroke/TIA after bivalent Pfizer-BioNTech or Moderna COVID-19 booster vaccination. Data from VSD and from CMS were presented to VRBPAC on January 26.

VSD analyses have been updated with data through February 4, 2023. Some of the previous presentation and analyses were modified following feedback from VaST at the January call.

Ischemic stroke in ≥ 65-year age group

- In the VSD rapid cycle analysis, there is a statistical signal (detected November 27, 2022) for ischemic stroke/TIA after bivalent Pfizer-BioNTech COVID-19 booster vaccination during the 1–21 days (risk interval) after vaccination vs. a comparison period of 22–42 days after vaccination. The rate ratio has slowly attenuated from 1.92 to 1.36 and recently has only intermittently met signaling criteria.
  - There was temporal clustering of ischemic stroke/TIA codes in days 13–22 following receipt of the bivalent Pfizer-BioNTech COVID-19 booster vaccine.
  - Among 24 intial cases from the Kaiser Permanente Northern California that were chart reviewed, 22 were confirmed as incident cases.
  - In a secondary analysis, when the comparison group was drawn from persons eligible to receive a bivalent Pfizer-BioNTech COVID-19 booster dose but had not received it, there was no statistical signal for ischemic stroke/TIA (adjusted rate ratio 1.07).
  - Supplemental analyses suggest comparison interval (22–42 days) rates were lower than expected.
  - There was no statistical signal for ischemic stroke/TIA 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.
- During the sample chart review of cases in the risk interval, it was noted that many adults aged ≥ 65 years had concomitant administration of bivalent Pfizer-BioNTech COVID-19 booster vaccine and influenza vaccine (most received high-dose).
  - Analyses evaluating concomitant administration of bivalent Pfizer-BioNTech COVID-19 booster vaccine and high-dose or adjuvanted influenza vaccine showed a rate ratio of 1.65 (95% CI 1.02–2.72; p-value 0.04).
  - Analyses evaluating bivalent Pfizer COVID-19 booster vaccination without concomitant high-dose or adjuvanted influenza vaccine showed a rate ratio of 1.19 (95% CI 0.87–1.62).

- Separate analyses did not detect an elevated rate ratio for ischemic stroke/TIA after influenza vaccine alone.

Ischemic stroke in 18–64-year age group

- In the rapid cycle analysis, there was no statistical signal for ischemic stroke/TIA after bivalent Pfizer-BioNTech COVID-19 booster or bivalent Moderna COVID-19 booster vaccination.

Myocarditis following bivalent COVID-19 booster vaccination

- While not part of the primary presentation to VaST, back-up slides included data on myocarditis/pericarditis. VaST noted that there were limited doses administered to males in the age groups of most interest (30–39 years: n=82,191 doses; 18–29 years: n=50,687 doses; 12–17 years: n=48,066 doses). There was one case in a male (18–29 year age group) and no cases in females.

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 has been attenuating over time. A signal has not been observed in two other active vaccine safety monitoring systems in the United States, nor in data from other countries. The US systems differ from each other in their definition of stroke (VSD includes TIA while CMS does not) and comparitor groups.
- Previous surveillance in the VSD and other systems found no evidence of increased risk of ischemic stroke/TIA after the primary series or monovalent COVID-19 booster vaccines for either Pfizer-BioNTech or Moderna products.
- VaST would like to see other data on concomitant administration of bivalent COVID-19 booster and influenza vaccination. It is unclear whether the increased rate ratio is due to one or the other vaccines, to concomitant administration, or to other factors such as unmeasured confounding.
- VaST highlighted several areas for further exploration:
  - Assess the impact of concomitant/recent respiratory viral infections (e.g., COVID-19, influenza) on risk of ischemic stroke/TIA.
  - The presentation highlighted some potential drivers for the observed lower incidence of ischemic stroke/TIA in the vaccinated comparator group, which could be contributing to the increased rate ratio. These should be explored further.
- VaST will continue to review data from additional analyses planned from VSD, CMS and the VA.
- Current data in VSD, based on small numbers, do not raise additional concerns about myocarditis following bivalent COVID-19 booster vaccination.

Table 1. COVID-19 vaccine monitoring systems reviewed by the VaST – Pfizer BioNTech (recommended for use in persons age ≥ 6 months)

Red indicates updated or new data this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Population data through 1/23/22	All health events, adverse events of special interest[a]	US population	313.0 million Pfizer-BioNTech doses administered	Descriptive and empirical Bayesian data mining and other		Anaphylaxis associated with vaccination, first detected by reports from UK and early reporting in the US; assessed by follow-up with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021)
6 month-4 year primary series data through 7/31/22	All health events, adverse events of special interest[a]		692,485 doses administered		321 VAERS reports, 6 serious • Fever was the most frequently reported AE • Administration errors were the next most frequently reported AE	Additional data needed VaST members expressed concerns about administration errors, how to prevent them
5–11-year-old primary series data through 4/24/22	All health events, adverse events of special interest[a]		17,859,728 doses administered		9,001 reports; 97% non-serious • Median age 8 years • Sex: 47% male; 47% female 20 verified myocarditis reports • Overall reporting rate: 0.94 per 1 million doses administered • < 1 per million for males following dose 1 and females following dose 1 and 2 • 2.2 per million for males following dose 2	No concerns raised

5–11-year-old first booster dose data through 7/31/22	All health events, adverse events of special interest[a]		466,716 booster doses administered		581 reports; 99% non-serious • Median age 9 years • Sex: 51% male; 47% females Administration errors are the most common reports	No concerns raised
First booster dose data for persons aged ≥12 years through 4/11/22			93,118,318 1st mRNA COVID-19 booster vaccinations administered		47,014 non-serious reports following 1st booster of mRNA COVID-19 vaccination • Headache, pyrexia, and pain: 3 most common non-serious 5,049 serious reports following 1st booster mRNA COVID-19 vaccination	No concerns raised
Second booster dose data for persons aged ≥50 years through 7/10/22			16,961,827 2nd mRNA COVID-19 booster vaccinations administered		8,073 non-serious reports following 2nd booster mRNA COVID-19 vaccination • COVID-19, fatigue, and headache: 3 most common non-serious 442 serious reports following 2nd booster mRNA COVID-19 vaccination	No concerns raised
Bivalent booster dose data for persons ≥ 12 years through 9/25/22	All health events, adverse events of special interest[a]		4.7 million persons aged 12+ years received Pfizer-BioNTech bivalent booster vaccination		1,236 non-serious reports following either mRNA bivalent booster dose • Vaccination errors were the most commonly reported AE (30%) 33 serious reports following either mRNA bivalent booster dose • 3 reports of myocarditis, 2 pericarditis, and 3 deaths	No concerns raised but further review needed after more doses administered
Co-administration data through 6/30/2022	All health events, adverse events of special interest[a]				1,663 reports following co-administration with a Pfizer-BioNTech vaccination 1,332 non-serious reports and 253 serious reports across both mRNA vaccines	No concerns raised but further review needed after more doses administered

					• 47 death reports – causes of death consistent with all-cause mortality for age groups	
Myocarditis/pericarditis first booster data through 5/26/22			93.4 million 1st mRNA COVID-19 booster vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-29 years in 7-day window following either booster dose exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 15.3 in males aged 12-15 years • 24.1 in males aged 16-17 years • 9.9 in males aged 18-24 years • 4.8 in males aged 25-29 years	There appears to be some risk of myocarditis/pericarditis after a booster dose. Further analyses ongoing.
Myocarditis/pericarditis primary series data through 5/26/22			398.4 million mRNA COVID-19 primary series vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-49 years in 7-day window following dose 2 exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 38.9 in males aged 18-24 years • 15.2 in males aged 25-29 years • 7.5 in males aged 30-39 years • 3.3 in males aged 40-49 years	Warning added to EUA fact sheets June 25, and information provided in update of CDC's clinical guidance and MMWR article. Information included in FDA materials after full approval on Aug 22. Further work being done to define myocarditis risk.
Myocarditis/pericarditis 5–17-year-old primary series data through 5/26/22			54.9 million doses administered (Dose 1: 27.7; Dose 2: 23.3; Dose 3: 3.8 million)		972 preliminary myocarditis reports 635 verified reports met the CDC case definition for myocarditis. • .2 reporting rate, males aged 5-11 years following dose 1	No new concerns raised

					• 2.6 reporting rate, males aged 5-11 years following dose 2	
MOVING data for persons aged 12-29 years presented on 12/12/22					60 myocarditis patients interviewed, across all vaccines, 1-year post-myocarditis dx 63 physicians interviewed, across all vaccines, 1-year post-myocarditis dx 83% of healthcare providers indicated the patient was fully or probably recovered	Further follow-up needed
Tinnitus and hearing loss data through 11/6/22					7,026 tinnitus reports to VAERS • 21.6 reports per million doses administered (18+ years) 197 sudden hearing loss reports • 0.6 reports per million doses administered (18+ years) 949 reports of 'permanent disability' and 157 reports of 'hospitalization' for tinnitus or sudden hearing loss	No concerns raised
Pregnancy data through 7/29/22					4,487 pregnancy-related reports to VAERS (2,424 after Pfizer). Safety profile of pregnancy reports after COVID-19 vaccines appears reassuring, and primary series reports are comparable to booster doses.	No concerns raised

GBS data through 1/28/22					104 verified cases of GBS following Pfizer-BioNTech vaccination • Median age: 57.5 years • Hospitalized: 96 • Deaths: 3 Observed number of confirmed GBS reports lower than than expected.	No concerns raised
Death reporting rates data through 11/17/21					For each vaccine, across all sex and age groups, the observed reporting rate for death events was much lower than the number of expected all cause deaths	No concerns raised
Menstrual irregularties data through 1/7/22					558 reports of post-menopausal bleeding reported to VAERS after COVID-19 vaccine (239 after Pfizer). Few PMB cases were classified as serious VAERS reports (3 reported after Pfizer).	No concerns raised
VA ADERS Data through 4/03/2022	All health events	VA employees and Veteran patients	1.9M 1st doses 1.8M 2nd doses 848,841 booster doses	Descriptive	10.8% serious reports and 89.2% non-serious reports	No concerns raised
DoD VAERS Data through 12/31/2021	All health events, adverse events of special interest	Active duty and beneficiaries	4.1 million Pfizer-BioNTech vaccines administered	Descriptive	12 cases myocarditis/pericarditis after Pfizer-BioNTech dose 1 41 cases of myocarditis/pericarditis after Pfizer-BioNTech dose 2 • 111.5 cases per million in males aged 12-17 years • 52.6 cases per million in males aged 18-24 years • 21.5 cases per million in males aged 25-39 years Observed > expected in males (<17, 18-24, and 25-39) after dose 2	Follow-up and evaluation continuing

Indian Health Services (IHS) VAERS Presented on 2/06/23	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	724 total AVE reports • 488 medically attended health impact events	No new concerns raised
Active Surveillance						
V-safe Booster dose data through 4/10/22		Vaccinees who enroll	369,841 v-safe participants who received Pfizer-BioNTech primary series received booster doses (336,618 had Pfizer-BioNTech primary series)	Descriptive	Local and systemic reactions for persons aged 18+ years reported less frequently following booster dose than dose 2 for mRNA vaccines. Similar or slightly more reports or reactions among persons aged 12-17 years following booster compared to dose 2 for mRNA vaccines.	No concerns raised
5–11-year data (primary series) through 4/24/22					49,396 participants with a Pfizer-BioNTech vaccination • Injection site pain most frequently reported reaction • Reactions were more frequently reported after dose 2 than 1	No concerns raised
6 month-4 year data through 7/10/22		Vaccinees who enroll	14,036 v-safe participants who received Pfizer-BioNTech	Descriptive	Reactogenicity 6 months-2 years-olds: • 18.8% reported any injection site reaction following dose 1 and 18.3% following dose 2 • 55.7% reported any systemic reaction following dose 1 and 47.1% following dose 2 Reactogenicity 3-4 year-olds: • 38.3% reported any injection site reaction following dose 1 and 26.3% following dose 2	No concerns raised

					• 31.5% reported any systemic reaction following dose 1 and 29.6% following dose 2	
Pregnant women reactogenicity data through 2/13/22 Data through 4/10/22					6,338 pregnant participants reported a booster dose. • Patterns of reporting after receiving a booster dose while pregnant are consistent with the general population 5,052 pregnant participants reported homologous mRNA booster while pregnant. • Reporting frequency for some systemic reactions differ between dose 2 and booster dose, with some differences in frequency of reporting noted depending on whether participant was pregnant for both doses or only booster dose.	No concerns raised No concerns raised
Menstrual irregularities data through 1/22					63,815 people across all vaccines reported responses likely related to menstruation • Common themes: menstrual timing and menstrual severity.	No concerns raised
Bivalent booster dose data for persons ≥ 12 years through 9/25/22		Vaccinees who enroll	28,568 v-safe participants reported receiving Pfizer-BioNTech bivalent booster dose	Descriptive	Across both mRNA bivalent vaccines, reporting frequencies of reactions and health impacts were similar to those after 1st and 2nd booster vaccination Approximately one-third reported co-administration	No concerns raised but further review needed after more doses administered
Simultaneous booster and influenza vaccine study data through 5/1/22		Vaccinees who enroll	526,829 v-safe participants reported		60,390 participants: simultaneous Pfizer-BioNTech booster and influenza	No concerns raised but further review needed after more doses administered

			receiving Pfizer-BioNTech booster dose		vaccinations; 466,439 participants: Pfizer-BioNTech booster alone Injection site and systemic reactions slightly more frequent following simultaneously administered. No evidence of a difference in severity.	
V-safe Pregnancy Registry Data through 8/1/22		Vaccinees who enroll	22,944 participants enrolled across all vaccines	Descriptive	22,951 total pregnancies. Pregnancy and neonatal outcome frequencies support safety of the COVID-19 vaccination.	Phase 2 Infant and maternal follow-up through 12 months of age/pregnancy end to start soon.
Department of Veterans Affairs (VA) Active Surveillance System RCA data through 10/28/22	Pre-specified health outcomes[a]	Veteran Patients	2.0 million first doses administered; 1.9 million second doses administered	Descriptive; historical comparator analysis	The only signal is for anaphylaxis following dose 1 of Pfizer-BioNTech.	No new concerns raised
RCA booster dose data through 3/26/22	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	838,337 Pfizer-BioNTech booster doses administered	Descriptive; historical comparator analysis	No signals, including for myocarditis/pericarditis or anaphylaxis, but pericarditis cases observed among those ≥40 years	No concerns raised, but follow-up in other safety systems needed
Bivalent booster presented on 1/09/23	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	377k Pfizer-BioNTech bivalent doses administered	Descriptive; historical comparator analysis	No signals observed; rate ratio for ischemic stroke/TIA following Pfizer-BioNTech bivalent vaccine <1	No concerns raised
Target trial emulation data presented on 9/19/22	All-cause mortality	Eligible Veterans	228,130 patients reached end of follow-up (100,253 Pfizer-BioNTech)	Discrete time logistic regression	Day 8 and day 28 all-cause mortality are statistically similar across all vaccines Day 60 all-cause mortality is significantly different across all vaccines • 11% reduction in risk in vaccinated group	No concerns raised
Vaccine Safety Datalink (VSD) RCA data through 1/15/22	Pre-specified health outcomes[a]	Patients enrolled in participating	9.0 million doses of Pfizer-	Vaccinated concurrent comparison,	21-day risk interval - signaled	Further monitoring and analyses of other potential signals ongoing.

		health care organization	BioNTech administered	sequential analyses	• Myocarditis/pericarditis (combined dose 1&2 and dose 2 alone) • VTE (combined dose 1&2 and dose 2 alone) • AMI (dose 2) <u>42-days risk interval - signaled</u> • Myocarditis/pericarditis (dose 2) • Seizures (dose2)	
First booster dose data through 8/13/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	2.8 million patients ≥18 years 265k patients 12-17 years 94,791 patients 5-11 years	Vaccinated concurrent comparison, sequential analyses	No statistical signal for pre-specified outcomes for Pfizer-BioNTech boosters for patients aged 12+ years. • Myocarditis/pericarditis signal for combined Pfizer-BioNTech and Moderna analysis, elevated risk highest in adolescent and young adult males No statistical signal for pre-specified outcomes for booster doses across mRNA vaccines for patients aged 5-11 years.	Further monitoring and analyses of needed
Bivalent dose data through 12/31/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	1.6 million patients received Pfizer-BioNTech bivalent booster dose	Vaccinated concurrent comparison, sequential analyses	There was an elevated rate ratio for ischemic stroke/TIA in persons 18-64 years, but there was no signal	Further review and analysis is needed
Bivalent dose ischemic stroke updated analysis data presented on 2/13/23	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	580k patients received Pfizer-BioNTech bivalent booster dose	Vaccinated concurrent comparison, sequential analyses	There was a statistical signal for ischemic stroke/TIA in persons 65+ years; attenuated in recent weeks. • Rate ratio of 1.36 (CI: 1.05-1.76)	Further review and analysis is needed

					Bivalent Pfizer-BioNTech and same-day co-administration of high-dose or adjuvanted flu vaccine, RR = 1.65 (95% CI 1.02–2.72).	
VSD simultaneous and co-administered vaccine data through 10/8/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	~230,000 patients administered either bivalent mRNA booster		No analyses, only vaccine doses administered presented	No concerns raised but further review needed after more doses administered
6 month-4-year primary series data through 8/13/22	Pre-specified health outcomes[a]		31,784 first doses of Pfizer-BioNTech administered; 18,729 second doses of Pfizer-BioNTech administered		No statistical signals identified	No concerns raised
5–11-year primary series data presented 5/22			817,217 doses of Pfizer-BioNTech administered		No statistical signals identified	No concerns raised
First booster dose data through 8/20/22			2.9 million doses of Pfizer-BioNTech booster administered following Pfizer-BioNTech primary series ages 5 and older	Vaccinated concurrent comparison, sequential analyses	<u>0-7 days risk-window</u> • 7.21 (95% CI: 2.04-29.66) for myocarditis/pericarditis events in persons aged 12-17 years • 4.81 (95% CI: 1.55-16.81) for myocarditis/pericarditis events in persons aged 18-39 years <u>0-21 days risk window</u> • No point estimate (95% CI: 2.66-∞) for myocarditis/myopericarditis events in persons aged 40+ years <u>0-7 or 0-21 days risk window</u>	Finding consistent with past analyses

					• Rate ratios for **pericarditis** not significantly elevated among persons aged 40+ years	
Head-to-Head myocarditis/pericarditis presented on 1/15/22					Head-to-head comparisons: risk of myocarditis/pericarditis was higher after Moderna than after Pfizer. 1.61 adjusted rate ratio for persons aged 18-39 years	No new concerns raised
Tinnitus and hearing loss presented on 11/14/22			4,068,513 doses of Pfizer-BioNTech; 2,467,865 booster doses of Pfizer-BioNTech following mRNA vaccines	Tree-scan, *ad hoc* temporal scans and descriptive	No clusters of hearing-related outcomes for any tree scan analyses *Ad hoc* temporal scan analysis - most likely cluster starts on Day 33, ~12 days after dose 2 78/10,000 person-years after Pfizer-BioNTech	No concerns raised Tinnitus after vaccination similar to recent global background incidence estimate
Tree scan analysis data presented 5/2/22			4,068,513 doses of Pfizer-BioNTech; 1,142,736 booster doses of Pfizer-BioNTech following mRNA vaccines		Patients 12-17 years and 18-39 years had a signal for myocarditis/pericarditis, chest pain, and breathing abnormalities following dose 2 using the 7-day window.	No additional serious adverse events identified using this data mining approach
KPSEM data through 12/13/21			6,194 surveys completed for children aged 5-11 years		~1% of respondents reported tachycardia or chest pain 0-7 days following vaccination • No documented myocarditis cases in the medical records 6.9% reported 'other symptoms' following dose 1 and 1.3% reported seeking medical care for symptoms following dose 1	No concerns raised

					5.6% reported 'other symptoms' following dose 2 and 1.4% reported seeking medical care for symptoms following dose 2	
Menstrual irregularities data through 12/2021	Post-menopausal bleeding	Women ≥45 years, KPNW	48,438 vaccinated women		79 cases of post-menopausal bleeding identified (53 after Pfizer). No cases had COVID-19 vaccination documented as a likely cause.	No concerns raised
Vaccine Safety Datalink (VSD) Mortality Study Vaccinated through 5/31/21 and death data through 7/31/21	Deaths	VSD sites enrolled in the mortality study; vaccinated before 5/31 and number of deaths before 7/31	3,453,126 vaccines administered	Matched cohort analysis	Individuals who received Pfizer-BioNTech COVID-19 vaccine had lower mortality risk after dose 1 and dose 2 vs unvaccinated comparators. • 0.41 (0.38-0.44) RR for mortality of Pfizer-BioNTech vaccine dose 1 recipients versus unvaccinated comparison group 0.34 (0.33-0.36) RR for mortality of Pfizer-BioNTech dose 2 recipients versus unvaccinated comparison	No concerns raised
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and Medicaid Services (CMS)[b] Data presented on 3/14/22	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)	NA	Historical comparator and sequential analyses	RCA statistical signals reported to VaST previously for PE, AMI, DIC, ITP, investigated in self-controlled case series with post vacc control interval • Consistent evidence of an elevated risk of PE	Inconclusive evidence for AMI, ITP; Consistently elevated risk for PE; numbers too small for DIC

					• Elevated risk for AMI that was attenuated after exclusion of cases with hx of COVID-19 disease in past year ITP: no elevated risk	
Booster dose data through 3/5/22	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)	3.2 million patients who received Pfizer-BioNTech primary series received booster doses (23.1 million had Pfizer-BioNTech primary series)	Historical comparator analysis	Signal for Bell's palsy following Pfizer-BioNTech booster among those without a prior COVID-19 diagnosis • Signal for AMI, ITP, myocarditis/pericarditis, and PE following Pfizer-BioNTech booster in those with a prior COVID-19 diagnosis	Inconclusive evidence, further analysis of booster data is needed
Bivalent dose data presented on 1/09/23	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)		Historical comparator analysis	No signal for ischemic stroke following Pfizer-BioNTech bivalent booster vaccination	No concerns raised
FDA - BEST Initiative Myocarditis/pericarditis data presented on 3/14/22	Myocarditis/Pericarditis	5 FDA BEST partners; males 18-25 and 18-35 years	16.9 million doses administered	Retrospective comparator analysis	1.43 (95% CI: 0.88,2.34) incidence rate ratio when comparing Moderna vs Pfizer-BioNTech in males aged 18-25 years in IP/ED/OP settings. .88 (95% CI: 0.67,1.15) incidence rate for males aged 18-25 years in IP/ED/OP settings	Results do not support a significant risk difference between the 2 mRNA vaccines for males aged 18-25 years and18-35 years IRRs attenuated for 18-35 years old and when restricted to IP/ED
FDA - BEST Initiative[b] Optum Data through 11/13/21	Pre-specified health outcomes[a]	Patients enrolled in Optum pre-adjudicated claims, 0-64 years	Total doses 5.0 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in Optum data following Pfizer-BioNTech	Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.

FDA - BEST Initiative HealthCore Data through 10/4/21	Pre-specified health outcomes[a]	Patients enrolled in BCBS 0-64 years	Total doses 5.5 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in HealthCore data following Pfizer-BioNTech	Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.
NPTC Vaccine Sentinel Survey Data presented on 2/6/23		Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	1,063 total AVE reports • 457 medically attended health impact events • 23 potential AESIs	No concerns raised
Vaccine Trials (Manufacturer)					• See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 2. COVID-19 vaccine monitoring systems reviewed by the VaST – Moderna (recommended for use in persons age ≥ 6 months)

Red indicates new results this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Population data through 1/23/26	All health events, adverse events of special interest[a]	US population	203.0 million Moderna doses administered	Descriptive and empirical Bayesian data mining		Anaphylaxis associated with vaccination, first detected by early reporting in US; assessed by follow-up with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021)
6 month-5 year data through 7/31/22	All health events, adverse events of special interest[a]		359,025 doses administered		346 VAERS reports, 6 serious • Fever was the most frequently reported AE	Additional data are needed to derive any insights
First booster dose data for persons aged ≥12 years through 4/11/22			93,118,318 1st mRNA COVID-19 booster vaccination administered		47,014 non-serious reports following 1st booster of mRNA COVID-19 vaccination • Headache, pyrexia, pain: 3 most common non-serious reports 5,049 serious reports following 1st booster of mRNA COVID-19 vaccination	No concerns raised
Bivalent booster dose data for persons ≥ 18 years through 9/25/22	All health events, adverse events of special interest[a]		2.6 million persons aged 18+ years received Moderna bivalent booster vaccination		1,236 non-serious reports following either mRNA bivalent booster dose • Vaccination errors were the most commonly reported AE (30%) 33 serious reports following either mRNA bivalent booster dose • 3 reports of myocarditis, 2 pericarditis, and 3 deaths	No concerns raised but further review needed after more doses administered

Co-administration data through 6/30/2022	All health events, adverse events of special interest[a]				786 reports following co-administration with a Moderna vaccination 1,332 non-serious reports and 253 serious reports across both mRNA vaccines • 47 death reports – causes of death consistent with all-cause mortality for age groups	No concerns raised; but further review needed after more doses administered
Myocarditis/pericarditis first booster data through 5/26/22			93.4 million 1st mRNA COVID-19 booster vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-29 years in 7-day window following either booster dose exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 9.9 in males aged 18-24 years • 4.8 in males aged 25-29 years	There appears to be some risk of myocarditis/pericarditis after a booster dose. Further analyses ongoing.
Myocarditis/pericarditis primary series data through 5/26/22			398.4 million mRNA COVID-19 primary series vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-49 years in 7-day window following dose 2 exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 38.9 in males aged 18-24 years • 15.2 in males aged 25-29 years • 7.5 in males aged 30-39 years • 3.3 in males aged 40-49 years	Warning added to EUA fact sheets June 2021, and information provided in update of CDC's clinical guidance and MMWR article. Information included in FDA materials after full approval on Aug 2021. Further work being done to define myocarditis risk.
MOVING data for persons aged 12-29 years presented on 12/12/22					60 myocarditis patients interviewed, across all vaccines, 1-year post-myocarditis dx	Further follow-up needed

					63 physicians interviewed, across all vaccines, 1-year post-myocarditis dx 83% of healthcare providers indicated the patient was fully or probably recovered	
Tinnitus and hearing loss data through 11/6/22					5,280 tinnitus reports to VAERS • 22.7 reports per million doses administered (18+ years) 125 sudden hearing loss reports • 0.5 reports per million doses administered (18+ years) 601 reports of 'permanent disability' and 125 reports of 'hospitalization' for tinnitus or sudden hearing loss	No concerns raised
TTS data through 8/4/21					2 confirmed TTS reports to VAERS	No concerns raised
GBS data through 1/28/22					72 verified cases of GBS following Moderna vaccination • Median age: 63.0 years • Hospitalized: 97 • Deaths: 5 Observed number of confirmed GBS reports was lower than than expected.	No concerns raised
Death reporting rates data through 11/17/21					For each vaccine, across all sex and age groups, observed reporting rate for death events much lower than the number of expected all cause deaths	No concerns raised

