From: "Menschik, David" [redacted]
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
Date: Fri, 10 Sep 2021 11:57:44 +0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-update98forOS_9921.docx

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

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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: "Menschik, David" [redacted]
To: "Shimabukuro, Tom (CDC)" [redacted]
Cc: "Nair, Narayan" [redacted]
Subject: RE: [EXTERNAL] FW: Weekly data mining
Date: Wed, 23 Jun 2021 18:06:28 +0000
Importance: Normal

No, I wish!
(If there is a compelling business need and approved, we can ask our contractor to construct new reports with different age brackets though in the past reconstructing reports with different parameters has taken a long while…)

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, June 23, 2021 1:33 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] FW: Weekly data mining

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

Thanks David. Can you do customized age groups? I'm not asking you do anything, just wondering. Thanks.

From: Menschik, David [redacted]
Sent: Wednesday, June 23, 2021 12:08 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: [EXTERNAL] FW: Weekly data mining

Sure Tom – the age brackets are: 0-1, 2-8, 9-18, 19-44, 45-64, and ≥65 years (corresponding to columns F through K respectively in the weekly excel spreadsheet per below)

Best,
David

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, June 23, 2021 11:37 AM
To: Menschik, David [redacted]
Subject: [EXTERNAL] FW: Weekly data mining

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

Hi David – Would you be able to address Frank's question/issue? Thanks.
Tom

From: Destefano, Frank (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Wednesday, June 23, 2021 9:31 AM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: Weekly data mining

It would be informative to know how they define the age groups. What I see is an "Adult" and "Teen" group. Maybe it's not showing up because they are not specifying the right age group of 12-29 or 12-39?

Frank DeStefano, MD, MPH

From: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Sent: Tuesday, June 22, 2021 12:08 PM
To: Destefano, Frank (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: FW: Weekly data mining

I'm perplexed that myocarditis isn't alerting for either of the mRNA vaccines. I'm wondering if it's getting washout out in the half million reports.

From: Menschik, David [redacted]
Sent: Tuesday, June 22, 2021 6:51 AM
To: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Zinderman, Craig E (FDA/CBER) [redacted]; Nair, Narayan (FDA/CBER) [redacted]; Alimchandani, Meghna (FDA/CBER) [redacted]; Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted]; Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]; Harrington, Theresa (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: Weekly data mining

Good morning John and Tom,

Attached please find a list of all (i.e., unvetted and regardless of notability) PTs with data mining alerts (i.e., EB05 ≥2) for all EUA SARS-CoV-2 vaccine VAERS reports from our weekly 'US Signals Summary Table' ('as of date' 6/18/21). Please feel free to share this hypothesis generating output with your team/command chain, though this is not intended to be shared more broadly.

Thanks,
David

From: "Jason, Christopher" [redacted]
To: "Bazel, Samaneh" [redacted], "Alimchandani, Meghna" [redacted] "Day, Brendan" [redacted], "Nair, Narayan" [redacted]
Subject: Pfizer Biontech Bivalent ISR 3-6
Date: Mon, 24 Jul 2023 14:47:24 +0000
Importance: Normal
Attachments: 2023_06_Pfizer-BioNTech_COVID-19_Vaccine_Bivalent_Q.pdf

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Dear All

Please find attached the COVID Pfizer Bivalent ISR for march to June. I have uploaded a copy to the shared drive.

Sincerely,
Chris

Pfizer-BioNTech COVID-19 Vaccine, Bivalent
EUA 27034

Samaneh Bazel
Samaneh Bazel -S
Digitally signed by Samaneh Bazel -S
Date: 2023.07.20 11:56:35 -04'00'

Quarterly Surveillance Report for Pfizer-BioNTech COVID-19 Vaccine, Bivalent
Surveillance Interval: April 01, 2023 – July 01, 2023

Christopher R. Jason -S
Digitally signed by Christopher R. Jason -S
Date: 2023.07.22 17:18:00 -04'00'

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. 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 (BO).

Reviewer comment:

Overall there were half the number of reports in VAERS (n = 6323) than the previous surveillance quarter (n = 12,146), possibly due to less vaccine uptake. Most U.S. reports for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were non-serious (n= 3,608; 70.7%) 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.

The most frequently reported PTs overall 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.

Medication error PTs during this surveillance period were consistent with those previously reported (Table 6). Among the 15 reports of "Product Use Issue" (5 serious), eleven were U.S reports, seven of which were follow up reports, with only one serious initial report of a patient infected with COVID-19, 157 days after vaccination without explanation for product use issue. 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 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 or the need for further regulatory action. Routine surveillance will continue.

3 DEATH REPORTS

There were a total of 96 death reports during this surveillance period. A separate, BO, QQ_CSS analysis on 7/13/23, yielded 93 initial death reports, including one pediatric death under 18 years of age during this surveillance period. Eight cases (8.6%) reported at least one concomitant vaccine. Among events with available vaccination to symptom onset interval data (N = 87), the mean and median reported onset interval was 57 day(s) and 9 day(s) respectively with range of 0 to 254 days. Among events with available age data (N = 67), the mean and median ages were 77 years and 80 years respectively. Among events with available sex data (N = 90), 39 (43.3%) were female.

All US death reports (n = 43, 46.2%) during the surveillance period were individually reviewed. Forty US cases reported multiple comorbidities and 24 cases were confounded by Covid-19 infection. Five patients expired within a week after receiving the bivalent Pfizer vaccine: two from cardiac events not further specified, one from unspecified respiratory event, and two from unknown causes. Seven other deaths occurred between 1 week and 1 month post vaccination: 1 death from Covid infection, 1 death from acute coronary thrombus with other comorbidities, and 5 others not specified. Due to limited medical information, role of vaccine could not be assessed in these cases. Notable US deaths are discussed further below.

Notable US Deaths

ID	Age (years)	Sex	Adverse Event	Summary
[redacted]	1	M	Cardiopulmonary arrest	1 year old apparently healthy male found unresponsive while napping, after eating cereal earlier, and died same day, 22 days after coadministration of Bivalent Pfizer booster and MMR vaccines. Per PCP VAERS form, patient had received 2 primary doses of Moderna Covid-19 vaccine previously on unknown dates. In ER fingerstick glucose was < 10 mg/dL and tox screen was negative. Bedside limited ultrasound showed no cardiac activity and no pericardial effusion. Per ER physician notes:

				"possible aspiration/choking from emesis while napping, respiratory failure leading to cardiac arrest. Could also have been primary cardiac or neurologic, although no obvious infectious, ischemic, metabolic, traumatic cause by history or exam, although limited diagnostics during ongoing CPR." Cause of death was noted in ER as cardiopulmonary arrest. Autopsy report was notable only for "pulmonary congestion and edema," with "no signs of injury or congenital malformation." *Reviewer Comment: Available information suggests aspiration event. DPV will follow case for any further information.*
[redacted]	76	F	Ischemic stroke	Consumer report of a 76Y F with hx of HTN, DM type 2, hyperlipidemia, and atherosclerosis, stable on corresponding medications, experienced ischemic stroke 57 days after Pfizer bivalent booster vaccine and expired the next day. Per reporter patient had no prior symptoms and had 4 doses of Moderna vaccine prior to receiving the Pfizer bivalent booster. *Reviewer Comment: Given patient's comorbidities and latency since vaccination, role of vaccine cannot be determined.*

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 US CASES

ID	Age (years)	Sex	Adverse Event	Summary

[redacted]	67	F	ANCA vasculitis, acute renal failure.	67Y F with hx of RA, developed ANCA vasculitis and ARF 30 days after bivalent vaccine. *Reviewer Comment: Unlabeled events. Although ANCA vasculitis occurred post vaccination, it can also occur with RA. Additionally, RA can predispose to renal disease. Further information is needed for assessment.*
[redacted]	0.5	M	Status epilepticus	5 mo M developed status epilepticus with fever, one day after coadministration of Covid bivalent, Vaxelis, and Rotateq vaccines. Admitted for sepsis evaluation. *Reviewer Comment: Status epilepticus is an unlabeled event, but case is confounded by multiple vaccines coadministration. Febrile seizures can occur after vaccination, but status epilepticus is less likely. Further information is needed.*
[redacted]	68	F	Ventricular hypokinesis, takotsubo cardiomyopathy	68Y F with no prior cardiac history, s/p recent bladder operation for unknown indication, developed Takotsubo cardiomyopathy 2 days after receiving Pfizer bivalent vaccine. *Reviewer Comment: Unlabeled event. This case is confounded by recent bladder surgery for unknown cause with limited medical information. Additionally, the patient's symptoms began during a 6-mile walk. However, the proximity to vaccination suggests vaccine role. Although Takotsubo cardiomyopathy is rare, it has been reported along other cardiac events after Covid mRNA vaccines, especially myocarditis and pericarditis, which are labeled events for the Pfizer mRNA vaccines. To date there are 2 other cases of Takotsubo cardiomyopathy reported after the*

				Pfizer ba.4-5 bivalent vaccine in VAERS. *A query in business objects on 7/13/23 using LLT "Takotsubo syndrome" also yielded 70 reports (including 24 US reports) for the Pfizer monovalent vaccine. A PubMed search on 7/13/23, using keywords "Takotsubo" and "Covid vaccines" yielded only articles on Takotsubo syndrome after the Pfizer monovalent vaccine (or other Covid-19 vaccines), and not the Pfizer bivalent vaccine.*
[redacted]	61	F	IGA nephropathy	61Y F with history of Crohn's disease, developed fever, chills, vomiting, and hematuria one day after Pfizer bivalent vaccine and was diagnosed with IGA nephropathy several days later. No further information is provided. *Reviewer Comment: Unlabeled event. IGA nephropathy could be triggered by Crohn's disease. However, given proximity of vaccination to onset of symptoms, the role of vaccine cannot be ruled out.*
[redacted]	50	F	Gastroparesis, PSBO	50Y F with history of HTN, developed sudden PSBO 40 days after Pfizer bivalent vaccine x 3, then underwent bowel resection with ensuing gastroparesis. *Reviewer Comment: PSBO is an unlabeled event. Further information is needed to assess. Gastroparesis is more likely due to bowel resection.*
[redacted]	65	M	ALS	65Y M with no prior medical history, with bilateral arms/hands pain and weakness beginning 2 days post vaccination with Pfizer bivalent vaccine, getting progressively worse, diagnosed with ALS 3 months post vaccination.

				Reviewer Comment: Unlabeled event. Role of vaccine cannot be ruled out, given the proximity of event to vaccination.
[redacted]	48	M	Parsonage-Turner syndrome, Brachial Plexopathy, Right Phrenic nerve palsy, Right diaphragm paralysis	48Y M with DM type 2, HTN, hyperlipidemia, gout, GERD, developed Parsonage-Turner syndrome -- brachial plexopathy, resulting in R phrenic nerve palsy, paralysis of R hemidiaphragm, impaired R lung ventilation, 23 days after vaccination. *Reviewer Comment: Unlabeled event. Given latency of symptoms since vaccination, the role of vaccine cannot be ruled out. However, more medical information is needed.*
[redacted]	40	M	Autoimmune rhombencephalitis	40Y M with no past medical history, developed gradual lethargy 6 weeks post vaccination, which progressed over the next 6 months to numbness and tingling in hands, feet, and slurring of speech; he was diagnosed with autoimmune rhombencephalitis and hospice was recommended. Life flighted to 2nd. alternate facility for stem cell transplant. Currently in inpatient rehabilitation. Cannot walk, cannot use arms for eating dressing or grasping objects. Speech remains difficult. *Reviewer Comment: Unlabeled event. Given limited information about medical workup for other etiologies, role of vaccine cannot be elucidated.*
[redacted]	78	F	Transverse myelitis	78Y F with history of A-fib, HTN, hyperlipidemia, osteoporosis, developed left lower extremity weakness and left thigh numbness 6 days after coadministration of influenza and Pfizer bivalent vaccine with MRI findings of Transverse myelitis. She did not have any recent

				illness and other workup was negative. *<u>Reviewer Comment</u>: Unlabeled event. Proximity to vaccination and negative workup for other etiologies point to vaccine causal role, but case is confounded by coadministration of influenza vaccine. Transverse myelitis is an AESI followed closely for the Pfizer vaccine.*

<u>Reviewer comment</u>: Review of VAERS data and medically notable reports did not identify new safety concerns for the Pfizer bivalent vaccine during the surveillance period. The reported AESIs showed a similar or decreased trend as compared to the previous quarterly surveillance, except for increased reports of acute MI (n = 87) vs previous quarterly reports (n = 32). Review of acute MI cases, however, revealed that majority of vaccination dates were between September and December 2022 with only 6 reports of acute MI in 2023. Additionally, the majority of the reports did not have further medical information and a meaningful analysis could not be performed.

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 7/10/23, with a data lock point of 7/7/23. Preferred terms (PTs) with corresponding EB05 values are shown in the table below.

Event	US EB05 20230707	US N 20230707	US Serious EB05 20230707	US Serious N 20230707	World EB05 20230707	World N 20230707
Off label use	2.56	142	0.975	7	0.978	386
Product use issue	2.50	133	1.139	8	4.17	285
Drug ineffective	2.17	1867	1.105	21	1.25	2325
Incorrect product formulation administered	2.02	1536	0.779	2	2.51	1536
Product storage error	1.67	4251			2.07	4251

<u>Reviewer comment:</u>

There are no new data mining findings compared to previous surveillance period. The previously reported signal for ischemic stroke has resolved.

6 CASE SERIES

None.

7 NOTABLE PUBLICATIONS

A literature search of PubMed conducted on 7/10/23 for 'Pfizer-BioNTech COVID-19 Vaccine Bivalent' with a date range of 4/1/23 through 7/1/23 and yielded the following safety related articles:

Piechotta V et al. "Safety and effectiveness of vaccines against COVID-19 in children aged 5-11 years: a systematic review and meta-analysis." *Lancet Child Adolesc Health*. 2023 Jun;7(6):379-391. doi: 10.1016/S2352-4642(23)00078-0. Epub 2023 Apr 18.

The authors performed a systematic review and meta-analysis aimed to assess the safety and efficacy or effectiveness of All COVID-19 vaccines, including the Pfizer bivalent vaccine, approved in the EU for children aged 5-11 years up to January 23, 2023. Authors concluded that In children aged 5-11 years, mRNA vaccines are moderately effective against infections with the omicron variant, but probably protect well against COVID-19 hospitalizations. Additionally, vaccines were "reactogenic but probably safe."

Ehmsen S, et al. "BQ.1.1, XBB.1, and XBB.1.5 neutralization after bivalent mRNA COVID-19 booster in patients with cancer." *Cancer Cell*. 2023 Apr 10;41(4):649-650. doi: 10.1016/j.ccell.2023.02.003. Epub 2023 Feb 9.

Authors evaluated the neutralizing capacity to current SARS-CoV-2 variants in patients with cancer before and after receiving the BNT162b2 bivalent mRNA vaccine booster. They concluded that "Bivalent vaccine provides some protection against BQ.1.1 but fails to protect against XBB.1 and XBB.1.5 in patients with cancer."

Wagenhäuser I, et al. "Bivalent BNT162b2 mRNA original/omicron BA.4-5 booster vaccination: adverse reactions and inability to work compared with the monovalent COVID-19 booster." *Clin Microbiol Infect*. 2023 Apr;29(4):554-556. doi: 10.1016/j.cmi.2023.01.008. Epub 2023 Jan 16.

Study comparing 104 four healthcare workers who received a fourth dose of COVID-19 vaccine with either the original, monovalent Pfizer vaccine or bivalent vaccine (between 8/13/21 to 10/28/22), showed higher rate of adverse reactions among participants receiving the bivalent vaccine (87.5% [95% CI, 77.2%–93.5%; 56/64]) compared with those receiving the monovalent vaccine (52.5% [95% CI, 37.5%–67.1%; 21/40]) vaccine (p = 0.0002). Per authors there was a trend towards an increased rate of inability to work and intake of as-needed medication following bivalent vaccination.

Reviewer comment: No further regulatory action is indicated based on the above literature search. DPV will continue to monitor.