Pregnancy data through 7/29/2022					4,487 pregnancy-related reports to VAERS (1,736 after Moderna). Safety profile of pregnancy reports after COVID-19 vaccines appears reassuring, and primary series reports are comparable to booster doses.	No concerns raised
Menstrual irregularities data through 1/7/22					558 reports of post-menopausal bleeding reported to VAERS after COVID-19 vaccine (145 after Moderna). Few PMB cases were classified as serious VAERS reports (2 reported after Moderna).	No concerns raised
VA ADERS Data through 4/03/2022	All health events	VA employees and Veteran patients	2.1M 1st doses 2M 2nd doses	Descriptive	8% serious; 92% nonserious	No concerns raised
DoD VAERS Data through 12/31/2021	All health events, adverse events of special interest	Active duty and beneficiaries	2.2 million Moderna vaccines administered	Descriptive	8 cases myocarditis/pericarditis after Moderna dose 1 23 cases with myocarditis/pericarditis after Moderna dose 2 • 104.5 cases per million in males aged 18-24 years • 22.7 cases per million in males aged 25-39 years Observed > expected in males (18-24, and 25-39) after dose 2	Follow-up and evaluation continuing
Indian Health Services (IHS) VAERS Presented on 2/06/23	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	612 total AVE reports • 426 medically attended health impact events	No new concerns raised
Active Surveillance						
V-safe Booster dose data through 4/10/22		Vaccinees who enroll	351,619 v-safe participants who received Moderna	Descriptive	Local and systemic reactions for persons aged 18+ years were reported less frequently following	No concerns raised

			primary series received booster doses (311,374 had Moderna primary series)		booster dose than dose 2 for mRNA vaccines. Similar or slightly more reports or reactions among persons aged 12-17 years following booster compared to dose 2 for mRNA vaccines.	
6 month-5 year data through 7/19/22		Vaccinees who enroll	7,879 v-safe participants who received Moderna	Descriptive	Reactogenicity 6 months-2 year-olds: • 19.0% reported any injection site reaction following dose 1 and 29.2% following dose 2 • 55.5% reported any systemic reaction following dose 1 and 59.8% following dose 2 Reactogenicity 3-5 year-olds: • 31.9% reported any injection site reaction following dose 1 and 47.9% following dose 2 • 34.2% reported any systemic reaction following dose 1 and 51.8% following dose 2	No concerns raised
Reactogenicity after booster doses in pregnant persons data through 2/13/22 Data through 4/10/22					4,552 pregnant participants reported a booster dose. • Patterns of reporting after receiving a booster dose while pregnant are consistent with the general population 5,052 pregnant participants reported homologous mRNA booster while pregnant. • Reporting frequency for some systemic reactions differ between dose 2 and booster dose, with some differences in frequency of reporting noted depending on	No concerns raised No concerns raised

					whether participant was pregnant for both doses or only booster dose.	
Menstrual irregularities data through 1/22					63,815 people across all vaccines reported responses likely related to menstruation • Common themes: menstrual timing and menstrual severity	No concerns raised
Bivalent booster dose data for persons ≥ 12 years through 9/25/22		Vaccinees who enroll	22,813 v-safe participants reported receiving Moderan bivalent booster dose	Descriptive	Across both mRNA bivalent vaccines, reporting frequencies of reactions and health impacts were similar to those described after 1st and 2nd booster vaccination Approximately one-third reported co-administration	No concerns raised; but further review needed after more doses administered No concerns raised
Simultaneous booster and influenza vaccine study data through 5/1/22		Vaccinees who enroll	453,270 v-safe participants reported receiving Moderna booster dose		30,633 participants: simultaneous Moderna booster and influenza vaccine; 422,637 participants: Moderna booster alone Injection site and systemic reactions slightly more frequent following simultaneous administration. No evidence of a difference in severity.	No concerns raised; but further review needed after more doses administered
V-safe Pregnancy Registry Data through 1/31/2022		Vaccinees who enroll	22,944 participants enrolled across all vaccines	Descriptive	22,951 total pregnancies. Pregnancy and neonatal outcome frequencies support safety of the COVID-19 vaccination.	Phase 2 Infant and maternal follow-up through 12 months of age/pregnancy end to start soon.
Department of Veterans Affairs (VA) Active Surveillance System RCA data through 10/28/22	Pre-specified health outcomes[a]	Veteran Patients	2.2 million first doses administered; 2.0 million second doses administered	Descriptive; historical comparator analysis	The only signal is for anaphylaxis following dose 2 of Moderna vaccine	No new concerns raised

RCA booster dose data through 3/26/22	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	955,454 booster doses administered	Descriptive; historical comparator analysis	No signals, including for myocarditis or pericarditis or anaphylaxis but pericarditis cases observed among those ≥40 years	No concerns raised, but followup in other safety systems needed
Bivalent booster presented on 1/09/23	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	376k Moderna bivalent doses administered	Descriptive; historical comparator analysis	No signals observed; rate ratio for ischemic stroke/TIA following Moderna bivalent booster vaccine <1	No concerns raised
Target trial emulation data presented on 9/19/22	All-cause mortality	Eligible Veterans	228,130 patients reached end of follow-up (114,621 Moderna)	Discrete time logistic regression	Day 8 and day 28 all-cause mortality are statistically similar across all vaccines Day 60 all-cause mortality is significantly different across all vaccines • 11% reduction in risk in vaccinated group	No concerns raised
Vaccine Safety Datalink (VSD) RCA data through 1/15/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	5.9 million doses of Moderna administered	Vaccinated concurrent comparison, sequential analyses	21-day risk interval - signaled • No signal for myocarditis/pericarditis, AMI, seizures, VTE, PE, and Bell's Palsy 42-days risk interval - signaled • AMI (dose 2) • No signal for myocarditis/pericarditis, AMI, seizures, VTE, PE, and Bell's Palsy	Further monitoring and analyses of other potential signals ongoing
6 month-4-year primary series data through 8/13/22	Pre-specified health outcomes[a]		334,466 first doses of Moderna administered; 17,940 second doses of Moderna administered		No statistical signals identified	No concerns raised

First booster dose data through 8/13/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	2.3 million patients ≥18 years who received a Moderna booster dose	Vaccinated concurrent comparison, sequential analyses	No statistical signal for pre-specified outcomes for Moderna boosters for patients aged ≥12 years • Myocarditis/pericarditis signal for combined Pfizer-BioNTech and Moderna analysis; elevated risk highest in adolescent and young adult males No statistical signal for pre-specified outcomes for booster doses across mRNA vaccines for patients aged 5-11 years	Further monitoring and analyses of ongoing
Rate ratio data through 1/15/2022					In 18–39 year-olds, 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 males	
First booster dose data through 8/20/2022			2.0 million doses of Moderna booster administered following Moderna primary series; age 6 and older	Vaccinated concurrent comparison, sequential analyses	<u>0-7 days risk-window</u> • Rate ratio for myocarditis/pericarditis was 3.27 (0.82-14.23) in persons aged 18-39 years <u>0-7 or 0-21 days risk window</u> • Rate ratios for **pericarditis** not significantly elevated among persons aged 40+ years	Finding consistent with past analyses
Head-to-Head myocarditis/pericarditis presented on 1/15/22					Head-to-head comparisons: risk of myocarditis/pericarditis was higher after Moderna than after Pfizer.	No new concerns raised

					1.61 adjusted rate ratio for persons aged 18-39 years	
Bivalent dose data through 10/8/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	91,626 persons received bivalent booster dose of Moderna	Vaccinated concurrent comparison, sequential analyses	There were no statistical signals for any pre-specified surveillance outcomes. • 1 verified case of acute pericarditis in male aged 35-39	No concerns raised but further review needed after more doses administered
VSD simultaneous and co-administered vaccine data through 10/8/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	~230,000 patients administered either bivalent mRNA booster	Descriptive and stratified RCA	No analyses, only vaccine doses administered presented	No concerns raised but further review needed after more doses administered o concerns raised.
Tinnitus and hearing loss presented on 11/14/22			2,559,563 doses of Moderna; 1,873,849 booster doses of Moderna following mRNA vaccines	Tree-scan, *ad hoc* temporal scans and descriptive	No clusters of hearing-related outcomes for any tree scan analyses Most likely cluster starts on Day 41, ~13 days after dose 2 for most 107/10,000 person-years after Moderna	No concerns raised Tinnitus after vaccination similar to recent global background incidence estimate
Tree scan analysis data presented 5/2/22			2,559,563 doses of Moderna; 841,216 booster doses of Moderna following mRNA vaccines		Patients 18-39 years and 40-64 years had a signal for urticaria and unspecified allergy following Moderna booster (following mRNA vaccines) in the 10-16 days window.	No additional serious adverse events identified using this data mining approach
Menstrual irregularities data through 12/2021	Post-menopausal bleeding	Women ≥45 years, KPNW	48,438 vaccinated women		79 cases of post-menopausal bleeding identified (23 after Moderna). No cases had COVID-19 vaccine documented as a likely cause.	No concerns raised.
Vaccine Safety Datalink (VSD) Mortality Study	Deaths	VSD sites enrolled in the mortality study; vaccinated	2,604,066 vaccines administered	Matched cohort analysis	Individuals who received Moderna COVID-19 vaccine had lower mortality risk after dose 1 and dose 2 than unvaccinated comparators.	No concerns raised

Vaccinated through 5/31/21 and death data through 7/31/21		before 5/31 and number of deaths before 7/31			• 0.34 (0.32-0.37) RR for mortality of Moderna vaccine dose 1 recipients versus unvaccinated comparison group • 0.31 (0.30-0.33) RR for mortality of Moderna vaccine dose 2 recipients versus unvaccinated comparison group	
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and Medicaid Services (CMS)[b] Data through 3/14/22	Pre-specified health outcomes[a]	CMS population 65 and above enrolled in Fee-for-Service (FFS)	NA	Historical comparator analysis	RCA statistical signals reported to VaST previously for PE, AMI, DIC, ITP, investigated in self-controlled case series with post vacc control interval • AMI, ITP: no evidence of risk • PE: Elevated risk for PE; attenuated after exclusion of cases with hx of COVID-19 disease	No evidence of elevated risk for AMI or ITP; inconclusive evidence for PE; numbers too small for DIC
Booster dose data through 3/5/22	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)	3.4 million who received Moderna primary series received booster doses (3.2 million had Moderna primary series)	Historical comparator analysis	No signals for following booster dose of Moderna in patients without a prior COVID-19 diagnosis Signal for AME and PE following Moderna booser dose in patients with a prior COVID-19 diagnosis	Inconclusive evidence, further analysis of booster data is needed for further discussion
Bivalent dose data presented on 1/09/23	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)		Historical comparator analysis	No signal for ischemic stroke following Moderna bivalent booster vaccination	No concerns raised

FDA - BEST Initiative Myocarditis/pericarditis data presented on 3/14/22	Myocarditis/Pericarditis	5 FDA BEST partners; males aged 18-25 and 18-35 years	10.6 million doses administered	Retrospective comparator analysis	1.43 (95% CI: 0.88,2.34) IRR comparing Moderna vs Pfizer-BioNTech in males aged 18-25 years in IP/ED/OP;1.27 (95% CI: 0.88,1.84) incidence rate for males aged 18-25 years in IP/ED/OP settings	Results do not support a significant risk difference between the 2 mRNA vaccines for males aged 18-25 years IRRs attenuated for 18-35 years old and when restricted to IP/ED
FDA - BEST Initiative[b] Optum Data through 11/13/21	Pre-specified health outcomes[a]	Patients enrolled in Optum pre-adjudicated claims, 0-64 years	Total doses 2.4 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in Optum data following Moderna	No concerns raised Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.
FDA - BEST Initiative HealthCore Data through 10/4/21	Pre-specified health outcomes[a]	Patients enrolled in BCBS 0-64 years	Total doses 2.9 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in HealthCore data following Moderna	No concerns raised Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.
NPTC Vaccine Sentinel Survey Data presented on 2/6/23		Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	617 total AVE reports • 195 medically attended health impact events • 18 potential AESIs	No concerns raised
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received [c]at the time of vaccination

Table 3. COVID-19 vaccine monitoring systems reviewed by the VaST – Janssen/Johnson & Johnson (recommended for use in persons age ≥ 18 years)

Red indicates new results this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Population data through 11/7/21; TTS data through 12/6/21	All health events, adverse events of special interest[a]	US population	16.4 million total doses administered	Descriptive and empirical Bayesian data mining	54 confirmed TTS reports to VAERS (37 in females) • 3.83/million doses administered • 10.60/million, females 30-39 yrs • 9.02/million, females 40-49 yrs	Further discussions by ACIP CVWG needed; earlier, warnings and other information had been provided in updated EUA and MMWR, and reflected in clinical guidance
TTS death data through 12/2/21					9 TTS deaths, all after dose 1 • Median age: 45 yrs (range: 28-62) • 7 female and 2 male • Median time from admission to death: 1 day (range: 0-2)	
Booster dose data through 11/5/21					201,653 additional Janssen doses administered • 58.5 non-serious reports per 100,000 doses • 2.0 serious reports per 100,000 doses	No concerns raised
Myocarditis/pericarditis data through 10/6/21					71 reports of myocarditis/pericarditis	No concerns raised
GBS data through 1/28/22					59 verified cases of GBS following Janssen/J&J vaccination • Median age: 57.0 years • Hospitalized: 80 • Deaths: 1	Warning added to EUA fact sheets July 12, other information provided in CDC's clinical guidance. Further reivew and adjudication of cases needed in VAERS and investigation in different systems.

					Observed number of GBS cases following Janssen/J&J vaccine was 2-3 times greater than expected in both post-vaccination intervals	
Pregnancy data through 2/11/22					327 pregnancy-related reports to VAERS. Disproportional reporting for 'prolonged labor' after Janssen (n = 10, confounding factors present).	No concerns raised
Death reporting rates data through 11/17/21					For each vaccine, across all sex and age groups, the observed reporting rate for death events was much lower than the number of expected all cause deaths Bayesian data mining identified mortality due to COVID-19 disease (vaccine failure) following the Ad26.COV2.S vaccine	
Menstrual irregularities data through 1/7/22					558 reports of post-menopausal bleeding reported to VAERS after COVID-19 vaccine (44 after Janssen). Few PMB cases were classified as serious VAERS reports (1 reported after Janssen).	No concerns raised
VA ADERS Data through 4/03/22	All health events	VA employees and Veteran patients	329,701 vaccines administered	Descriptive	No signals were detected	No concerns raised
DoD VAERS Data through 12/31/21	All health events, adverse events of special interest	Active duty and beneficiaries	264 thousand Janssen/J&J vaccines administered	Descriptive	4 cases with myocarditis/pericarditis after Janssen/J&J vaccine	No concerns raised
Indian Health Services (IHS) VAERS Presented on 2/06/23	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	62 total AVE reports • 50 medically attended health impact events	No new concerns raised

Active Surveillance						
V-safe Booster dose data through 4/10/22		Vaccinees who enroll	8,260 v-safe participants who received Janssen primary series received booster doses (7,775 had Janssen for their primary series)	Descriptive	Currently not enough data to describe reactogenicity.	No concerns raised
Menstrual irregularities data through 1/22					63,815 people across all vaccines reported responses likely related to menstruation • Common themes: menstrual timing and menstrual severity	No concerns raised
V-safe Pregnancy Registry Data through 1/31/2022		Vaccinees who enroll	22,944 participants enrolled across all vaccines	Descriptive	22,951 total pregnancies. Pregnancy and neonatal outcome frequencies support safety of the COVID-19 vaccination.	Phase 2 Infant and maternal follow-up through 12 months of age/pregnancy end to start soon.
Department of Veterans Affairs (VA) Active Surveillance System RCA data through 10/28/22	Pre-specified health outcomes[a]	Veteran Patients	380k doses of Janssen/J&J administered	Descriptive; historical comparator analysis	No signals for anaphylaxis, myocarditis/pericarditis, GBS, TTS, or other AESIs	No new concerns raised
Target trial emulation data presented on 9/19/22	All-cause mortality	Eligible Veterans	228,130 patients reached end of follow-up (10,853 Janssen/J&J)	Discrete time logistic regression	Day 8 and day 28 all-cause mortality are statistically similar across all vaccines Day 60 all-cause mortality is significantly different across all vaccines • 11% reduction in risk in vaccinated group	No concerns raised

Vaccine Safety Datalink (VSD) Bell's palsy data through 1/15/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	500,000 doses of Janssen/J&J administered	Vaccinated comparator analysis.	Bell's palsy signaled using a 42-day risk interval	Further analysis of Bell's palsy ongoing
GBS data through 9/25/21					10 confirmed cases of GBS following vaccination within 1-98 days	Further analysis of GBS following ongoing
Booster dose data through 4/12/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	254,973 patients who received Janssen primary series received booster doses (70,607 had Janssen for their primary series)	Vaccinated concurrent comparison, sequential analyses	There were no signals for any prespecified outcomes for Janssen booster doses with Janssen as a primary series	No concerns raised
VSD simultaneous and co-administered vaccine data through 3/26/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	15.9 million persons aged ≥5 years administered COVID-19 vaccine	Descriptive and stratified RCA	Small number of outcomes observed among persons who received simultaneous vaccines and/or co-admin vaccines when stratified by outcome, COVID-19 vaccine manufacturer and dose, vaccine family, and age group • 1,925 persons received simultaneous vaccines and co-administered vaccines • 194,885 persons received any co-administered vaccine • 100,802 persons received any simultaneous vaccine	No concerns raised. The next steps include conducting analysis comparing observed vs expected from non-simultaneous/-co-administered doses.

Tinnitus and hearing loss presented on 11/14/22			417,854 doses of Janssen; 65,238 booster doses of Janssen following Janssen vaccines	Tree-scan, *ad hoc* temporal scans and descriptive	No clusters of hearing-related outcomes for tree scan analyses No likely cluster found 85/10,000 person-years after Janssen	No concerns raised Tinnitus after vaccination similar to recent global background incidence estimate
Tree scan analysis data presented 5/2/22			417,854 doses of Janssen; 75,489 booster doses of mRNA following Janssen; 30,452 booster doses of Janssen following Janssen		Patients 65+ years had a signal for difficulty walking and muscle weakness following Janssen primary dose in the 1-2 day window.	No additional serious adverse events identified using this data mining approach
Menstrual irregularities data through 12/2021	Post-menopausal bleeding	Women ≥45 years, KPNW	48,438 vaccinated women		79 cases of post-menopausal bleeding identified (3 after Janssen). No cases had COVID-19 documented as a likely cause.	No concerns raised
Vaccine Safety Datalink (VSD) Mortality Study Vaccinated through 5/31/21 and death data through 7/31/21	Deaths	VSD sites enrolled in the mortality study; vaccinated before 5/31 and number of deaths before 7/31	1,346,445 vaccines administered	Matched cohort analysis	Individuals who received Janssen/J&J COVID-19 vaccine had lower mortality risk after dose 1 and dose 2than unvaccinated comparators. • 0.54 (0.49-0.59) RR for mortality of Janssen/J&J vaccine dose 1 recipients versus unvaccinated comparison group	No concerns raised
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					

FDA - Centers for Medicare and Medicaid Services (CMS)[b] Data through 3/14/2022	Pre-specified health outcomes[a]	CMS population 65 and above enrolled in Fee-for-Service (FFS)	Total doses 487 thousand	Historical comparator analysis	RCA statistical signal for anaphylaxis in CMS data following Janssen • AMI, PE: no evidence of risk • ITP and DIC: sample size too small to make any conclusions	No concerns raised
FDA - BEST Initiative[b] Optum Data through 11/13/21	Pre-specified health outcomes[a]	Patients enrolled in Optum pre-adjudicated claims, 0-64 years	Total doses 260 thousand	Historical comparator and sequential analyses	No RCA statistical signals for in Optum data following Janssen	No concerns raised
FDA - BEST Initiative HealthCore Data through 10/4/21	Pre-specified health outcomes[a]	Patients enrolled in BCBS 0-64 years	Total doses 338 thousand	Historical comparator and sequential analyses	No RCA statistical signals in HealthCore data following Janssen	No concerns raised
NPTC Vaccine Sentinel Survey Data presented on 2/6/23		Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	69 total AVE reports • 29 medically attended health impact events • 4 potential AESIs	No concerns raised
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5. for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 4. COVID-19 vaccine monitoring systems reviewed by the VaST – Novavax (recommended for use in persons age ≥ 18 years)

Red indicates new results this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Dose data through 9/11/22	All health events, adverse events of special interest[a]	US population	24,125 total doses administered	Descriptive and empirical Bayesian data mining	62 VAERS reports • 5 serious reports No reports of death or myocarditis	Awaiting additional data
Active Surveillance						
V-safe Dose data through 9/11/22		Vaccinees who enroll	179 v-safe registrants reported receiving a dose of Novavax	Descriptive	Currently not enough data to describe reactogenicity.	Awaiting additional data
Vaccine Safety Datalink (VSD) Data through 9/11/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	<600 doses of Novavax administered	Vaccinated comparator analysis.	Currently not enough data to describe reactogenicity.	Awaiting additional data
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5. for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 5. Health systems and pre-specified health outcomes

	VAERS	VSD	VA	DMSS	CMS	BEST
Acute disseminated encephalomyelitis (ADEM)	x[1,2]	x	x	x		
Acute myocardial infarction	x	x	x	x	x	x
Anaphylaxis	x	x[3]	x	x	x	x
Appendicitis	x	x	x	x	x	x
Acute respiratory distress syndrome (ARDS)		x[3]	x	x		
Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)	x[1]		x	x		
Ataxia	x[1,2]					
Autoimmune disease	x[1]					
Bell's palsy	x	x	x	x	x	x
Chronic inflammatory demyelinating polyneuropathy (CIDP)	x[1,2]					
COVID-19	x[1]					
Death	x			x		
Disseminated intravascular coagulation (DIC)	x	x	x	x	x	x
Encephalomyelitis/Encephalitis					x	x
Encephalitis	x	x	x			
Encephalomyelitis	x[1,2]	x	x			
Encephalopathy	x[1,2]	x	x	x		
Guillain-Barré syndrome (GBS)	x	x	x	x	x	x
Immune thrombocytopenic purpura (ITP)		x	x	x	x	x
Kawasaki disease	x	x				
Meningitis	x[1,2]		x	x		
Meningoencephalitis	x[1,2]	x	x	x		
Multiple sclerosis (MS)	x[1,2]					
Multisystem Inflammatory Syndrome in Adults (MIS-A)	x	x[3]	x[3]	x	x[6]	x[6]
Multisystem Inflammatory Syndrome in Children (MIS-C)	x	x[3]				x[6]
Myelitis	x[1,2]	x	x	x		
Myocarditis / pericarditis	x	x	x	x	x	x
Narcolepsy / cataplexy	x	x[3]	x	x	x[4]	x[4]
Non-anaphylactic allergic reactions	x[1]					

Optic neuritis (ON)	x[1,2]					
Seizures / convulsions (convulsion is now an LLT under PT seizure)	x	x	x			
Stroke	x	x	x			
Non-hemorrhagic stroke (NHS)					x	x
Hemorrhagic stroke (HS)					x	x
Thrombocytopenia	x	x				
Thrombosis with thrombocytopenia syndrome (TTS) and/or CVST	x	x			x	x
Thrombosis at uncommon site (including intracranial, intraabdominal, portal, renal, or other veins) with thrombocytopenia					x	x
Thrombosis at common site (AMI, DVT, HS, NHS, or PE) with thrombocytopenia					x	x
Transverse myelitis (TM)	x	x	x		x	x
Vaccination during pregnancy/adverse pregnancy outcomes	x					
Venous thromboembolism (VTE)	x	x	x		x	x
Pulmonary embolism	-	x	x		x	x
Deep vein thrombosis	-	-	x		x	x

[1]Health outcomes are monitored, but adverse event reports are not abstracted
[2]Diagnoses are grouped and monitored as "Other clinically serious neurologic AEs" in VAERS
[3]Health outcomes are counted, and no sequential analysis is conducted
[4]Only includes narcolepsy
[5]Only list outcomes that are currently included in the RCA.
[6]Only included in the descriptive analysis not the RCA, as MIS requires a COVID-19 diaganosis and therefore historical rates cannot be estimated.

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From: "Alimchandani, Meghna" [redacted]
To: "Forshee, Richard" [redacted]
Cc: "Nair, Narayan" [redacted]
Subject: RE: Safety of bivalent COVID-19 vaccines
Date: Wed, 10 May 2023 13:32:30 +0000
Importance: Normal
Attachments: 2023_03_Pfizer-BioNTech_COVID-19_Vaccine_Bivalent_Q.pdf; 2023_3_ModernaCOVID-19Bivalent_Q.pdf
Inline-Images: image001.png; image002.png; image003.jpg; image004.jpg; image005.jpg; image006.jpg; image007.jpg

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Hello Rich,

We are sharing the most recent internal surveillance reports for the bivalent vaccines for your reference; thanks. (Note that these are internal analysis generated by the medical officers from VAERS queries.)
Thanks!

Best,
Meghna

From: Forshee, Richard [redacted]
Sent: Tuesday, May 2, 2023 1:23 PM
To: Alimchandani, Meghna [redacted]
Cc: Nair, Narayan [redacted]
Subject: RE: Safety of bivalent COVID-19 vaccines

Thank you, Meghna!

From: Alimchandani, Meghna [redacted]
Sent: Tuesday, May 2, 2023 1:11 PM
To: Forshee, Richard [redacted]
Cc: Nair, Narayan [redacted]
Subject: RE: Safety of bivalent COVID-19 vaccines

Hi Rich,

I believe the most recent memo documenting VAERS data for bivalent are in the decision memos (https://www.fda.gov/media/167258/download and https://www.fda.gov/media/167306/download).

- As of April 5, 2023, there were 35,690,430 booster doses of Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) administered in the U.S.
    - In recipients of any age and all doses, the most frequently reported PTs from VAERS data were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain.
- As of April 5, 2023, there were 20,076,974 booster doses of Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) administered in the U.S.
    - In recipients of any age and all doses, the most frequently reported PTs from VAERS data were headache, pyrexia, fatigue, chills, pain, pain in extremity, nausea, dizziness, myalgia, and injection site pain.

I'm checking with the BCS to see if we can get you a more detailed summary of bivalent safety data.

Thanks

Meghna

From: Forshee, Richard [redacted]
Sent: Tuesday, May 2, 2023 12:23 PM
To: Nair, Narayan [redacted] Alimchandani, Meghna [redacted]
Subject: Safety of bivalent COVID-19 vaccines

Hi Narayan and Meghna,

I've been asked to give a presentation about the safety of the bivalent COVID-19 vaccines. What sort of data do we have from VAERS?

Thanks,
--Rich

Richard Forshee, Ph.D. (he/him/his)
Deputy Director, CBER/OBPV

Typical Day at White Oak: Thursday

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

Pfizer-BioNTech COVID-19 Vaccine, Bivalent
EUA 27034

Samaneh Bazel

APPROVED
By Samaneh Bazel at 1:53 pm, May 02, 2023

Quarterly Surveillance Report for Pfizer-BioNTech COVID-19 Vaccine, Bivalent
Surveillance Interval: January 01, 2023 – March 31, 2023

APPROVED
By Christopher Jason at 2:15 pm, May 02, 2023

1 PRODUCT DETAILS

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent contains equal amounts of modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 (original) and modRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 (Omicron BA.4/BA.5). As of 4/18/23, the Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use for all doses administered to individuals 6 months of age and older. The monovalent Pfizer-BioNTech COVID-19 Vaccine is no longer authorized for use in the United States. Please see the latest EUA Letter of Authorization (LOA), and product EUA Fact Sheets for additional details.

2 REVIEW OF TABLES AND TRENDS

Please refer to the attachment at the end of the memo for the tables generated by Business Objects.

Reviewer comment:

Most U.S. reports for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were non-serious (n= 7301; 79%) during the surveillance period. Of note, foreign reports may be for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent encoding Original/Omicron BA.1 (not authorized for use in the U.S.) or Original/Omicron BA.4/BA.5.

Majority of the most frequently reported PTs overall (Table 5) are consistent with PTs reported for the monovalent vaccine, PTs previously reported for the bivalent vaccine, and with the known safety profile for the monovalent and bivalent vaccine or signs/symptoms of COVID-19 or viral illness. However, cerebrovascular accident (CVA) was not noted in the most frequently reported PTs in previous surveillance reports. Most CVA reports were from US consumers with other pre-existing medical conditions and limited medical information:

> *Among all 116 events of CVA, 111 (95.7%) were reported as serious and 10 (8.6%) involved a fatality. The dates of vaccination ranged from 9/9/22 to 3/12/23, with majority between September and December 2022. Among events with available vaccination to symptom onset interval data (N = 104), the mean and median reported onset interval was 26 day(s) and 11 day(s) respectively. Upon manual review of US cases (n=90; 77.6%), 50 individuals reported a stroke event within 21 days after receiving the bivalent vaccine and 16 individuals between day 22 to day 41 post vaccination. Among events with available age*

data (N = 90), the mean and median ages were 72 years and 73 years respectively. Majority of individuals were 65 years of age and older, but there were 16 individuals less than 65 years of age with an age range of 35 to 64 years.

A previous concern for increased rate of strokes post Pfizer Covid-19 vaccine, Bivalent in adults 65 years of age and older in the first 21 days after a Pfizer Bivalent booster dose as compared with days 22-42 following vaccination was first raised by the CDC on Jan 13, 2023, based on data from the Vaccine Safety Datalink (VSD).[1] However, this signal was not confirmed in multiple other safety databases, such as the sponsor's global safety database, the Centers for Medicare and Medicaid Services or Veterans Affairs databases, or in reports from other countries.[1] Further CDC analyses showed that the risk of stroke in the first 3 weeks after the booster dose was similar to unboosted comparators who have completed the primary series, and the risk of ischemic stroke in boosted individuals 22-42 days following vaccination was actually lower than the unboosted comparators in the same interval.[2] Subsequently there was an increase in the number of ischemic stroke reports submitted to VAERS, suggestive of stimulated reporting. However, no particular safety trends have been identified for ischemic stroke or cerebral/cerebellar infarct after Pfizer-BioNTech COVID-19 Vaccine, Bivalent to date.

Medication error PTs during this surveillance period were consistent with those previously reported and almost all reports were non-serious (Table 6). Among the 60 reports of "Product Use Issue" (18 serious), 23 were U.S reports (2 serious); both serious US cases were consumer reports that described co-administration of influenza vaccine as "off label use". All 16 serious foreign reports also described co-administration with influenza vaccine, with 11 reports describing "product use for unapproved combination." Of note per CDC guidelines the Pfizer-BioNTech bivalent vaccine may be co-administered with influenza vaccines. The EUA Fact Sheet for Healthcare Providers Administering Vaccine contains instructions for storage/handling, product preparation, and administration. The sponsor also monitors medication error reports and provides a summary to FDA in periodic safety update reports.

Review of PTs and/or reports within the SOC "Pregnancy, Puerperium, and Perinatal Conditions" did not suggest new safety concerns (Table 8). The safety of the vaccine in pregnancy is being studied in post-authorization studies conducted by the sponsor.

Review of the most frequent PTs for death reports (Table 9) was consistent with the previous surveillance quarter and did not reveal patterns suggesting new safety concerns. Review of the Business Objects query does not indicate the need for further regulatory action. Routine surveillance will continue.

3 DEATH REPORTS

There were a total of 154 deaths, including one pediatric death under 18 years of age during this surveillance period. All U.S. death reports (n=75; 49%) were individually reviewed during the surveillance period. Twelve (16%) reported at least one concomitant vaccine. Among events with available vaccination to symptom onset interval data (N = 64), the mean and median reported onset interval was 48 day(s) and 17 day(s) respectively with range of 0 to 167 days. Among events with available age data (N = 66), the mean and median ages were 75 years and 81 years respectively.

Deaths that were considered notable include deaths that in the reviewer's judgment were suspicious for being due to the vaccine or did not have an alternate etiology and could plausibly be due to the vaccine.

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.*

[redacted]	13	F	Probable Infectious (viral or bacterial) myocarditis, Ventricular tachycardia, cardiac arrest	Patient with PMH iron deficiency, type 1 DM, vit D deficiency, experienced elevated blood sugars, chest pain and rapid heart rate, seen at ED with abnormal EKG (1st degree AV block and possible septal infarct), with eventual V-tach, and cardiac arrest. Onset of symptoms 18-days post- and death 22 days post-vaccination with 3rd dose. Autopsy was declined by family. Per post-mortem exam notes, cardiology was consulted with working COD as infectious myocarditis. *Reviewer comment: Due to concurrent type 1 DM with elevated glucose, and limited clinical details and postmortem exam, an infectious etiology for myocarditis is possible, but role of vaccine cannot be ruled out, given proximity of events to vaccination.*
[redacted]	80	M	GBS, respiratory failure, shock, cardiac arrest, death	Patient who received Pfizer bivalent vaccine and influenza vaccine on same day, developed fever, urinary incontinence, and headaches one day post vaccination with ensuing fatigue diagnosed as hypokalemia. Had recurrent fatigue, itchy skin daily headaches 2 weeks later with subsequent falls and behavior changes, with onset of respiratory difficulties and sensorimotor changes including movement difficulties, tingling in hands and dysphagia 3 weeks post vaccination. Was diagnosed with GBS that caused respiratory failure with eventual shock and cardiac arrest 27 days post vaccination. *Reviewer comment: GBS is unlabeled for Pfizer Covid vaccines and is an adverse event of special interest in post authorization studies being conducted by the sponsor, FDA's BEST, and CDC's VSD. At this time,*

				no signals have been reported for GBS from post-authorization studies. Surveillance will continue.

Reviewer comment: *No patterns were identified that suggested new safety concerns requiring further regulatory action. Death reports will continue to be monitored.*

4 OTHER MEDICALLY NOTABLE CASES

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; L vertebral artery dissection	Patient with PMH of COVID-19 in April 2022 experienced three TIA events (17Dec2022; 20Dec2022; 24Dec2022) + several small acute infarcts in Lt posterior Cerebellum. Additional acute infarct in occipital subcortical white matter. The patient was hospitalized for transient ischemic attack for 2 days. Polymerase chain reaction: (23Dec2022) Negative. Onset 2-days post-4th dose (bivalent) administered on 12/15/22. Primary symptom was weakness on left side and when prolonged occurrence took place on 23Dec2022. However, patient complaining of progressive headaches since few months prior to events and reportedly vomited the same day after vaccination. Head CT, MR Angio WNL. Sars-Cov-2 PCR and coagulopathy workup were all WNL. Family history includes sister with brain cavernous malformation and father with two small benign brain tumors. Pt d/c home on aspirin for one month with f/u appt with neuro, cardiology, and peds heme/onc. However, patient subsequently developed more TIAs on 1/28/23 and 2/23/23 with eventual diagnosis of dissection of left vertebral artery on CTA, 71 days post vaccination. *<u>Reviewer comment:</u> Per MFR, no further information is expected for this report. This case was reviewed by division leadership. History of recurrent headaches prior to vaccination and unusual family history could suggest possible other etiologies for ensuing strokes and vomiting post vaccination could have*

				precipitated insidious onset of vertebral artery dissection; however, the role of vaccine cannot be fully excluded in the face of close proximity to event onset. 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). To date there have been no other reports of ischemic stroke or vertebral artery dissection after the bivalent vaccine in individuals less than 18 years of age. DPV will continue to monitor.
[redacted]	38	M	Acute leukemia, thrombocytopenia	A 38-year-old male patient with hx of sickle cell anemia, received the Pfizer bivalent vaccine on 10/21/22 as dose 4 (booster) and was hospitalized with profound thrombocytopenia on 11/21/22 with onset of back pain and fatigue two weeks prior. Bone marrow biopsy concerning for acute leukemia and for 5 days. SARS-CoV-2 test: Negative. *Reviewer comment:* *Case is confounded due to PMH of sickle cell anemia which could increase risk of leukemia, however further medical records are not available. Will continue to monitor.* (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 (MOGAD)	Patient with PMH ADHD and anxiety experienced severe headache 19-days post-3rd dose and subsequent seizure 3 days later and was diagnosed with Rhino/Entero and Adenovirus. After several weeks of headaches, she was admitted to the hospital on a month later and underwent testing which diagnosed MOGAD, treated with steroid taper. Patient presented to ED again 2 months later with recurring acute on chronic headache. Repeat MRI showed some resolution of previous brain lesions, but possible new lesions and signal intensity in both optic nerves were noted. Patient admitted to neurology service. No follow up report available since February 2023. *Reviewer comment:* *Initial presentation is confounded due to concurrent viral illness. However, role of vaccine cannot be ruled out due to proximity to symptom onset.* 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 et al.

				"*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 Imaging Abnormal; Nerve Injury	Patient report: "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 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 3 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.*
[redacted]	39	F	CVST	Patient with no PMH and no meds, developed progressive headache and neck pain 2 – 3 days post vaccine, and had imaging almost a month later. Brain CT/MRI on 11/17/22 showed dural venous sinus thrombosis, treated with anticoagulation. Despite

				anticoagulation, 6 weeks later had massive PE that had an acute and chronic component. Unresponsive to thrombolytics and thrombectomy attempt. Required ECMO, still hospitalized (as of 2/2/23). *Reviewer comment: Re-review if medical records become available, unable to assess further at this time.*
[redacted]	14	F	MOGAD	Foreign report of patient with no PMH, received BNT162b2 omi ba.4-5 as dose 4 (booster) and developed difficulty walking due to pain in LEs 11 days later with subsequent urinary and defecation disorder, diagnosed as myelitis. Patient had abnormal brain and spine lesions noted 19 days after vaccination with a positive serum MOG antibody diagnosed as MOGAD. Patient was recovering 48 days after the vaccination with steroid treatment. *Reviewer comment: Given inflammatory nature of MOGAD with close temporal association to vaccination, vaccine role cannot be ruled out.*

Reviewer comment: Review of VAERS data and medically notable reports did not identify new safety concerns for Comirnaty during the surveillance period.

5 DATA MINING FINDINGS

Datamining for Pfizer-BioNTech COVID-19 Vaccine, Bivalent was conducted using the Empirica Signal Signals tab "US/World Signals Summary Table" on 4/19/23, with a data lock point of 4/14/23. Preferred terms (PTs) with corresponding EB05 values are shown in the table below. Notable/New PTs are discussed in reviewer comment below.

Event	US EB05 20230414	US N 20230414	US Serious EB05 20230414	US Fatal EB05 20230414	US Fatal N 20230414	World EB05 20230414	World N 20230414
Blood test normal	1.085	120	2.073			1.373	188

Incorrect product formulation administered	1.974		0.783			2.486	1477
Off label use	2.69		0.974	0.863	2	0.957	338
Product preparation error	1.71		0.752			2.023	145
Product use issue	2.601		1.049	0.857	1	4.223	266

Reviewer comment:

US PTs with an EB05 ≥ 2 included product use issue and off label use, which are consistent with previous review. Normal blood test is not an adverse event

Of note, *Ischemic stroke appeared as a new data mining finding on February 02, 2023, for US serious reports with an EB05 ≥ 2, but not for overall US reports. This coincided with the previously discussed stimulated reporting of cases after CDC concern for a possible signal for increased risk of ischemic stroke in January 2023, which was resolved upon further analysis. No particular safety trends have been identified for ischemic stroke or cerebral/cerebellar infarct after Pfizer-BioNTech COVID-19 Vaccine, Bivalent to date. Additionally, the stroke signal has resolved from Empirica Signal as of 4/14/23.*

6 CASE SERIES

Myocarditis/Pericarditis

In line with previous surveillance reports, a Business Objects AESI Screening Report query was run for Pfizer-BioNTech COVID-19 Vaccine, Bivalent for the current review period on 4/20/23 for reports related to myocarditis or pericarditis. The following PTs were included: autoimmune myocarditis; autoimmune pericarditis; chronic myocarditis; eosinophilic myocarditis; hypersensitivity myocarditis; immune-mediated myocarditis; myocarditis; myopericarditis; pericarditis; pericarditis adhesive; pericarditis constrictive; pleuropericarditis.

The query returned 89 reports (including 30 US reports; 33.7%) with 5 fatalities (5.6%), 3 of which were from US. Among reports with available vaccination to symptom onset interval data (N = 67), 36 cases (including 8 from US) occurred within 7 days of vaccination, with a mean and median reported onset interval of 20 day(s) and 4 day(s) respectively. Among reports with available age data (N = 54), the mean and median ages were 46 years and 46 years respectively, with an age range of 12 to 91 (including 6 adolescents, 4 of whom were from US. Among reports with available sex data (N = 85), 41 (48.2%) were female.

Reviewer comment: Post-EUA safety surveillance reports received by FDA and CDC identified increased reporting rates of myocarditis and pericarditis following the monovalent Pfizer-BioNTech COVID-19 Vaccine particularly within 7 days following administration of the second dose of the 2-dose primary series. Reporting rates for medical chart-confirmed myocarditis in VAERS following monovalent vaccination have been higher among males under 40 years of age than among females and older males and have been highest in males 12 through 17 years of age (Shimabukuro, 2022). Myocarditis and pericarditis are labeled events. The Sponsor is conducting post authorization/ post-marketing studies to assess known serious risks of myocarditis and pericarditis. Reports of myocarditis and pericarditis from this surveillance period do not suggest new safety concerns. Routine monitoring will continue.

7 NOTABLE PUBLICATIONS

A literature search of PubMed conducted on 4/7/23 for 'Pfizer-BioNTech COVID-19 Vaccine Bivalent' with a date range of 1/1/23 through 3/31/23 and yielded the following safety related articles:

Abara W.E. et al. "Reports of Guillain-Barré Syndrome After COVID-19 Vaccination in the United States." *JAMA Network Open.* 2023 Feb 1;6(2):e2253845. doi: 10.1001/jamanetworkopen.2022.53845. A retrospective cohort study using US VAERS reports between December 2020 to January 2022 to evaluate GBS reports and compare reporting patterns within 21 and 42 days after vaccination with Ad26.COV2.S (Janssen), BNT162b2 (Pfizer-BioNTech), and mRNA-1273 (Moderna) COVID-19 vaccines. The study found disproportionate reporting and imbalances after Ad26.COV2.S vaccination only, and no associations between mRNA COVID-19 vaccines and risk of GBS were observed.

Winokur, P. et al. "Bivalent Omicron BA.1-Adapted BNT162b2 Booster in Adults Older than 55 Years." *The New England journal of medicine* vol. 388,3 (2023): 214-227. doi:10.1056/NEJMoa2213082. In an ongoing phase 3 trial of adults older than 55 years who had previously received three 30-µg doses of the BNT162b2 vaccine, were randomized to receive a booster dose of the original monovalent BNT162b2, a BA.1 adapted monovalent BNT162b2, or a Bivalent BA.1 adapted BNT162b2. Per authors, "monovalent or bivalent omicron BA.1-adapted vaccines had a safety profile similar to that of BNT162b2 (30 µg), induced substantial neutralizing responses against ancestral and omicron BA.1 strains, and, to a lesser extent, neutralized BA.4, BA.5, and BA.2.75 strains."

Yonker L. M. et al. "Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis." *Circulation.* Vol 147, No. 11. January 4, 2023. Immunoprofiling of 16 vaccinated adolescents and young adults who developed myocarditis between January 2021 through February 2022, revealed that the mRNA vaccine-induced immune responses did not differ between individuals who developed myocarditis and

individuals who did not. However, free spike antigen was detected in the blood of patients who developed post-mRNA vaccine myocarditis, but not in asymptomatic vaccinated control subjects. These results do not alter the risk-benefit ratio favoring vaccination against COVID-19 to prevent severe clinical outcomes given that postvaccine myocarditis is a rare complication and the study is limited by the relatively small sample size.

Reviewer comment: No further regulatory action is indicated based on the above literature search. DPV Leadership is aware of the Yonker et al article noted above and DPV will continue to monitor.

8 SPONSOR'S ABBREVIATED SUMMARY MONTHLY SAFETY REPORT

The sponsor submitted an Abbreviated Summary Monthly Safety Report (aSMSR) in PBRER format on 4/7/23 (STN 125742.290; reporting period 2/16/23 to 3/15/23), which included the monovalent and bivalent vaccines. During the reporting period for the aSMSR, no actions were taken for BNT162b2 vaccines for safety reasons. Per review memo: "during this reporting period, there has been no new significant safety information changing the characterization of this risk." (page 20) "The results are generally similar to those reported in the previous abbreviated SMSR #13 (reporting period 16 January 2023 through 15 February 2023). No newly elevated groups were identified as compared to the results in SMSR #13." (page 32).

Overview of signals addressed or under evaluation during the reporting interval: Menstrual Irregularities, status ongoing, category not yet determined; Myositis, status closed, category no risk. (pages 20 and 403). Routine monitoring will continue.

Reviewer comment: A separate memo summarizing the review findings from the aSMSR was prepared and uploaded to CBER Connect. No further regulatory action is indicated based upon the information provided in the aSMSR.

9 SUMMARY OF QUERY AND INFORMATION REQUESTS DURING THE SURVEILLANCE PERIOD

9.1 Query for Acute Disseminated Encephalomyelitis (ADEM) for Pfizer-BioNTech COVID-19 Vaccine, Monovalent and Bivalent

A request from MHRA regarding ADEM in February 2023 prompted a review of this AE. "A cumulative VAERS query was run using the QQ_LL query in Business Objects on January 20, 2023, for reports with the Preferred Term "Acute Disseminated Encephalomyelitis" (ADEM) for the Pfizer-BioNTech COVID-19 Vaccine (monovalent and bivalent) among individuals of all ages with the following U.S. VAERS event reports:

- 24 total U.S. events reported (23 following receipt of monovalent vaccine and 1 following bivalent vaccine)
- 22 (91.7%) non-fatal serious and 1 (4.2%) death
- 14 (58.3%) females and 10 (41.7%) males
- Median age=57 years (range=11-84 years, including one report of ADEM in a pediatric-aged individual; 2 events with age field=unknown)
- Median onset=8 days post-vaccination (range=1-78 days; 3 events with time to onset not reported)
- 9 (37.5%) events reported following dose 1; 5 (20.8%) events following dose 2; 1 (4.2%) event following dose 3; 1 (4.2%) event following dose 4; 0 (0%) events following dose 5; and 8 (33.3%) events with unknown dose number/dose not reported
- U.S. reporting rate of 0.06 events reported per million doses of monovalent Pfizer-BioNTech COVID-19 Vaccine administered and 0.03 events reported per million doses of bivalent Pfizer-BioNTech COVID-19 Vaccine administered (dose data from CDC COVID Data Tracker: Vaccinations in the US, accessed on January 23, 2023)

VAERS query results showed reported events of ADEM that were temporally associated with receipt of the Pfizer-BioNTech COVID-19 Vaccine, monovalent and bivalent. Most events were non-fatal serious, and deaths were also reported; this is consistent with the condition of ADEM. A study examining ADEM in the U.S. found the incidence of ADEM associated pediatric hospitalizations to be 0.5 per 100,000 children per year during the study period from 2006 through 2014[3]. A population-based U.S. study in Minnesota among individuals of all ages found the incidence of ADEM to be increasing over time with an incidence of 0.1 per 100,000 person-years from 1995-2005 and 0.2 per 100,000 from 2006-2015[4]. The VAERS reporting rate of ADEM following the Pfizer-BioNTech COVID-19 Vaccine, monovalent and bivalent, is low in the context of background rates from the literature. Encephalomyelitis is an adverse event of special interest (AESI) being assessed in post-authorization safety studies being conducted by the sponsor, and in FDA BEST and CDC VSD COVID-19 safety surveillance studies."

9.2 IR response to cumulative safety and causality assessment of thromboembolic events following receipt of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent

The sponsor submitted an analysis of thromboembolic events post Pfizer-BioNTech COVID-19 monovalent and bivalent vaccines on 1/24/23 (STN #125742/ 245.2) in response to FDA information request. According to the sponsor, available safety data from medical literature, clinical trials, and spontaneous safety database did not identify a causal association with Comirnaty or the Bivalent BNT162b2 (Original and Omicron BA.4/BA.5) vaccine at the time of the query (DLP 12/15/22). Per sponsor, individual review of the cumulative thromboembolic event reports (those with sufficient evaluable detail) for the bivalent vaccine in the Pfizer safety database, noted "patients with risk factors for such events. No other notable trends in the cases (e.g., dose number, manufacturer, concomitant influenza vaccination) were identified." Per sponsor there

was no evidence to date that thromboembolic events, including ischemic stroke, were a safety signal or risk of the bivalent Pfizer vaccine. These events will continue to be reviewed per routine pharmacovigilance.

Subsequently there was an internal DPV query on 3/1/23, looking at stroke events in individuals > 65 years of age after receipt of bivalent vaccine, but no safety signals were identified.

9.3 Query for Seizures in children less than 2 years and 2 – 4 years for Pfizer BioNTech COVID-19 Vaccine, Monovalent and Bivalent

FDA leadership requested a review of the adverse event of seizure associated with the Pfizer vaccines in children less than 4 years of age. A cumulative VAERS query was run using the QQ_LL query in Business Objects on February 21, 2023 for reports for the Pfizer-BioNTech COVID-19 Vaccine (monovalent and bivalent) among individuals ages less than 2 years of age and 2 years to 4 years of age. “The queries for both age groups returned no reports for the bivalent vaccine…an observed to expected (O/E) analysis did not show an elevated rate of seizures in individuals in either age group receiving the [Monovalent] vaccine compared to background rate.”

9.4 Chest Pain Query

A request for review of the adverse event of chest pain was submitted by Australia for the International Post-Market Surveillance (IPMS) Teleconference in March 2023. As part of review, a search in VAERS was run on March 16, 2023, using the PT “chest pain” for Pfizer COVID monovalent and bivalent vaccines in the US. There were 16,112 events for the Pfizer COVID monovalent vaccine, of which 5,974 were serious and 385 involved a fatality. Additionally there were 285 events for Pfizer COVID bivalent vaccine of which 92 were serious and 4 involved a fatality. “Comparing this to the search for the PT “non cardiac chest pain” in which the Pfizer COVID monovalent vaccine returned 52 events and bivalent vaccine returned no events, reveals the difficulty in using VAERS to explore chest pain as a symptom. Given the variety of underlying causes for chest pain unrelated to a specific syndrome, this is a diagnosis of exclusion difficult for postmarketing surveillance to assess.”

10 CONCLUSIONS

The results from this quarterly surveillance report do not indicate a need for regulatory action. Continue routine surveillance.

REFERENCES

1. “*CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older*.” January 13, 2023. **CDC**. https://stacks.cdc.gov/view/cdc/123602

2. N Klein. "*Update on Original COVID-19 Vaccine and COVID-19 Vaccine Bivalent Effectiveness and Safety*." **Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting**. January 26, 2023. https://www.fda.gov/media/165307/download

3. Bhatt P et al. "*Temporal Trends of Pediatric Hospitalizations with Acute Disseminated Encephalomyelitis in the United States: An Analysis from 2006 to 2014 using National Inpatient Sample*." **J Pediatr**. 2019 Mar;206:26-32.e1. doi: 10.1016/j.jpeds.2018.10.044. Epub 2018 Dec 6. PMID: 30528761.

4. Dubey D et al. "*Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis*." **Ann Neurol**. 2018 Jan;83(1):166-177. doi: 10.1002/ana.25131. PMID: 29293273; PMCID: PMC6011827.

VAERS Internal Surveillance Report

Surveillance Period (Completed Dates): **1/1/23 to 3/31/23**

Report Run Date: **4/13/23**

Vaccine Name: **COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))**

Report By: **Samaneh.Bazel**

1. Event Counts by Location and Seriousness

	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
US	9,240	1,930	75	128	639	123	3	1,178
Foreign	2,318	2,313	79	127	422	213	0	1,607
Total	**11,558**	**4,243**	**154**	**255**	**1,061**	**336**	**3**	**2,785**

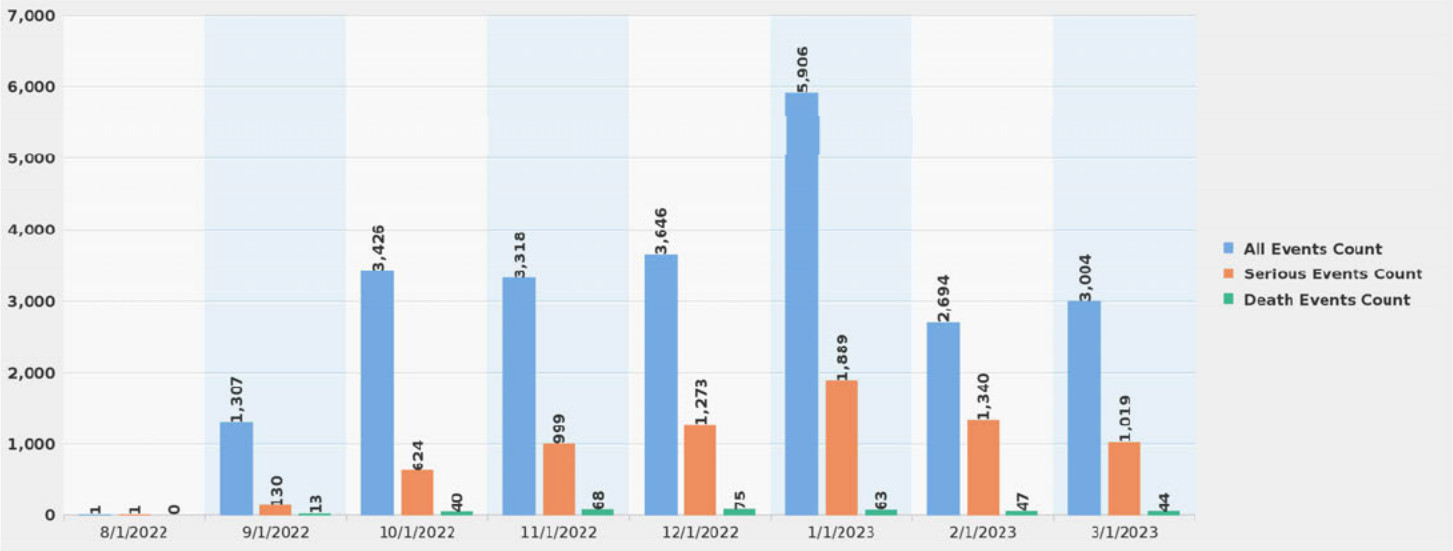
Note: One event can be counted in multiple serious subcategories if reported differently by multiple reporters

2. Event Counts by Age Group

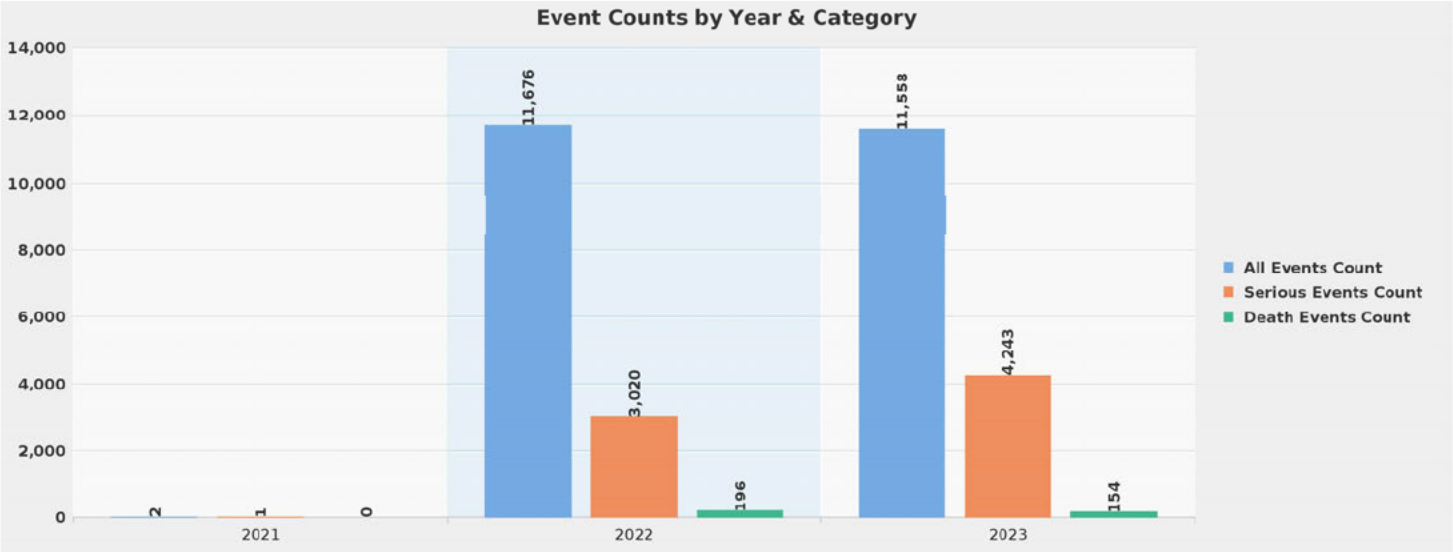
	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
<1 Year	34	0	0	0	0	0	0	0
1 to <3 Years	75	0	0	0	0	0	0	0
3 to <7 Years	186	2	0	0	2	1	0	0
7 to <17 Years	590	41	1	2	20	5	0	16
17 to <65 Years	5,331	1,412	17	79	277	115	3	1,018
>= 65 Years	3,528	1,267	85	101	552	91	0	606
Not Reported	1,821	1,523	51	73	210	124	0	1,147
Total	**11,558**	**4,243**	**154**	**255**	**1,061**	**336**	**3**	**2,785**