8 SPONSOR'S ABBREVIATED SUMMARY MONTHLY SAFETY REPORT

The most recent Abbreviated Summary Monthly Safety Report (aSMSR #16) in PBRER format was submitted on 6/12/23 (STN 125742.300; reporting period 4/16/23 to 5/15/23), which included the monovalent and bivalent vaccines. During the reporting period for the aSMSR, no actions were taken for BNT162b2 vaccines for safety reasons. A total of 9,781,940 doses were distributed for the BNT162b2 Bivalent (Original and Omicron BA.4/BA.5) for this reporting period (543,979,490 cumulative).

Per review memo: "During the reporting period, no actions were taken for safety reasons by a HA with respect to the authorized BNT162b2 vaccines (page 7). According to the manufacturer, there is no data at this time to suggest that the safety concerns for the bivalent presentations are different from those of BNT162b2 Original (page 15). According to the manufacturer, based on the evaluation of cumulative safety data and the benefit-risk analysis, no changes to the Reference Safety Information (RSI), or additional risk minimization activities are warranted (page 17).
Myocarditis and Pericarditis: "The results are generally similar to those reported in the previous abbreviated SMSR #15 (reporting period 3/16/2323 through 4/1523). No newly elevated groups were identified as compared to the results in SMSR #15" (page 25).
Overview of signals addressed or under evaluation during the reporting interval: Menstrual Irregularities, status ongoing, category not yet determined (pages 16 and 345)."

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 QUERY AND INFORMATION REQUESTS DURING THE SURVEILLANCE PERIOD

No information requests were received during this surveillance period.

10 CONCLUSIONS

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

VAERS Internal Surveillance Report

(Confidential - Deliberative/Predecisional)

Surveillance Period (Completed Dates): **4/1/23 to 7/1/23**

Report Run Date: **7/6/23**

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	5,079	1,489	45	45	879	49	0	550
Foreign	1,210	1,208	51	43	266	107	0	802
Total	**6,289**	**2,697**	**96**	**88**	**1,145**	**156**	**0**	**1,352**

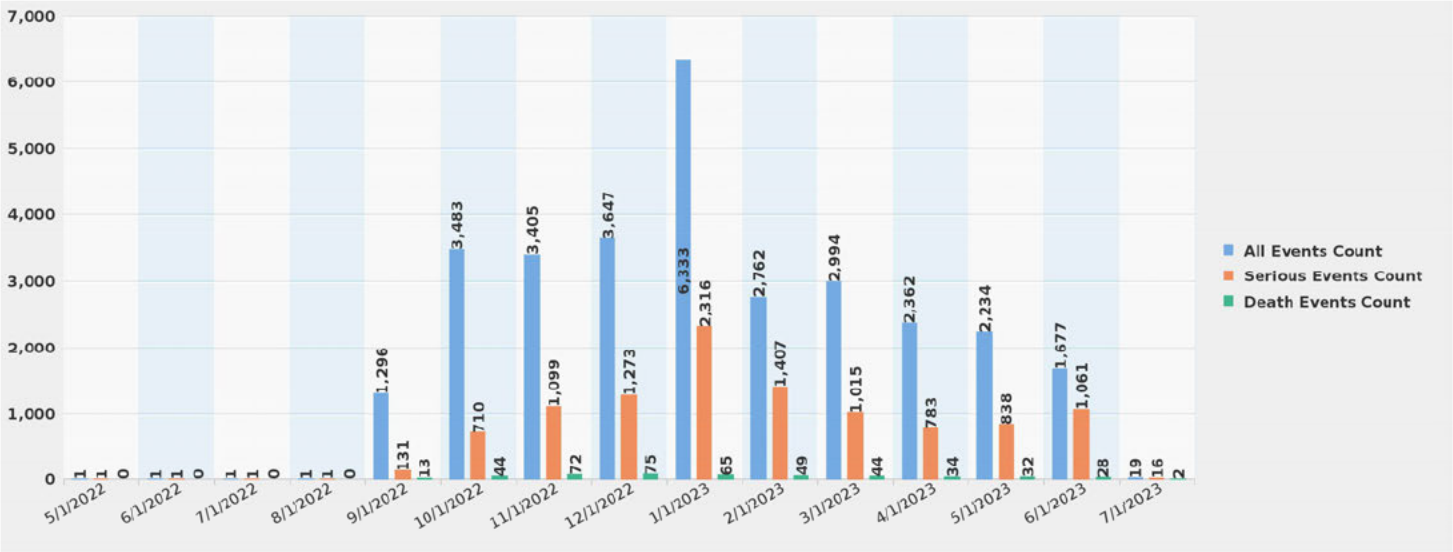
Note: One event can be counted in multiple serious subcategories if reported differently by multiple reporters

2. Event Counts by Age Group

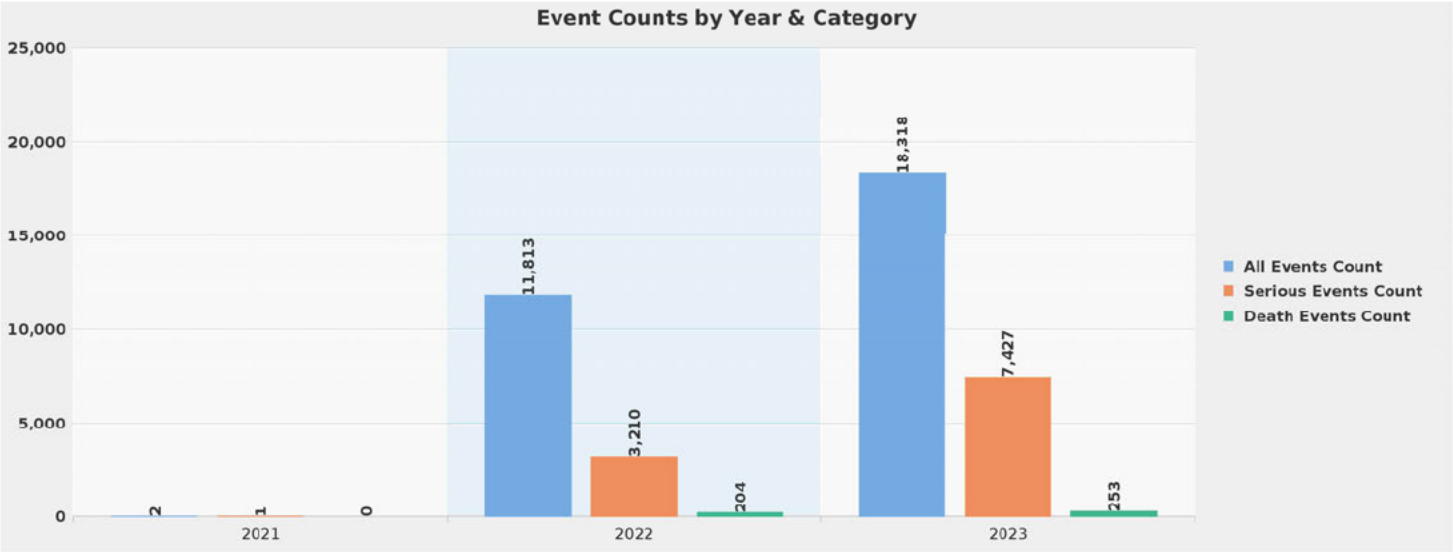
	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
<1 Year	32	1	0	1	1	0	0	0
1 to <3 Years	55	1	1	0	1	0	0	0
3 to <7 Years	146	1	0	0	0	0	0	1
7 to <17 Years	495	9	0	0	4	1	0	4
17 to <65 Years	2,040	728	12	21	282	39	0	399
>= 65 Years	2,502	1,037	57	33	706	41	0	272
Not Reported	1,022	922	26	33	152	75	0	676
Total	**6,289**	**2,697**	**96**	**88**	**1,145**	**156**	**0**	**1,352**

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
COVID-19	1,612	5,736	1	1	0	848	25
EXPIRED PRODUCT ADMINISTERED	724	1,449	2	12	10	0	0
PRODUCT STORAGE ERROR	638	4,247	3	2	-1	0	0
FATIGUE	635	3,018	4	3	-1	199	5
DRUG INEFFECTIVE	576	2,299	5	6	1	576	1
COUGH	569	2,103	6	7	1	102	4
PYREXIA	556	2,764	7	5	-2	178	7
HEADACHE	467	2,914	8	4	-4	153	1
PAIN	373	2,024	9	8	-1	99	1
NO ADVERSE EVENT	340	1,922	10	9	-1	0	0
MALAISE	317	1,446	11	13	2	104	5
OROPHARYNGEAL PAIN	316	1,212	12	18	6	23	0
DYSPNOEA	295	1,307	13	15	2	170	12
INTERCHANGE OF VACCINE PRODUCTS	257	1,120	14	19	5	242	5
RESPIRATORY TRACT CONGESTION	253	890	15	22	7	15	3
CHILLS	228	1,534	16	11	-5	81	2
PAIN IN EXTREMITY	217	1,353	17	14	-3	98	3
RHINORRHOEA	199	793	18	24	6	10	0
ASTHENIA	193	925	19	21	2	118	8
ARTHRALGIA	183	1,015	20	20	0	96	2
ACUTE RESPIRATORY FAILURE	181	302	21	42	21	180	12
DIZZINESS	174	1,256	22	17	-5	88	1
CONDITION AGGRAVATED	164	667	23	30	7	104	9
NAUSEA	150	1,282	24	16	-8	81	3
NASOPHARYNGITIS	139	462	25	34	9	9	0
HYPOXIA	137	242	26	45	19	137	12
VOMITING	131	715	27	27	0	77	3
DIARRHOEA	130	675	28	28	0	63	2
MYALGIA	122	888	29	23	-6	74	0
FEELING ABNORMAL	120	750	30	26	-4	25	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
INCORRECT PRODUCT FORMULATION ADMINISTERED	113	1,535	31	10	-21	1	0
VACCINATION FAILURE	110	470	32	33	1	110	1
CHEST PAIN	107	646	33	31	-2	71	2
NASAL CONGESTION	105	418	34	38	4	6	0
HYPOTENSION	104	259	35	44	9	96	9
SYMPTOM RECURRENCE	102	133	36	50	14	98	0
ACUTE MYOCARDIAL INFARCTION	89	149	37	48	11	89	4
INCORRECT DOSE ADMINISTERED	88	762	38	25	-13	2	1
INFLUENZA LIKE ILLNESS	85	320	39	40	1	27	0
WRONG PRODUCT ADMINISTERED	85	668	39	29	-10	45	1
RESPIRATORY FAILURE	84	134	41	49	8	84	5
ATRIAL FIBRILLATION	83	290	42	43	1	56	7
DECREASED APPETITE	82	421	43	37	-6	33	2
RASH	81	566	44	32	-12	31	0
PALPITATIONS	76	449	45	35	-10	45	0
PNEUMONIA	76	228	45	47	2	58	8
FALL	74	351	47	39	-8	61	8
PRODUCTIVE COUGH	74	235	47	46	-1	17	1
THROAT IRRITATION	73	318	49	41	-8	4	0
HYPOAESTHESIA	71	444	50	36	-14	39	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	724	1,449	1	3	2	0	0
PRODUCT STORAGE ERROR	638	4,247	2	1	-1	0	0
INCORRECT PRODUCT FORMULATION ADMINISTERED	113	1,535	3	2	-1	1	0
INCORRECT DOSE ADMINISTERED	88	762	4	4	0	2	1
WRONG PRODUCT ADMINISTERED	85	668	5	5	0	45	1
INAPPROPRIATE SCHEDULE OF PRODUCT ADMINISTRATION	46	299	6	9	3	4	0
EXTRA DOSE ADMINISTERED	43	444	7	6	-1	1	0
PRODUCT PREPARATION ISSUE	32	327	8	8	0	0	0
PRODUCT PREPARATION ERROR	27	170	9	11	2	0	0
PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE	26	344	10	7	-3	1	0
POOR QUALITY PRODUCT ADMINISTERED	15	142	11	12	1	0	0
PRODUCT USE ISSUE	15	283	11	10	-1	5	0
PRODUCT ADMINISTRATION ERROR	13	95	13	14	1	0	0
VACCINATION ERROR	10	43	14	15	1	0	0
MEDICATION ERROR	8	99	15	13	-2	3	0
CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR	5	28	16	17	1	0	0
INCORRECT ROUTE OF PRODUCT ADMINISTRATION	5	37	16	16	0	4	0
PRODUCT ADMINISTERED AT INAPPROPRIATE SITE	4	21	18	18	0	2	0
ACCIDENTAL OVERDOSE	2	3	19	20	1	1	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
WRONG TECHNIQUE IN PRODUCT USAGE PROCESS	2	11	19	19	0	2	0
DEVICE DIFFICULT TO USE	1	1	21	24	3	1	1
PRODUCT PACKAGING CONFUSION	1	2	21	22	1	0	0
UNINTENTIONAL MEDICAL DEVICE REMOVAL	1	2	21	22	1	1	1
WRONG PATIENT RECEIVED PRODUCT	1	3	21	20	-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	9	45	1	1	0	4	0
ABORTION SPONTANEOUS	5	17	2	3	1	0	0
MATERNAL EXPOSURE DURING PREGNANCY	5	26	2	2	0	5	1
MATERNAL EXPOSURE BEFORE PREGNANCY	3	7	4	5	1	0	0
PREGNANCY	3	6	4	6	2	0	0
ABORTION MISSED	2	5	6	7	1	1	0
FAILURE TO THRIVE	2	9	6	4	-2	2	0
FOETAL GROWTH RESTRICTION	2	4	6	9	3	1	0
ABORTION SPONTANEOUS COMPLETE	1	1	9	22	13	1	0
ANTIPHOSPHOLIPID SYNDROME	1	3	9	12	3	0	0
BRADYCARDIA NEONATAL	1	1	9	22	13	1	0
BRIEF RESOLVED UNEXPLAINED EVENT	1	2	9	13	4	1	0
CHRONIC VILLITIS OF UNKNOWN ETIOLOGY	1	1	9	22	13	0	0
DELIVERY	1	5	9	7	-2	1	0
EXPOSURE VIA BREAST MILK	1	1	9	22	13	1	0
FOETAL CARDIAC ARREST	1	1	9	22	13	1	1
FOETAL DEATH	1	4	9	9	0	1	0
FOETAL EXPOSURE DURING PREGNANCY	1	2	9	13	4	1	0
FOETAL HEART RATE DECELERATION ABNORMALITY	1	2	9	13	4	1	0
FOETAL HYPOKINESIA	1	2	9	13	4	1	0
HAEMORRHAGE IN PREGNANCY	1	2	9	13	4	0	0
MECONIUM STAIN	1	1	9	22	13	0	0
NEONATAL ASPIRATION	1	1	9	22	13	1	0
PERINATAL DEPRESSION	1	1	9	22	13	1	0
PERINEAL ABSCESS	1	1	9	22	13	1	0
POSTPARTUM HAEMORRHAGE	1	2	9	13	4	1	0
PRE-ECLAMPSIA	1	2	9	13	4	1	0
PREMATURE BABY	1	1	9	22	13	1	0
PREMATURE DELIVERY	1	4	9	9	0	0	0
PREMATURE RUPTURE OF MEMBRANES	1	1	9	22	13	1	0
PREMATURE SEPARATION OF PLACENTA	1	2	9	13	4	0	0
RETAINED PRODUCTS OF CONCEPTION	1	1	9	22	13	0	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
TACHYCARDIA FOETAL	1	2	9	13	4	1	0
THIRD STAGE POSTPARTUM HAEMORRHAGE	1	1	9	22	13	1	0
Count:	34						

9. Most Frequent PTs with Death

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
COVID-19	25	63	1	1	0
ACUTE RESPIRATORY FAILURE	12	35	16	23	7
DYSPNOEA	12	58	9	11	2
HYPOXIA	12	36	20	25	5
CONDITION AGGRAVATED	9	31	18	20	2
HYPOTENSION	9	25	25	24	-1
ASTHENIA	8	30	14	16	2
PYREXIA	7	34	5	4	-1
FATIGUE	5	22	2	2	0
INTERCHANGE OF VACCINE PRODUCTS	5	26	10	14	4
MALAISE	5	32	8	9	1
COUGH	4	22	4	6	2
NAUSEA	3	15	19	12	-7
PAIN IN EXTREMITY	3	6	13	10	-3
RESPIRATORY TRACT CONGESTION	3	6	11	17	6
VOMITING	3	18	21	18	-3
ARTHRALGIA	2	9	15	15	0
CHEST PAIN	2	12	24	21	-3
CHILLS	2	10	12	8	-4
DIARRHOEA	2	6	22	19	-3
DIZZINESS	1	11	17	13	-4
DRUG INEFFECTIVE	1	5	3	5	2
HEADACHE	1	8	6	3	-3
PAIN	1	7	7	7	0
VACCINATION FAILURE	1	4	23	22	-1
Count:	25				

Input Summary

*** Query Name:Query 1 ***

Select Only One Vaccine Name COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))
Report Date (Start): 4/1/2023 12:00:00 AM
Report Date (End): 7/1/2023 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)
Age unknown - If specifying age(s), select 'Unknown' here to include unknown ages (Optional)
Enter 'FR' to exclude foreign reports (otherwise, leave blank) (Optional)

From: "Menschik, David" [redacted]
To: "Nair, Narayan" [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Fri, 3 Dec 2021 14:32:10 +0000
Importance: Normal

(I discussed at length with Hannah and she expressed understanding…)

From: Menschik, David
Sent: Friday, December 03, 2021 9:31 AM
To: Narayan Nair (Narayan.Nair@fda.hhs.gov) [redacted]
Subject: FW: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

FYI

From: Menschik, David
Sent: Friday, December 03, 2021 9:29 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Hi Hannah,

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

Best,
David and Bethany

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

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

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

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

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

All the very best,
Hannah

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

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

Dear Dr. Rosenblum,

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

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

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

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

Editorial points - IMPORTANT:

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

Authorship and reporting guidelines:

1. Please check that all author name spellings and affiliations are correct.
2. Please indicate any authors who are full professors.