Note: One event can be counted in multiple age bands and/or serious subcategories if reported differently by multiple reporters

3. Event Counts for Surveillance Period and Prior 12 Months



4. Event Counts for Surveillance Period Year and Prior 5 Years



5. Most Frequent Preferred Terms (PTs)

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
PRODUCT STORAGE ERROR	2,852	3,613	1	2	1	0	0
COVID-19	2,564	4,562	2	1	-1	1,469	23
HEADACHE	1,147	2,416	3	3	0	438	3
FATIGUE	1,076	2,399	4	4	0	449	5
DRUG INEFFECTIVE	1,023	1,792	5	6	1	1,023	3
PYREXIA	960	2,260	6	5	-1	395	9
COUGH	903	1,713	7	7	0	170	9
NO ADVERSE EVENT	682	1,631	8	9	1	1	1
PAIN	655	1,709	9	8	-1	208	1
MALAISE	543	1,139	10	12	2	206	6
OROPHARYNGEAL PAIN	501	1,006	11	17	6	51	3
DYSPNOEA	485	1,010	12	16	4	317	20
INCORRECT PRODUCT FORMULATION ADMINISTERED	481	1,468	13	10	-3	2	0
CHILLS	455	1,271	14	11	-3	205	4
INTERCHANGE OF VACCINE PRODUCTS	418	818	15	18	3	397	8
PAIN IN EXTREMITY	418	1,087	15	13	-2	241	3
NAUSEA	394	1,063	17	14	-3	257	4
RESPIRATORY TRACT CONGESTION	384	745	18	20	2	20	1
EXPIRED PRODUCT ADMINISTERED	375	670	19	24	5	0	0
DIZZINESS	370	1,045	20	15	-5	215	4
ASTHENIA	341	732	21	21	0	211	10
RHINORRHOEA	339	661	22	25	3	26	1
ARTHRALGIA	318	773	23	19	-4	203	2
MYALGIA	275	699	24	22	-2	173	1
FEELING ABNORMAL	265	653	25	26	1	81	4
DIARRHOEA	249	531	26	29	3	139	3
CHEST PAIN	248	511	27	31	4	179	3
CONDITION AGGRAVATED	239	530	28	30	2	143	10
VOMITING	214	560	29	28	-1	132	4
VACCINATION FAILURE	211	374	30	37	7	211	2
EXTRA DOSE ADMINISTERED	207	413	31	36	5	1	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
NASOPHARYNGITIS	202	374	32	37	5	41	1
PALPITATIONS	194	347	33	41	8	136	2
WRONG PRODUCT ADMINISTERED	181	595	34	27	-7	97	3
LYMPHADENOPATHY	170	417	35	35	0	115	0
NASAL CONGESTION	160	355	36	40	4	10	0
INCORRECT DOSE ADMINISTERED	150	675	37	23	-14	25	0
DECREASED APPETITE	149	340	38	42	4	86	3
RASH	148	485	39	32	-7	51	1
HYPOAESTHESIA	143	362	40	39	-1	89	1
PRURITUS	139	425	41	34	-7	70	0
HEART RATE INCREASED	132	300	42	44	2	82	4
CHEST DISCOMFORT	129	302	43	43	0	65	0
THROAT IRRITATION	125	267	44	47	3	10	0
INSOMNIA	122	256	45	48	3	66	0
BACK PAIN	116	285	46	45	-1	75	2
CEREBROVASCULAR ACCIDENT	116	174	46	50	4	111	10
VACCINATION SITE PAIN	115	280	48	46	-2	97	0
INFLUENZA LIKE ILLNESS	114	234	49	49	0	69	0
SYNCOPE	113	436	50	33	-17	69	2
Count:	50						

6. Most Frequent PTs Within HLGT 'MEDICATION ERRORS AND OTHER PRODUCT USE ERRORS AND ISSUES'

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
PRODUCT STORAGE ERROR	2,852	3,613	1	1	0	0	0
INCORRECT PRODUCT FORMULATION ADMINISTERED	481	1,468	2	2	0	2	0
EXPIRED PRODUCT ADMINISTERED	375	670	3	4	1	0	0
EXTRA DOSE ADMINISTERED	207	413	4	6	2	1	0
WRONG PRODUCT ADMINISTERED	181	595	5	5	0	97	3
INCORRECT DOSE ADMINISTERED	150	675	6	3	-3	25	0
POOR QUALITY PRODUCT ADMINISTERED	95	125	7	12	5	1	0
INAPPROPRIATE SCHEDULE OF PRODUCT ADMINISTRATION	92	256	8	10	2	7	0
MEDICATION ERROR	84	91	9	13	4	3	0
PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE	74	327	10	7	-3	3	0
PRODUCT PREPARATION ISSUE	64	298	11	8	-3	0	0
PRODUCT USE ISSUE	60	264	12	9	-3	45	3
PRODUCT PREPARATION ERROR	33	145	13	11	-2	0	0
PRODUCT ADMINISTRATION ERROR	29	82	14	14	0	4	0
VACCINATION ERROR	19	36	15	15	0	0	0
INCORRECT ROUTE OF PRODUCT ADMINISTRATION	12	32	16	16	0	8	1
CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR	8	23	17	17	0	0	0
PRODUCT ADMINISTERED AT INAPPROPRIATE SITE	5	20	18	18	0	1	0
WRONG TECHNIQUE IN PRODUCT USAGE PROCESS	2	10	19	19	0	1	0
CONTRAINDICATED PRODUCT ADMINISTERED	1	1	20	23	3	1	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
INCOMPLETE COURSE OF VACCINATION	1	5	20	20	0	0	0
PRODUCT PACKAGING CONFUSION	1	2	20	21	1	0	0
UNINTENTIONAL MEDICAL DEVICE REMOVAL	1	1	20	23	3	0	0
WRONG PATIENT RECEIVED PRODUCT	1	2	20	21	1	0	0
Count:	24						

7. Most Frequent PTs with Malfunction Flag = Yes

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
Count:	0						

8. Most Frequent PTs Within SOC 'PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS'

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
EXPOSURE DURING PREGNANCY	16	38	1	1	0	5	0
MATERNAL EXPOSURE DURING PREGNANCY	13	21	2	2	0	11	0
ABORTION SPONTANEOUS	6	12	3	3	0	4	0
FAILURE TO THRIVE	4	7	4	4	0	3	1
ANTIPHOSPHOLIPID SYNDROME	2	3	5	9	4	2	1
DELIVERY	2	4	5	6	1	1	0
MATERNAL EXPOSURE BEFORE PREGNANCY	2	5	5	5	0	1	0
MORNING SICKNESS	2	2	5	11	6	1	0
PREMATURE DELIVERY	2	3	5	9	4	2	0
SCALP HAEMATOMA	2	2	5	11	6	2	1
ABORTION INCOMPLETE	1	2	11	11	0	0	0
ABORTION MISSED	1	4	11	6	-5	0	0
BIOCHEMICAL PREGNANCY	1	1	11	17	6	1	0
BRIEF RESOLVED UNEXPLAINED EVENT	1	1	11	17	6	1	0
CENTRAL NERVOUS SYSTEM LYMPHOMA	1	1	11	17	6	1	0
HAEMORRHAGE IN PREGNANCY	1	1	11	17	6	0	0
INDUCED LABOUR	1	1	11	17	6	1	0
LABOUR PAIN	1	1	11	17	6	1	0
MATERNAL EXPOSURE DURING BREAST FEEDING	1	1	11	17	6	1	0
PLACENTA PRAEVIA	1	2	11	11	0	0	0
PREGNANCY	1	4	11	6	-5	1	0
PREMATURE SEPARATION OF PLACENTA	1	2	11	11	0	1	0
SUPPRESSED LACTATION	1	2	11	11	0	1	0
UTERINE HYPERTONUS	1	1	11	17	6	1	0
Count:	24						

9. Most Frequent PTs with Death

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
COVID-19	23	42	1	1	0
DYSPNOEA	20	47	10	13	3
ASTHENIA	10	20	17	18	1
CONDITION AGGRAVATED	10	24	24	24	0
COUGH	9	15	6	6	0
PYREXIA	9	26	5	4	-1

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
INTERCHANGE OF VACCINE PRODUCTS	8	19	12	15	3
MALAISE	6	26	8	9	1
FATIGUE	5	16	3	3	0
CHILLS	4	8	11	8	-3
DIZZINESS	4	10	16	12	-4
FEELING ABNORMAL	4	6	21	21	0
NAUSEA	4	11	14	11	-3
VOMITING	4	14	25	22	-3
CHEST PAIN	3	9	23	25	2
DIARRHOEA	3	5	22	23	1
DRUG INEFFECTIVE	3	4	4	5	1
HEADACHE	3	6	2	2	0
OROPHARYNGEAL PAIN	3	3	9	14	5
PAIN IN EXTREMITY	3	3	12	10	-2
ARTHRALGIA	2	8	19	16	-3
MYALGIA	1	4	20	19	-1
PAIN	1	5	7	7	0
RESPIRATORY TRACT CONGESTION	1	3	15	17	2
RHINORRHOEA	1	3	18	20	2
Count:	25				

Input Summary

*** Query Name:Query 1 ***

Select Only One Vaccine Name COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))
Report Date (Start): 1/1/2023 12:00:00 AM
Report Date (End): 3/31/2023 11:59:59 PM
Vaccination Date (Start) (Optional)
Vaccination Date (End) (Optional)
Vaccination Date Unknown Flag - If specifying vaccination dates, select 'Yes' to include reports with unknown vaccination dates (otherwise, leave blank) (Optional)
Age (Start) (Optional)
Age (End) (Optional)
Age unknown - If specifying age(s), select 'Unknown' here to include unknown ages (Optional)
Enter 'FR' to exclude foreign reports (otherwise, leave blank) (Optional)

Moderna COVID-19 Vaccine, Bivalent STN#125752/EUA27073
Review Period: 1/1/23 – 3/31/23 FDA Authorization Date: 8/31/2022

Quarterly Surveillance Report for Moderna COVID-19 Vaccine, Bivalent
Surveillance Period: January 1, 2023 to March 31, 2023

1. The Business Objects VAERS Internal Surveillance Report (VISR) query was run on April 5, 2023 for Moderna COVID-19 Vaccine, Bivalent for the surveillance period January 1, 2023 to March 31, 2023. All tables of report counts by age, location, most common PT, medication error and malfunction, and pregnancy are presented in Reports 1-9 in the attached document.

Reviewer Comment: Data in Business Objects queries do not suggest a new safety concern.

2. Death Reports

Deaths During Surveillance Period

The following death report was considered notable:

ID	Age/Sex	COD	Case Summary
[redacted]	2y/F	Unknown, pending investigation	Patient was found dead 1 day after receiving Moderna COVID-19 Vaccine, Bivalent and annual Flulaval flu vaccine. Had a history of a seizure 6 months prior to death, EEG was performed at that time (no results included in VAERS).

Reviewer Comments:
Death reports were individually reviewed, most death reports concern patients with COVID-19 infection or alternate/plausible etiologies for cause of death, the majority of death reports cannot be directly attributed solely to Moderna COVID-19 Vaccine, Bivalent.

3. Other Medically Notable Cases

ID	Age/Sex	Case Summary
[redacted]	38y/M	This report is from a non-study case report publication. Patient presented with a sudden central scotoma in the left eye 3 days after vaccination with second booster dose of Moderna COVID-19, Bivalent. No previous significant refractive error. Diagnosed with atypical bilateral serous retinal detachment with Roth spot, felt to be consistent with acute idiopathic maculopathy
[redacted]	24y/M	Developed idiopathic transverse myelitis 30 days after vaccination, also had received an unknown formulation of influenza vaccine 2 days prior to development of symptoms.
[redacted]	39y/M	History of high functioning autism, developed headache and photosensitivity 10 days after vaccination, MRI normal. 32 days after vaccination, developed confusion and left arm numbness. Repeat MRI revealed significant bilateral (right > left) medial temporal enhancing lesions, suggestive of encephalitis. Viral studies and quantiferon gold negative. Rheumatologic and oncologic workup was negative. Subsequent imaging showed improvement in brain lesions but discovered a cervical spine lesion.
[redacted]	58y/F	Eleven days after vaccine, developed severe bullous urticaria, with large open ulcers all over the body including oral cavity, skin peeling, feet and toes

		blistering rash. Had persisted for 4 months at the time of the report.

Reviewer Comments:
Report [redacted] *is a foreign report. In the publication, the authors concluded that the vaccine was probably causal for the adverse event due to the temporal relationship and the absence of other potential causes. The remainder of the reports are domestic. With the second and third reports, alternate causes were not found according to the latest documents available within VAERS. FDA will continue close surveillance for any similar cases.*

4. Data Mining Findings[1]

Data mining for Moderna COVID-19 Vaccine, Bivalent was conducted using the Empirica 8.0 Signals run on April 5, 2023. The data lock point was March 31, 2023. The PTs with an EB05≥2 are shown below. PTs are discussed in reviewer comment below.

Event	US EB05 20230331	US Serious EB05 20230331	US Fatal EB05 20230331	US Infant EB05 20230331	US Child EB05 20230331	US Teen EB05 20230331
Accidental underdose	**9.675**				0.648	0.534
Circumstance or information capable of leading to medication error	**2.014**				0.524	
Device connection issue	**6.911**					
Incorrect dose administered	**3.072**			0.874	1.08	0.772
Incorrect product formulation administered	1.25	0.747	0.857	1.922	1.47	**2.587**
No adverse event	**2.488**	0.735		0.672	1.202	1.231
Poor quality product administered	**2.009**				0.709	0.434
Product temperature excursion issue	**2.725**				0.918	0.699
Syringe issue	**2.679**					0.519
Underdose	**6.733**				0.335	1.069

[1] Data mining findings are subject to a number of potential limitations and are to be regarded as "hypothesis generating." Data mining findings do not imply causality.

Wrong product administered	**2.173**			0.741	0.962	1.388

Reviewer Comments:
Data mining findings demonstrate that PTs with disproportionate reports are in the category of medication errors and were not disproportionate in serious or fatal cases. No specific disproportionate reporting of medication errors were noted in the pediatric age group.

5. Publications

A literature search of PubMed on April 5, 2023 using the keywords, (mRNA-1273.222 OR Moderna bivalent) AND safety and a date range of January 1, 2023 to March 31, 2023 yielded two new articles relevant to safety in humans in the current review period. The titles and abstracts of the articles were reviewed, and articles relevant to safety are described in the table below.

Article Citation	Safety Conclusions	Regulatory Implications
Jacobs JW, Booth GS, Adkins BD. Analysis of hematologic adverse events reported to a national surveillance system following COVID-19 bivalent booster vaccination. Ann Hematol. 2023 Apr;102(4):955-959. doi: 10.1007/s00277-023-05136-2. Epub 2023 Feb 16. PMID: 36795118; PMCID: PMC9933824.	In reviewing VAERS reports, adverse hematologic events are rare following vaccination with COVID-19 bivalent booster from all manufacturers (1.05 per million doses), and most cannot be definitively attributed to vaccination. Three reports of possible ITP and one report of possible VITT highlight the need for ongoing surveillance as new formulations are authorized.	Continue with pharmacovigilance activities as currently being performed.
Hause AM, Marquez P, Zhang B, Su JR, Myers TR, Gee J, Panchanathan SS, Thompson D, Shimabukuro TT, Shay DK. 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 Jan 13;72(2):39-43. doi: 10.15585/mmwr.mm7202a5. PMID: 36634021; PMCID: PMC9869731.	Preliminary review of safety reporting to the VAERS database from the first 11 weeks after authorization of Moderna COVID-19 Local and systemic reactions reported after receipt of a bivalent booster dose are consistent with those reported after a monovalent booster dose; serious adverse events are rare.	Continue with pharmacovigilance activities as currently being performed.

Additional Product Information

Monthly Summary Safety Reports 17, 18, and 19 were reviewed during the reporting period. There were no new safety issues identified in these three reports. Three validated signals, “Myositis”, “Amenorrhea [reevaluation],” and “Pemphigus and pemphigoid”), two of which (“Amenorrhea [reevaluation]” and “Pemphigus and pemphigoid”) were evaluated and closed as refuted signals.

Product Details

The Moderna COVID-19 Vaccine, Bivalent is a 50-µg formulation which contains total mRNA encoding the SARS-CoV-2 spike glycoproteins (S-2P) from Omicron BA.4/.5 strain (25µg mRNA) and Wuhan-Hu-1 strain (25µg mRNA, Original strain). The Bivalent Vaccine is supplied in a multiple-dose vial with a dark blue cap and gray border; the label will specify that it is the “Bivalent” product. It is supplied as a frozen suspension that does not contain a preservative and must be thawed prior to administration.

Conclusion

The results from this quarterly surveillance report do not indicate a need for further regulatory action. Continue routine surveillance.

VAERS Internal Surveillance Report

Surveillance Period (Completed Dates): **1/1/23 to 3/31/23**

Report Run Date: **4/5/23**

Vaccine Name: **COVID19 (COVID19 (MODERNA BIVALENT))**

Report By: **Sarada.Panchanathan**

1. Event Counts by Location and Seriousness

	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
US	5,161	470	51	51	328	59	0	68
Foreign	173	163	14	15	61	9	0	85
Total	**5,334**	**633**	**65**	**66**	**389**	**68**	**0**	**153**

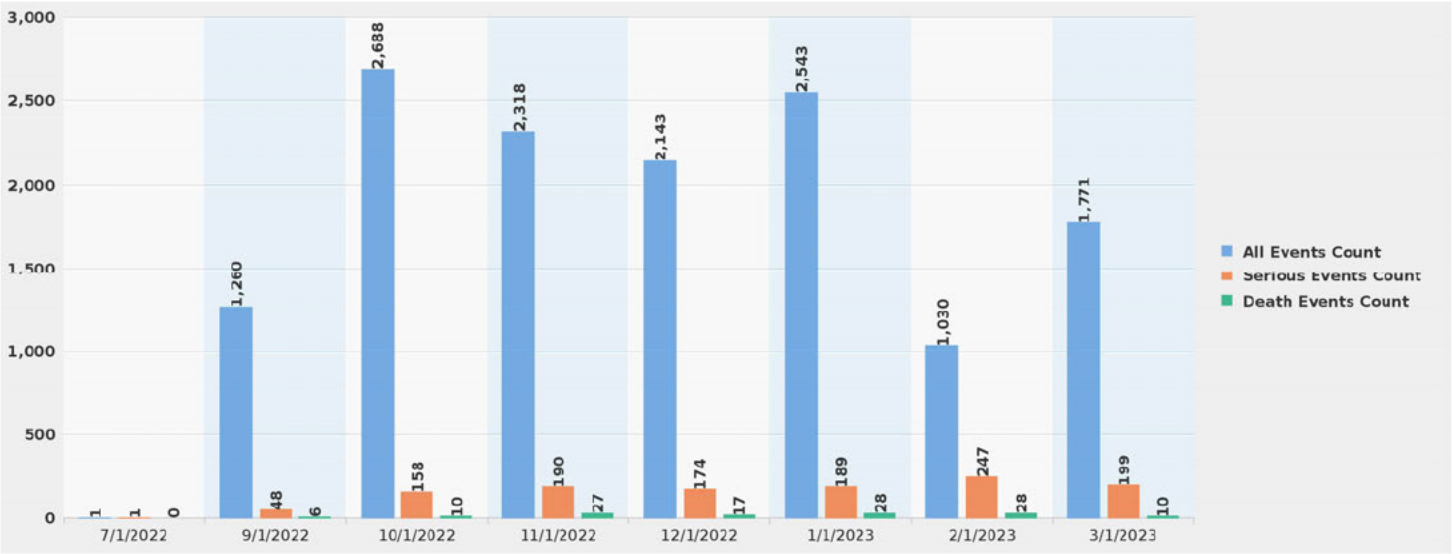
Note: One event can be counted in multiple serious subcategories if reported differently by multiple reporters

2. Event Counts by Age Group

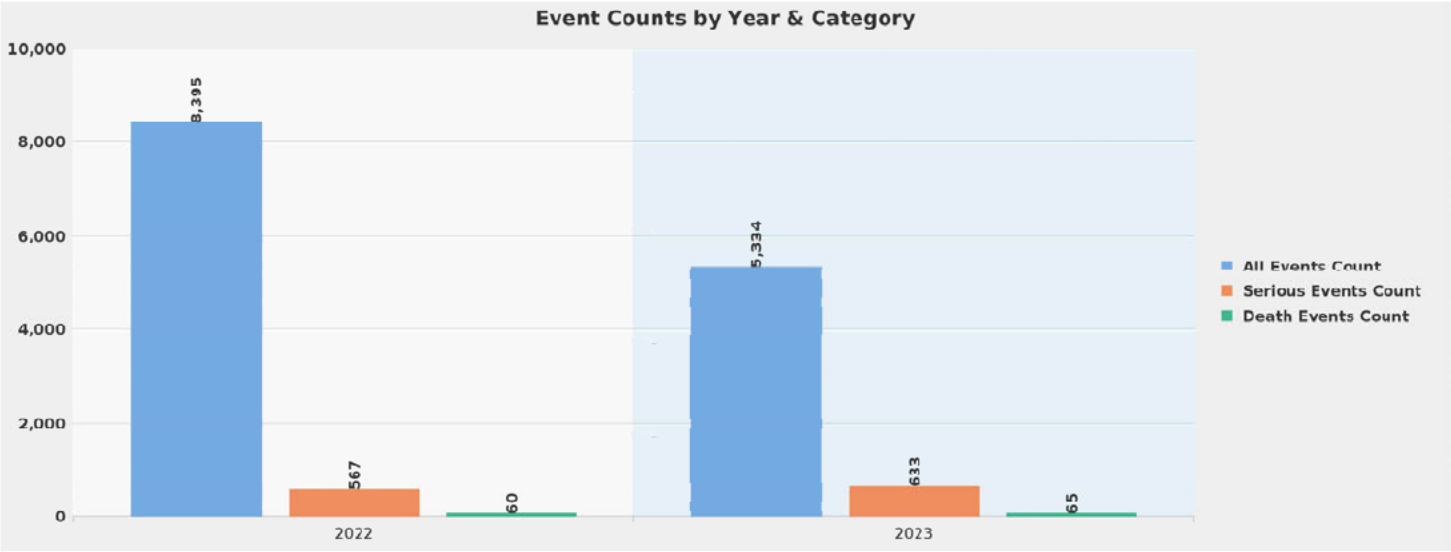
	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
<1 Year	22	0	0	0	0	0	0	0
1 to <3 Years	63	1	1	0	0	0	0	0
3 to <7 Years	79	4	0	0	3	0	0	1
7 to <17 Years	88	31	0	1	15	1	0	14
17 to <65 Years	2,055	187	13	22	100	34	0	50
>= 65 Years	1,907	319	34	35	259	27	0	28
Not Reported	1,121	91	17	8	12	6	0	60
Total	**5,334**	**633**	**65**	**66**	**389**	**68**	**0**	**153**

Note: One event can be counted in multiple age bands and/or serious subcategories if reported differently by multiple reporters

3. Event Counts for Surveillance Period and Prior 12 Months



4. Event Counts for Surveillance Period Year and Prior 5 Years



5. Most Frequent Preferred Terms (PTs)

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
NO ADVERSE EVENT	1,550	3,726	1	1	0	0	0
COVID-19	1,130	1,861	2	2	0	201	9
EXPIRED PRODUCT ADMINISTERED	865	1,421	3	3	0	0	0
COUGH	646	1,071	4	8	4	47	1
PRODUCT STORAGE ERROR	621	961	5	10	5	0	0
PYREXIA	566	1,325	6	5	-1	71	1
FATIGUE	528	1,255	7	6	-1	42	2
UNDERDOSE	470	1,371	8	4	-4	0	0
HEADACHE	451	1,199	9	7	-2	40	2
PAIN	403	1,035	10	9	-1	30	1
OROPHARYNGEAL PAIN	371	645	11	13	2	9	0
RESPIRATORY TRACT CONGESTION	316	506	12	20	8	14	0
MALAISE	281	534	13	17	4	23	1
RHINORRHOEA	252	435	14	23	9	5	0
CHILLS	212	716	15	11	-4	18	0
INCORRECT PRODUCT FORMULATION ADMINISTERED	209	507	16	19	3	0	0
DYSPNOEA	195	460	17	22	5	73	9
POOR QUALITY PRODUCT ADMINISTERED	178	628	18	14	-4	0	0
PAIN IN EXTREMITY	165	589	19	16	-3	23	1
NASOPHARYNGITIS	153	241	20	36	16	4	0
PRODUCT TEMPERATURE EXCURSION ISSUE	152	618	21	15	-6	0	0
DIZZINESS	146	533	22	18	-4	35	1
ASTHENIA	143	355	23	29	6	52	3
EXTRA DOSE ADMINISTERED	143	326	23	32	9	0	0
NAUSEA	131	500	25	21	-4	34	2
WRONG PRODUCT ADMINISTERED	131	416	25	25	0	0	0
FEELING ABNORMAL	127	367	27	26	-1	12	0
NASAL CONGESTION	122	228	28	39	11	4	0
ARTHRALGIA	119	433	29	24	-5	12	0
CONDITION AGGRAVATED	118	280	30	33	3	49	4

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
RASH	105	358	31	27	-4	14	0
CHEST PAIN	104	233	32	37	5	43	2
MYALGIA	103	356	33	28	-5	17	1
DIARRHOEA	92	251	34	34	0	24	1
INCORRECT DOSE ADMINISTERED	88	654	35	12	-23	1	0
SNEEZING	85	140	36	46	10	3	0
VOMITING	85	251	36	34	-2	32	1
CHEST DISCOMFORT	83	192	38	41	3	24	0
PRURITUS	82	332	39	31	-8	8	0
EXPOSURE TO SARS-COV-2	81	117	40	48	8	3	0
THROAT IRRITATION	81	156	40	44	4	2	0
URTICARIA	74	230	42	38	-4	5	0
INJECTION SITE PAIN	71	339	43	30	-13	7	0
INAPPROPRIATE SCHEDULE OF PRODUCT ADMINISTRATION	68	189	44	42	-2	0	0
VACCINE BREAKTHROUGH INFECTION	65	98	45	50	5	46	0
MOBILITY DECREASED	62	179	46	43	-3	13	2
ERYTHEMA	60	206	47	40	-7	5	1
DECREASED APPETITE	58	139	48	47	-1	11	1
IMMUNISATION REACTION	55	144	49	45	-4	2	0
PRODUCTIVE COUGH	54	113	50	49	-1	3	0
Count:	50						