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

Title/summary:

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

Methods:

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

Results:

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

Discussion:

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

Additional requirements:

22. Please provide the text, tables, and figures in an editable format (eg, EPS files, PowerPoint files, depending on software used to produce them. If figures are composed of photographs or other images, high resolution files

(300dpi or greater) should be provided. More information can be found here: https://www.thelancet.com/for-authors/forms?section=artwork.

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

Reviewers' Comments:

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

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

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

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

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

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

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

There is a lot of data represented in this report but also of interest to know what happened with reporting of events as the vaccine rollout matured. Is it possible to show data from the first 3 months versus second 3 months.

Women were more likely to be over-represented during the initial three months in view of healthcare rollout. It would be of interest if the reporting of any of the events including reactogenic events changed as time went on and there was more societal familiarity with these.

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

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

Reviewer #5: This article provides a picture of reports of AEFI in the first six months of utilization of mRNA COVID-19 vaccines in the United States. I think that similar reports are highly desirable to reassure the population about vaccine safety and therefore priority is high. However, in the attempt of providing more information, the study goes beyond the simple description of reports from VAERS and providing a survey of data collected by v-safe. Unfortunately, the authors made this step without providing important information to the readers. With the current information I cannot establish whether and to what extent the results deserve to be discussed with more caution.
Specific comments
Introduction (page 3) "We reviewed VAERS and v-safe […] vaccines were administered". Instead of providing a simple descriptive report of the data collected in these two databases the authors 1) calculated a rate of report of death and compared that with that expected in an unspecified vaccinated population and 2) performed a disproportionality analysis. These are objectives to be declared in the and text and in the abstract.
For the above mentioned analysis the authors did not included in the methods important information.

For the disproportionality analysis we have no information on the dataset. What were the vaccines included in the dataset? What was the proportion of COVID-19 vaccines? For the latter question, the authors reported in the limitation that in the analyzed period (we know only that they included reports up to June 14th, 2021 but we have not the initial date) the great majority of reports was for the vaccines of interest. If this proportion is over 90% the possibility of identifying a signal was likely close to zero. So, why performing such an analysis?
For the comparison of mortality rates we have not information about the comparator: does it refers to mortality following immunization with any vaccine? From the reference number 20 it seems that this rate was calculated (how?) only for COVID-19 vaccines? So what is the rationale for this comparison? Estimating the under-reporting of fatal cases? Estimating the number of reports over a mortality for any cause that was attributed to vaccines (not accidental) by reporters? What was the period in which mortality was calculated in the reference? 14 days after vaccination or longer? In summary, I think that these two rates cannot be compared or should be interpreted in a different way, at least with the details of information provided by the authors.
Page 7: "there were 4,496 reports of death…." Were all these reports from US? Did the VAERS include reports from other countries? I suppose these fatal cases have been occurred all in the US since the authors used this number to estimate the reporting rate for fatal cases using the number of doses of vaccines administered in the US. If this is the case, it should be clearly stated.
Page 8: "During the analytic period, 7,914,583 mRNA COVID-19 vaccine recipients […]". How many patients dropped out after the initial enrolment? In case the drop-out is quite high (as I suppose) the authors should compare the population included in the analysis with the population dropped out to check for a possible selection that could have had an impact on the results.
Page 10 "Analysis of deaths reported to VAERS demonstrated lower than expected reported mortality rates compared to background mortality rates". Besides my doubt about comparability given the lack of essential information, why the authors wrote "than expected"? I would have bet whatever I have that the rate was lower than that estimated for a background mortality for two reasons: 1) under-reporting and 2) background mortality include death for any cause while VAERS includes only deaths that have been somehow associated with the immunization. The authors included an interpretation similar to mine in the "limitations" section. So they likely expected this results as well.

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

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

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

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

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

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

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

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

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

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

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

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

TECHNICAL INFORMATION:

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

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

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

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

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In summary, the signed statements we require are:

- Authors' contribution and signatures
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Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Anderson, Steven" [redacted]
To: "Nair, Narayan" [redacted] "Forshee, Richard" [redacted]
Subject: RE: F/u on Pfizer Bivalent
Date: Thu, 2 Mar 2023 16:04:38 +0000
Importance: Normal
Inline-Images: image008.png; image009.png; image010.png; image011.png; image012.jpg; image013.jpg; image014.jpg; image015.jpg; image016.jpg

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Dear Narayan,

Thank you for sharing these additional analyses - these results are helpful in understanding the situation. It seems like there is no signal here. I will note the large number/proportion of reports after the announcement which suggests the small increases may have been due to stimulated reporting.

Regards,

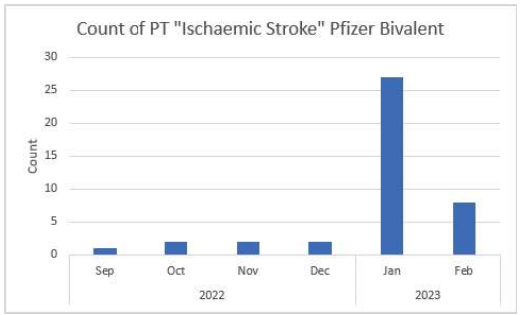
Steve

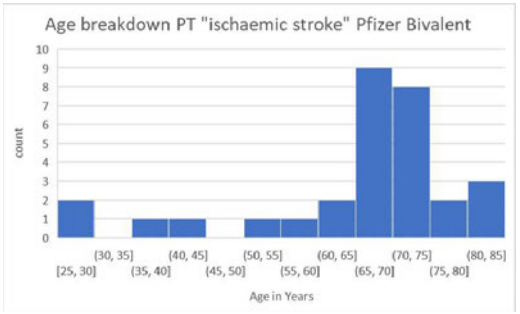
Steve Anderson, Ph.D., M.P.P.
Director
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U. S. Food & Drug Administration
[redacted]

Phone
email: [redacted]

From: Nair, Narayan [redacted]
Sent: Wednesday, March 1, 2023 11:39 AM
To: Anderson, Steven [redacted]; Forshee, Richard [redacted]
Subject: RE: F/u on Pfizer Bivalent

Dear Steve,
The EB05 for ages 65 and older was 1.029 so it did not reach significance. It has not reached significance in prior runs. Thus far the only run that has reached significance has been for US serious (all ages for Feb 28) all other data mining runs including overall (including foreign reports), overall US reports, fatal US reports and US reports broken down by various age groups have not reached significance. As of today we have 42 US VAERS reports of ischemic stroke following the Pfizer bivalent vaccine. Of note 32 of these were received on or after Jan 13, when the VSD data on ischemic stroke was released publicly.





Note there are 2 with unknown age

Narayan

From: Anderson, Steven [redacted]
Sent: Tuesday, February 28, 2023 11:43 AM
To: Nair, Narayan [redacted]; Forshee, Richard [redacted]
Subject: RE: F/u on Pfizer Bivalent

Narayan,

Thank you for the update. Do we know the EB05 for ages 65 and older? Can you say more about the periods of evaluation for prior trend versus post-mid-January 2023 when the public notification appeared and if it could be stimulated reporting as you mention?
Have the reports been evaluated?

Thank you,

steve

Steve Anderson, Ph.D., M.P.P.
Director
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U. S. Food & Drug Administration
[redacted]

Phone [redacted]
email: [redacted]

From: Nair, Narayan [redacted]
Sent: Tuesday, February 28, 2023 11:29 AM
To: Anderson, Steven [redacted] Forshee, Richard [redacted]
Subject: F/u on Pfizer Bivalent

Dear Steve and Rich,
While Deb Thompson was doing her 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			0.664	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

Overall we have a small number of reports- 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.

As you know at best Data mining is hypothesis generating and I am wondering if this is overall related to stimulated reporting. Given we don't have any data mining alerts for the overall US cases, and the low reporting rate, I still feel our passive surveillance data does not reveal any type of signal for the Pfizer bivalent vaccine. We will continue to keep a close eye on this.

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

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

Subject: [EXTERNAL] VaST - Draft minutes and report from January 9, 2023 (CONFIDENTIAL)

Date: Fri, 13 Jan 2023 18:02:33 +0000

Importance: Normal

Attachments: 2023-01-09_-_VaST_minutes_draft_confidential.docx; 2023-01-09_-_VaST_Report_and_Data_Table_draft_confidential.docx

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Dear VaST members and participants,

Attached are the draft minutes and report from the VaST call this week. The first 2 pages of the report summarize the VaST assessment from the closed session. Please let us know if there are any corrections or edits.

At present, you should have a VaST call on your schedule for January 23. We likely will be changing the schedule for January and will notify all soon. Of note, on Thursday, January 26, there is a VRBPAC meeting. Information about that call is posted:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-january-26-2023-meeting-announcement

Regards,
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
January 9, 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, Keipp Talbot (VaST chair), Bob Hopkins (NVAC-chair), Lisa Jackson, 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), Mary Rubin (HRSA), Timothy Styles (HRSA)

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

CDC: Karen Broder, Margaret Cortese, Julianne Gee, Monica Godfrey, Elisha Hall, Anne Hause, Rita Helfand, Jessica MacNeil, Lauri Markowitz (CDC Co-lead), Paige Marquez, Michael McNeil, Sarah Meyer, Alanna Moorer, Pedro Moro, Danielle Moulia, Tanya Myers, Kristen Nordlund, Sara Oliver, Sierra Scarbrough, Martha Sharan, David Shay, John Su, Evelyn Twentyman, Megan Wallace, Eric Weintraub, Melinda Wharton (CDC Co-lead), Jared Woo

Technical SMEs: Steve Anderson (FDA), Ed Belongia (VSD), James Donahue (VSD), Peter Donoforio (VUMC), Bruce Fireman (VSD), Rich Forshee (FDA), Kristin Goddard (VSD), George Grimes (HRSA), Kayla Hanson (VSD), Nicky Klein (VSD), Ned Lewis (VSD), Narayan Nair (FDA), Azadeh Shoaibi (FDA), Kawsar Talaat (JHU), Ousseny Zerbo (VSD)

Agenda

Signal detection/signal assessment for bivalent COVID-19 booster vaccination in active surveillance:

- Vaccine Safety Datalink COVID-19 RCA: Preliminary Analyses of Ischemic Stroke after Pfizer Bivalent Booster Dose, Nicky Klein (KPNC)
- Centers for Medicare & Medicaid Services (verbal update), Rich Forshee (FDA)
- Veterans Affairs (verbal update), Fran Cunningham (VA)

Administrative issues and announcements - Co-chairs and Co-leads

- Reminders about COI and confidentiality
- Doses distributed: 942,343,115; Doses administered: 665,076,272 (last updated: January 5)
  - Doses distributed: Pfizer-BioNTech: 566,920,395; Pfizer-BioNTech(bivalent): 70,300,080; Moderna: 342,955,820; Moderna (bivalent): 33,615,200 Janssen/J&J: 31,439,600; Novavax: 1,027,300; Other: 0
  - Doses administered: Pfizer-BioNTech: 396,267,682; Pfizer-BioNTech(bivalent): 30,933,298; Moderna: 248,998,772; Moderna (bivalent): 17,536,128 Janssen/J&J: 18,954,913; Novavax: 70,373; Other: 784,532
  - At least one dose: 268,546,218; Primary series: 229,254,623; Bivalent booster dose (people ≥ 5-years): 48,229,842
  - 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).

Vaccine Safety Datalink COVID-19 RCA: Preliminary Analyses of Ischemic Stroke after Pfizer Bivalent Booster Dose – Dr. Nicky Klein (KPNC)

Dr. Klein presented the preliminary analysis of ischemic stroke following Pfizer-BioNTech COVID-19 bivalent booster vaccination. There were 2.2 million (Moderna: 650k; Pfizer-BioNTech: 1.6 million) doses of bivalent boosters administered, of which, 820k doses (Moderna: 280k; Pfizer-BioNTech: 540k) were in persons ≥ 65-years old.

There was a signal for stroke following Pfizer-BioNTech bivalent COVID-19 vaccine in persons ≥65 years, a rate ratio of 1.5-2 (CI: 1.16-2.07). There was significant temporal clustering in the 11-22 day risk-window. KPNC reviewed 24 cases in persons ≥65 years following Pfizer-BioNTech bivalent vaccine. 22 were incident ischemic stroke and none had a history of stroke or TIA. 14 patients had flu vaccine co-administered on the same day. There was an elevated rate ratio for persons 18-64 years, but there was no statistical signal. In previous analyses, there was no evidence of increased risk after primary series or monovalent booster.

Discussion and questions

1. Was flu circulating during these time periods? Flu is also associated with strokes.
    - There was substantial Flu A in Northern California during this period. They do not have immediate information on flu and/or respiratory viruses at other sites.
2. Do rates differ comparing bivalent only, bivalent + flu (HD), HD flu?
    - VSD is looking at rates by concomitant flu vaccine and they are a little higher in those with concomitant HD flu but the data are too sparse to draw strong conclusions. In the past 2 weeks, the rates with and without concomitant HD flu have converged.
3. What is the race/ethnicity of stroke patients?
    - The additional slides (slide 23) include a race/ethnicity breakdown of the stroke cases following Pfizer-BioNTech bivalent booster in the 1-21 day window.
4. Any changes in race/ethnicity in the <65 year-old cohort compared to ≥65 year-old?
    - The race/ethnicity breakdown for persons 18-64 years is similar (see slide 24).
5. Have subgroups within the ≥65 year age group been explored?
    - To date, VSD has looked at age groups and at concomitant HD flu vaccine. Other subgroups not yet been explored.
6. Is there a concern about the imbalance of accumulation of person-time & events contributing later in the post-vax window; how is the potential source of imbalance removed?
    - There was a bigger imbalance at the beginning of data collection and stability comes more with time. It has a second order effect because they have the same amount of forward time for the event to be reported.
7. Once a signal is found it is considered a signal. How are additional data taken into account after a signal is found?
    - The purpose of continued evaluation of data is to check if it was in fact a signal. This could be due to late arriving data, specific sub-groups, or other comparators and/or other methods that need to be taken into account.
8. Can you describe what you were seeing in the Moderna analysis?
    - VSD has not seen the same elevated rate ratios for Moderna. The most recent weekly analysis for Moderna in persons ≥65 years for stroke had a rate ratio of 1.05 (CI: 0.69-1.59), p-value: 0.450. For persons 18-64 years, the rate ratio for stroke was 0.63 (CI:0.23 - 1.64), p-value 0.889.
9. Have the weekly estimates for Moderna decreased over time, akin to Pfizer estimates?
    - The rate ratios have fluctuated over the last 5 weeks (not consistently decreasing or increasing), with RRs all roughly around 1. The absence of a signal for Moderna is relevant

for the earlier questions about flu circulation. Moderna vaccines were used later when flu activity was higher.

10. Was there a requirement of receipt of previous vaccines? Were they homologous or did you see heterologous doses?
    - The criteria were that individuals that were eligible for a booster. There was no distinction in previous # of vaccines, heterologous, or homologous. The only other requirement was a vaccine 4+ months prior.
11. VaST members discussed reviewing background rates and whether there is actually a protective effect. The infection block effect is a plausible explanation for the differences we see between the risk and comparison intervals, but it does not explain the clustering in the risk interval. There is the same relationship with influenza disease and stroke.
12. VaST members discussed if there were any clinical differences (i.e. more comorbidities) between patients who received vaccine earlier vs later.

Centers for Medicare & Medicaid Services (verbal update) – Dr. Rich Forshee (FDA)

Dr. Forshee gave a verbal update on the CMS historical comparator analysis for evaluating stroke. The analysis has some differences compared with the VSD analysis – the outcome does not include transient ischemic attack (TIA), only ischemic stroke, and the risk interval is 1-28 days, compared to 1-21 days in VSD. Importantly, the comparator group is different. There has not been a signal for ischemic stroke following bivalent Pfizer-BioNTech or Moderna booster vaccination.

Discussion and questions

1. What dates are being used for the historical comparator?
    - 2019 data were used for the historical comparator analysis.
2. What are the adjustments?
    - The rates are directly adjusted for age, sex, race. The seasonality adjustment is added when FDA runs the RCA. There are more adjustments when a signal is found.
    - For Pfizer-BioNTech, the analysis has reached the prespecified limit of outcome detection.
    - FDA is now working on a more robust analysis.

Veterans Affairs (verbal update) – Dr. Fran Cunningham (VA)

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

Combined Systems Safety Monitoring Report
January 9, 2023
Confidential - DRAFT

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

VSD findings:

- ≥ 65-year age group
  - In the rapid cycle analysis, there is a statistical signal for ischemic stroke/transient ischemic attack (TIA) after bivalent Pfizer-BioNTech COVID-19 booster vaccination during the period 1-21 days after vaccination vs. a comparison period of 22-42 days after vaccination, with a rate ratio that ranges from 1.5 to 2.0.
    - There is temporal clustering of ischemic stroke/TIA codes in days 11-22 following receipt of the bivalent Pfizer-BioNTech COVID-19 booster vaccine.
    - 22/24 cases available for chart review were confirmed as incident cases.
  - In a secondary analysis, when the comparison group was drawn from persons eligible to receive a bivalent COVID-19 booster dose but had not received it, there was no statistical signal for ischemic stroke/TIA.
  - During chart review, it was noted that many adults ≥ 65 years had concomitant administration of bivalent Pfizer-BioNTech COVID-19 booster vaccine and influenza vaccine (most received high dose).
  - There is 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. Bivalent Moderna COVID-19 booster doses were administered later in the calendar year and fewer were co-administered with influenza vaccine.
  - Previous surveillance 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.
- 18–64-year age group
  - In the rapid cycle analysis, there is no statistical signal for ischemic stroke/transient ischemic attack after bivalent Pfizer-BioNTech COVID-19 booster vaccination or bivalent Moderna COVID-19 booster vaccination.

CMS and VA findings:

- In the CMS rapid cycle analysis, there is no statistical signal for ischemic stroke after Pfizer-BioNTech or Moderna COVID-19 booster vaccination.
- In the VA rapid cycle analysis, there is no statistical signal for ischemic stroke/TIA after Pfizer-BioNTech or Moderna COVID-19 booster vaccination.
- Both the CMS and VA rapid cycle analyses use historical comparison groups.
  - In contrast, the VSD rapid cycle analysis uses vaccinated concurrent comparators and analyzes events occurring in vaccinated people in a risk period compared to events

occurring in vaccinated people in a comparison period. The FDA/CMS and VA historical comparator and the VSD vaccinated concurrent comparator analyses are complementary methodologies that look at different datasets using different methods and help increase the robustness of U.S. vaccine safety monitoring efforts.

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 not been observed in two other active vaccine safety monitoring systems in the United States.
- 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
  - Consider potential drivers for the observed lower incidence of ischemic stroke/TIA among the vaccinated comparator group on the reducing risk of complications due to disease with COVID-19 or influenza during the comparison window
  - Estimate risk of ischemic stroke/TIA following concomitant administration of COVID-19 booster dose and other vaccinations vs. separate day vaccination
- VaST will continue to review data from additional analyses planned from VSD, CMS and the VA.

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 Population data through 7/11/22; VAERS data presented 7/18/22	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	3.7 million vaccines administered across all vaccines	Descriptive	635 total AE 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	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 preliminary analysis data through 12/31/22	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	540k 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 • Rate ratio of 1.5-2 (CI: 1.16-2.07)	Further review and analysis is needed

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> • 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. 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 5.6% reported 'other symptoms' following dose 2 and 1.4% reported	No concerns raised

					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 • Elevated risk for AMI that was attenuated after exclusion of	Inconclusive evidence for AMI, ITP; Consistently elevated risk for PE; numbers too small for DIC

					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	Total doses 5.5 million	Historical comparator and	RCA statistical signal for anaphylaxis in HealthCore data following Pfizer-BioNTech	Further monitoring and analyses of myocarditis/pericarditis in younger age groups ongoing.

		0-64 years		sequential analyses		
NPTC Vaccine Sentinel Survey Data presented on 7/18/22		Persons who identify as American Indian/Alaska Native	3.7 million vaccines administered across all vaccines	Descriptive	1,036 total AE reports • 456 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 Population data through 7/11/22; VAERS data presented 7/18/22	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	3.7 million vaccines administered across all vaccines	Descriptive	579 total AE reports • 406 medically attended health impact events	No 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 7/18/22)		Persons who identify as American Indian/Alaska Native	3.7 million vaccines administered across all vaccines	Descriptive	606 total AE reports • 194 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 Population data through 7/11/22; VAERS data presented 7/18/22	All health events, adverse events of special interest[a]	Persons who identify as American Indian/Alaska Native	3.7 million vaccines administered across all vaccines	Descriptive	59 total AE reports • 47 medically attended health impact events	No 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 7/18/22		Persons who identify as American Indian/Alaska Native	3.7 million vaccines administered across all vaccines	Descriptive	69 total AE 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.

From: "Welsh, Kerry" [redacted]
To: "Nair, Narayan" [redacted]
Subject: FW: IR for TEE
Date: Mon, 19 Dec 2022 19:44:22 +0000
Importance: Normal
Attachments: 2022_11_Pfizer-BioNTech_COVID-19_Vaccine_-_Bivalent_M.pdf
Inline-Images: image001.png; image002.jpg; image003.jpg; image004.jpg; image005.jpg; image006.jpg

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Narayan,

The four notable cases of TEE for Pfizer Bivalent start on pg 4 under the notable cases section of the last SR, which includes three reports mentioning VITT. There are potential alternate causes or insufficient info but thought were relevant in the overall concern for thrombotic events.

Best,
Kerry

From: Thompson, Deborah [redacted]
Sent: Monday, December 19, 2022 1:30 PM
To: Welsh, Kerry [redacted]
Subject: RE: IR for TEE

Thanks, Kerry!

Deb

From: Welsh, Kerry [redacted]
Sent: Monday, December 19, 2022 1:27 PM
To: Thompson, Deborah [redacted]
Cc: Alimchandani, Meghna [redacted]; Nair, Narayan [redacted]
Subject: RE: IR for TEE

Hi Deb,

This looks good me. Looping in Division for awareness.

Yes, I think we'll need to change to something along the lines of "FDA is evaluating mRNA COVID-19 vaccines...." for Moderna. I'll ask Soumya to draft a similar IR for Moderna Bivalent. Thanks!

Best,
Kerry

From: Thompson, Deborah [redacted]
Sent: Monday, December 19, 2022 1:20 PM
To: Welsh, Kerry [redacted]
Subject: IR for TEE

Hi Kerry,

Please see the attached draft IR for Pfizer regarding reports of TEE. I didn't single out ischemic stroke, but mentioned the reports of CVST/PE/VITT, as examples of notable reports that triggered the IR. Pfizer recently questioned why we were asking about glomerulonephritis and SJS/TEN, so wanted to provide something more concrete than just a general IR.

However, something more general might be needed for Moderna.

Please let me know if you have any edits/comments.

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

Monthly Surveillance Report for Pfizer-BioNTech COVID-19 Vaccine, Bivalent
Surveillance Period: November 1, 2022 – November 30, 2022

Reviewer comments on Business Objects Query: During the surveillance period, the Pfizer-BioNTech COVID-19 Vaccine was authorized for use as a single booster dose in individuals 5 years of age and older. Reports in VAERS for younger individuals (Table 2) may represent unauthorized use of the vaccine, medication errors, and/or misclassification of the vaccine given. The majority (70.4%) of reports for the Pfizer bivalent vaccine were non-serious during the surveillance period (Table 1), although there was a higher percentage of serious reports for this surveillance period (29.6%) as compared to the prior surveillance period (15.8%). Serious reports were individually reviewed.

The most frequently reported PTs (Table 5) are consistent with PTs reported for the monovalent vaccine and with the known safety profile for the monovalent and bivalent vaccine or signs/symptoms of COVID-19. Review of PTs does not suggest new safety concerns for the bivalent vaccine. The EUA Fact Sheet includes Warnings and Precautions for myocarditis, pericarditis, and syncope. Lymphadenopathy is also a labeled event.

Medication error PTs during this surveillance period were consistent with those previously reported for the monovalent vaccine and almost all reports were non-serious (Table 6). The EUA Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) 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 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.

Notable U.S. Death Reports

There were 25 U.S. death reports received during this surveillance period. All U.S. death reports were individually reviewed during the surveillance period. 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.

Summary of Notable U.S. Death Reports Following Pfizer-BioNTech COVID-19, Bivalent Vaccination, November 1, 2022 – November 30, 2022

ID	Age (years)	Sex	Summary
[redacted]	66	M	Patient with PMH AORTIC VALVE STENOSIS; CHRONIC KIDNEY DISEASE; DIALYSIS; HYPERTENSION had dialysis on the morning of 11/4, received the covid vaccine (dose 5) and then went to a dermatologic office for a skin

			check. While he was getting checked he became unresponsive. CPR was started, patient came to the ER and ACLS care was given. Patient expired. *Reviewer comment: This individual with chronic medical conditions died the same day of vaccination. Medical records and additional information are not available at this time, which precludes further assessment of this report.*
[redacted]	67	F	Patient with PMH High blood pressure, IBS/GI issues and recent history of bronchitis was running on treadmill and collapsed, eyes rolled back and strange breathing for a few minutes, then stopped breathing, CPR given, patient died. Onset 3-days post-4th dose. *Reviewer comment: This individual experienced sudden death 3-days post-vaccination. ER records mention possible acute coronary syndrome vs cardiac dysrhythmia vs pulmonary embolism. It is unknown if an autopsy was performed.*
[redacted]	29	F	Patient received flu vaccine and COVID bivalent booster and died 3-days later from an unknown heart issue. Report from pharmacist not directly involved with patient – was a friend from yoga class. Reporter saw online that individual died suddenly from what her partner described as an unknown heart issue. Reporter saw she recently had vaccines administered and wanted to make sure it was reported to VAERS. *Reviewer comment: This is a hearsay report. Medical records and additional information are not available at this time, which precludes further assessment of this report.*

Reviewer comment: Review of death reports during the surveillance period found deaths that were temporally associated with vaccination. However, reports contained limited details and/or additional information was not available regarding other potential contributing factors or likely causes of death. No new safety concerns requiring further regulatory action were identified. Death reports will continue to be monitored.

U.S. Medically Notable Reports

Medically notable reports are based on reviewer judgement and may include reports of serious, unlabeled events that were suspicious for being due to the vaccine or that did not have an alternate etiology and could plausibly be due to the vaccine, atypical or rare life-threatening events, or serious, labeled events with unusual presentations or clinical courses.

Summary of U.S. Medically Notable Reports Following Pfizer-BioNTech COVID-19, Bivalent Vaccination, November 1, 2022 – November 30, 2022

ID	Age (years)	Sex	Adverse Event	Summary

[redacted]	67	F	GBS	Patient with PMH of chondrosarcoma presented to the emergency department 5-days post-5th dose for evaluation of gradually worsening of weakness in both legs and back pain that started same day post-vaccination. She also received an influenza vaccine a few days AFTER symptoms started. A CT thoracic and lumbar spine with contrast showed no central canal stenosis. Neurology was consulted. LP was done which revealed albumino-cytological dissociation. Given concern for post-vaccine mediated Guillain Barre Syndrome (GBS), patient was started on IVIG. Completed 5 days of IVIG with mild improvement. Transferred to acute inpatient rehab unit to continue rehabilitation. *Reviewer comment:* *GBS is an adverse event of special interest (AESI) that is being monitored by the FDA BEST Initiative, CDC Vaccine Safety Datalink (VSD), and post-authorization studies being conducted by the sponsor. An internal DPV observed to expected (O/E) analysis tool was used to calculate a crude O/E for GBS after receipt of the bivalent vaccine using the following assumptions: 28-day risk window, 7 cumulative U.S. cases among all ages since initial bivalent authorization, 26,941,088 bivalent doses administered in U.S. per CDC COVID tracker, and a conservative background rate of 1 per 100,000 person-years (Gubernot, 2021). The O/E=0.339 (95% CI=0.136-0.698). The O/E is below 1 and does not suggest a new safety concern at this time. Surveillance will continue.*
[redacted]	6	F	Miller Fisher syndrome	Patient with PMH of ear infection developed Miller Fisher syndrome - started with fatigue and headache on 10/27, developed diplopia and fever (fever lasted ~3 days) on 10/29 as well as weakness. Onset 3-days post-unk dose. Admitted and evaluated - ultimately treated with IVIG. MRI brain 10/31/22 with enhancement of bilateral CN III-VIII; MRI spine 11/1/22 with patchy enhancement of nerve roots of cauda equina; CSF studies 11/1/22:- Protein 76- Glucose 59- 12 WBC (11%N, 42%L, 47%Macro)- 0 RBC- Meningitis/encephalitis panel and culture negative- CSF oligoclonal bands pending. Other tests: 11/1- Lyme serology negative- EBV serology negative- Respiratory pathogen

				panel with +Rhino/enterovirus. *Reviewer comment:* *No medical records available at this time. This individual was positive for rhinovirus and enterovirus; viral infections are known to precede symptom onset of Miller Fisher syndrome and GBS. Please see comments above regarding safety surveillance for GBS and a crude O/E analysis.*
[redacted]	67	M	Bilateral pulmonary emboli, Suspicion for Vaccine Induced Thrombotic Thrombocytopenia	Patient with PMH ANGINA PECTORIS; ANXIETY; DYSLIPIDAEMIA; ESSENTIAL HYPERTENSION; GASTROOESOPHAGEAL REFLUX DISEASE; GOUT; HYPERLIPIDAEMIA; ISCHAEMIC CARDIOMYOPATHY; MIGRAINE; OBSTRUCTIVE SLEEP APNOEA SYNDROME presented to ER 10/20/2022 and diagnosed with Bilateral PE w/right heart strain; heparin infusion started. Onset 24 days post-5th dose (vaccinated on 9/26/22). Left ICA CVA on heparin a few hours later, occlusion lysed with tenecteplase, and mechanical thrombectomy 10/20/2022. Patient was intubated in the ER and transferred to the intensive care unit. Gross Hematuria - anticoagulation was held for a period of time while bleeding. Anticoagulation switched to Argatroban and eventually transitioned to warfarin. Extensive DVT left lower extremity discovered on imaging 11/3/2022. Of note previous admission to the hospital on 10/16/2022 for Ileus small bowel and previous admission for 5 Vessel CABG 10/7/2022, discharged on 10/12/2022 raising concern for Heparin induced thrombocytopenia however testing is not clear between HIT/T or VITT see lab results below. Declining platelets as follows 9/2/2022 204 k/mL; 192k/mL pre-CABG ; 120k/mL 10/7/2022 after heparin/ protamine on the bypass machine - no further challenge with heparin until 10/20/2022; 10/8 125; 10/9 111; 10/10 114; 10/11 146; 10/12 188; 10/16; 209; 10/17 194 10/20 143 pre heparin; 10/21 91; 10/22 65; Argatroban started on 10/22; 10/23 86; 10/24 platelets continue to rise to 335 k/mL on 11/7/2022. Heparin platelet antibody positive 10/22/22, Serotonin release assay (SRA) negative 10/22/22. Repeat SRA sent 11/2/2022 - negative. Hep-Ind Thrombocytopenia PF4 Ab IgG (used [illegible]