6. Most Frequent PTs Within HLGT 'MEDICATION ERRORS AND OTHER PRODUCT USE ERRORS AND ISSUES'

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
EXPIRED PRODUCT ADMINISTERED	865	1,421	1	1	0	0	0
PRODUCT STORAGE ERROR	621	961	2	2	0	0	0
INCORRECT PRODUCT FORMULATION ADMINISTERED	209	507	3	5	2	0	0
POOR QUALITY PRODUCT ADMINISTERED	178	628	4	4	0	0	0
EXTRA DOSE ADMINISTERED	143	326	5	7	2	0	0
WRONG PRODUCT ADMINISTERED	131	416	6	6	0	0	0
INCORRECT DOSE ADMINISTERED	88	654	7	3	-4	1	0
INAPPROPRIATE SCHEDULE OF PRODUCT ADMINISTRATION	68	189	8	9	1	0	0
CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR	34	67	9	11	2	0	0
PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE	23	123	10	10	0	1	0
PRODUCT PREPARATION ERROR	14	19	11	15	4	0	0
PRODUCT ADMINISTRATION ERROR	13	38	12	12	0	1	0
TRANSCRIPTION MEDICATION ERROR	13	13	12	18	6	0	0
ACCIDENTAL UNDERDOSE	11	311	14	8	-6	0	0
VACCINATION ERROR	9	10	15	20	5	0	0
PRODUCT USE ISSUE	7	15	16	17	1	0	0
INCORRECT ROUTE OF PRODUCT ADMINISTRATION	6	30	17	13	-4	0	0
PRODUCT ADMINISTERED AT INAPPROPRIATE SITE	5	27	18	14	-4	1	0
MEDICATION ERROR	4	9	19	21	2	0	0
ACCIDENTAL OVERDOSE	3	13	20	18	-2	0	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
PRODUCT ADMINISTRATION INTERRUPTED	1	1	21	24	3	0	0
PRODUCT DOSE OMISSION ISSUE	1	2	21	23	2	0	0
WRONG PATIENT RECEIVED PRODUCT	1	4	21	22	1	0	0
WRONG TECHNIQUE IN PRODUCT USAGE PROCESS	1	19	21	15	-6	0	0
Count:	24						

7. Most Frequent PTs with Malfunction Flag = Yes

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
Count:	0						

8. Most Frequent PTs Within SOC 'PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS'

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
MATERNAL EXPOSURE DURING BREAST FEEDING	15	16	1	2	1	1	0
EXPOSURE DURING PREGNANCY	10	25	2	1	-1	1	0
MATERNAL EXPOSURE DURING PREGNANCY	6	14	3	3	0	0	0
ABORTION SPONTANEOUS	2	4	4	4	0	0	0
DELIVERY	1	2	5	6	1	1	0
EXPOSURE VIA BREAST MILK	1	3	5	5	0	1	0
FOETAL DEATH	1	2	5	6	1	0	0
FOETAL HYPOKINESIA	1	1	5	8	3	0	0
FOETAL VASCULAR MALPERFUSION	1	1	5	8	3	0	0
MATERNAL EXPOSURE BEFORE PREGNANCY	1	1	5	8	3	0	0
PRE-ECLAMPSIA	1	1	5	8	3	0	0
PRETERM PREMATURE RUPTURE OF MEMBRANES	1	1	5	8	3	0	0
UMBILICAL CORD THROMBOSIS	1	1	5	8	3	0	0
Count:	13						

9. Most Frequent PTs with Death

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
DEATH	52	101	21	25	4
COVID-19	9	17	1	1	0
DYSPNOEA	9	19	8	11	3
ATRIAL FIBRILLATION	5	6	23	24	1
CONDITION AGGRAVATED	4	10	13	14	1
ASTHENIA	3	7	11	13	2
LETHARGY	3	6	25	23	-2
CHEST PAIN	2	5	14	17	3
FATIGUE	2	4	4	3	-1
HEADACHE	2	2	5	4	-1
HEART RATE INCREASED	2	4	24	21	-3
MOBILITY DECREASED	2	3	18	19	1
NAUSEA	2	2	12	10	-2
COUGH	1	5	2	5	3
DECREASED APPETITE	1	2	20	22	2
DIARRHOEA	1	3	16	15	-1
DIZZINESS	1	2	10	9	-1
ERYTHEMA	1	1	19	18	-1

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
MALAISE	1	3	7	8	1
MYALGIA	1	1	15	12	-3
PAIN IN EXTREMITY	1	2	9	7	-2
PAIN	1	3	6	6	0
PALPITATIONS	1	2	21	20	-1
PYREXIA	1	2	3	2	-1
VOMITING	1	2	17	15	-2
Count:	25				

Input Summary

*** Query Name:Query 1 ***

Select Only One Vaccine Name COVID19 (COVID19 (MODERNA BIVALENT))
Report Date (Start): 1/1/2023 12:00:00 AM
Report Date (End): 3/31/2023 12:00:00 AM
Vaccination Date (Start) (Optional)
Vaccination Date (End) (Optional)
Vaccination Date Unknown Flag - If specifying vaccination dates, select ‘Yes’ to include reports with unknown vaccination dates (otherwise, leave blank) (Optional)
Age (Start) (Optional)
Age (End) (Optional)
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Quarterly Surveillance Report for Moderna COVID-19 Vaccine, Bivalent
Surveillance Period: January 1, 2023 to March 31, 2023

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Reviewer Comment: Data in Business Objects queries do not suggest a new safety concern.

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The following death report was considered notable:

ID	Age/Sex	COD	Case Summary
[redacted]	2y/F	Unknown, pending investigation	Patient was found dead 1 day after receiving Moderna COVID-19 Vaccine, Bivalent and annual Flulaval flu vaccine. Had a history of a seizure 6 months prior to death, EEG was performed at that time (no results included in VAERS).

Reviewer Comments:
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3. Other Medically Notable Cases

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[redacted]	24y/M	Developed idiopathic transverse myelitis 30 days after vaccination, also had received an unknown formulation of influenza vaccine 2 days prior to development of symptoms.
[redacted]	39y/M	History of high functioning autism, developed headache and photosensitivity 10 days after vaccination, MRI normal. 32 days after vaccination, developed confusion and left arm numbness. Repeat MRI revealed significant bilateral (right > left) medial temporal enhancing lesions, suggestive of encephalitis. Viral studies and quantiferon gold negative. Rheumatologic and oncologic workup was negative. Subsequent imaging showed improvement in brain lesions but discovered a cervical spine lesion.
[redacted]	58y/F	Eleven days after vaccine, developed severe bullous urticaria, with large open ulcers all over the body including oral cavity, skin peeling, feet and toes

		blistering rash. Had persisted for 4 months at the time of the report.

Reviewer Comments:
Report [redacted] is a foreign report. In the publication, the authors concluded that the vaccine was probably causal for the adverse event due to the temporal relationship and the absence of other potential causes. The remainder of the reports are domestic. With the second and third reports, alternate causes were not found according to the latest documents available within VAERS. FDA will continue close surveillance for any similar cases.

4. Data Mining Findings[1]

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Reviewer Comments:
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Monthly Summary Safety Reports 17, 18, and 19 were reviewed during the reporting period. There were no new safety issues identified in these three reports. Three validated signals, “Myositis”, “Amenorrhea [reevaluation],” and “Pemphigus and pemphigoid”), two of which (“Amenorrhea [reevaluation]” and “Pemphigus and pemphigoid”) were evaluated and closed as refuted signals.

Product Details

The Moderna COVID-19 Vaccine, Bivalent is a 50-µg formulation which contains total mRNA encoding the SARS-CoV-2 spike glycoproteins (S-2P) from Omicron BA.4/.5 strain (25µg mRNA) and Wuhan-Hu-1 strain (25µg mRNA, Original strain). The Bivalent Vaccine is supplied in a multiple-dose vial with a dark blue cap and gray border; the label will specify that it is the "Bivalent" product. It is supplied as a frozen suspension that does not contain a preservative and must be thawed prior to administration.

Conclusion

The results from this quarterly surveillance report do not indicate a need for further regulatory action. Continue routine surveillance.

From: "Thompson, Deborah" [redacted]
To: "Nair, Narayan" [redacted] "Alimchandani, Meghna" [redacted] "Welsh, Kerry" [redacted] "Jason, Christopher" [redacted] "Bazel, Samaneh" [redacted]
Subject: Data Mining for Pfizer Bivalent: Ischemic Stroke
Date: Tue, 28 Feb 2023 15:54:32 +0000
Importance: Normal
Attachments: Empirica_data_Pfizer_Bivalent_DLP_2.24.23.xls; QQ_LL_Pfizer_Bivalent_Ischemic_Stroke_Run_on_2.28.23.xlsx; 125742.245.2_response-20dec2023-ir-safety-assessment.pdf
Inline-Images: image001.png; image002.jpg; image003.jpg; image004.jpg; image005.jpg; image006.jpg; image007.png

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Hi Narayan, Meghna, Kerry, Chris, and Sam,

While doing my weekly surveillance review for the Pfizer bivalent COVID-19 vaccine, ischemic stroke appeared as a new data mining finding with an EB05>2 for US serious, although the EB05=1.01 for overall US:

Drug	Event	US EB05 20230224	US Serious EB05 20230224	US Fatal EB05 20230224	US Infant EB05 20230224	US Child EB05 20230224	US Teen EB05 20230224	US Adult1 EB05 20230224	US Adult2 EB05 20230224	US Adult3 EB05 20230224	US Female EB05 20230224	US Male EB05 20230224
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Incorrect product formulation	1.965			6.099	3.335	2.815	2.022	1.232	0.909	1.849	1.969
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Ischaemic stroke	1.01	2.056	0.855				0.707	0.53	1.029	0.867	0.98
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Off label use	2.773	0.977	0.86		0.62	0.654	1.275	1.788	3.074	2.609	1.969
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Product preparation error	1.91			0.664	1.227	1.063	5.39	1.103	1.625	1.36	2.205
COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))	Product use issue	2.844	1.047	0.854		0.53	0.743	1.381	2.534	2.384	2.569	1.964

The QQ-LL report for Pfizer bivalent for ischemic stroke shows a total of 53 reports (41 US and 12 foreign).

Among the 41 US reports:

- 39 (95.1%) non-fatal serious/OMIC reports and 2 (4.9%) death reports
- 19 (46.3%) females and 22 (53.7%) males
- Median age=69 years (range=20-90 years)
- Median onset=21 days post-vax (range=0-128 days)
- US reporting rate=1.19 reports per million doses administered (CDC COVID Data Tracker: Vaccinations in the US)

I've also attached the recent IR response from Pfizer, which evaluated thromboembolic events (TEE) following the Pfizer bivalent vaccine and concluded that there is no evidence that TEE, including ischemic stroke, are a safety signal or risk of the bivalent vaccine.

I'm wondering if you are aware of any updates from CDC VSD or BEST on the monitoring/assessment of ischemic stroke following the Pfizer bivalent vaccine?

Please let me know if you have any questions or need any additional information.

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
[redacted]

FDA U.S. FOOD & DRUG ADMINISTRATION

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Bivalent BNT162b2 (Original and Omicron BA.4/BA.5)

Response to FDA (CBER) Request for Information

Thromboembolic events and Pfizer-BioNTech Bivalent BNT162b2 (Original and Omicron BA.4/BA.5) COVID-19 Vaccine

24 January 2023

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACCESS	vACcine Covid-19 monitoring readinESS
ACS	acute coronary syndrome
AESI	adverse events of special interest
AER	adverse event report
AF	atrial fibrillation
AMI	acute myocardial infarction
APF4	antiplatelet factor 4
ARS	Agenzia regionale di sanità
aSMSR	Abbreviated Summary Monthly Safety Report
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (Pharmacoepidemiologic Research in Public Health Systems)
BLA	Biologics License Application
BNT	BioNTech
CBER	Center for Biologics Evaluation and Research
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPRD	Clinical Practice Research Datalink
CVST	cerebral venous sinus thrombosis
DCE-AU	Danish Centre for Environment and Energy- Aarhus University
DIC	disseminated intravascular coagulation
DM	diabetes mellitus
DVT	deep vein thrombosis
ED	emergency department
EEA	European Economic Area
FDA	Food and Drug Administration
GePaRD	German Pharmacoepidemiological Research Database
HC	high cholesterol
HCP	healthcare professional
HIT	heparin-induced thrombocytopenia
HTN	hypertension
ICU	intensive care unit
LL	lower limit
LMWH	low molecular weight heparin
LV	left ventricle
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Abbreviation	Definition
NSAIDS	nonsteroidal anti-inflammatory drug
O/E	observed/expected
OSA	obstructive sleep apnea
PCR	polymerase chain reaction
PE	pulmonary emboli
PT	Preferred Term
PY	person-years
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (The Information System for Research in Primary Care)
SLE	systemic lupus erythematosus
SMQ	standardized MedDRA query
SNDS	Supplement to a New Drug Submission
TIA	transient ischemic attack
TTP	thrombotic thrombocytopenic purpura
TTS	thrombosis with thrombocytopenia syndrome
UL	upper limit
US	United States
UTI	urinary tract infection
VAERS	vaccine adverse event reporting system

1. INTRODUCTION

Reference is made to the information request received by Pfizer via e-mail on 20 Dec 2022 from the FDA, CBER from Alexandria Edwards, PharmD. (CBER) to Gosia Mineo (Pfizer Inc) regarding arterial, venous and mixed thromboembolic events after receiving Bivalent BNT162b2 (Original and Omicron BA.4/BA.5) BNT COVID-19 mRNA vaccine. CBER requested we provide the results from this assessment in the next aSMSR which is due in January 2023. On 21 Dec 2022, Pfizer informed CBER that aSMSR 11 (16 Nov 2022 to 15 Dec 2022) was planned to be submitted on 06 Jan 2023 and proposed to provide the request for information in a separate report and submit it to the BLA 125742 by end of January 2023. CBER agreed to this proposal on 22 Dec 2022.

The FDA (CBER) requests in ***bold italics*** are followed by Pfizer-BioNTech's responses in plain text below.

2. CBER REQUEST FOR INFORMATION

We have received VAERS reports of embolic and thrombotic events, including ischemic stroke, transient ischemic attacks, cerebral venous sinus thrombosis (CVST) and pulmonary emboli (PE), for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Three reports mention concern for vaccine-induced immune thrombotic thrombocytopenia (VITT) (VAERS #2502144, #2514229, and #2507203). Please perform a cumulative safety and causality assessment of embolic and thrombotic events following receipt of the Pfizer-BioNTech COVID-19 Vaccine, Bivalent.

3. RESPONSE

3.1. BACKGROUND

Thromboembolic events and TTS are AESI for Comirnaty (including the BNT16b2 bivalent vaccines) and are monitored by Pfizer on behalf of BioNTech. This document is written in response to the above FDA request and pertains to Bivalent BNT162b2 (Original and Omicron BA.4/BA.5) vaccine (herein referred to as *Bivalent Comirnaty*).

3.2. SAFETY DATABASE

Pfizer's safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious adverse events reported from clinical studies regardless of causality.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include length of time since marketing, market share of the drug, publicity about a drug or an adverse event, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.

Because many external factors influence whether or not an adverse event is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.

An accumulation of AERs does not necessarily indicate that a particular adverse event was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.

The safety database was searched for all cases reported cumulatively for BNT162b2, BNT162b2 OMI BA.4-5 (Bivalent Comirnaty) through 15 Dec 2022 with a PT falling into the MedDRA version 25.1 Embolic and thrombotic events SMQ. This SMQ consists of 3 "sub-SMQs:"

1. Embolic and thrombotic events, arterial SMQ (40 cases)
2. Embolic and thrombotic events, venous SMQ and (67 cases)
3. Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous SMQ (75 cases)

Eighteen cases appeared in more than 1 of the 3 sub-SMQs. Seventeen of the 18 are in either the arterial or venous SMQ plus the vessel type unspecified/mixed SMQ and will be discussed in Section 3.2.3 with the unspecified/mixed cases. The remaining overlapping case (PV202200103847) is in both the venous and arterial SMQs and will be discussed in Section 3.2.1 with the arterial cases.

3.2.1. Cases in Embolic and Thrombotic Events, Arterial SMQ

Of the 40 total reports in this arterial SMQ, 14 overlapped with the other embolic and thrombotic SMQs: 4 overlapped with the venous SMQ, 13 overlapped with the unspecified/mixed SMQ and 3 overlapped with both the venous and the unspecified/mixed SMQ; leaving 27 unique cases.

The 27 cases (26 unique plus 1 overlapping with venous SMQ, AER PV202200103847), were reported between 17 Oct 2022 and 15 Dec 2022 and included 15 females and 11 males (1 case did not specify sex). Ages ranged from 37 to 94 years (mean 74.7); 1 case did not specify age. Fifteen cases were medically confirmed and 12 were not; all cases were classified as serious. Cases were reported from Germany (11), Japan (6), Spain, Italy, France (2 each) and Finland, Portugal, Sweden and US (1 each). Dose number was specified in all but 6 cases; 1 case occurred after Dose 2, twelve (12) occurred after Dose 4 and 8 occurred after Dose 5. A large majority of reporters were unable to specify the manufacturers of the

previous COVID-19 vaccine the patients received prior to Bivalent Comirnaty. There were 10 death reports; narrative line listings of the death cases are in Appendix 1.

3.2.1.1. Cardiovascular Events (19 Cases)

- Nine AMIs and 2 ACSs ranging from the same day to 24 days after vaccination; outcomes were: 4 deaths (1 in patient with concomitant COVID-19), 3 recovering or recovered with sequelae, and 4 with unknown outcomes. All patients except 2 with no known or reported medical history, had risk factors for heart disease including known coronary artery disease, valvular cardiac disease, HTN, DM, HC, and atrial fibrillation. One of the 11 cases were notable for concurrent thrombocytopenia:

    1. An 88-year-old man with known COPD, CHF and LV dysfunction had an ACS occurring 24 days after Dose 4 (previous COVID-19 vaccine doses from an unknown manufacturer) and was also reported to have concurrent immune thrombocytopenia (platelet nadir 2000), treated with IVIg, corticosteroids and responding to rituximab (APF4 testing not mentioned); his hospital course was also complicated by a UTI and nosocomial pneumonia, however he was recovering from the thrombocytopenia and ACS at the time of the report.

- Five cases in which AMI or a cardiac event was assumed by the reporter because all outcomes were deaths with no autopsies in patients with risk factors for cardiac disease including known cardiac disorders, HTN, DM, HC; 1 patient had cirrhosis and hepatocellular carcinoma.

- One case of aortic dissection in a 79-year-old woman with known aortic dissection, HTN and SLE who died 1 day following Dose 4 (no autopsy performed but progression of aortic dissection was suspected).

- One case of stress cardiomyopathy (Takotsubo syndrome) in a 59-year-old woman with a history of migraine and 3 miscarriages who presented with chest pain 13 days following Dose 4 and had not recovered at the time of the report.

3.2.1.2. Cerebrovascular Events (6 Cases)

- Two cases of TIA, 1 in a 65-year-old man with DM on the same day as a booster (dose number not known) of Bivalent Comirnaty with no concomitant vaccinations reported and previous COVID-19 vaccine doses from an unknown manufacturer; and 2 in a 93-year-old man with known vascular disease and leukoencephalopathy who received Bivalent Comirnaty with no concomitant vaccinations as the Dose 2 of his primary series of COVID-19 vaccination (Dose 1 was Comirnaty) and was reported to have a TIA 1 day later. Both patients recovered.

- Four cases of ischemic stroke in women aged 37 to 88 years; 3 of whom had risk factors including HTN, TTP, previous stroke, valvular cardiac disease and DM (outcomes recovered, recovered with sequelae and recovering) and 1 with no

specified medical history (outcome unknown); the events occurred from the same day to 3 days following Dose 4 (4 cases) and Dose 5 (1 case). Two of the cases described a heterologous course of COVID-19 vaccination (Spikevax) and 2 had previous COVID-19 vaccine doses from an unknown manufacturer; none had concomitant influenza vaccination with Bivalent Comirnaty.

3.2.1.3. Other Arterial Events (3 Cases)

- Transient blindness in a 61-year-old woman with no medical history provided, occurring 1 day following Dose 4 and recovered in 4 days (not medically confirmed); previous COVID-19 vaccines were of an unknown manufacturer and no concomitant vaccinations with Bivalent Comirnaty reported

- Left axillary artery thrombus in a 94-year-old woman with a history of an unspecified cardiac disorder occurring 4 days following an unspecified dose, recovering at the time of the report; previous COVID-19 vaccines were of an unknown manufacturer and no concomitant vaccinations with Bivalent Comirnaty reported

- Retinal artery occlusion in a 71-year-old man with a history of HTN, occurring 6 days following Dose 4, recovered with sequelae; previous COVID-19 vaccines were of an unknown manufacturer and no concomitant vaccinations with Bivalent Comirnaty reported

3.2.2. Cases in Embolic and Thrombotic Events, Venous SMQ

Of the 67 total reports in this venous SMQ, 1 overlapped with the arterial SMQ, 4 overlapped with the unspecified/mixed SMQ and 3 overlapped with both the arterial and unspecified/mixed SMQ; leaving 59 unique cases.

The 59 cases were reported between 13 Oct 2022 and 14 Dec 2022 and included 32 females and 26 males (1 case did not specify sex). Ages ranged from 35 to 94 years (mean 69.1); 2 cases did not specify age. Forty-four (44) cases were medically confirmed and 15 were not; 55 cases were classified as serious and 4 as non- serious. Cases were reported from Germany and Spain (14 each), Italy (6), Denmark (5), Austria and the US (4 each), France (3), Japan, Luxembourg and Sweden (2 each), and Estonia, Portugal and Canada (1 each). Dose number was specified in all but 11 cases; 2 cases occurred after Dose 1, 6 cases occurred after Dose 3, 37 occurred after Dose 4 and 3 occurred after Dose 5. Many reporters were unable to specify the manufacturer of previous COVID-19 vaccines received prior to their booster doses with Bivalent Comirnaty; many reported heterogeneous COVID-19 vaccination courses, mainly with Spikevax. There were 5 death reports; narrative line listings of the death cases are in Appendix 2.

3.2.2.1. Pulmonary Emboli and Limb Thrombosis (53 Cases)

- Thirty-one cases of PE ranging from the same day to 31 days after Bivalent Comirnaty; outcomes were: 5 deaths (patients ranged in age from 65 to 81 years and had significant comorbidities including COPD, OSA, DM, HTN, cancer (2), infection

and 1 patient was wheelchair bound with a neurodegenerative condition); 15 recovering or recovered, 3 not recovered and 8 with unknown outcomes. Many patients (except 9 with no known or reported medical history), had risk factors for thromboembolic events including previous thromboembolic events, COVID-19, genetic thrombophilia, malignancies, overweight/obesity, valvular cardiac conditions and estrogen use.

- Thirteen cases of extremity thrombosis included 5 leg thrombosis (4 of which were specifically noted as superficial), 5 leg DVTs, 1 saphenous vein thrombosis and 2 upper extremity DVTs. Patients ranged in age from 35 to 90 years of age. Five individuals had unknown outcomes, 6 were recovered or recovering and 2 had not recovered at the time of the reports. Medical history was not provided for 6 patients; the remainder had medical histories that included chronic venous insufficiency, obesity, DVT, COVID-19, HC and cancer.

- Nine cases described both extremity thrombosis and PE in individuals ranging in age from 55 to 84 years. Five of the individuals had clear risk factors for PE/DVT including prior PE, cancer, recent travel, and estrogen use. Outcome in 6 of the individuals was recovering, in 1 individual not recovered and in 2 individuals unknown.

3.2.2.2. Cerebral Venous Sinus Thrombosis (2 Cases)

- Two cases of CVST. A non-HCP case described a 39-year-old woman with unspecified medical history who was reported to have a CVST 13 days after Dose 4 with Bivalent Comirnaty. Previous COVID-19 vaccinations had been with Comirnaty (Doses 1 and 2) and Spikevax (Dose 3). No clinical details (including imaging reports) were provided. She had not recovered at the time of the report. In the second report, a 52-year-old woman with headache and sinusitis initially treated with NSAIDs and antibiotics was found to have CVST on MRI 7 weeks following Dose 3 with Bivalent Comirnaty. Primary COVID-19 vaccinations were from an unknown manufacturer. She was recovering at the time of the report.

3.2.2.3. Other Venous Events (4 Cases)

- Three non-medically confirmed cases described thrombosis in unspecified anatomic locations from 1 to 12 days after vaccination with Bivalent Comirnaty but provided little other information.

- One non-medically confirmed case described an ophthalmic vein thrombosis in a 59-year-old female with HTN occurring 23 days after Bivalent Comirnaty vaccination (dose number unspecified). Primary COVID-19 vaccination was from an unknown manufacturer; she was recovered with sequelae at the time of the report.

3.2.3. Cases in Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous SMQ

Of the 75 total reports in this SMQ, 16 overlapped with the other embolic and thrombotic event SMQs: 12 were also in the arterial SMQ, 7 were in the venous SMQ and 3 were in all 3 of the SMQs; leaving 59 unique cases. All 75 cases are discussed in this section

The 75 cases (59 unique plus 16 overlapping with other embolic and thrombotic SMQs), were reported between 15 Sep 2022 and 14 Dec 2022 and included 39 females and 34 males (2 cases did not specify sex). Ages ranged from 42 to 89 years (mean 68.7); 9 cases did not specify age. Forty-three (43) cases were medically confirmed and 32 were not; all cases except 1 were classified as serious. Cases were reported from Germany (19), US and Japan (16 each), Spain (6), Italy (4), Denmark (3), Austria, Czech Republic, France (2 each) and Estonia, Finland, Norway, Portugal and Sweden (1 each).

Upon individual case review, 18 case narratives failed to describe details consistent with the occurrence of a thrombotic or embolic event. These cases were eliminated from further review.

In the remaining 57 cases, dose number was specified in 47 cases: 1 case occurred after Dose 1, 4 cases occurred after Dose 3, 29 after Dose 4 and 13 after Dose 5; 10 cases occurred after an unspecified dose number. Most cases did not provide the manufacturer of previous COVID-19 vaccines received ("manufacturer unknown"), a smaller number reported homologous dosing with BNT162b2 or Comirnaty and even fewer reported heterologous dosing. There were 7 death reports; narrative line listings of the death cases are in Appendix 3

3.2.3.1. Arterial Events (34 Cases)

- Thirty cases of cerebrovascular events (1 also reporting an MI), cerebral infarctions and/or cerebellar infarctions were presumed to be of arterial origin. None described accompanying venous events unless noted below. Time to onset from vaccination in these cases ranged from the same day to 17 days post-vaccination and, when specified, patients ranged in age from 43 to 89 years. One was reported after Dose 1, 4 were reported after Dose 3, 14 after Dose 4, 6 after Dose 5 and 5 after an unspecified chronologic dose. Fifteen of the reports provided no data on medical history, 2 reported that the patients had no relevant medical conditions and in the remaining 13 cases, all described risk factors for thromboembolic disease (such as known coronary artery disease, cerebral infarction, atrial fibrillation, previous DVT/PE, smoking, DM and HTN), except for a 64-year-old woman who was reported to have only asthma. Five of the 30 cases described concomitant influenza vaccination with the Bivalent Comirnaty dose; 8 described homologous COVID-19 vaccine use, 4 described heterologous COVID-19 vaccinations and 17 referred to an unknown manufacturer of the previous COVID-19 vaccines. One of the 30 cases was notable for concurrent thrombocytopenia:

1. A 65-year-old woman with HTN, DM and valvular cardiac disease (echocardiogram in 2019) was reported to have previous AstraZeneca (Dose 1) and Comirnaty (Dose 2) COVID-19 vaccines. She also had asymptomatic but PCR positive COVID-19, 8 days prior to receiving Dose 3 (Bivalent Comirnaty) and concomitant influenza (Seqirus) vaccination. Twenty-one days later she presented to the emergency room with hemiparesis and report of cough and congestion since the last vaccination. She underwent a CT angiography and was found to have thrombi in the aortic arch and descending aorta and an embolic left hemisphere ischemic stroke. A complicated hospitalization ensued, and she was reported to have a "multifactorial" thrombocytopenia (platelets ranged from 88 K to 114 K) and DIC. She died after 8 days in the hospital and the reported cause of death was thromboembolic stroke. It was not reported if an autopsy was performed.