				VITT assay) positive 10/22/22. *Reviewer comment:* *No medical records available at this time. This individual had a recent history of 5-vessel CABG and had declining platelets pre-CABG and after heparin on the bypass machine. The report indicates that lab testing was not clear to differentiate between HIT or VITT. Thrombosis with thrombocytopenia syndrome (TTS) has been reported to occur following COVID-19 vaccination and is a labeled event for the Janssen COVID-19 vaccine. The sponsor reviewed the topic of TTS following the Pfizer-BioNTech COVID-19 Vaccine at several time points during 2021 in Summary Monthly Safety Reports (SMSRs) and concluded that the review did not indicate the presence of a causal association with the Pfizer-BioNTech COVID-19 Vaccine (19736.335, 19736.366, 19736.409, 19736.453, 19736.491). Thrombotic and embolic events are AESIs being monitored by CDC's VSD, FDA's BEST, and in post-authorization/post-market safety studies being conducted by the sponsor.*
[redacted]	36	M	STEMI, thrombosis	Patient with HTN, 6-days post-vax on 11/1/22 had STEMI thought to be due to embolic thrombi requiring aspiration thrombectomy. 11/2/22 had another STEMI due to embolic thrombi requiring aspiration thrombectomy. Patient is a 36-year-old man with history of hypertension and possible MI (age 21, self-reported) who presented with acute onset substernal chest pain radiating to both arms and was found to have STEMI with 100% occlusions with thrombi (no underlying plaque) of both LAD and RCA now s/p aspiration and thrombectomy of both arteries on 11/1 persistent ST elevation, then found to have 100% occluded posterolateral branch artery in the setting of heavy thrombus burden s/p second aspiration thrombectomy and stent placement on 11/2. He was then started on DAPT and apixaban, with plan for triple therapy (DAPT/apixaban) for a month (stop aspirin 12/1/22) followed by dual therapy (P2y12/DOAC) for at least 1 year. Hypercoagulable workup was unrevealing. Had Left heart catheterization 11/1/22, 11/2/22. Transesophageal echocardiogram, Transthoracic echocardiogram performed

				Reviewer comment: No medical records are available at this time, which precludes further assessment of this case. Thrombotic and embolic events are AESIs being monitored by CDC's VSD, FDA's BEST, and in post-authorization/post-market safety studies being conducted by the sponsor. The sponsor conducted a safety review of thromboembolic events in the SMSR for September 2021 (19736.536), including case reviews, O/E analysis, and literature review, and concluded the totality of evidence did not support a causal association between thromboembolic events and the vaccine. Monitoring will continue.
[redacted]	30	M	CVST, possible VITT	Patient with PMH of ASTHMA, ECZEMA, ALLERGIC RHINITIS, HX OF COVID 19 (6/8/2022), and history of gynecomastia surgery 1-month prior to vaccination and on the following medications: ibuprofen, tylenol, oxycodone, fexofenadine, fluticasone, albuterol, triamcinolone, clindamycin, hydrocortisone experienced difficulty speaking, right facial droop, and right-sided weakness 2-days post-vax (vax on 11/4/22). Diagnosed with cerebral venous sinus thrombosis superior sagittal sinus and left convexity cortical vein, intracranial hemorrhage, and cerebral edema; required decompressive craniotomy, endovascular venous thrombectomy, and platelet transfusion. Reported as "DIC picture" with platelets low at 52,000 (were 211,000 pre-vax in Sept 2022), d-dimer elevated >4.0 (more specific value not found in records), INR 1.7, low fibrinogen <60. Reported as "highly suspicious for COVID vaccine induced immune thrombocytopenia (VITT)." Negative lupus anticoagulant, negative Factor V Leiden, protein C activity level low (59, ref range=70-130%), antithrombin III activity normal, negative anti-cardiolipin antibody, ESR=2 (normal), SARS-CoV-2 not detected. No history of heparin exposure, PF4 antibody test=0.328 OD (ref range<=0.399 OD). Med records show ongoing hospitalization through at least 11/21/22, patient non-verbal with severe cognitive impairment, requires total assist. *Reviewer comment:* This individual developed

				CVST and possible VITT, although the PF4 antibody test was within the reference range. A negative PF4 antibody test makes VITT less likely but does not exclude the diagnosis. (Greinacher, 2022) In addition, the onset was 2-days post-vaccination; VITT has a more likely onset 5-30 days post-vaccination. (Greinacher, 2022) Please see above comments regarding previous sponsor evaluations of TTS and safety surveillance for thromboembolic events. In addition, the sponsor previously evaluated cases of cerebral venous thrombosis (CVT) following the Pfizer-BioNTech COVID-19 Vaccine in response to questions from Swissmedic, including case reviews, clinical trial data, literature review, and O/E analyses (cumulatively through November 24, 2021), and concluded the evidence did not support a conclusion that Comirnaty is causally associated with CVT (19736.709). The sponsor performed an additional analysis of CVST through April 15, 2022 and again concluded that given the totality of evidence of data on CVST and Comirnaty, including O/E analyses, AE reports, literature review, and in context of the millions of doses administered, that a causal association between Comirnaty and CVST was not concluded and that no changes to the labeling or risk management documents were warranted. Routine monitoring will continue.
[redacted]	80	F	Multiple pulmonary emboli, possible VITT	Patient with pancreatic carcinoma experienced increased shortness of breath 9-days post-bivalent vaccine. She went to the emergency department, and they completed a CT scan of her chest and found lots of clots. She was then hospitalized and placed on supportive care with anti-coagulants. Reported that testing that shows vaccine-induced Thrombotic Thrombocytopenia. Antibody test positive October 24, 2022 (no values provided). Reported via V-safe. CT Angio 10/24: Multiple pulmonary emboli and cardiac thrombus, 11/22: High PF4 antibody levels *<u>Reviewer comment:</u> This individual has pancreatic carcinoma which is a confounding condition for blood clots. The report mentions high PF4 antibody levels and VITT, although no lab values were available. Other laboratory*

				results, including platelet counts, and medical records are not available. This report will be re-reviewed pending additional information.
[redacted]	35	M	Visual disturbance, cyclitis	Patient with no chronic or long-standing health conditions experienced symptoms in both eyes roughly 2-4 weeks after the first COVID vaccine (Moderna Lot#025J20-2A, Jan 2021) and had initial 24–48-hour flu-like symptoms post-vax. Second shot (Moderna Lot#042L20A) was administered in Feb 2021 along with increased eye related symptoms. Initial symptoms included blurred vision, headaches/migraines, vertigo, and sensitivity to lights which included haloing and star-bursting. Initially sought care with optometrist but was referred to Medical Center for additional assessment between Feb-April 2021. Ophthalmology initial assessment that symptoms were presenting as Fuchs Heterochronic cyclitis, bilateral (treatment recommended optical steroids and artificial tears). Symptoms stabilized but failed to resolve during tapering treatments through July/Aug 2021. Referred to cornea specialist with an appointment Nov 2021. Specialist assessment could not provide positive diagnosis but did not believe symptoms were related to Fuchs Heterochronic cyclitis. Specialist could not confirm correlation with COVID virus or COVID vaccine but recommended continue Ophthalmologist directed treatments. Third COVID shot (Moderna Lot#035C21A) was administered on Dec 2021, which presented increased eye related symptoms shortly after. Symptoms again stabilized through spring/summer 2022 with suspected tie to COVID vaccine. Fourth shot (Pfizer Bivalent Lot#GJ5342) was administered October 2022, which again presented with increased eye related symptoms 2-3 weeks after the shot. Followed up with Ophthalmology who recommended not taking any additional COVID vaccines, submit CDC adverse effect report, and to seek military medical waiver from future COVID vaccines. HLA-B27 Blood Test Negative, No suspected correlation to 2013 Lasik surgery, Fuchs Heterochronic cyclitis-like symptoms present at all times in both eyes. *Reviewer comment: This individual*

				experienced Fuchs Heterochronic cyclitis-like symptoms following each mRNA COVID-19 vaccine. Fuchs Heterochronic cyclitis is a chronic, low grade anterior segment inflammation that accounts for 2-3% of all uveitis cases and has an unknown etiology, although there is consensus that an immunologic reaction is involved. (Bonfioli, 2009) However, the report indicates that ophthalmology assessment ultimately did not believe symptoms were related to Fuchs Heterochronic cyclitis. No medical records are available at this time, however, the positive re-challenge in this case, suggests a potential relationship to mRNA COVID-19 vaccines. The sponsor has previously evaluated ophthalmology topics including blindness and visual disturbances (19736.453), optic neuritis (19736.335), and uveitis (19736.536 and 19736.782); based on the totality of evidence, these events were not found to be a risk and/or causally associated with exposure to Comirnaty. Monitoring will continue.
[redacted]	66	F	ITP	Patient with PMH Diabetes mellitus; hypertension; obstructive sleep apnea; pulmonary hypertension and on meds of Tylenol PM Extra Strength; atorvastatin; bumetanide; buspirone; cholestyramine; cyanocobalamin; dexamethasone; ergocalciferol; escitalopram; losartan; melatonin; pantoprazole; pioglitazone; potassium chloride; sildenafil; triamcinolone admitted to hospital for thrombocytopenia with platelet count of 12k. Patient received COVID-19 booster 8-days prior, and flu shot 12-days prior to symptom onset. Underwent extensive workup, which noted elevated ANA levels. Patient noted previously high ANA levels 8/2022 during autoimmune workup. Report indicated that patient presumed to have vaccine induced ITP and was treated with dexamethasone. Platelet count recovered, and patient was discharged from hospital in stable condition. *<u>Reviewer comment:</u> No medical records available at this time. This individual had undergone a previous autoimmune work-up for unknown reasons and was noted to have high ANA levels. The individual was also noted to be on pantoprazole, which is labeled for thrombocytopenia. The sponsor has*

				previously evaluated the risk of ITP and the potential signal was closed as "no risk" in August 2021 (19736.453).

Reviewer comment: Four U.S. medically notable reports concerned thromboembolic events, with three reports mentioning concern for VITT. Assessment of three of these reports (including two of the potential VITT reports) was limited by lack of medical records and/or confounding factors. The fourth report with available medical records [redacted] *was for a 30-year-old male with a history of gynecomastia surgery in the month prior to vaccination who experienced CVST with thrombocytopenia 2-days post-vaccination; PF4 antibody test result was within the reference range which is not supportive of VITT. AESIs, including thromboembolic events, CVST, and TTS, are being monitored in CDC and FDA safety surveillance systems, and in post-authorization studies being conducted by the sponsor.*

Case Series Analyses:

Myocarditis/Pericarditis

A Business Objects AESI Screening Report query was run for Pfizer-BioNTech COVID-19 Vaccine, Bivalent for the current surveillance period on December 14, 2022 for reports related to myocarditis or pericarditis. The following PTs were included: AUTOIMMUNE MYOCARDITIS;AUTOIMMUNE PERICARDITIS;EOSINOPHILIC MYOCARDITIS;HYPERSENSITIVITY MYOCARDITIS;IMMUNE-MEDIATED MYOCARDITIS;MYOCARDITIS;PERICARDITIS;PERICARDITIS ADHESIVE;PERICARDITIS CONSTRICTIVE;PLEUROPERICARDITIS.

The query returned a total of five U.S. reports, including one non-fatal serious report (no death reports). The median age=56 years (range=33-73 years). The median onset=7 days post-vaccination (range=1-20 days). Reports were for 2 (40.0%) females and 3 (60.0%) males. The one non-fatal serious report was for a 56-year-old female with a history of hypertension and flu-like symptoms (negative for COVID) with onset 17-days post-bivalent dose. Cardiology note indicated likely infective endocarditis of the aortic valve; 1 bottle positive for Streptococcus and transthoracic echo showed evidence of moderate size vegetation on the aortic valve.

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.

Sponsor's Abbreviated Summary Monthly Safety Report

The sponsor submitted an Abbreviated Summary Monthly Safety Report (aSMSR) on December 8, 2022 (STN 125742/243; reporting period October 16, 2022 to November 15,

2022), which included the monovalent and bivalent vaccines. During the reporting period for the aSMSR, no actions were taken for BNT162b2 for safety reasons. A potential safety signal for dermatomyositis has an ongoing evaluation. This signal was from a serious AE (SAE) from a non-vaccine Pfizer-sponsored clinical trial for an immunomodular investigational product. The sponsor evaluated a signal for hemophagocytic lymphohistiocytosis (HLH) and closed the signal as "no risk."

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

Data Mining Findings[1]

Data mining was conducted using the Empirica Signal "US Signals Summary Table" with a data lock point of December 9, 2022. PTs with an EB05≥2 for the U.S. overall and/or subgroups are shown below.

Preferred Terms with an EB05≥2 for the U.S. overall or subgroups, Pfizer-BioNTech COVID-19 Vaccine, Bivalent

Event	US EB05 20221209	US Child EB05 20221209	US Teen EB05 20221209	US Adult1 EB05 20221209	US Adult2 EB05 20221209	US Adult3 EB05 20221209	US Female EB05 20221209	US Male EB05 20221209
Incorrect dose administered	1.859	**2.184**	1.842	1.011	1.266	1.178	1.737	1.873
Incorrect product formulation administered	**3.724**	**5.778**	**4.967**	**5.135**	**2.573**	1.586	**3.451**	**3.778**
Off label use	**3.819**	0.492	0.525	1.38	**2.714**	**4.523**	**3.76**	**2.264**
Product use issue	**3.834**	0.505	0.561	**2.223**	**4.493**	**3.493**	**3.636**	**2.323**
Syncope	1.825	0.759	1.444	**2.424**	1.187	0.867	1.697	1.673
Unresponsive to stimuli	1.422		1.431	**3.392**	0.529	0.533	1.161	1.374
Wrong product administered	**2.765**	0.923	1.668	**4.992**	**2.65**	**2.041**	**2.742**	**2.427**

Reviewer comment: PTs with an EB05≥2 primarily included medication errors and off label use. Prior review of reports of "loss of consciousness" and "unresponsive to stimuli" frequently revealed events of fainting/syncope, with some reports also involving seizures or seizure-like activity. A few death reports also included the PT "unresponsive to stimuli." Syncope is a labeled event and is included in Warnings and Precautions of the EUA Fact Sheet. Herpes zoster is no longer a PT with an EB05≥2 for any subgroup. Data mining findings did not reveal patterns suggesting new safety concerns. Continued surveillance using data mining will continue.

Publications

A literature search of PubMed was conducted on December 14, 2022 for 'Pfizer-BioNTech COVID-19 Vaccine, Bivalent' with a date range of November 1, 2022 through November 30, 2022: 2022/11/01:2022/11/30[Date - Publication] AND ("bnt162

vaccine"[MeSH Terms] OR ("bnt162"[All Fields] AND "vaccine"[All Fields]) OR "bnt162 vaccine"[All Fields] OR "pfizer biontech covid 19 vaccine"[All Fields]) AND ("bivalence"[All Fields] OR "bivalency"[All Fields] OR "bivalent"[All Fields] OR "bivalently"[All Fields] OR "bivalents"[All Fields]))

The search returned two articles. Review of abstracts did not identify new safety concerns for the bivalent vaccine.

Reviewer comment: *No further regulatory action is indicated based on the above literature search.*

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).

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use as a single booster dose to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals ≥5 years of age and as the third dose in the primary series for individuals aged 6 months through 4 years. Please see the EUA Letter of Authorization (LOA), and product EUA Fact Sheets for additional details.

Conclusions

The findings from this monthly surveillance report for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent did not reveal new safety concerns requiring further regulatory action at this time. Routine surveillance will continue, along with routine surveillance reports.

References

Bonfioli AA, Curi AL, Orefice F. Fuchs' heterochromic cyclitis. Semin Ophthalmol. 2005 Jul-Sep;20(3):143-6. doi: 10.1080/08820530500231995. PMID: 16282147.

Greinacher A, Langer F, Makris M, Pai M, Pavord S, Tran H, Warkentin TE. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Update on diagnosis and management considering different resources. J Thromb Haemost. 2022 Jan;20(1):149-156. doi: 10.1111/jth.15572. Epub 2021 Nov 10. PMID: 34693641; PMCID: PMC8646430.

Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, Duffy J, Harrington T, McNeil MM, Broder K, Su J, Kamidani S, Olson CK, Panagiotakopoulos L, Shimabukuro T, Forshee R, Anderson S, Bennett S. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016. Epub 2021 May 14. PMID: 34088506; PMCID: PMC8118666.

Shimabukuro, T. Myocarditis following mRNA COVID-19 vaccination; presented to the Advisory Committee on Immunization Practices on July 19, 2022. Available at: ACIP July 19, 2022 Presentation Slides | Immunization Practices | CDC; Accessed on October 14, 2022.

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[1] The minimum standard analysis is the “US Signals Summary Table.” Data mining covers the entire post-authorization period for this product. 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.

VAERS Internal Surveillance Report

Surveillance Period (Completed Dates): **11/1/22 to 11/30/22**

Report Run Date: **12/12/22**

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

Report By: **Deborah.Thompson**

1. Event Counts by Location and Seriousness

	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
US	2,763	442	25	33	164	29	0	244
Foreign	533	532	40	35	145	61	0	297
Total	3,296	974	65	68	309	90	0	541

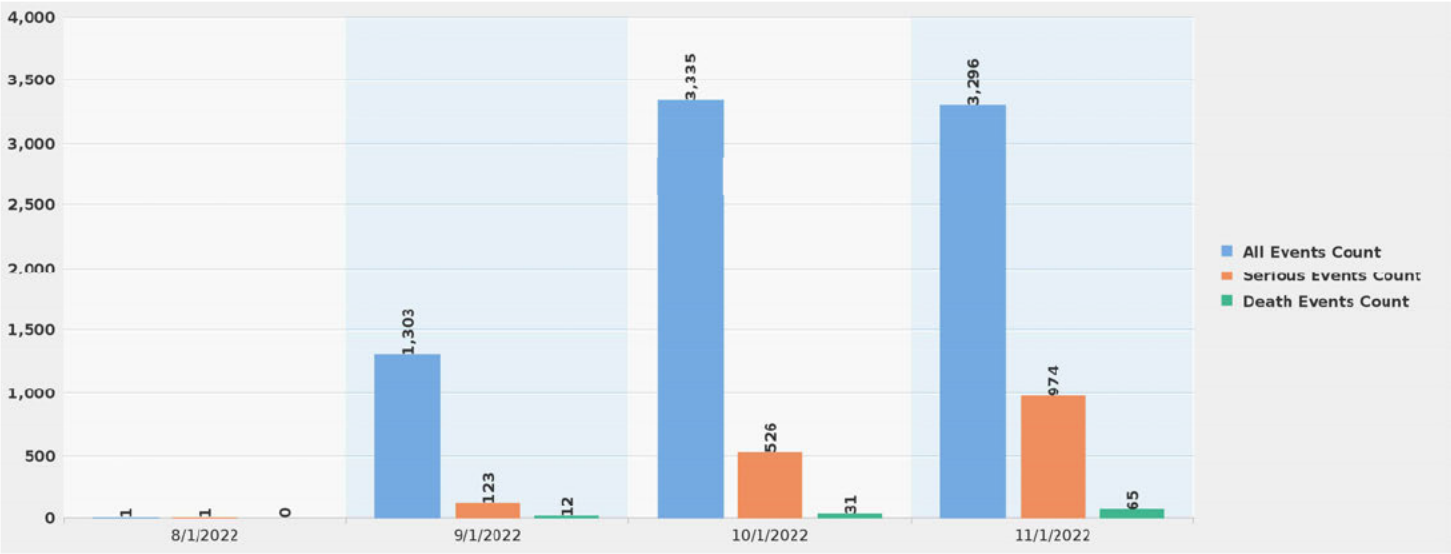
Note: One event can be counted in multiple serious subcategories if reported differently by multiple reporters

2. Event Counts by Age Group

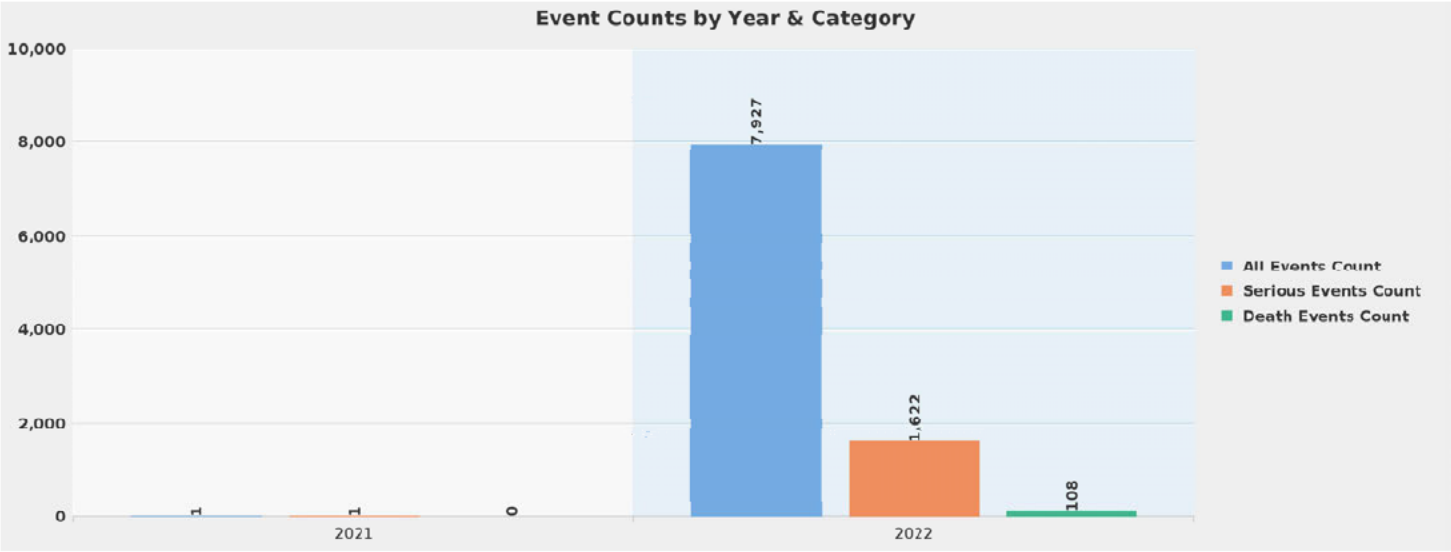
	All	Serious	Deaths	Life Threatening	Hospitalization	Disability	Birth Defect	OMIC
<1 Year	7	0	0	0	0	0	0	0
1 to <3 Years	4	1	0	0	0	0	0	1
3 to <7 Years	137	2	0	0	1	0	0	1
7 to <17 Years	455	7	0	0	2	0	0	5
17 to <65 Years	1,310	298	9	19	76	43	0	178
>= 65 Years	944	351	36	29	167	24	0	143
Not Reported	440	316	20	20	63	23	0	213
Total	3,296	974	65	68	309	90	0	541

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
COVID-19	376	908	1	1	0	265	5
FATIGUE	282	846	2	3	1	78	3
HEADACHE	269	859	3	2	-1	73	1
INCORRECT PRODUCT FORMULATION ADMINISTERED	267	798	4	5	1	0	0
NO ADVERSE EVENT	261	679	5	7	2	1	0
PYREXIA	261	840	5	4	-1	94	1
PAIN	235	729	7	6	-1	45	2
INCORRECT DOSE ADMINISTERED	215	435	8	12	4	0	0
DRUG INEFFECTIVE	188	417	9	13	4	188	0
PAIN IN EXTREMITY	179	517	10	11	1	34	0
DIZZINESS	169	529	11	9	-2	39	2
NAUSEA	169	527	11	10	-1	78	3
CHILLS	158	593	13	8	-5	49	0
COUGH	144	354	14	16	2	22	2
MALAISE	128	363	15	14	-1	60	5
DYSPNOEA	127	328	16	19	3	75	9
INTERCHANGE OF VACCINE PRODUCTS	127	244	16	27	11	105	3
PRODUCT PREPARATION ISSUE	126	196	18	33	15	0	0
ARTHRALGIA	124	333	19	18	-1	46	0
WRONG PRODUCT ADMINISTERED	118	360	20	15	-5	16	1
SYNCOPE	99	258	21	25	4	31	3
PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE	96	220	22	30	8	2	0
MYALGIA	94	296	23	20	-3	48	0
VOMITING	91	260	24	24	0	39	1
OROPHARYNGEAL PAIN	88	246	25	26	1	9	0
RASH	87	272	26	21	-5	3	0
ASTHENIA	85	265	27	23	-4	40	2
FEELING ABNORMAL	80	238	28	29	1	24	1
CONDITION AGGRAVATED	78	177	29	37	8	34	5
INJECTION SITE PAIN	75	272	30	21	-9	7	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
PRURITUS	75	241	30	28	-2	8	0
UNEVALUABLE EVENT	75	110	30	49	19	3	0
OFF LABEL USE	73	166	33	39	6	43	6
PRODUCT USE ISSUE	73	149	33	45	12	43	6
PRODUCT STORAGE ERROR	71	342	35	17	-18	0	0
LYMPHADENOPATHY	67	204	36	31	-5	21	0
EXPIRED PRODUCT ADMINISTERED	60	161	37	41	4	0	0
PARAESTHESIA	58	158	38	42	4	18	0
RHINORRHOEA	58	157	38	43	5	6	1
DIARRHOEA	56	200	40	32	-8	22	0
HYPOAESTHESIA	56	175	40	38	-2	19	1
LOSS OF CONSCIOUSNESS	56	165	40	40	0	24	4
VACCINATION FAILURE	56	105	40	50	10	56	1
URTICARIA	54	181	44	34	-10	11	0
CHEST PAIN	53	179	45	36	-9	24	1
PRODUCT PREPARATION ERROR	53	76	45	51	6	0	0
RESPIRATORY TRACT CONGESTION	52	124	47	48	1	0	0
HYPERHIDROSIS	51	181	48	34	-14	17	1
EXTRA DOSE ADMINISTERED	47	151	49	44	-5	2	0
BACK PAIN	46	132	50	46	-4	17	2
INAPPROPRIATE SCHEDULE OF PRODUCT ADMINISTRATION	46	132	50	46	-4	5	1
Count:	51						

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
INCORRECT PRODUCT FORMULATION ADMINISTERED	267	798	1	1	0	0	0
INCORRECT DOSE ADMINISTERED	215	435	2	2	0	0	0
PRODUCT PREPARATION ISSUE	126	196	3	6	3	0	0
WRONG PRODUCT ADMINISTERED	118	360	4	3	-1	16	1
PRODUCT ADMINISTERED TO PATIENT OF INAPPROPRIATE AGE	96	220	5	5	0	2	0
PRODUCT USE ISSUE	73	149	6	9	3	43	6
PRODUCT STORAGE ERROR	71	342	7	4	-3	0	0
EXPIRED PRODUCT ADMINISTERED	60	161	8	7	-1	0	0
PRODUCT PREPARATION ERROR	53	76	9	11	2	0	0
EXTRA DOSE ADMINISTERED	47	151	10	8	-2	2	0
INAPPROPRIATE SCHEDULE OF PRODUCT ADMINISTRATION	46	132	11	10	-1	5	1
PRODUCT ADMINISTRATION ERROR	26	45	12	12	0	1	0
POOR QUALITY PRODUCT ADMINISTERED	11	14	13	13	0	0	0
CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR	8	13	14	16	2	0	0
PRODUCT ADMINISTERED AT INAPPROPRIATE SITE	5	13	15	16	1	1	0
INCORRECT ROUTE OF PRODUCT ADMINISTRATION	3	14	16	13	-3	1	0
VACCINATION ERROR	3	14	16	13	-3	0	0
ACCIDENTAL OVERDOSE	1	2	18	20	2	0	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta	Serious	Deaths
INCOMPLETE COURSE OF VACCINATION	1	4	18	19	1	0	0
PRODUCT COMMUNICATION ISSUE	1	2	18	20	2	0	0
WRONG PATIENT	1	2	18	20	2	0	0
WRONG TECHNIQUE IN PRODUCT USAGE PROCESS	1	7	18	18	0	0	0
Count:	22						

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	7	13	1	1	0	1	0
ABORTION SPONTANEOUS	3	4	2	2	0	2	1
FOETAL GROWTH RESTRICTION	2	2	3	4	1	2	1
MATERNAL EXPOSURE DURING PREGNANCY	2	3	3	3	0	2	0
ABORTION MISSED	1	1	5	5	0	1	0
AMNIORRHOEA	1	1	5	5	0	1	0
CEREBRAL PALSY	1	1	5	5	0	1	1
ECTOPIC PREGNANCY	1	1	5	5	0	0	0
FOETAL DEATH	1	1	5	5	0	1	1
FOETAL EXPOSURE DURING PREGNANCY	1	1	5	5	0	1	0
FOETAL HYPOKINESIA	1	1	5	5	0	1	0
Count:	11						

9. Most Frequent PTs with Death

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
DYSPNOEA	9	16	10	11	1
OFF LABEL USE	6	11	18	21	3
PRODUCT USE ISSUE	6	11	18	24	6
CONDITION AGGRAVATED	5	7	17	19	2
COVID-19	5	11	1	1	0
MALAISE	5	12	9	8	-1
LOSS OF CONSCIOUSNESS	4	5	21	22	1
FATIGUE	3	6	2	3	1
INTERCHANGE OF VACCINE PRODUCTS	3	7	10	15	5
NAUSEA	3	4	6	7	1
SYNCOPE	3	4	13	14	1
ASTHENIA	2	6	15	12	-3
COUGH	2	4	8	10	2
DIZZINESS	2	3	6	6	0
PAIN	2	3	5	5	0
CHEST PAIN	1	1	24	18	-6
FEELING ABNORMAL	1	2	16	16	0
HEADACHE	1	2	3	2	-1
HYPERHIDROSIS	1	3	25	17	-8
HYPOAESTHESIA	1	1	21	20	-1
PYREXIA	1	4	4	4	0

MedDRA Preferred Term	All (Report Period)	All (Ever)	Period Rank (All)	Cumulative Rank (All)	Rank Delta
RHINORRHOEA	1	2	20	23	3
VACCINATION FAILURE	1	1	21	25	4
VOMITING	1	5	14	13	-1
WRONG PRODUCT ADMINISTERED	1	2	12	9	-3
Count:	25				

Input Summary

*** Query Name:Query 1 ***

Select Only One Vaccine Name COVID19 (COVID19 (PFIZER-BIONTECH BIVALENT))
Report Date (Start): 11/1/2022 12:00:00 AM
Report Date (End): 11/30/2022 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)
Age unknown - If specifying age(s), select ‘Unknown’ here to include unknown ages (Optional)
Enter 'FR' to exclude foreign reports (otherwise, leave blank) (Optional)

Monthly Surveillance Report for Pfizer-BioNTech COVID-19 Vaccine, Bivalent
Surveillance Period: November 1, 2022 – November 30, 2022

Reviewer comments on Business Objects Query: During the surveillance period, the Pfizer-BioNTech COVID-19 Vaccine was authorized for use as a single booster dose in individuals 5 years of age and older. Reports in VAERS for younger individuals (Table 2) may represent unauthorized use of the vaccine, medication errors, and/or misclassification of the vaccine given. The majority (70.4%) of reports for the Pfizer bivalent vaccine were non-serious during the surveillance period (Table 1), although there was a higher percentage of serious reports for this surveillance period (29.6%) as compared to the prior surveillance period (15.8%). Serious reports were individually reviewed.

The most frequently reported PTs (Table 5) are consistent with PTs reported for the monovalent vaccine and with the known safety profile for the monovalent and bivalent vaccine or signs/symptoms of COVID-19. Review of PTs does not suggest new safety concerns for the bivalent vaccine. The EUA Fact Sheet includes Warnings and Precautions for myocarditis, pericarditis, and syncope. Lymphadenopathy is also a labeled event.

Medication error PTs during this surveillance period were consistent with those previously reported for the monovalent vaccine and almost all reports were non-serious (Table 6). The EUA Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) 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 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.

Notable U.S. Death Reports

There were 25 U.S. death reports received during this surveillance period. All U.S. death reports were individually reviewed during the surveillance period. 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.