- Four cardiac ischemic events occurred in this dataset. One case was already noted in the description of arterial cerebrovascular events above. The remaining 3 cases described a 64-year-old male smoker with HC and HTN who had Bivalent Comirnaty (Dose 4) and 16 days later was reported to have an AMI and cardiac failure with a ventricular thrombus; he recovered with sequelae; a 53-year-old male with Factor V Leiden mutation who had Bivalent Comirnaty (Dose 4) and unknown manufacturer of previous COVID-19 vaccinations, and 1 day later was reported to have an acute right coronary artery occlusion; he recovered. The remaining case was notable for concomitant thrombocytopenia:

    1. An 80-year-old woman with a history of HC and HTN and no history of known COVID-19 received Dose 5 of Bivalent Comirnaty and 1 day later was brought to the hospital for chest pain; she was reported to have had exertional chest pressure prior to this incident. She had received influenza vaccine (manufacturer Biken) 26 days prior to Dose 5 of Bivalent Comirnaty. She underwent a cardiac catheterization and coronary artery stent placement and was in the ICU for 2 days. She was reported to also have TTS (outcome unknown), however there are no clinical details, lab values (such as platelet count or APF4) or discussion of the basis for the diagnosis. She was recovering from the AMI at the time of the report.

- One TIA was described in an 80-year-old woman with a history of carotid endarterectomy and stroke who had 3 previous Comirnaty vaccinations; she was reported to have a TIA (recovered) on the same day as Dose 4.

3.2.3.2. Venous Events (13 Cases)

- Ten reports described PEs, DVTs, or unspecified extremity thrombosis in patients ranging in age from 50 to 80 years of age. Time to onset ranged from the same day of vaccination to 14 days after vaccination (3 unspecified); and the events occurred after Dose 4 in 5 cases and Dose 5 in 2 cases (3 unspecified). One case of PE and 1 of

superficial thrombosis provided very little clinical detail; the remaining cases described patients with risk factors such as HTN, cancer, DM, obesity, history of thrombophlebitis and Factor V Leiden mutation. Three patients were recovered or recovering, 2 had not recovered at the time of the report and outcome was unknown in 5 cases. One case was notable for concomitant thrombocytopenia:

1. A 70-year-old man with a risk factor of prostate cancer on hormone therapy received Dose 5 of COVID-19 vaccination with Bivalent Comirnaty (previous COVID-19 vaccinations from an unknown manufacturer). The following day he noted exertional shortness of breath and 8 days after vaccination he was hospitalized and diagnosed with PE and DVT. His platelet count on the day of admission was 18.6 K and although he was reported to have TTS, it was noted that Anti-PF4 antibody and anti-HIT antibody tests were not performed. The patient had no history of heparin administration and DIC and antiphospholipid syndrome were reported to be excluded. The patient was recovering at the time of the report.

- Two reports described CNS venous thrombosis

1. A 62-year-old woman with history of cerebrovascular arteriovenous malformation and previous cerebral thrombosis had an unspecified dose of Bivalent Comirnaty (primary COVID-19 vaccine series from an unknown manufacturer) and 3 days later was hospitalized for dizziness and cerebral thrombosis. CT and MRI results were not provided. She was started on unspecified anticoagulation therapy and outcome was not recovered at the time of the report.

2. A 72-year-old woman with HC and HTN received Bivalent Comirnaty (Dose 4); previous COVID-19 vaccines included Spikevax for Doses 1, 2 and 3. Two days later, he was hospitalized due to a transient expressive “phatic” with impaired psychomotor skills. She was reported to have acute thrombosis of cortical veins (fronto-dorsal and parietal) bilaterally and subarachnoid hemorrhage. She was recovering at the time of the report.

- One report described a thrombosed hemorrhoid in a 42-year-old male with rheumatoid arthritis and a recent 200 km bicycle ride, 6 days after Dose 4 of Bivalent Comirnaty (previous COVID-19 vaccines were from unknown manufacturer); outcome was unknown.

3.2.3.3. Unspecified or Mixed Arterial-Venous Events (10 Cases)

- Nine cases reported unspecified thromboembolic events or cerebrovascular disorders. Three of the 9 cases provided scant detail (PTs Thrombosis, Cerebrovascular disorder) precluding meaningful assessment (outcomes unknown). The remaining 6 cases described unspecified thromboembolic (1 cases), cerebrovascular or cardiovascular disorders (2 cases), DIC following streptococcal sepsis (1 case) and

intracranial hemorrhagic events (2 cases) in patients ranging in age from 66 to 87 years of age occurring from the same day up to 25 days after Bivalent Comirnaty vaccination. Five of the 6 cases provided medical histories such as stroke, cancer, HTN, DM, Parkinson's disease, atrial fibrillation, except for 1 case with no relevant medical history that would be considered a risk factor for thromboembolic events; 4 cases had an outcome of death and 2 of recovering. Four of the 6 cases described previous COVID-19 vaccinations from an unknown manufacturer. One of the 6 cases was notable for concomitant thrombocytopenia:

1. A 79-year-old woman with a history of breast cancer, lymph node excision and recurrent left upper extremity cellulitis received Dose 5 of COVID-19 vaccination with Bivalent Comirnaty (previous COVID-19 vaccines were from unknown manufacturer). The day after vaccination the patient had injection site pain, redness and swelling and malaise and the following day had lower extremity weakness. She presented to the ED and was found to have abnormal labs including platelet count of 7.2 K (nadir 1.9 K). She was hospitalized in the ICU for sepsis from cellulitis with purpura at the vaccination site on her left arm and redness spreading to her trunk. She died the following day of multi-organ failure from a severe invasive streptococcal infection. Autopsy was not performed.

- One case described both an arterial (cerebral infarction) and venous (PE) event and was also notable for thrombocytopenia.

1. An 84-year-old woman with an extensive medical history including polyarthrosis, DVT and PE on anticoagulation received her influenza vaccine and Bivalent Comirnaty (COVID-19 vaccine Dose 4); previous vaccinations had been with Comirnaty. At the same time, she also switched from LMWH to edoxaban for anticoagulation. One day following vaccination, she was brought to the ED for disorientation. A head CT showed no acute hemorrhage or ischemia however there were subacute/chronic small infarcts in the regions of the anterior and posterior circulation that appeared to be of an embolic nature. Her hospitalization was complicated by stress cardiomyopathy and HIT and she died after 8 days of hospitalization. The reported cause of death was "multiple cerebral infarcts of embolic etiology within systemic coagulopathy."

3.3. CLINICAL TRIAL DATA

In the current Pfizer-run clinical trials studying Bivalent BNT162b2 (Original and Omicron BA.4/BA.5) vaccine, Study C4591044 and Study C4591048, there have been no thromboembolic events reported in participants to date.

3.4. LITERATURE

Pfizer searched the literature databases Medline, Biosis and Embase for bivalent BNT162b2 BA.4/BA.5 (Tozinameran/Famtozinameran) and embolic and thrombotic events, including

ischemic stroke, TIAs, CVST and PE as well as vaccine-induced immune thrombotic thrombocytopenia and TTS. No relevant articles were retrieved.

3.5. OBSERVED TO EXPECTED ANALYSES

The MAH conducted unadjusted O/E analyses for embolic and thrombotic cases reported cumulatively through 18 Dec 2022 in the US and EEA (US/EEA). Observed cases were defined using the PTs provided in Appendix 4 Table 3. In Table 1, O/E results using 21- and 42-day risk windows post Pfizer-BioNTech Bivalent Omicron BA.4/BA.5 vaccines are provided using select population-based background rates for calculation of the expected cases in the denominator and all spontaneous reports of observed cases reported in the US/EEA in the numerator. Analyses were restricted to the US/EEA only because data specific to the Pfizer-BioNTech Bivalent Omicron BA.4/BA.5 were available for these regions.

Sources of background incidence rates for embolic and thrombotic events are referenced in Table 1. Where available, rates were obtained from the ACCESS project, as recommended by guidance from European Medicines Agency[1]. ACCESS includes a consortium of 10 data sources from 7 European countries (Denmark, Germany, France, Italy, Netherlands, Spain, United Kingdom). These data sources include health insurance data (GePaRD, SNDS), hospitalization record linkage data (PHARMO, Danish registries [DCE-AU], SIDIAP, ARS), or data from general practitioners (CPRD, PEDIANET, BIFAP, FISABIO). A rate from a single data provider was selected for each AESI based on the range of observed values, type of care typically sought for the AESI (eg, hospital or general practitioner), and relevant characteristics of the databases, as described in the ACCESS User Guide.[2] In general, a data provider with a mid-range rate within these criteria was chosen for the primary overall analyses. Incidence rates were then averaged for the most recent 3 years of data available prior to 2020 within each data access provider. For AESIs not available through the ACCESS project, incidence rates were identified in the literature. If a plausible range of background rates was identified across multiple data sources, a single rate from the low end of the range was selected. This conservative approach is more likely to identify a signal than an approach using a higher background rate.

The expected case counts were calculated using the background incidence rates, the estimated number of Pfizer-BioNTech bivalent Omicron BA.4/BA.5 vaccine doses reported through 15 Dec 2022,[3],[4] and the length of risk windows. The estimate of administered doses does not reflect COVID-19 vaccine doses administered in countries that did not publicly report.

Based on the observed cases through 18 Dec 2022, selected background rates, and the estimated number of exposure PY through 15 Dec 2022, O/E ratios were well below 1 for both risk windows of 21- and 42-days. This suggests that the number of observed cases is not higher than expected in the absence of Pfizer-BioNTech Bivalent Omicron BA.4/BA.5 vaccines overall and within the queried strata.

Table 1. Observed to Expected (O/E) Analyses for Spontaneously Reported Cases of Embolic and Thrombotic Events After the Pfizer-BioNTech Bivalent Omicron BA.4/BA.5 Vaccine in US/EEA Countries, Cumulative Period Through 18 Dec 2022

Stratification	Observed Cases	Time at risk (PY)[a]	Background Rate Per 100,000 PY	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21-day risk window							
US/EEA							
Arterial thromboembolism, broad	19	2,276,515	323.67[5]	7,368	**0.003**	0.002	0.004
Arterial thromboembolism, narrow	3	2,276,515	323.67[5]	7,368	**0.000**	0.000	0.001
CVST	1	2,276,515	0.76[5]	17	**0.058**	0.001	0.322
Coronary artery disease	1	2,276,515	175.95[6]	4,006	**0.000**	0.000	0.001
DVT	13	2,276,515	50.00[7]	1,138	**0.011**	0.006	0.020
Ischemic stroke	31	2,276,515	237.40[5]	5,404	**0.006**	0.004	0.008
Limb ischemia	1	2,276,515	260.00[8]	5,919	**0.000**	0.000	0.001
Pulmonary embolus	34	2,276,515	30.00[7]	683	**0.050**	0.034	0.070
Thrombotic thrombocytopenia syndrome	0	2,276,515	2.39[5]	54	--	--	--
Venous thromboembolism, broad	61	2,276,515	209.38[5]	4,767	**0.013**	0.010	0.016
Venous thromboembolism, narrow	50	2,276,515	209.38[5]	4,767	**0.010**	0.008	0.014
42-day							
US/EEA							
Arterial thromboembolism, broad	21	4,063,581	323.67[5]	13,153	**0.002**	0.001	0.002
Arterial thromboembolism, narrow	3	4,063,581	323.67[5]	13,153	**0.000**	0.000	0.001
CVST	2	4,063,581	0.76[5]	31	**0.065**	0.008	0.234
Coronary artery disease	1	4,063,581	175.95[6]	7,150	**0.000**	0.000	0.001
DVTs	14	4,063,581	50.00[7]	2,032	**0.007**	0.004	0.012
Ischemic stroke	33	4,063,581	237.40[5]	9,647	**0.003**	0.002	0.005
Limb ischemia	1	4,063,581	260.00[8]	10,565	**0.000**	0.000	0.001
Pulmonary embolus	37	4,063,581	30.00[7]	1,219	**0.030**	0.021	0.042
Thrombotic thrombocytopenia syndrome	0	4,063,581	2.39[5]	97	--	--	--
Venous thromboembolism, broad	70	4,063,581	209.38[5]	8,508	**0.008**	0.006	0.010
Venous thromboembolism, narrow	56	4,063,581	209.38[5]	8,508	**0.007**	0.005	0.005

a. Exposure data through 15 Dec 2022

The MAH is also including observed versus expected analyses for ischemic stroke with detail by age stratification Table 2. All O/E ratios are well below 1 for both 21-day and 42-day risk windows.

Table 2. Observed to Expected (O/E) Analyses for Spontaneously Reported Cases of Ischemic Stroke After the Pfizer-BioNTech Bivalent Omicron BA.4/BA.5 Vaccine in US/EEA Countries, Cumulative Period Through 18 Dec 2022

Stratification	Observed Cases	Time at risk (PY)[a]	Background Rate Per 100,000 PY	Expected Cases	O/E Ratio	95% CI LL	95% CI UL
21-day							
US/EEA							
<5 years	0	0	1.93	0.00	--	--	--
5-11 years	0	27,448	1.93	0.53	--	--	--
12_17 years	0	50,403	1.93	0.97	--	--	--
18_24 years	0	60,915	5.27	3.21	--	--	--
25_49 years	3	429,459	18.96	81.43	**0.037**	0.008	0.108
50_59 years	3	353,979	81.86	289.77	**0.010**	0.002	0.030
60+ years	25	1,354,311	544.59	7375.37	**0.003**	0.002	0.005
Overall, US/EEA	31	2,276,515	237.40	5404.45	**0.006**	0.004	0.008
42-day							
US/EEA							
<5 years	0	0	1.93	0.00	--	--	--
5-11 years	0	49,869	1.93	0.96	--	--	--
12_17 years	0	91,224	1.93	1.76	--	--	--
18_24 years	0	109,656	5.27	5.78	--	--	--
25_49 years	3	771,692	18.96	146.31	**0.021**	0.004	0.060
50_59 years	4	626,942	81.86	513.21	**0.008**	0.002	0.020
60+ years	26	2,414,198	544.59	13147.36	**0.002**	0.001	0.003
Overall, US/EEA	33	4,063,581	237.40	9646.94	**0.003**	0.002	0.005

a. Exposure data through 15 Dec 2022

There are several limitations to O/E analyses for signal detection. The observed case counts are likely to be underestimated due to the spontaneous reporting nature with passive safety surveillance. Additional reasons for underestimations include incomplete reporting and lags in reporting. Spontaneous reporting systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine are more likely to be reported even if they do not meet the clinical definition. Conversely, events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association. Furthermore, some observed cases were missing time to onset information. Missing values were imputed according to the known distribution of time to onset among observed cases.

Regarding the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported

vaccine administrations is complete and accurate when in fact not all countries administering vaccine have reported to the data source. Also, country-specific[9] dose volume data are dynamic and specific to the date of download from the websites, and subject to retrospective updates at the country level. The expected count also assumes the background rates of the COVID-19 vaccinated population in the absence of vaccination is the same as those in the historical cohort. The background rates used in these analyses are derived from studies prior to the COVID-19 era and from individual countries. It is possible that the delivery of healthcare, population demographics, and the underlying health status of the populations used for the background rate estimates differ from those expected in the vaccinated population.

The risk windows for embolic and thrombotic events following Pfizer-BioNTech COVID-19 vaccines are unclear. Misspecification of risk windows could potentially under-estimate the risk estimates. We queried 21- and 42-day risk windows to cover a wide range of periods during which one is expected to be at risk of this acute event if there is a causal association between the event and vaccination.

3.6. SUMMARY AND CONCLUSION

Based on the totality of safety information available, thromboembolic events have not been identified as a risk with the use of Comirnaty (Original) vaccine.

The safety information available for Bivalent BNT162b2 (Original and Omicron BA.4/BA.5) vaccine and thromboembolic events at this time includes clinical trial data for ongoing Pfizer-run trials, in which thromboembolic events have not so far been reported, O/E analyses which are well below 1 for these events, and post-authorization reports from the Pfizer safety database which have not shown thromboembolic events to have an EB05>2. Upon individual review of the cumulative thromboembolic event reports for Bivalent Comirnaty in the Pfizer safety database, those providing sufficient detail generally describe patients with risk factors for such events. No other notable trends in the cases (eg, dose number, manufacturer, concomitant influenza vaccination) were identified. There is no evidence at this time that thromboembolic events, including ischemic stroke, are a safety signal or risk of Bivalent Comirnaty. These events will continue to be reviewed per routine pharmacovigilance.

4. APPENDICES

4.1. Appendix 1: Death Cases - Arterial

Narrative Line Listing Arterial Embolic NLL

4.2. Appendix 2: Death Cases - Venous

Narrative Line Listing Venous Embolic_NLL

4.3. Appendix 3: Death Cases - Unspecified/Mixed

Narrative Line Listing Unspecified Mixed Embolic_NLL

4.4. Appendix 4: PTs Used to Identify Spontaneously Reported Embolic and Thrombotic Events for O/E Analyses

Table 3. Preferred Terms (PT) Used to Identify Spontaneously Reported Embolic and Thrombotic Events

AESI	PTs
Arterial thromboembolism, broad	Administration site thrombosis, Adrenal thrombosis, Aneurysm thrombosis, Antiphospholipid syndrome, Aortic aneurysm thrombosis, Aortic embolus, Aortic thrombosis, Application site thrombosis, Arterial thrombosis, Arteriovenous fistula thrombosis, Arteriovenous graft site stenosis, Arteriovenous graft thrombosis, Atheroembolism, Atrial thrombosis, Basilar artery thrombosis, Blue toe syndrome, Brain stem embolism, Brain stem thrombosis, Cardiac ventricular thrombosis, Carotid arterial embolus, Carotid artery thrombosis, Cerebellar artery thrombosis, Cerebellar embolism, Cerebral artery embolism, Cerebral artery thrombosis, Cerebral microembolism, Cerebral septic infarct, Cerebral thrombosis, Cerebrospinal thrombotic tamponade, Coronary artery embolism, Coronary artery thrombosis, Coronary bypass thrombosis, Device related thrombosis, Disseminated intravascular coagulation, Disseminated intravascular coagulation in newborn, Embolia cutis medicamentosa, Embolic cerebellar infarction, Embolic cerebral infarction, Embolic stroke, Embolism, Embolism arterial, Femoral artery embolism, Graft thrombosis, Heparin-induced thrombocytopenia, Hepatic artery embolism, Hepatic artery thrombosis, Hepatic vascular thrombosis, Hypothenar hammer syndrome, Iliac artery embolism, Implant site thrombosis, Infective thrombosis, Infusion site thrombosis, Injection site thrombosis, Instillation site thrombosis, Intracardiac mass, Intracardiac thrombus, Intrapericardial thrombosis, Lambl's excrescences, Mahler sign, Medical device site thrombosis, Mesenteric artery embolism, Mesenteric artery thrombosis, Microembolism, Moyamoya disease, Ophthalmic artery occlusion, Ophthalmic artery thrombosis, Ophthalmic vascular thrombosis, Paraneoplastic thrombosis, Paroxysmal nocturnal haemoglobinuria, Peripheral artery thrombosis, Peripheral embolism, Post thrombotic retinopathy, Post thrombotic syndrome, Postoperative thrombosis, Precerebral artery embolism, Precerebral artery thrombosis, Prosthetic cardiac valve thrombosis, Renal artery thrombosis, Renal embolism, Renal vascular thrombosis, Renal-limited thrombotic microangiopathy, Retinal artery embolism, Retinal artery occlusion, Retinal artery thrombosis, Retinal vascular thrombosis, Septic embolus, Shunt thrombosis, Spinal artery embolism, Spinal artery thrombosis, Splenic artery thrombosis, Splenic embolism, Spontaneous heparin-induced thrombocytopenia syndrome, Subclavian artery embolism, Subclavian

	artery thrombosis, Thrombosis, Thrombosis in device, Thrombosis mesenteric vessel, Thrombotic cerebral infarction, Thrombotic microangiopathy, Thrombotic stroke, Truncus coeliacus thrombosis, Umbilical cord thrombosis, Vascular graft thrombosis, Vascular pseudoaneurysm thrombosis, Vascular stent thrombosis, Vertebral artery thrombosis
Arterial thromboembolism, narrow	Aneurysm thrombosis, Basilar artery thrombosis, Brain stem embolism, Brain stem thrombosis, Carotid arterial embolus, Carotid artery thrombosis, Cerebellar artery thrombosis, Cerebellar embolism, Cerebral artery embolism, Cerebral artery thrombosis, Cerebral microembolism, Cerebral septic infarct, Coronary artery embolism, Coronary artery thrombosis, Coronary bypass thrombosis, Embolic cerebellar infarction, Embolic cerebral infarction, Embolic stroke, Precerebral artery embolism, Precerebral artery thrombosis, Thrombotic cerebral infarction, Thrombotic stroke, Vertebral artery thrombosis
Coronary artery disease	Coronary artery disease
Cerebral venous sinus thrombosis	Cerebral venous sinus thrombosis, Cerebral venous thrombosis, Sigmoid sinus thrombosis, Superior sagittal sinus thrombosis, Transverse sinus thrombosis
Deep vein thrombosis	Deep vein thrombosis
Ischemic stroke	Basal ganglia infarction, Basal ganglia stroke, Basilar artery thrombosis, Brain stem stroke, Cerebral infarction, Cerebral thrombosis, Cerebral venous sinus thrombosis, Cerebrovascular accident, Ischaemic stroke, Lacunar infarction, Pituitary infarction, Thalamic stroke, Thrombotic stroke
Limb ischemia	Peripheral ischaemia
Pulmonary embolus	Pulmonary embolism
Thrombotic thrombocytopenia syndrome	Thrombosis with thrombocytopenia syndrome
Venous thromboembolism, broad	Administration site thrombosis, Adrenal thrombosis, Antiphospholipid syndrome, Application site thrombosis, Arterial thrombosis, Arteriovenous fistula thrombosis, Arteriovenous graft site stenosis, Arteriovenous graft thrombosis, Aseptic cavernous sinus thrombosis, Axillary vein thrombosis, Brachiocephalic vein thrombosis, Budd-Chiari syndrome, Catheter site thrombosis, Cavernous sinus thrombosis, Cerebral thrombosis, Cerebral venous sinus thrombosis, Cerebral venous thrombosis, Cerebrospinal thrombotic tamponade, Deep vein thrombosis, Deep vein thrombosis postoperative, Device related thrombosis, Disseminated intravascular coagulation, Disseminated intravascular coagulation in newborn, Embolic pneumonia, Embolism, Embolism venous, Graft thrombosis, Heparin-induced thrombocytopenia, Hepatic vascular thrombosis, Hepatic vein embolism, Hepatic vein thrombosis, Implant site thrombosis, Infective thrombosis, Infusion site thrombosis, Injection site thrombosis, Instillation site thrombosis, Jugular vein embolism, Jugular vein thrombosis, Lemierre syndrome, Mahler sign, Medical device site thrombosis, Mesenteric vein embolism, Mesenteric vein thrombosis, Metastatic pulmonary embolism, Microembolism, Obstetrical pulmonary embolism, Ophthalmic vein thrombosis, Ovarian vein thrombosis, Paget-Schroetter syndrome, Papillophlebitis, Paradoxical embolism, Paraneoplastic thrombosis, Paroxysmal nocturnal haemoglobinuria, Pelvic venous thrombosis, Penile vein thrombosis, Peripheral vein thrombosis, Peripheral vein thrombus extension, Portal pyaemia, Portal vein embolism, Portal vein thrombosis, Portosplenomesenteric venous thrombosis, Post procedural pulmonary embolism, Post thrombotic retinopathy, Post thrombotic syndrome, Postoperative thrombosis, Postpartum thrombosis, Postpartum venous thrombosis, Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary microemboli, Pulmonary thrombosis, Pulmonary tumour thrombotic microangiopathy, Pulmonary veno-occlusive disease, Pulmonary venous thrombosis, Renal vascular thrombosis, Renal vein embolism, Renal vein

	thrombosis, Retinal vascular thrombosis, Retinal vein occlusion, Retinal vein thrombosis, Septic embolus, Septic pulmonary embolism, Shunt thrombosis, Sigmoid sinus thrombosis, Spermatic vein thrombosis, Splenic thrombosis, Splenic vein thrombosis, Spontaneous heparin-induced thrombocytopenia syndrome, Stoma site thrombosis, Subclavian vein thrombosis, Superior sagittal sinus thrombosis, Thrombophlebitis, Thrombophlebitis migrans, Thrombophlebitis neonatal, Thrombophlebitis septic, Thrombosis, Thrombosis corpora cavernosa, Thrombosis in device, Thrombosis mesenteric vessel, Transverse sinus thrombosis, Umbilical cord thrombosis, Vaccination site thrombosis, Vascular graft thrombosis, Vascular stent thrombosis, Vena cava embolism, Vena cava thrombosis, Venous recanalisation, Venous thrombosis, Venous thrombosis in pregnancy, Venous thrombosis limb, Venous thrombosis neonatal, Vessel puncture site thrombosis, Visceral venous thrombosis
Venous thromboembolism, narrow	Axillary vein thrombosis, Brachiocephalic vein thrombosis, Catheter site thrombosis, Cerebral venous sinus thrombosis, Cerebral venous thrombosis, Deep vein thrombosis, Deep vein thrombosis postoperative, Embolic pneumonia, Jugular vein embolism, Jugular vein thrombosis, Lemierre syndrome, Metastatic pulmonary embolism, Obstetrical pulmonary embolism, Paget-Schroetter syndrome, Peripheral vein thrombosis, Peripheral vein thrombus extension, Post procedural pulmonary embolism, Pulmonary artery thrombosis, Pulmonary embolism, Pulmonary microemboli, Pulmonary thrombosis, Pulmonary tumour thrombotic microangiopathy, Pulmonary veno-occlusive disease, Pulmonary venous thrombosis, Sigmoid sinus thrombosis, Subclavian vein thrombosis, Superior sagittal sinus thrombosis, Thrombophlebitis, Thrombophlebitis migrans, Thrombophlebitis neonatal, Thrombophlebitis septic, Transverse sinus thrombosis, Venous thrombosis limb

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Document Approval Record

Document Name:	January 2023 Covid-19 Vaccine FDA Information Request_CBER_VAERS reports of embolic and thrombotic events
Document Title:	January 2023 Covid-19 Vaccine FDA Information Request_CBER_VAERS reports of embolic and thrombotic events

Signed By:	Date(GMT)	Signing Capacity
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Subject: [EXTERNAL] VaST - Draft minutes and report from February 27, 2023 (CONFIDENTIAL)

Date: Fri, 3 Mar 2023 13:55:18 +0000

Importance: Normal

Attachments: 2023-02-27_-_VaST_minutes_draft_confidential.docx; 2023-02-27_-_VaST_Report_and_Data_Table_draft_confidential.docx

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sender and know the content is safe.

Dear VaST members and participants,

Attached are the draft minutes and report from the VaST call this week. Please let us know if there are any corrections or edits.

The next VaST calls this month are:
March 20 – DoD summary presentation
March 27 – VSD summary presentation

Regards and many thanks to all,
Lauri Markowitz and Melinda Wharton

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

VaST meeting notes
February 27, 2023
Confidential - DRAFT

Presentations and verbal updates are briefly summarized in meeting notes. Chat notes not answered verbally on the call are available and some have been incorporated into the minutes.