Summary of Notable U.S. Death Reports Following Pfizer-BioNTech COVID-19, Bivalent Vaccination, November 1, 2022 – November 30, 2022

ID	Age (years)	Sex	Summary
[redacted]	66	M	Patient with PMH AORTIC VALVE STENOSIS; CHRONIC KIDNEY DISEASE; DIALYSIS; HYPERTENSION had dialysis on the morning of 11/4, received the covid vaccine (dose 5) and then went to a dermatologic office for a skin

			check. While he was getting checked he became unresponsive. CPR was started, patient came to the ER and ACLS care was given. Patient expired. *Reviewer comment: This individual with chronic medical conditions died the same day of vaccination. Medical records and additional information are not available at this time, which precludes further assessment of this report.*
[redacted]	67	F	Patient with PMH High blood pressure, IBS/GI issues and recent history of bronchitis was running on treadmill and collapsed, eyes rolled back and strange breathing for a few minutes, then stopped breathing, CPR given, patient died. Onset 3-days post-4th dose. *Reviewer comment: This individual experienced sudden death 3-days post-vaccination. ER records mention possible acute coronary syndrome vs cardiac dysrhythmia vs pulmonary embolism. It is unknown if an autopsy was performed.*
[redacted]	29	F	Patient received flu vaccine and COVID bivalent booster and died 3-days later from an unknown heart issue. Report from pharmacist not directly involved with patient – was a friend from yoga class. Reporter saw online that individual died suddenly from what her partner described as an unknown heart issue. Reporter saw she recently had vaccines administered and wanted to make sure it was reported to VAERS. *Reviewer comment: This is a hearsay report. Medical records and additional information are not available at this time, which precludes further assessment of this report.*

Reviewer comment: Review of death reports during the surveillance period found deaths that were temporally associated with vaccination. However, reports contained limited details and/or additional information was not available regarding other potential contributing factors or likely causes of death. No new safety concerns requiring further regulatory action were identified. Death reports will continue to be monitored.

U.S. Medically Notable Reports

Medically notable reports are based on reviewer judgement and may include reports of serious, unlabeled events that were suspicious for being due to the vaccine or that did not have an alternate etiology and could plausibly be due to the vaccine, atypical or rare life-threatening events, or serious, labeled events with unusual presentations or clinical courses.

Summary of U.S. Medically Notable Reports Following Pfizer-BioNTech COVID-19, Bivalent Vaccination, November 1, 2022 – November 30, 2022

ID	Age (years)	Sex	Adverse Event	Summary

[redacted]	67	F	GBS	Patient with PMH of chondrosarcoma presented to the emergency department 5-days post-5th dose for evaluation of gradually worsening of weakness in both legs and back pain that started same day post-vaccination. She also received an influenza vaccine a few days AFTER symptoms started. A CT thoracic and lumbar spine with contrast showed no central canal stenosis. Neurology was consulted. LP was done which revealed albumino-cytological dissociation. Given concern for post-vaccine mediated Guillain Barre Syndrome (GBS), patient was started on IVIG. Completed 5 days of IVIG with mild improvement. Transferred to acute inpatient rehab unit to continue rehabilitation. *<u>Reviewer comment:</u> GBS is an adverse event of special interest (AESI) that is being monitored by the FDA BEST Initiative, CDC Vaccine Safety Datalink (VSD), and post-authorization studies being conducted by the sponsor. An internal DPV observed to expected (O/E) analysis tool was used to calculate a crude O/E for GBS after receipt of the bivalent vaccine using the following assumptions: 28-day risk window, 7 cumulative U.S. cases among all ages since initial bivalent authorization, 26,941,088 bivalent doses administered in U.S. per CDC COVID tracker, and a conservative background rate of 1 per 100,000 person-years (Gubernot, 2021). The O/E=0.339 (95% CI=0.136-0.698). The O/E is below 1 and does not suggest a new safety concern at this time. Surveillance will continue.*
[redacted]	6	F	Miller Fisher syndrome	Patient with PMH of ear infection developed Miller Fisher syndrome - started with fatigue and headache on 10/27, developed diplopia and fever (fever lasted ~3 days) on 10/29 as well as weakness. Onset 3-days post-unk dose. Admitted and evaluated - ultimately treated with IVIG. MRI brain 10/31/22 with enhancement of bilateral CN III-VIII; MRI spine 11/1/22 with patchy enhancement of nerve roots of cauda equina; CSF studies 11/1/22:- Protein 76- Glucose 59- 12 WBC (11%N, 42%L, 47%Macro)- 0 RBC- Meningitis/encephalitis panel and culture negative- CSF oligoclonal bands pending. Other tests: 11/1- Lyme serology negative- EBV serology negative- Respiratory pathogen

				panel with +Rhino/enterovirus. *<u>Reviewer comment:</u> No medical records available at this time. This individual was positive for rhinovirus and enterovirus; viral infections are known to precede symptom onset of Miller Fisher syndrome and GBS. Please see comments above regarding safety surveillance for GBS and a crude O/E analysis.*
[redacted]	67	M	Bilateral pulmonary emboli, Suspicion for Vaccine Induced Thrombotic Thrombocytopenia	Patient with PMH ANGINA PECTORIS; ANXIETY; DYSLIPIDAEMIA; ESSENTIAL HYPERTENSION; GASTROOESOPHAGEAL REFLUX DISEASE; GOUT; HYPERLIPIDAEMIA; ISCHAEMIC CARDIOMYOPATHY; MIGRAINE; OBSTRUCTIVE SLEEP APNOEA SYNDROME presented to ER 10/20/2022 and diagnosed with Bilateral PE w/right heart strain; heparin infusion started. Onset 24 days post-5th dose (vaccinated on 9/26/22). Left ICA CVA on heparin a few hours later, occlusion lysed with tenecteplase, and mechanical thrombectomy 10/20/2022. Patient was intubated in the ER and transferred to the intensive care unit. Gross Hematuria - anticoagulation was held for a period of time while bleeding. Anticoagulation switched to Argatroban and eventually transitioned to warfarin. Extensive DVT left lower extremity discovered on imaging 11/3/2022. Of note previous admission to the hospital on 10/16/2022 for Ileus small bowel and previous admission for 5 Vessel CABG 10/7/2022, discharged on 10/12/2022 raising concern for Heparin induced thrombocytopenia however testing is not clear between HIT/T or VITT see lab results below. Declining platelets as follows 9/2/2022 204 k/mL; 192k/mL pre-CABG ; 120k/mL 10/7/2022 after heparin/ protamine on the bypass machine - no further challenge with heparin until 10/20/2022; 10/8 125; 10/9 111; 10/10 114; 10/11 146; 10/12 188; 10/16; 209; 10/17 194 10/20 143 pre heparin; 10/21 91; 10/22 65; Argatroban started on 10/22; 10/23 86; 10/24 platelets continue to rise to 335 k/mL on 11/7/2022. Heparin platelet antibody positive 10/22/22, Serotonin release assay (SRA) negative 10/22/22. Repeat SRA sent 11/2/2022 - negative. Hep-Ind Thrombocytopenia PF4 Ab IgG (used on [redacted]

				VITT assay) positive 10/22/22. Reviewer comment: *No medical records available at this time. This individual had a recent history of 5-vessel CABG and had declining platelets pre-CABG and after heparin on the bypass machine. The report indicates that lab testing was not clear to differentiate between HIT or VITT. Thrombosis with thrombocytopenia syndrome (TTS) has been reported to occur following COVID-19 vaccination and is a labeled event for the Janssen COVID-19 vaccine. The sponsor reviewed the topic of TTS following the Pfizer-BioNTech COVID-19 Vaccine at several time points during 2021 in Summary Monthly Safety Reports (SMSRs) and concluded that the review did not indicate the presence of a causal association with the Pfizer-BioNTech COVID-19 Vaccine (19736.335, 19736.366, 19736.409, 19736.453, 19736.491). Thrombotic and embolic events are AESIs being monitored by CDC's VSD, FDA's BEST, and in post-authorization/post-market safety studies being conducted by the sponsor.*
[redacted]	36	M	STEMI, thrombosis	Patient with HTN, 6-days post-vax on 11/1/22 had STEMI thought to be due to embolic thrombi requiring aspiration thrombectomy. 11/2/22 had another STEMI due to embolic thrombi requiring aspiration thrombectomy. Patient is a 36-year-old man with history of hypertension and possible MI (age 21, self-reported) who presented with acute onset substernal chest pain radiating to both arms and was found to have STEMI with 100% occlusions with thrombi (no underlying plaque) of both LAD and RCA now s/p aspiration and thrombectomy of both arteries on 11/1 persistent ST elevation, then found to have 100% occluded posterolateral branch artery in the setting of heavy thrombus burden s/p second aspiration thrombectomy and stent placement on 11/2. He was then started on DAPT and apixaban, with plan for triple therapy (DAPT/apixaban) for a month (stop aspirin 12/1/22) followed by dual therapy (P2y12/DOAC) for at least 1 year. Hypercoagulable workup was unrevealing. Had Left heart catheterization 11/1/22, 11/2/22. Transesophageal echocardiogram, Transthoracic echocardiogram performed

				Reviewer comment: *No medical records are available at this time, which precludes further assessment of this case. Thrombotic and embolic events are AESIs being monitored by CDC's VSD, FDA's BEST, and in post-authorization/post-market safety studies being conducted by the sponsor. The sponsor conducted a safety review of thromboembolic events in the SMSR for September 2021 (19736.536), including case reviews, O/E analysis, and literature review, and concluded the totality of evidence did not support a causal association between thromboembolic events and the vaccine. Monitoring will continue.*
[redacted]	30	M	CVST, possible VITT	Patient with PMH of ASTHMA, ECZEMA, ALLERGIC RHINITIS, HX OF COVID 19 (6/8/2022), and history of gynecomastia surgery 1-month prior to vaccination and on the following medications: ibuprofen, tylenol, oxycodone, fexofenadine, fluticasone, albuterol, triamcinolone, clindamycin, hydrocortisone experienced difficulty speaking, right facial droop, and right-sided weakness 2-days post-vax (vax on 11/4/22). Diagnosed with cerebral venous sinus thrombosis superior sagittal sinus and left convexity cortical vein, intracranial hemorrhage, and cerebral edema; required decompressive craniotomy, endovascular venous thrombectomy, and platelet transfusion. Reported as "DIC picture" with platelets low at 52,000 (were 211,000 pre-vax in Sept 2022), d-dimer elevated >4.0 (more specific value not found in records), INR 1.7, low fibrinogen <60. Reported as "highly suspicious for COVID vaccine induced immune thrombocytopenia (VITT)." Negative lupus anticoagulant, negative Factor V Leiden, protein C activity level low (59, ref range=70-130%), antithrombin III activity normal, negative anti-cardiolipin antibody, ESR=2 (normal), SARS-CoV-2 not detected. No history of heparin exposure, PF4 antibody test=0.328 OD (ref range<=0.399 OD). Med records show ongoing hospitalization through at least 11/21/22, patient non-verbal with severe cognitive impairment, requires total assist. *Reviewer comment:* *This individual developed*

				CVST and possible VITT, although the PF4 antibody test was within the reference range. A negative PF4 antibody test makes VITT less likely but does not exclude the diagnosis. (Greinacher, 2022) In addition, the onset was 2-days post-vaccination; VITT has a more likely onset 5-30 days post-vaccination. (Greinacher, 2022) Please see above comments regarding previous sponsor evaluations of TTS and safety surveillance for thromboembolic events. In addition, the sponsor previously evaluated cases of cerebral venous thrombosis (CVT) following the Pfizer-BioNTech COVID-19 Vaccine in response to questions from Swissmedic, including case reviews, clinical trial data, literature review, and O/E analyses (cumulatively through November 24, 2021), and concluded the evidence did not support a conclusion that Comirnaty is causally associated with CVT (19736.709). The sponsor performed an additional analysis of CVST through April 15, 2022 and again concluded that given the totality of evidence of data on CVST and Comirnaty, including O/E analyses, AE reports, literature review, and in context of the millions of doses administered, that a causal association between Comirnaty and CVST was not concluded and that no changes to the labeling or risk management documents were warranted. Routine monitoring will continue.
[redacted]	80	F	Multiple pulmonary emboli, possible VITT	Patient with pancreatic carcinoma experienced increased shortness of breath 9-days post-bivalent vaccine. She went to the emergency department, and they completed a CT scan of her chest and found lots of clots. She was then hospitalized and placed on supportive care with anti-coagulants. Reported that testing that shows vaccine-induced Thrombotic Thrombocytopenia. Antibody test positive October 24, 2022 (no values provided). Reported via V-safe. CT Angio 10/24: Multiple pulmonary emboli and cardiac thrombus, 11/22: High PF4 antibody levels *<u>Reviewer comment:</u> This individual has pancreatic carcinoma which is a confounding condition for blood clots. The report mentions high PF4 antibody levels and VITT, although no lab values were available. Other laboratory*

				results, including platelet counts, and medical records are not available. This report will be re-reviewed pending additional information.
[redacted]	35	M	Visual disturbance, cyclitis	Patient with no chronic or long-standing health conditions experienced symptoms in both eyes roughly 2-4 weeks after the first COVID vaccine (Moderna Lot#025J20-2A, Jan 2021) and had initial 24–48-hour flu-like symptoms post-vax. Second shot (Moderna Lot#042L20A) was administered in Feb 2021 along with increased eye related symptoms. Initial symptoms included blurred vision, headaches/migraines, vertigo, and sensitivity to lights which included haloing and star-bursting. Initially sought care with optometrist but was referred to Medical Center for additional assessment between Feb-April 2021. Ophthalmology initial assessment that symptoms were presenting as Fuchs Heterochronic cyclitis, bilateral (treatment recommended optical steroids and artificial tears). Symptoms stabilized but failed to resolve during tapering treatments through July/Aug 2021. Referred to cornea specialist with an appointment Nov 2021. Specialist assessment could not provide positive diagnosis but did not believe symptoms were related to Fuchs Heterochronic cyclitis. Specialist could not confirm correlation with COVID virus or COVID vaccine but recommended continue Ophthalmologist directed treatments. Third COVID shot (Moderna Lot#035C21A) was administered on Dec 2021, which presented increased eye related symptoms shortly after. Symptoms again stabilized through spring/summer 2022 with suspected tie to COVID vaccine. Fourth shot (Pfizer Bivalent Lot#GJ5342) was administered October 2022, which again presented with increased eye related symptoms 2-3 weeks after the shot. Followed up with Ophthalmology who recommended not taking any additional COVID vaccines, submit CDC adverse effect report, and to seek military medical waiver from future COVID vaccines. HLA-B27 Blood Test Negative, No suspected correlation to 2013 Lasik surgery, Fuchs Heterochronic cyclitis-like symptoms present at all times in both eyes. *Reviewer comment:* This individual

				experienced Fuchs Heterochronic cyclitis-like symptoms following each mRNA COVID-19 vaccine. Fuchs Heterochronic cyclitis is a chronic, low grade anterior segment inflammation that accounts for 2-3% of all uveitis cases and has an unknown etiology, although there is consensus that an immunologic reaction is involved. (Bonfioli, 2009) However, the report indicates that ophthalmology assessment ultimately did not believe symptoms were related to Fuchs Heterochronic cyclitis. No medical records are available at this time, however, the positive re-challenge in this case, suggests a potential relationship to mRNA COVID-19 vaccines. The sponsor has previously evaluated ophthalmology topics including blindness and visual disturbances (19736.453), optic neuritis (19736.335), and uveitis (19736.536 and 19736.782); based on the totality of evidence, these events were not found to be a risk and/or causally associated with exposure to Comirnaty. Monitoring will continue.
[redacted]	66	F	ITP	Patient with PMH Diabetes mellitus; hypertension; obstructive sleep apnea; pulmonary hypertension and on meds of Tylenol PM Extra Strength; atorvastatin; bumetanide; buspirone; cholestyramine; cyanocobalamin; dexamethasone; ergocalciferol; escitalopram; losartan; melatonin; pantoprazole; pioglitazone; potassium chloride; sildenafil; triamcinolone admitted to hospital for thrombocytopenia with platelet count of 12k. Patient received COVID-19 booster 8-days prior, and flu shot 12-days prior to symptom onset. Underwent extensive workup, which noted elevated ANA levels. Patient noted previously high ANA levels 8/2022 during autoimmune workup. Report indicated that patient presumed to have vaccine induced ITP and was treated with dexamethasone. Platelet count recovered, and patient was discharged from hospital in stable condition. *<u>Reviewer comment:</u> No medical records available at this time. This individual had undergone a previous autoimmune work-up for unknown reasons and was noted to have high ANA levels. The individual was also noted to be on pantoprazole, which is labeled for thrombocytopenia. The sponsor has*

				previously evaluated the risk of ITP and the potential signal was closed as "no risk" in August 2021 (19736.453).