Participants
Workgroup members: Kathy Edwards, Bob Hopkins (NVAC-chair), Veronica McNally, Jennifer Nelson, Laura Riley, Rob Schechter, Pat Whitley-Williams

Ex officio and liaison participants: Tatiana Beresnev (NIH), Matthew Clark (IHS), Karen Farizo (FDA), Jeff Kelman (CMS), Valerie Marshall (HHS), Timothy Styles (HRSA)

Federal Partners: Fran Cunningham (VA), Margaret Ryan (DoD)

CDC: Karen Broder, Julianne Gee, Monica Godfrey, Anne Hause, Rita Helfand, Lauri Markowitz (CDC Co-lead), Paige Marquez, Mike McNeil, Alanna Moorer, Pedro Moro, Sara Oliver, Sierra Scarbrough, David Shay, Tom Shimabukuro, John Su, Evelyn Twentyman, Eric Weintraub, Melinda Wharton (CDC Co-lead), Jared Woo

Technical SMEs: Steve Anderson (FDA), Rich Forshee (FDA), Yun Lu (FDA), Azadeh Shoaibi (FDA)

Agenda
Update on Original COVID-19 Vaccine and COVID-19 Vaccine Bivalent Safety, Dr. Rich Forshee, FDA

Administrative issues and announcements - Co-chairs and Co-leads
- Reminders about COI and confidentiality
- Next planned VaST meetings are on 3/20 and 3/27
- Doses distributed: 963,131,415; Doses administered: 671,582,379 (last updated: February 24)
  - Doses distributed: Pfizer-BioNTech: 580,931,295; Pfizer-BioNTech(bivalent): 79,726,460; Moderna: 349,537,120; Moderna (bivalent): 37,655,900; Janssen/J&J: 31,547,200; Novavax: 1,115,800; Other: N/A
  - Doses administered: Pfizer-BioNTech: 400,441,248; Pfizer-BioNTech(bivalent): 34,314,082; Moderna: 251,252,512; Moderna (bivalent): 19,444,661 Janssen/J&J: 18,979,373; Novavax: 79,668; Other: 829,578
  - At least one dose: 269,459,752; Primary series: 229,996,296; Bivalent booster dose: 53,350,658
  - These data are posted on the CDC website and are updated regularly (https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total).

Update on Original COVID-19 Vaccine and COVID-19 Vaccine Bivalent Safety – Dr. Rich Forshee (FDA)
Dr. Forshee presented a brief overview of the CBER Active Surveillance Program (BEST Initiative) and then summarized safety surveillance analyses for: 1) adverse events following bivalent COVID-19 mRNA vaccine booster doses in a rapid cycle analysis (RCA), and 2) self-controlled analysis for potential adverse events after monovalent COVID-19 mRNA vaccines.

In the RCA, several age groups were evaluated. There were 4.3 million persons aged 65+ years who received the bivalent Pfizer-BioNTech bivalent vaccine and 3.0 million persons aged 65+ years who

received the bivalent Moderna vaccine. There was no signal for non-hemorrhagic stroke (not including transient ischemic attack) or any other adverse event of special interest following the bivalent COVID-19 vaccine in the 65+ year population. In the database, 38% of Medicare recipients who received a bivalent Pfizer-BioNTech COVID-19 booster received a seasonal influenza vaccination on the same day. There was no signal for non-hemorrhagic stroke in the 65+ year population following concomitant influenza vaccination. In the 18–35 year-old population, there was a signal for myocarditis following bivalent Pfizer-BioNTech vaccination. FDA is planning a formal epidemiologic study of COVID-19 vaccine and influenza vaccine coadministration in 2023–2024.

The self-controlled analysis was conducted to follow-up potential associations for six adverse events following primary series and monovalent booster dose administration detected in the FDA RCA for the original monovalent COVID-19 mRNA vaccine in persons aged 65+ years. The self-controlled analysis did not find an increased risk for acute myocardial infarction, immune thrombocytopenia, disseminated intravascular coagulation, or myocarditis/pericarditis; results for pulmonary embolism were not consistent. There was a small, elevated risk of Bell's palsy after COVID-19 mRNA vaccination. The results are currently on a pre-print server (Evaluation of Potential Adverse Events Following COVID-19 mRNA Vaccination Among Adults Aged 65 Years and Older: A Self-Controlled Study in the U.S | medRxiv).

Discussion and questions

1. Are statistical signals for myopericarditis attenuating going from primary series to the bivalent dose?
   - The sequential surveillance analysis isn't designed to compare rates across different doses. The RCA analyzes outcomes compared to a threshold and cannot address trends or association.
2. Are there any hypotheses concerning the difference in findings between the first analyses for the monovalent COVID-19 vaccine primary series and in the self-controlled analyses?
   - It is possible that there is statistical noise, we may have not been able to control for time factors.
3. How appropriate are 2019 historical data for use during a pandemic with broad health effects?
   - FDA did a comprehensive study on historical rates before deciding to use 2019 data for sequential analysis. There were large variations in healthcare utilization compared to 2020.
4. Does FDA have plans to use other comparison groups for sequential analyses?
   - FDA is exploring use of concurrent comparator groups, similar to what is used in the Vaccine Safety Datalink.

Combined Systems Safety Monitoring Report
February 27, 2023
Confidential – DRAFT

The VaST session on February 27, 2023 included an FDA presentation on safety monitoring data for the bivalent COVID-19 vaccine booster vaccine and for the original COVID-19 vaccine.

Bivalent COVID-19 booster vaccination

VaST appreciated the overview of the FDA safety monitoring systems and the focused summary of the study design for the Rapid Cycle Analysis (RCA) near real-time surveillance in CMS, which uses historical comparators.

The RCA found a signal for myocarditis/pericarditis following the bivalent Pfizer-BioNTech COVID-19 booster among 18-35 year-olds. Among persons aged 65 years and older, there was no statistical signal for ischemic stroke after bivalent Pfizer-BioNTech or Moderna COVID-19 booster vaccination in any age group. (These data from CMS were presented to VRBPAC on January 26 and to ACIP on February 24.) The analysis in this age group also found no signal for any of the other prespecified outcomes. The following outcomes have completed their surveillance period: acute myocardial infarction, deep vein thrombosis, non-hemorrhagic stroke (for both bivalent Moderna and Pfizer BioNTech COVID-19 vaccine), Bell's palsy, pulmonary embolus, and common site thrombosis with thrombocytopenia (for bivalent Pfizer-BioNTech COVID-19 vaccine).

VaST felt the findings were reassuring regarding ischemic stroke in persons aged 65 years and older, particularly given the large number of bivalent COVID-19 vaccine booster doses in the CMS analysis (larger than for the Vaccine Safety Datalink [VSD]), but also expressed reservations recognizing the potential limitations given the historical comparators used. VaST members noted that FDA was discussing use of concomitant comparators, as does VSD, and felt that use of those would be helpful.

Although the CMS analysis did not find a statistical signal for ischemic stroke following bivalent Pfizer-BioNTech or Moderna COVID-19 booster vaccinations, due to the findings in VSD, FDA is planning a formal epidemiologic study regarding coadministration with influenza vaccine. VaST members felt this was an excellent next step and requested more information about plans for the study.

Evaluation of potential adverse events following monovalent COVID-19 mRNA vaccination among adults aged 65 years and older: a self-controlled study

Available at: https://doi.org/10.1101/2023.01.19.23284803

This study, now available as a pre-preprint, is a further evaluation of statistical signals identified by FDA earlier in CMS sequential analyses. In the further analyses presented to VaST, there was no increased risk for acute myocardial infarction, immune thrombocytopenia, myocarditis/pericarditis, or disseminated intravascular coagulation; results were not consistent for pulmonary embolus. There was a small, elevated risk of Bell's palsy after monovalent COVID-19 mRNA vaccine booster vaccination (both products).

VaST felt that a strength of the analysis is statistical power but a limitation is the lack of medical record review for Bell's palsy; review of a sample of records is still in progress. VaST requested information about whether other international safety monitoring systems had detected statistical signals for Bell's palsy.

Table 1. COVID-19 vaccine monitoring systems reviewed by the VaST – Pfizer BioNTech (recommended for use in persons age ≥ 6 months)

Red indicates updated or new data this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Population data through 1/23/22	All health events, adverse events of special interest[a]	US population	313.0 million Pfizer-BioNTech doses administered	Descriptive and empirical Bayesian data mining and other		Anaphylaxis associated with vaccination, first detected by reports from UK and early reporting in the US; assessed by follow-up with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021)
6 month-4 year primary series data through 7/31/22	All health events, adverse events of special interest[a]		692,485 doses administered		321 VAERS reports, 6 serious • Fever was the most frequently reported AE • Administration errors were the next most frequently reported AE	Additional data needed VaST members expressed concerns about administration errors, how to prevent them
5–11-year-old primary series data through 4/24/22	All health events, adverse events of special interest[a]		17,859,728 doses administered		9,001 reports; 97% non-serious • Median age 8 years • Sex: 47% male; 47% female 20 verified myocarditis reports • Overall reporting rate: 0.94 per 1 million doses administered • < 1 per million for males following dose 1 and females following dose 1 and 2 • 2.2 per million for males following dose 2	No concerns raised

5–11-year-old first booster dose data through 7/31/22	All health events, adverse events of special interest[a]		466,716 booster doses administered		581 reports; 99% non-serious • Median age 9 years • Sex: 51% male; 47% females Administration errors are the most common reports	No concerns raised
First booster dose data for persons aged ≥12 years through 4/11/22			93,118,318 1st mRNA COVID-19 booster vaccinations administered		47,014 non-serious reports following 1st booster of mRNA COVID-19 vaccination • Headache, pyrexia, and pain: 3 most common non-serious 5,049 serious reports following 1st booster mRNA COVID-19 vaccination	No concerns raised
Second booster dose data for persons aged ≥50 years through 7/10/22			16,961,827 2nd mRNA COVID-19 booster vaccinations administered		8,073 non-serious reports following 2nd booster mRNA COVID-19 vaccination • COVID-19, fatigue, and headache: 3 most common non-serious 442 serious reports following 2nd booster mRNA COVID-19 vaccination	No concerns raised
Bivalent booster dose data for persons ≥ 12 years through 9/25/22	All health events, adverse events of special interest[a]		4.7 million persons aged 12+ years received Pfizer-BioNTech bivalent booster vaccination		1,236 non-serious reports following either mRNA bivalent booster dose • Vaccination errors were the most commonly reported AE (30%) 33 serious reports following either mRNA bivalent booster dose • 3 reports of myocarditis, 2 pericarditis, and 3 deaths	No concerns raised but further review needed after more doses administered
Co-administration data through 6/30/2022	All health events, adverse events of special interest[a]				1,663 reports following co-administration with a Pfizer-BioNTech vaccination 1,332 non-serious reports and 253 serious reports across both mRNA vaccines	No concerns raised but further review needed after more doses administered

					• 47 death reports – causes of death consistent with all-cause mortality for age groups	
Myocarditis/pericarditis first booster data through 5/26/22			93.4 million 1st mRNA COVID-19 booster vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-29 years in 7-day window following either booster dose exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 15.3 in males aged 12-15 years • 24.1 in males aged 16-17 years • 9.9 in males aged 18-24 years • 4.8 in males aged 25-29 years	There appears to be some risk of myocarditis/pericarditis after a booster dose. Further analyses ongoing.
Myocarditis/pericarditis primary series data through 5/26/22			398.4 million mRNA COVID-19 primary series vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-49 years in 7-day window following dose 2 exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 38.9 in males aged 18-24 years • 15.2 in males aged 25-29 years • 7.5 in males aged 30-39 years • 3.3 in males aged 40-49 years	Warning added to EUA fact sheets June 25, and information provided in update of CDC's clinical guidance and MMWR article. Information included in FDA materials after full approval on Aug 22. Further work being done to define myocarditis risk.
Myocarditis/pericarditis 5–17-year-old primary series data through 5/26/22			54.9 million doses administered (Dose 1: 27.7; Dose 2: 23.3; Dose 3: 3.8 million)		972 preliminary myocarditis reports 635 verified reports met the CDC case definition for myocarditis. • .2 reporting rate, males aged 5-11 years following dose 1	No new concerns raised

					• 2.6 reporting rate, males aged 5-11 years following dose 2	
MOVING data for persons aged 12-29 years presented on 12/12/22					60 myocarditis patients interviewed, across all vaccines, 1-year post-myocarditis dx 63 physicians interviewed, across all vaccines, 1-year post-myocarditis dx 83% of healthcare providers indicated the patient was fully or probably recovered	Further follow-up needed
Tinnitus and hearing loss data through 11/6/22					7,026 tinnitus reports to VAERS • 21.6 reports per million doses administered (18+ years) 197 sudden hearing loss reports • 0.6 reports per million doses administered (18+ years) 949 reports of 'permanent disability' and 157 reports of 'hospitalization' for tinnitus or sudden hearing loss	No concerns raised
Pregnancy data through 7/29/22					4,487 pregnancy-related reports to VAERS (2,424 after Pfizer). Safety profile of pregnancy reports after COVID-19 vaccines appears reassuring, and primary series reports are comparable to booster doses.	No concerns raised

GBS data through 1/28/22					104 verified cases of GBS following Pfizer-BioNTech vaccination • Median age: 57.5 years • Hospitalized: 96 • Deaths: 3 Observed number of confirmed GBS reports lower than than expected.	No concerns raised
Death reporting rates data through 11/17/21					For each vaccine, across all sex and age groups, the observed reporting rate for death events was much lower than the number of expected all cause deaths	No concerns raised
Menstrual irregularties data through 1/7/22					558 reports of post-menopausal bleeding reported to VAERS after COVID-19 vaccine (239 after Pfizer). Few PMB cases were classified as serious VAERS reports (3 reported after Pfizer).	No concerns raised
VA ADERS Data through 4/03/2022	All health events	VA employees and Veteran patients	1.9M 1st doses 1.8M 2nd doses 848,841 booster doses	Descriptive	10.8% serious reports and 89.2% non-serious reports	No concerns raised
DoD VAERS Data through 12/31/2021	All health events, adverse events of special interest	Active duty and beneficiaries	4.1 million Pfizer-BioNTech vaccines administered	Descriptive	12 cases myocarditis/pericarditis after Pfizer-BioNTech dose 1 41 cases of myocarditis/pericarditis after Pfizer-BioNTech dose 2 • 111.5 cases per million in males aged 12-17 years • 52.6 cases per million in males aged 18-24 years • 21.5 cases per million in males aged 25-39 years Observed > expected in males (<17, 18-24, and 25-39) after dose 2	Follow-up and evaluation continuing

Indian Health Services (IHS) VAERS Presented on 2/06/23	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	724 total AVE reports • 488 medically attended health impact events	No new concerns raised
Active Surveillance						
V-safe Booster dose data through 4/10/22		Vaccinees who enroll	369,841 v-safe participants who received Pfizer-BioNTech primary series received booster doses (336,618 had Pfizer-BioNTech primary series)	Descriptive	Local and systemic reactions for persons aged 18+ years reported less frequently following booster dose than dose 2 for mRNA vaccines. Similar or slightly more reports or reactions among persons aged 12-17 years following booster compared to dose 2 for mRNA vaccines.	No concerns raised
5–11-year data (primary series) through 4/24/22					49,396 participants with a Pfizer-BioNTech vaccination • Injection site pain most frequently reported reaction • Reactions were more frequently reported after dose 2 than 1	No concerns raised
6 month-4 year data through 7/10/22		Vaccinees who enroll	14,036 v-safe participants who received Pfizer-BioNTech	Descriptive	Reactogenicity 6 months-2 years-olds: • 18.8% reported any injection site reaction following dose 1 and 18.3% following dose 2 • 55.7% reported any systemic reaction following dose 1 and 47.1% following dose 2 Reactogenicity 3-4 year-olds: • 38.3% reported any injection site reaction following dose 1 and 26.3% following dose 2	No concerns raised

					• 31.5% reported any systemic reaction following dose 1 and 29.6% following dose 2	
Pregnant women reactogenicity data through 2/13/22 Data through 4/10/22					6,338 pregnant participants reported a booster dose. • Patterns of reporting after receiving a booster dose while pregnant are consistent with the general population 5,052 pregnant participants reported homologous mRNA booster while pregnant. • Reporting frequency for some systemic reactions differ between dose 2 and booster dose, with some differences in frequency of reporting noted depending on whether participant was pregnant for both doses or only booster dose.	No concerns raised No concerns raised
Menstrual irregularities data through 1/22					63,815 people across all vaccines reported responses likely related to menstruation • Common themes: menstrual timing and menstrual severity.	No concerns raised
Bivalent booster dose data for persons ≥ 12 years through 9/25/22		Vaccinees who enroll	28,568 v-safe participants reported receiving Pfizer-BioNTech bivalent booster dose	Descriptive	Across both mRNA bivalent vaccines, reporting frequencies of reactions and health impacts were similar to those after 1st and 2nd booster vaccination Approximately one-third reported co-administration	No concerns raised but further review needed after more doses administered
Simultaneous booster and influenza vaccine study data through 5/1/22		Vaccinees who enroll	526,829 v-safe participants reported		60,390 participants: simultaneous Pfizer-BioNTech booster and influenza	No concerns raised but further review needed after more doses administered

			receiving Pfizer-BioNTech booster dose		vaccinations; 466,439 participants: Pfizer-BioNTech booster alone Injection site and systemic reactions slightly more frequent following simultaneously administered. No evidence of a difference in severity.	
V-safe Pregnancy Registry Data through 8/1/22		Vaccinees who enroll	22,944 participants enrolled across all vaccines	Descriptive	22,951 total pregnancies. Pregnancy and neonatal outcome frequencies support safety of the COVID-19 vaccination.	Phase 2 Infant and maternal follow-up through 12 months of age/pregnancy end to start soon.
Department of Veterans Affairs (VA) Active Surveillance System RCA data through 10/28/22	Pre-specified health outcomes[a]	Veteran Patients	2.0 million first doses administered; 1.9 million second doses administered	Descriptive; historical comparator analysis	The only signal is for anaphylaxis following dose 1 of Pfizer-BioNTech.	No new concerns raised
RCA booster dose data through 3/26/22	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	838,337 Pfizer-BioNTech booster doses administered	Descriptive; historical comparator analysis	No signals, including for myocarditis/pericarditis or anaphylaxis, but pericarditis cases observed among those ≥40 years	No concerns raised, but follow-up in other safety systems needed
Bivalent booster presented on 1/09/23	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	377k Pfizer-BioNTech bivalent doses administered	Descriptive; historical comparator analysis	No signals observed; rate ratio for ischemic stroke/TIA following Pfizer-BioNTech bivalent vaccine <1	No concerns raised
Target trial emulation data presented on 9/19/22	All-cause mortality	Eligible Veterans	228,130 patients reached end of follow-up (100,253 Pfizer-BioNTech)	Discrete time logistic regression	Day 8 and day 28 all-cause mortality are statistically similar across all vaccines Day 60 all-cause mortality is significantly different across all vaccines • 11% reduction in risk in vaccinated group	No concerns raised
Vaccine Safety Datalink (VSD) RCA data through 1/15/22	Pre-specified health outcomes[a]	Patients enrolled in participating	9.0 million doses of Pfizer-	Vaccinated concurrent comparison,	21-day risk interval - signaled	Further monitoring and analyses of other potential signals ongoing.

		health care organization	BioNTech administered	sequential analyses	• Myocarditis/pericarditis (combined dose 1&2 and dose 2 alone) • VTE (combined dose 1&2 and dose 2 alone) • AMI (dose 2) <u>42-days risk interval - signaled</u> • Myocarditis/pericarditis (dose 2) • Seizures (dose2)	
First booster dose data through 8/13/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	2.8 million patients ≥18 years 265k patients 12-17 years 94,791 patients 5-11 years	Vaccinated concurrent comparison, sequential analyses	No statistical signal for pre-specified outcomes for Pfizer-BioNTech boosters for patients aged 12+ years. • Myocarditis/pericarditis signal for combined Pfizer-BioNTech and Moderna analysis, elevated risk highest in adolescent and young adult males No statistical signal for pre-specified outcomes for booster doses across mRNA vaccines for patients aged 5-11 years.	Further monitoring and analyses of needed
Bivalent dose data through 12/31/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	1.6 million patients received Pfizer-BioNTech bivalent booster dose	Vaccinated concurrent comparison, sequential analyses	There was an elevated rate ratio for ischemic stroke/TIA in persons 18-64 years, but there was no signal	Further review and analysis is needed
Bivalent dose ischemic stroke updated analysis data presented on 2/13/23	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	580k patients received Pfizer-BioNTech bivalent booster dose	Vaccinated concurrent comparison, sequential analyses	There was a statistical signal for ischemic stroke/TIA in persons 65+ years; attenuated in recent weeks. • Rate ratio of 1.36 (CI: 1.05-1.76)	Further review and analysis is needed

					Bivalent Pfizer-BioNTech and same-day co-administration of high-dose or adjuvanted flu vaccine, RR = 1.65 (95% CI 1.02–2.72).	
VSD simultaneous and co-administered vaccine data through 10/8/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	~230,000 patients administered either bivalent mRNA booster		No analyses, only vaccine doses administered presented	No concerns raised but further review needed after more doses administered
6 month-4-year primary series data through 8/13/22	Pre-specified health outcomes[a]		31,784 first doses of Pfizer-BioNTech administered; 18,729 second doses of Pfizer-BioNTech administered		No statistical signals identified	No concerns raised
5–11-year primary series data presented 5/22			817,217 doses of Pfizer-BioNTech administered		No statistical signals identified	No concerns raised
First booster dose data through 8/20/22			2.9 million doses of Pfizer-BioNTech booster administered following Pfizer-BioNTech primary series ages 5 and older	Vaccinated concurrent comparison, sequential analyses	<u>0-7 days risk-window</u> • 7.21 (95% CI: 2.04-29.66) for myocarditis/pericarditis events in persons aged 12-17 years • 4.81 (95% CI: 1.55-16.81) for myocarditis/pericarditis events in persons aged 18-39 years <u>0-21 days risk window</u> • No point estimate (95% CI: 2.66-∞) for myocarditis/myopericarditis events in persons aged 40+ years <u>0-7 or 0-21 days risk window</u>	Finding consistent with past analyses

					• Rate ratios for **pericarditis** not significantly elevated among persons aged 40+ years	
Head-to-Head myocarditis/pericarditis presented on 1/15/22					Head-to-head comparisons: risk of myocarditis/pericarditis was higher after Moderna than after Pfizer. 1.61 adjusted rate ratio for persons aged 18-39 years	No new concerns raised
Tinnitus and hearing loss presented on 11/14/22			4,068,513 doses of Pfizer-BioNTech; 2,467,865 booster doses of Pfizer-BioNTech following mRNA vaccines	Tree-scan, *ad hoc* temporal scans and descriptive	No clusters of hearing-related outcomes for any tree scan analyses *Ad hoc* temporal scan analysis - most likely cluster starts on Day 33, ~12 days after dose 2 78/10,000 person-years after Pfizer-BioNTech	No concerns raised Tinnitus after vaccination similar to recent global background incidence estimate
Tree scan analysis data presented 5/2/22			4,068,513 doses of Pfizer-BioNTech; 1,142,736 booster doses of Pfizer-BioNTech following mRNA vaccines		Patients 12-17 years and 18-39 years had a signal for myocarditis/pericarditis, chest pain, and breathing abnormalities following dose 2 using the 7-day window.	No additional serious adverse events identified using this data mining approach
KPSEM data through 12/13/21			6,194 surveys completed for children aged 5-11 years		~1% of respondents reported tachycardia or chest pain 0-7 days following vaccination • No documented myocarditis cases in the medical records 6.9% reported 'other symptoms' following dose 1 and 1.3% reported seeking medical care for symptoms following dose 1	No concerns raised

					5.6% reported 'other symptoms' following dose 2 and 1.4% reported seeking medical care for symptoms following dose 2	
Menstrual irregularities data through 12/2021	Post-menopausal bleeding	Women ≥45 years, KPNW	48,438 vaccinated women		79 cases of post-menopausal bleeding identified (53 after Pfizer). No cases had COVID-19 vaccination documented as a likely cause.	No concerns raised
Vaccine Safety Datalink (VSD) Mortality Study Vaccinated through 5/31/21 and death data through 7/31/21	Deaths	VSD sites enrolled in the mortality study; vaccinated before 5/31 and number of deaths before 7/31	3,453,126 vaccines administered	Matched cohort analysis	Individuals who received Pfizer-BioNTech COVID-19 vaccine had lower mortality risk after dose 1 and dose 2 vs unvaccinated comparators. • 0.41 (0.38-0.44) RR for mortality of Pfizer-BioNTech vaccine dose 1 recipients versus unvaccinated comparison group 0.34 (0.33-0.36) RR for mortality of Pfizer-BioNTech dose 2 recipients versus unvaccinated comparison	No concerns raised
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and Medicaid Services (CMS)[b] Data presented on 3/14/22	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)	NA	Historical comparator and sequential analyses	RCA statistical signals reported to VaST previously for PE, AMI, DIC, ITP, investigated in self-controlled case series with post vacc control interval • Consistent evidence of an elevated risk of PE	Inconclusive evidence for AMI, ITP; Consistently elevated risk for PE; numbers too small for DIC

					• Elevated risk for AMI that was attenuated after exclusion of cases with hx of COVID-19 disease in past year ITP: no elevated risk	
Original vaccine primary series and booster dose Presented 2/27/23	AMI, ITP, DIC, myo/pericarditis, PE, Bell's Palsy	CMS population 65+		Self-controlled analysis of AEs identified in RCA	No increased risk for AMI, ITP, DIC, myo/pericarditis; Results not consistent for PE; Small elevated risk of Bell's Palsy	No concerns raised
Booster dose data through 3/5/22	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)	3.2 million patients who received Pfizer-BioNTech primary series received booster doses (23.1 million had Pfizer-BioNTech primary series)	Historical comparator analysis	Signal for Bell's palsy following Pfizer-BioNTech booster among those without a prior COVID-19 diagnosis • Signal for AMI, ITP, myocarditis/pericarditis, and PE following Pfizer-BioNTech booster in those with a prior COVID-19 diagnosis	Inconclusive evidence, further analysis of booster data is needed
Bivalent dose data presented on 2/27/23	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)		Historical comparator analysis	No signal for any AESI, including non-hemorrhagic stroke, following Pfizer-BioNTech bivalent booster vaccination	No concerns raised
FDA - BEST Initiative Myocarditis/pericarditis data presented on 3/14/22	Myocarditis/Pericarditis	5 FDA BEST partners; males 18-25 and 18-35 years	16.9 million doses administered	Retrospective comparator analysis	1.43 (95% CI: 0.88,2.34) incidence rate ratio when comparing Moderna vs Pfizer-BioNTech in males aged 18-25 years in IP/ED/OP settings. .88 (95% CI: 0.67,1.15) incidence rate for males aged 18-25 years in IP/ED/OP settings	Results do not support a significant risk difference between the 2 mRNA vaccines for males aged 18-25 years and 18-35 years IRRs attenuated for 18-35 years old and when restricted to IP/ED
FDA - BEST Initiative[b] Optum Data through 11/13/21	Pre-specified health outcomes[a]	Patients enrolled in Optum pre-adjudicated	Total doses 5.0 million	Historical comparator and	RCA statistical signal for anaphylaxis in Optum data following Pfizer-BioNTech	Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.

		claims, 0-64 years		sequential analyses		
FDA - BEST Initiative HealthCore Data through 10/4/21	Pre-specified health outcomes[a]	Patients enrolled in BCBS 0-64 years	Total doses 5.5 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in HealthCore data following Pfizer-BioNTech	Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.
NPTC Vaccine Sentinel Survey Data presented on 2/6/23		Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	1,063 total AVE reports • 457 medically attended health impact events • 23 potential AESIs	No concerns raised
Vaccine Trials (Manufacturer)					• See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 2. COVID-19 vaccine monitoring systems reviewed by the VaST – Moderna (recommended for use in persons age ≥ 6 months)

Red indicates new results this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Population data through 1/23/26	All health events, adverse events of special interest[a]	US population	203.0 million Moderna doses administered	Descriptive and empirical Bayesian data mining		Anaphylaxis associated with vaccination, first detected by early reporting in US; assessed by follow-up with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021)
6 month-5 year data through 7/31/22	All health events, adverse events of special interest[a]		359,025 doses administered		346 VAERS reports, 6 serious • Fever was the most frequently reported AE	Additional data are needed to derive any insights
First booster dose data for persons aged ≥12 years through 4/11/22			93,118,318 1st mRNA COVID-19 booster vaccination administered		47,014 non-serious reports following 1st booster of mRNA COVID-19 vaccination • Headache, pyrexia, pain: 3 most common non-serious reports 5,049 serious reports following 1st booster of mRNA COVID-19 vaccination	No concerns raised
Bivalent booster dose data for persons ≥ 18 years through 9/25/22	All health events, adverse events of special interest[a]		2.6 million persons aged 18+ years received Moderna bivalent booster vaccination		1,236 non-serious reports following either mRNA bivalent booster dose • Vaccination errors were the most commonly reported AE (30%) 33 serious reports following either mRNA bivalent booster dose • 3 reports of myocarditis, 2 pericarditis, and 3 deaths	No concerns raised but further review needed after more doses administered

Co-administration data through 6/30/2022	All health events, adverse events of special interest[a]				786 reports following co-administration with a Moderna vaccination 1,332 non-serious reports and 253 serious reports across both mRNA vaccines • 47 death reports – causes of death consistent with all-cause mortality for age groups	No concerns raised; but further review needed after more doses administered
Myocarditis/pericarditis first booster data through 5/26/22			93.4 million 1st mRNA COVID-19 booster vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-29 years in 7-day window following either booster dose exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 9.9 in males aged 18-24 years • 4.8 in males aged 25-29 years	There appears to be some risk of myocarditis/pericarditis after a booster dose. Further analyses ongoing.
Myocarditis/pericarditis primary series data through 5/26/22			398.4 million mRNA COVID-19 primary series vaccinations administered		Reporting rates of myocarditis/myopericarditis among males 12-49 years in 7-day window following dose 2 exceed background incidence of .2-2.2 per 1 million person 7-day risk period – across both mRNA vaccines combined • 38.9 in males aged 18-24 years • 15.2 in males aged 25-29 years • 7.5 in males aged 30-39 years • 3.3 in males aged 40-49 years	Warning added to EUA fact sheets June 2021, and information provided in update of CDC's clinical guidance and MMWR article. Information included in FDA materials after full approval on Aug 2021. Further work being done to define myocarditis risk.
MOVING data for persons aged 12-29 years presented on 12/12/22					60 myocarditis patients interviewed, across all vaccines, 1-year post-myocarditis dx	Further follow-up needed

					63 physicians interviewed, across all vaccines, 1-year post-myocarditis dx 83% of healthcare providers indicated the patient was fully or probably recovered	
Tinnitus and hearing loss data through 11/6/22					5,280 tinnitus reports to VAERS • 22.7 reports per million doses administered (18+ years) 125 sudden hearing loss reports • 0.5 reports per million doses administered (18+ years) 601 reports of 'permanent disability' and 125 reports of 'hospitalization' for tinnitus or sudden hearing loss	No concerns raised
TTS data through 8/4/21					2 confirmed TTS reports to VAERS	No concerns raised
GBS data through 1/28/22					72 verified cases of GBS following Moderna vaccination • Median age: 63.0 years • Hospitalized: 97 • Deaths: 5 Observed number of confirmed GBS reports was lower than than expected.	No concerns raised
Death reporting rates data through 11/17/21					For each vaccine, across all sex and age groups, observed reporting rate for death events much lower than the number of expected all cause deaths	No concerns raised

Pregnancy data through 7/29/2022					4,487 pregnancy-related reports to VAERS (1,736 after Moderna). Safety profile of pregnancy reports after COVID-19 vaccines appears reassuring, and primary series reports are comparable to booster doses.	No concerns raised
Menstrual irregularities data through 1/7/22					558 reports of post-menopausal bleeding reported to VAERS after COVID-19 vaccine (145 after Moderna). Few PMB cases were classified as serious VAERS reports (2 reported after Moderna).	No concerns raised
VA ADERS Data through 4/03/2022	All health events	VA employees and Veteran patients	2.1M 1st doses 2M 2nd doses	Descriptive	8% serious; 92% nonserious	No concerns raised
DoD VAERS Data through 12/31/2021	All health events, adverse events of special interest	Active duty and beneficiaries	2.2 million Moderna vaccines administered	Descriptive	8 cases myocarditis/pericarditis after Moderna dose 1 23 cases with myocarditis/pericarditis after Moderna dose 2 • 104.5 cases per million in males aged 18-24 years • 22.7 cases per million in males aged 25-39 years Observed > expected in males (18-24, and 25-39) after dose 2	Follow-up and evaluation continuing
Indian Health Services (IHS) VAERS Presented on 2/06/23	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	612 total AVE reports • 426 medically attended health impact events	No new concerns raised
Active Surveillance						
V-safe Booster dose data through 4/10/22		Vaccinees who enroll	351,619 v-safe participants who received Moderna	Descriptive	Local and systemic reactions for persons aged 18+ years were reported less frequently following	No concerns raised

			primary series received booster doses (311,374 had Moderna primary series)		booster dose than dose 2 for mRNA vaccines. Similar or slightly more reports or reactions among persons aged 12-17 years following booster compared to dose 2 for mRNA vaccines.	
6 month-5 year data through 7/19/22		Vaccinees who enroll	7,879 v-safe participants who received Moderna	Descriptive	Reactogenicity 6 months-2 year-olds: • 19.0% reported any injection site reaction following dose 1 and 29.2% following dose 2 • 55.5% reported any systemic reaction following dose 1 and 59.8% following dose 2 Reactogenicity 3-5 year-olds: • 31.9% reported any injection site reaction following dose 1 and 47.9% following dose 2 • 34.2% reported any systemic reaction following dose 1 and 51.8% following dose 2	No concerns raised
Reactogenicity after booster doses in pregnant persons data through 2/13/22 Data through 4/10/22					4,552 pregnant participants reported a booster dose. • Patterns of reporting after receiving a booster dose while pregnant are consistent with the general population 5,052 pregnant participants reported homologous mRNA booster while pregnant. • Reporting frequency for some systemic reactions differ between dose 2 and booster dose, with some differences in frequency of reporting noted depending on	No concerns raised No concerns raised

					whether participant was pregnant for both doses or only booster dose.	
Menstrual irregularities data through 1/22					63,815 people across all vaccines reported responses likely related to menstruation • Common themes: menstrual timing and menstrual severity	No concerns raised
Bivalent booster dose data for persons ≥ 12 years through 9/25/22		Vaccinees who enroll	22,813 v-safe participants reported receiving Moderan bivalent booster dose	Descriptive	Across both mRNA bivalent vaccines, reporting frequencies of reactions and health impacts were similar to those described after 1st and 2nd booster vaccination Approximately one-third reported co-administration	No concerns raised; but further review needed after more doses administered No concerns raised
Simultaneous booster and influenza vaccine study data through 5/1/22		Vaccinees who enroll	453,270 v-safe participants reported receiving Moderna booster dose		30,633 participants: simultaneous Moderna booster and influenza vaccine; 422,637 participants: Moderna booster alone Injection site and systemic reactions slightly more frequent following simultaneous administration. No evidence of a difference in severity.	No concerns raised; but further review needed after more doses administered
V-safe Pregnancy Registry Data through 1/31/2022		Vaccinees who enroll	22,944 participants enrolled across all vaccines	Descriptive	22,951 total pregnancies. Pregnancy and neonatal outcome frequencies support safety of the COVID-19 vaccination.	Phase 2 Infant and maternal follow-up through 12 months of age/pregnancy end to start soon.
Department of Veterans Affairs (VA) Active Surveillance System RCA data through 10/28/22	Pre-specified health outcomes[a]	Veteran Patients	2.2 million first doses administered; 2.0 million second doses administered	Descriptive; historical comparator analysis	The only signal is for anaphylaxis following dose 2 of Moderna vaccine	No new concerns raised

RCA booster dose data through 3/26/22	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	955,454 booster doses administered	Descriptive; historical comparator analysis	No signals, including for myocarditis or pericarditis or anaphylaxis but pericarditis cases observed among those ≥40 years	No concerns raised, but followup in other safety systems needed
Bivalent booster presented on 1/09/23	Pre-specified health outcomes[a]	Veteran Patients who received a booster dose	376k Moderna bivalent doses administered	Descriptive; historical comparator analysis	No signals observed; rate ratio for ischemic stroke/TIA following Moderna bivalent booster vaccine <1	No concerns raised
Target trial emulation data presented on 9/19/22	All-cause mortality	Eligible Veterans	228,130 patients reached end of follow-up (114,621 Moderna)	Discrete time logistic regression	Day 8 and day 28 all-cause mortality are statistically similar across all vaccines Day 60 all-cause mortality is significantly different across all vaccines • 11% reduction in risk in vaccinated group	No concerns raised
Vaccine Safety Datalink (VSD) RCA data through 1/15/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	5.9 million doses of Moderna administered	Vaccinated concurrent comparison, sequential analyses	21-day risk interval - signaled • No signal for myocarditis/pericarditis, AMI, seizures, VTE, PE, and Bell's Palsy 42-days risk interval - signaled • AMI (dose 2) • No signal for myocarditis/pericarditis, AMI, seizures, VTE, PE, and Bell's Palsy	Further monitoring and analyses of other potential signals ongoing
6 month-4-year primary series data through 8/13/22	Pre-specified health outcomes[a]		334,466 first doses of Moderna administered; 17,940 second doses of Moderna administered		No statistical signals identified	No concerns raised

First booster dose data through 8/13/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	2.3 million patients ≥18 years who received a Moderna booster dose	Vaccinated concurrent comparison, sequential analyses	No statistical signal for pre-specified outcomes for Moderna boosters for patients aged ≥12 years • Myocarditis/pericarditis signal for combined Pfizer-BioNTech and Moderna analysis; elevated risk highest in adolescent and young adult males No statistical signal for pre-specified outcomes for booster doses across mRNA vaccines for patients aged 5-11 years	Further monitoring and analyses of ongoing
Rate ratio data through 1/15/2022					In 18–39 year-olds, 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 males	
First booster dose data through 8/20/2022			2.0 million doses of Moderna booster administered following Moderna primary series; age 6 and older	Vaccinated concurrent comparison, sequential analyses	<u>0-7 days risk-window</u> • Rate ratio for myocarditis/pericarditis was 3.27 (0.82-14.23) in persons aged 18-39 years <u>0-7 or 0-21 days risk window</u> • Rate ratios for **pericarditis** not significantly elevated among persons aged 40+ years	Finding consistent with past analyses
Head-to-Head myocarditis/pericarditis presented on 1/15/22					Head-to-head comparisons: risk of myocarditis/pericarditis was higher after Moderna than after Pfizer.	No new concerns raised

					1.61 adjusted rate ratio for persons aged 18-39 years	
Bivalent dose data through 10/8/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	91,626 persons received bivalent booster dose of Moderna	Vaccinated concurrent comparison, sequential analyses	There were no statistical signals for any pre-specified surveillance outcomes. • 1 verified case of acute pericarditis in male aged 35-39	No concerns raised but further review needed after more doses administered
VSD simultaneous and co-administered vaccine data through 10/8/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	~230,000 patients administered either bivalent mRNA booster	Descriptive and stratified RCA	No analyses, only vaccine doses administered presented	No concerns raised but further review needed after more doses administered o concerns raised.
Tinnitus and hearing loss presented on 11/14/22			2,559,563 doses of Moderna; 1,873,849 booster doses of Moderna following mRNA vaccines	Tree-scan, *ad hoc* temporal scans and descriptive	No clusters of hearing-related outcomes for any tree scan analyses Most likely cluster starts on Day 41, ~13 days after dose 2 for most 107/10,000 person-years after Moderna	No concerns raised Tinnitus after vaccination similar to recent global background incidence estimate
Tree scan analysis data presented 5/2/22			2,559,563 doses of Moderna; 841,216 booster doses of Moderna following mRNA vaccines		Patients 18-39 years and 40-64 years had a signal for urticaria and unspecified allergy following Moderna booster (following mRNA vaccines) in the 10-16 days window.	No additional serious adverse events identified using this data mining approach
Menstrual irregularities data through 12/2021	Post-menopausal bleeding	Women ≥45 years, KPNW	48,438 vaccinated women		79 cases of post-menopausal bleeding identified (23 after Moderna). No cases had COVID-19 vaccine documented as a likely cause.	No concerns raised.
Vaccine Safety Datalink (VSD) Mortality Study	Deaths	VSD sites enrolled in the mortality study; vaccinated	2,604,066 vaccines administered	Matched cohort analysis	Individuals who received Moderna COVID-19 vaccine had lower mortality risk after dose 1 and dose 2 than unvaccinated comparators.	No concerns raised

Vaccinated through 5/31/21 and death data through 7/31/21		before 5/31 and number of deaths before 7/31			• 0.34 (0.32-0.37) RR for mortality of Moderna vaccine dose 1 recipients versus unvaccinated comparison group • 0.31 (0.30-0.33) RR for mortality of Moderna vaccine dose 2 recipients versus unvaccinated comparison group	
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and Medicaid Services (CMS)[b] Data through 3/14/22	Pre-specified health outcomes[a]	CMS population 65 and above enrolled in Fee-for-Service (FFS)	NA	Historical comparator analysis	RCA statistical signals reported to VaST previously for PE, AMI, DIC, ITP, investigated in self-controlled case series with post vacc control interval • AMI, ITP: no evidence of risk • PE: Elevated risk for PE; attenuated after exclusion of cases with hx of COVID-19 disease	No evidence of elevated risk for AMI or ITP; inconclusive evidence for PE; numbers too small for DIC
Original vaccine primary series and booster dose Presented 2/27/23	AMI, ITP, DIC, myo/pericarditis, PE, Bell's Palsy	CMS population 65+		Self-controlled analysis of AEs identified in RCA	No increased risk for AMI, ITP, DIC, myo/pericarditis; Results not consistent for PE and Bell's Palsy	No concerns raised
Booster dose data through 3/5/22	Pre-specified health outcomes[a]	CMS population 65+ enrolled in Fee-for-Service (FFS)	3.4 million who received Moderna primary series received booster doses (3.2 million had Moderna primary series)	Historical comparator analysis	No signals for following booster dose of Moderna in patients without a prior COVID-19 diagnosis Signal for AME and PE following Moderna booser dose in patients with a prior COVID-19 diagnosis	Inconclusive evidence, further analysis of booster data is needed for further discussion
Bivalent dose data presented on 2/27/23	Pre-specified health outcomes[a]	CMS population 65+ enrolled in		Historical comparator analysis	No signal for any AESI, including non-hemorrhagic stroke, following Moderna bivalent booster vaccination	No concerns raised

		Fee-for-Service (FFS)				
FDA - BEST Initiative Myocarditis/pericarditis data presented on 3/14/22	Myocarditis/Pericarditis	5 FDA BEST partners; males aged 18-25 and 18-35 years	10.6 million doses administered	Retrospective comparator analysis	1.43 (95% CI: 0.88,2.34) IRR comparing Moderna vs Pfizer-BioNTech in males aged 18-25 years in IP/ED/OP;1.27 (95% CI: 0.88,1.84) incidence rate for males aged 18-25 years in IP/ED/OP settings	Results do not support a significant risk difference between the 2 mRNA vaccines for males aged 18-25 years IRRs attenuated for 18-35 years old and when restricted to IP/ED
FDA - BEST Initiative[b] Optum Data through 11/13/21	Pre-specified health outcomes[a]	Patients enrolled in Optum pre-adjudicated claims, 0-64 years	Total doses 2.4 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in Optum data following Moderna	No concerns raised Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.
FDA - BEST Initiative HealthCore Data through 10/4/21	Pre-specified health outcomes[a]	Patients enrolled in BCBS 0-64 years	Total doses 2.9 million	Historical comparator and sequential analyses	RCA statistical signal for anaphylaxis in HealthCore data following Moderna	No concerns raised Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.
NPTC Vaccine Sentinel Survey Data presented on 2/6/23		Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	617 total AVE reports • 195 medically attended health impact events • 18 potential AESIs	No concerns raised
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received [c]at the time of vaccination

Table 3. COVID-19 vaccine monitoring systems reviewed by the VaST – Janssen/Johnson & Johnson (recommended for use in persons age ≥ 18 years)

Red indicates new results this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Population data through 11/7/21; TTS data through 12/6/21	All health events, adverse events of special interest[a]	US population	16.4 million total doses administered	Descriptive and empirical Bayesian data mining	54 confirmed TTS reports to VAERS (37 in females) • 3.83/million doses administered • 10.60/million, females 30-39 yrs • 9.02/million, females 40-49 yrs	Further discussions by ACIP CVWG needed; earlier, warnings and other information had been provided in updated EUA and MMWR, and reflected in clinical guidance
TTS death data through 12/2/21					9 TTS deaths, all after dose 1 • Median age: 45 yrs (range: 28-62) • 7 female and 2 male • Median time from admission to death: 1 day (range: 0-2)	
Booster dose data through 11/5/21					201,653 additional Janssen doses administered • 58.5 non-serious reports per 100,000 doses • 2.0 serious reports per 100,000 doses	No concerns raised
Myocarditis/pericarditis data through 10/6/21					71 reports of myocarditis/pericarditis	No concerns raised
GBS data through 1/28/22					59 verified cases of GBS following Janssen/J&J vaccination • Median age: 57.0 years • Hospitalized: 80 • Deaths: 1	Warning added to EUA fact sheets July 12, other information provided in CDC's clinical guidance. Further reivew and adjudication of cases needed in VAERS and investigation in different systems.

					Observed number of GBS cases following Janssen/J&J vaccine was 2-3 times greater than expected in both post-vaccination intervals	
Pregnancy data through 2/11/22					327 pregnancy-related reports to VAERS. Disproportional reporting for 'prolonged labor' after Janssen (n = 10, confounding factors present).	No concerns raised
Death reporting rates data through 11/17/21					For each vaccine, across all sex and age groups, the observed reporting rate for death events was much lower than the number of expected all cause deaths Bayesian data mining identified mortality due to COVID-19 disease (vaccine failure) following the Ad26.COV2.S vaccine	
Menstrual irregularities data through 1/7/22					558 reports of post-menopausal bleeding reported to VAERS after COVID-19 vaccine (44 after Janssen). Few PMB cases were classified as serious VAERS reports (1 reported after Janssen).	No concerns raised
VA ADERS Data through 4/03/22	All health events	VA employees and Veteran patients	329,701 vaccines administered	Descriptive	No signals were detected	No concerns raised
DoD VAERS Data through 12/31/21	All health events, adverse events of special interest	Active duty and beneficiaries	264 thousand Janssen/J&J vaccines administered	Descriptive	4 cases with myocarditis/pericarditis after Janssen/J&J vaccine	No concerns raised
Indian Health Services (IHS) VAERS Presented on 2/06/23	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	62 total AVE reports • 50 medically attended health impact events	No new concerns raised

Active Surveillance						
V-safe Booster dose data through 4/10/22		Vaccinees who enroll	8,260 v-safe participants who received Janssen primary series received booster doses (7,775 had Janssen for their primary series)	Descriptive	Currently not enough data to describe reactogenicity.	No concerns raised
Menstrual irregularities data through 1/22					63,815 people across all vaccines reported responses likely related to menstruation • Common themes: menstrual timing and menstrual severity	No concerns raised
V-safe Pregnancy Registry Data through 1/31/2022		Vaccinees who enroll	22,944 participants enrolled across all vaccines	Descriptive	22,951 total pregnancies. Pregnancy and neonatal outcome frequencies support safety of the COVID-19 vaccination.	Phase 2 Infant and maternal follow-up through 12 months of age/pregnancy end to start soon.
Department of Veterans Affairs (VA) Active Surveillance System RCA data through 10/28/22	Pre-specified health outcomes[a]	Veteran Patients	380k doses of Janssen/J&J administered	Descriptive; historical comparator analysis	No signals for anaphylaxis, myocarditis/pericarditis, GBS, TTS, or other AESIs	No new concerns raised
Target trial emulation data presented on 9/19/22	All-cause mortality	Eligible Veterans	228,130 patients reached end of follow-up (10,853 Janssen/J&J)	Discrete time logistic regression	Day 8 and day 28 all-cause mortality are statistically similar across all vaccines Day 60 all-cause mortality is significantly different across all vaccines • 11% reduction in risk in vaccinated group	No concerns raised

Vaccine Safety Datalink (VSD) Bell's palsy data through 1/15/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	500,000 doses of Janssen/J&J administered	Vaccinated comparator analysis.	Bell's palsy signaled using a 42-day risk interval	Further analysis of Bell's palsy ongoing
GBS data through 9/25/21					10 confirmed cases of GBS following vaccination within 1-98 days	Further analysis of GBS following ongoing
Booster dose data through 4/12/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	254,973 patients who received Janssen primary series received booster doses (70,607 had Janssen for their primary series)	Vaccinated concurrent comparison, sequential analyses	There were no signals for any prespecified outcomes for Janssen booster doses with Janssen as a primary series	No concerns raised
VSD simultaneous and co-administered vaccine data through 3/26/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	15.9 million persons aged ≥5 years administered COVID-19 vaccine	Descriptive and stratified RCA	Small number of outcomes observed among persons who received simultaneous vaccines and/or co-admin vaccines when stratified by outcome, COVID-19 vaccine manufacturer and dose, vaccine family, and age group • 1,925 persons received simultaneous vaccines and co-administered vaccines • 194,885 persons received any co-administered vaccine • 100,802 persons received any simultaneous vaccine	No concerns raised. The next steps include conducting analysis comparing observed vs expected from non-simultaneous/-co-administered doses.

Tinnitus and hearing loss presented on 11/14/22			417,854 doses of Janssen; 65,238 booster doses of Janssen following Janssen vaccines	Tree-scan, *ad hoc* temporal scans and descriptive	No clusters of hearing-related outcomes for tree scan analyses No likely cluster found 85/10,000 person-years after Janssen	No concerns raised Tinnitus after vaccination similar to recent global background incidence estimate
Tree scan analysis data presented 5/2/22			417,854 doses of Janssen; 75,489 booster doses of mRNA following Janssen; 30,452 booster doses of Janssen following Janssen		Patients 65+ years had a signal for difficulty walking and muscle weakness following Janssen primary dose in the 1-2 day window.	No additional serious adverse events identified using this data mining approach
Menstrual irregularities data through 12/2021	Post-menopausal bleeding	Women ≥45 years, KPNW	48,438 vaccinated women		79 cases of post-menopausal bleeding identified (3 after Janssen). No cases had COVID-19 documented as a likely cause.	No concerns raised
Vaccine Safety Datalink (VSD) Mortality Study Vaccinated through 5/31/21 and death data through 7/31/21	Deaths	VSD sites enrolled in the mortality study; vaccinated before 5/31 and number of deaths before 7/31	1,346,445 vaccines administered	Matched cohort analysis	Individuals who received Janssen/J&J COVID-19 vaccine had lower mortality risk after dose 1 and dose 2than unvaccinated comparators. • 0.54 (0.49-0.59) RR for mortality of Janssen/J&J vaccine dose 1 recipients versus unvaccinated comparison group	No concerns raised
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					

FDA - Centers for Medicare and Medicaid Services (CMS)[b] Data through 3/14/2022	Pre-specified health outcomes[a]	CMS population 65 and above enrolled in Fee-for-Service (FFS)	Total doses 487 thousand	Historical comparator analysis	RCA statistical signal for anaphylaxis in CMS data following Janssen • AMI, PE: no evidence of risk • ITP and DIC: sample size too small to make any conclusions	No concerns raised
FDA - BEST Initiative[b] Optum Data through 11/13/21	Pre-specified health outcomes[a]	Patients enrolled in Optum pre-adjudicated claims, 0-64 years	Total doses 260 thousand	Historical comparator and sequential analyses	No RCA statistical signals for in Optum data following Janssen	No concerns raised
FDA - BEST Initiative HealthCore Data through 10/4/21	Pre-specified health outcomes[a]	Patients enrolled in BCBS 0-64 years	Total doses 338 thousand	Historical comparator and sequential analyses	No RCA statistical signals in HealthCore data following Janssen	No concerns raised
NPTC Vaccine Sentinel Survey Data presented on 2/6/23		Persons who identify as American Indian/Alaska Native	2.34 million vaccines administered across all vaccines	Descriptive	69 total AVE reports • 29 medically attended health impact events • 4 potential AESIs	No concerns raised
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5. for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 4. COVID-19 vaccine monitoring systems reviewed by the VaST – Novavax (recommended for use in persons age ≥ 18 years)

Red indicates new results this week

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) Dose data through 9/11/22	All health events, adverse events of special interest[a]	US population	24,125 total doses administered	Descriptive and empirical Bayesian data mining	62 VAERS reports • 5 serious reports No reports of death or myocarditis	Awaiting additional data
Active Surveillance						
V-safe Dose data through 9/11/22		Vaccinees who enroll	179 v-safe registrants reported receiving a dose of Novavax	Descriptive	Currently not enough data to describe reactogenicity.	Awaiting additional data
Vaccine Safety Datalink (VSD) Data through 9/11/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	<600 doses of Novavax administered	Vaccinated comparator analysis.	Currently not enough data to describe reactogenicity.	Awaiting additional data
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html	

[a]See Table 5. for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 5. Health systems and pre-specified health outcomes

	VAERS	VSD	VA	DMSS	CMS	BEST
Acute disseminated encephalomyelitis (ADEM)	x[1,2]	x	x	x		
Acute myocardial infarction	x	x	x	x	x	x
Anaphylaxis	x	x[3]	x	x	x	x
Appendicitis	x	x	x	x	x	x
Acute respiratory distress syndrome (ARDS)		x[3]	x	x		
Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)	x[1]		x	x		
Ataxia	x[1,2]					
Autoimmune disease	x[1]					
Bell's palsy	x	x	x	x	x	x
Chronic inflammatory demyelinating polyneuropathy (CIDP)	x[1,2]					
COVID-19	x[1]					
Death	x			x		
Disseminated intravascular coagulation (DIC)	x	x	x	x	x	x
Encephalomyelitis/Encephalitis					x	x
Encephalitis	x	x	x			
Encephalomyelitis	x[1,2]	x	x			
Encephalopathy	x[1,2]	x	x	x		
Guillain-Barré syndrome (GBS)	x	x	x	x	x	x
Immune thrombocytopenic purpura (ITP)		x	x	x	x	x
Kawasaki disease	x	x				
Meningitis	x[1,2]		x	x		
Meningoencephalitis	x[1,2]	x	x	x		
Multiple sclerosis (MS)	x[1,2]					
Multisystem Inflammatory Syndrome in Adults (MIS-A)	x	x[3]	x[3]	x	x[6]	x[6]
Multisystem Inflammatory Syndrome in Children (MIS-C)	x	x[3]				x[6]
Myelitis	x[1,2]	x	x	x		
Myocarditis / pericarditis	x	x	x	x	x	x
Narcolepsy / cataplexy	x	x[3]	x	x	x[4]	x[4]
Non-anaphylactic allergic reactions	x[1]					

Optic neuritis (ON)	x[1,2]					
Seizures / convulsions (convulsion is now an LLT under PT seizure)	x	x	x			
Stroke	x		x			
Non-hemorrhagic stroke (NHS)		x			x	x
Hemorrhagic stroke (HS)		x			x	x
Thrombocytopenia	x	x				
Thrombosis with thrombocytopenia syndrome (TTS) and/or CVST	x	x			x	x
Thrombosis at uncommon site (including intracranial, intraabdominal, portal, renal, or other veins) with thrombocytopenia					x	x
Thrombosis at common site (AMI, DVT, HS, NHS, or PE) with thrombocytopenia					x	x
Transverse myelitis (TM)	x	x	x		x	x
Vaccination during pregnancy/adverse pregnancy outcomes	x					
Venous thromboembolism (VTE)	x	x	x		x	x
Pulmonary embolism	-	x	x		x	x
Deep vein thrombosis	-	-	x		x	x

[1]Health outcomes are monitored, but adverse event reports are not abstracted
[2]Diagnoses are grouped and monitored as "Other clinically serious neurologic AEs" in VAERS
[3]Health outcomes are counted, and no sequential analysis is conducted
[4]Only includes narcolepsy
[5]Only list outcomes that are currently included in the RCA.
[6]Only included in the descriptive analysis not the RCA, as MIS requires a COVID-19 diaganosis and therefore historical rates cannot be estimated.