Reviewer comment: Four U.S. medically notable reports concerned thromboembolic events, with three reports mentioning concern for VITT. Assessment of three of these reports (including two of the potential VITT reports) was limited by lack of medical records and/or confounding factors. The fourth report with available medical records ([redacted]) was for a 30-year-old male with a history of gynecomastia surgery in the month prior to vaccination who experienced CVST with thrombocytopenia 2-days post-vaccination; PF4 antibody test result was within the reference range which is not supportive of VITT. AESIs, including thromboembolic events, CVST, and TTS, are being monitored in CDC and FDA safety surveillance systems, and in post-authorization studies being conducted by the sponsor.

Case Series Analyses:

Myocarditis/Pericarditis

A Business Objects AESI Screening Report query was run for Pfizer-BioNTech COVID-19 Vaccine, Bivalent for the current surveillance period on December 14, 2022 for reports related to myocarditis or pericarditis. The following PTs were included: AUTOIMMUNE MYOCARDITIS;AUTOIMMUNE PERICARDITIS;EOSINOPHILIC MYOCARDITIS;HYPERSENSITIVITY MYOCARDITIS;IMMUNE-MEDIATED MYOCARDITIS;MYOCARDITIS;PERICARDITIS;PERICARDITIS ADHESIVE;PERICARDITIS CONSTRICTIVE;PLEUROPERICARDITIS.

The query returned a total of five U.S. reports, including one non-fatal serious report (no death reports). The median age=56 years (range=33-73 years). The median onset=7 days post-vaccination (range=1-20 days). Reports were for 2 (40.0%) females and 3 (60.0%) males. The one non-fatal serious report was for a 56-year-old female with a history of hypertension and flu-like symptoms (negative for COVID) with onset 17-days post-bivalent dose. Cardiology note indicated likely infective endocarditis of the aortic valve; 1 bottle positive for Streptococcus and transthoracic echo showed evidence of moderate size vegetation on the aortic valve.

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.

Sponsor's Abbreviated Summary Monthly Safety Report

The sponsor submitted an Abbreviated Summary Monthly Safety Report (aSMSR) on December 8, 2022 (STN 125742/243; reporting period October 16, 2022 to November 15,

2022), which included the monovalent and bivalent vaccines. During the reporting period for the aSMSR, no actions were taken for BNT162b2 for safety reasons. A potential safety signal for dermatomyositis has an ongoing evaluation. This signal was from a serious AE (SAE) from a non-vaccine Pfizer-sponsored clinical trial for an immunomodular investigational product. The sponsor evaluated a signal for hemophagocytic lymphohistiocytosis (HLH) and closed the signal as "no risk."

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

Data Mining Findings[1]

Data mining was conducted using the Empirica Signal "US Signals Summary Table" with a data lock point of December 9, 2022. PTs with an EB05≥2 for the U.S. overall and/or subgroups are shown below.

Preferred Terms with an EB05≥2 for the U.S. overall or subgroups, Pfizer-BioNTech COVID-19 Vaccine, Bivalent

Event	US EB05 20221209	US Child EB05 20221209	US Teen EB05 20221209	US Adult1 EB05 20221209	US Adult2 EB05 20221209	US Adult3 EB05 20221209	US Female EB05 20221209	US Male EB05 20221209
Incorrect dose administered	1.859	**2.184**	1.842	1.011	1.266	1.178	1.737	1.873
Incorrect product formulation administered	**3.724**	**5.778**	**4.967**	**5.135**	**2.573**	1.586	**3.451**	**3.778**
Off label use	**3.819**	0.492	0.525	1.38	**2.714**	**4.523**	**3.76**	**2.264**
Product use issue	**3.834**	0.505	0.561	**2.223**	**4.493**	**3.493**	**3.636**	**2.323**
Syncope	1.825	0.759	1.444	**2.424**	1.187	0.867	1.697	1.673
Unresponsive to stimuli	1.422		1.431	**3.392**	0.529	0.533	1.161	1.374
Wrong product administered	**2.765**	0.923	1.668	**4.992**	**2.65**	**2.041**	**2.742**	**2.427**

Reviewer comment: PTs with an EB05≥2 primarily included medication errors and off label use. Prior review of reports of "loss of consciousness" and "unresponsive to stimuli" frequently revealed events of fainting/syncope, with some reports also involving seizures or seizure-like activity. A few death reports also included the PT "unresponsive to stimuli." Syncope is a labeled event and is included in Warnings and Precautions of the EUA Fact Sheet. Herpes zoster is no longer a PT with an EB05≥2 for any subgroup. Data mining findings did not reveal patterns suggesting new safety concerns. Continued surveillance using data mining will continue.

Publications

A literature search of PubMed was conducted on December 14, 2022 for 'Pfizer-BioNTech COVID-19 Vaccine, Bivalent' with a date range of November 1, 2022 through November 30, 2022: 2022/11/01:2022/11/30[Date - Publication] AND (("bnt162

vaccine"[MeSH Terms] OR ("bnt162"[All Fields] AND "vaccine"[All Fields]) OR "bnt162 vaccine"[All Fields] OR "pfizer biontech covid 19 vaccine"[All Fields]) AND ("bivalence"[All Fields] OR "bivalency"[All Fields] OR "bivalent"[All Fields] OR "bivalently"[All Fields] OR "bivalents"[All Fields]))

The search returned two articles. Review of abstracts did not identify new safety concerns for the bivalent vaccine.

Reviewer comment: *No further regulatory action is indicated based on the above literature search.*

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).

The Pfizer-BioNTech COVID-19 Vaccine, Bivalent is authorized for use as a single booster dose to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals ≥5 years of age and as the third dose in the primary series for individuals aged 6 months through 4 years. Please see the EUA Letter of Authorization (LOA), and product EUA Fact Sheets for additional details.

Conclusions

The findings from this monthly surveillance report for the Pfizer-BioNTech COVID-19 Vaccine, Bivalent did not reveal new safety concerns requiring further regulatory action at this time. Routine surveillance will continue, along with routine surveillance reports.

References

Bonfioli AA, Curi AL, Orefice F. Fuchs' heterochromic cyclitis. Semin Ophthalmol. 2005 Jul-Sep;20(3):143-6. doi: 10.1080/08820530500231995. PMID: 16282147.

Greinacher A, Langer F, Makris M, Pai M, Pavord S, Tran H, Warkentin TE. Vaccine-induced immune thrombotic thrombocytopenia (VITT): Update on diagnosis and management considering different resources. J Thromb Haemost. 2022 Jan;20(1):149-156. doi: 10.1111/jth.15572. Epub 2021 Nov 10. PMID: 34693641; PMCID: PMC8646430.

Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, Duffy J, Harrington T, McNeil MM, Broder K, Su J, Kamidani S, Olson CK, Panagiotakopoulos L, Shimabukuro T, Forshee R, Anderson S, Bennett S. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016. Epub 2021 May 14. PMID: 34088506; PMCID: PMC8118666.

Shimabukuro, T. Myocarditis following mRNA COVID-19 vaccination; presented to the Advisory Committee on Immunization Practices on July 19, 2022. Available at: ACIP July 19, 2022 Presentation Slides | Immunization Practices | CDC; Accessed on October 14, 2022.

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[1] The minimum standard analysis is the “US Signals Summary Table.” Data mining covers the entire post-authorization period for this product. 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.

From: "Menschik, David" [redacted]
To: "Nair, Narayan" [redacted]
Subject: Data mining limitations
Date: Thu, 26 Oct 2023 18:29:10 +0000
Importance: Normal
Attachments: DE_VAERS_data_mining_methods_and_limitations_2021_03_DRAFT.pptx

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

Data Mining Introduction*

- Statistical method for identifying disproportionality (excess of reported AE for product relative to other products) in large database
- Can be useful for screening and hypothesis generating only
  - Evaluate findings in clinical and epidemiological context (e.g., unexpected?)
  - Compelling hypotheses should be explored (e.g., via case series analyses)
  - Statistical signal of disproportionality ≠ safety signal
- Absence of disproportionality does not confirm absence of safety signal nor negate a signal otherwise detected

*Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff (November 2019; Draft). Available at https://www.fda.gov/media/130216/download

DE VAERS Data Mining Methods

- Empirica™ Signal software (Oracle)
- Calculates Empiric Bayes Geometric Mean (EBGM) using observed to expected (O/E) vaccine-PT pair ratios
  - EBGM derived from statistical model (Multi-item Gamma Poisson Shrinker; MGPS) that accounts for instability from small numbers*
    - adjusted by age, gender and year received
- Vaccine-PT pairs ranked by lower 5% bound of 90% confidence interval around EBGM (EB05)
- Standard alert threshold: EB05 >2
- Weekly US summary table includes subset alerts for age (0-1, 2-8, 9-18, 19-44, 45-64, and ≥65 years), gender, and serious/fatal

*Szarfman A, Tonning JM, Doraiswamy PM. Pharmacovigilance in the 21st century: new systematic tools for an old problem. Pharmacotherapy. 2004 Sep;24(9):1099-104. doi: 10.1592/phco.24.13.1099.38090. PMID: 15460169.

Limitations of Data Mining Include:

- Impacted by stimulated reporting (e.g., V-safe, media reports)
- False alerts from statistical interaction (e.g., If vaccines X and Y often given concomitantly, statistical signal for vaccine X and AE Z may be driven by vaccine Y)
- MedDRA constraints (e.g., Signal X can be reflected in multiple PTs that individually do not reach alert threshold)
- Confounding (e.g., by indication)
- Other VAERS limitations (e.g., underreporting, variable reporting by source, incomplete reporting, duplicate reporting)

From: "Thompson, Deborah" [redacted]
To: "Nair, Narayan" [redacted], "Welsh, Kerry" [redacted]
Cc: "Alimchandani, Meghna" [redacted]
Subject: FW: DCC Login ID 2088124 loaded by DCC - DO NOT REPLY
Date: Mon, 30 Jan 2023 20:23:39 +0000
Importance: Normal
Attachments: 125742.245.2_response-20dec2023-ir-safety-assessment.pdf; appendix-1.pdf; appendix-2.pdf; appendix-3.pdf

---

Hi Narayan and Kerry,

Pfizer submitted an IR response to our inquiry regarding their assessment of TEE following receipt of the bivalent vaccine. They reviewed case reports, clinical trial data, and literature, and performed an O/E analysis. They concluded that there is no evidence that TEE, including ischemic stroke, is a safety signal or risk for the bivalent vaccine. That seems reasonable based on the information available at this time in their IR response.

It will be interesting to see what CDC's VSD finds in their signal evaluation work.

Please let me know if you have any questions or concerns or additional information you would like from Pfizer.

Thanks,

Deb

-----Original Message-----
From: OBPVIRs [redacted]
Sent: Thursday, January 26, 2023 4:29 PM
To: Thompson, Deborah [redacted]
Cc: Austin-Hansberry, Lori [redacted]
Subject: FW: DCC Login ID 2088124 loaded by DCC - DO NOT REPLY

Hi Deb,

Please see below the link to the COMIRNATY IR.

Kind regards,
Alexandria

-----Original Message-----
From: cbersecure@fda.hhs.gov [redacted]
Sent: Thursday, January 26, 2023 3:41 PM
To: CBEROBPVESUB [redacted] High, Sherrie [redacted]; CBEROBPVESUB [redacted]; Edwards, Alexandria [redacted]; CBER.RIB [redacted]>
Cc: CBER IT EDR [redacted]; CBER IT EDR [redacted]; CBER DCC EDR [redacted]>
Subject: DCC Login ID 2088124 loaded by DCC - DO NOT REPLY

This BLA AMENDMENT DCC Login ID 2088124 is now available in the CER.

This is an eCTD submission. Select the link to access the .enx file:

<https://cberconnect.fda.gov/regulatory/submissions/detail?folder-obj-id=0bbcaea683776521>

DESCRIPTION:

Applicant: BIONTECH MANUFACTURING GMBH / 2229

Product: COVID-19 VACCINE, MRNA

Indication: active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) in individuals 16 years of age and older.; active immunization to prevent coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV 2) in individuals 12 years of age and older.

Proprietary Name: COMIRNATY

APPLICATION INFORMATION:

Application Number: [redacted]

eCTD Sequence Number: [redacted]

CBER Receipt Date: 26-Jan-2023

If you need additional assistance with this submission, please contact ERIC Help Desk at [redacted].

PLEASE DO NOT REPLY TO THIS EMAIL. This is an automatically generated message.

Technical information for administrators - Process Track ID: [redacted]

Gateway Core ID: [redacted]

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
Maroko, Robert T	24-Jan-2023 16:31:53	Business Line Approver

Narrative Line Listing

BNT162B2, BNT162B2 OMI BA.4-5

Reporting Period: All Time

Total Number of Cases: 5

1.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	12-OCT-2022 - 12-OCT-2022
BNT162B2	COVID-19 immunisation	12-OCT-2022 - 12-OCT-2022
INFLUENZA VACCINE INACT SAG 4V	Influenza immunisation	12-OCT-2022 - 12-OCT-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Chronic obstructive pulmonary disease			ONGOING	
PATIENT	Hypertension			ONGOING	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Haematemesis	
DEATH	PATIENT	Pulmonary embolism	

Narrative

This is a spontaneous report received from a contactable reporter(s) (Physician) from the European Medicines Agency (EMA) EudraVigilance-WEB and product quality group. Regulatory number: DK-DKMA-WBS-[redacted](DKMA). Other Case identifier(s): DK-DKMA-ADR [redacted]DKMA).

An 80-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 12Oct2022 as dose 1, single (Lot number: GJ2552) intramuscular for covid-19 immunisation; influenza vaccine inact sag 4v (INFLUVAC TETRA), on 12Oct2022 as dose number unknown, single (Lot number: E18) intramuscular for influenza immunisation. The patient didn't receive BNT162b2 (COMIRNATY). The patient's relevant medical history included: "COPD" (ongoing); "Hypertension" (ongoing). The patient's concomitant medications were not reported.
The following information was reported: OFF LABEL USE (death, hospitalization) with onset 12Oct2022, outcome "fatal"; PRODUCT USE ISSUE (death, hospitalization) with onset 12Oct2022, outcome "fatal", described as "Product use for unapproved combination"; WRONG PRODUCT ADMINISTERED (death, hospitalization) with onset 12Oct2022, outcome "fatal", described as "Wrong vaccine administered"; HAEMATEMESIS (death, hospitalization) with onset 14Oct2022, outcome "fatal", described as "The patient is found on the toilet, bloody dark brow

1.AER Number: [redacted]

Narrative
n vomit in the toilet and at the dinner table"; PULMONARY EMBOLISM (death, hospitalization) with onset 14Oct2022, outcome "fatal", described as "The physician suspects lung embolism as the underlying cause of death". The patient was hospitalized for off label use, product use issue, wrong product administered, pulmonary embolism, haematemesis (start date: 2022). Therapeutic measures were taken as a result of pulmonary embolism, haematemesis. The patient date of death was 14Oct2022. Reported cause of death: "Lung embolism", "Vomiting blood". No autopsy was performed. Clinical course: The patient was brought to the hospital under cardiopulmonary resuscitation, which was stopped short after. Product Quality Group provided investigational results on 03Nov2022 for BNT162b2, BNT162b2 omi ba.4-5: The complaint for "PFIZER-BIONTECH COVID-19 VACCINE" was investigated. The investigation included reviewing the involved batch records, deviation investigation, an analysis of the complaint history for the reported lot and product type. The final scope was determined to be the associated lot(s) of the reported lot GJ2552. A complaint sample was not returned. No related quality issues were identified during the investigation. There is no impact on product quality, regulatory, validation and stability. PGS Puurs concludes that the reported defect is not representative of the quality of the batch and the batch remains acceptable. The NTM process determined that no regulatory notification was required. The reported defect could not be confirmed. No root cause or CAPA were identified as the complaint was not confirmed. No follow-up attempts are possible. No further information is expected. Follow-up (03Nov2022): This is a follow-up report from product quality group providing investigation results for batch number GJ2552. No follow-up attempts are possible. No further information is expected.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Off label use	SERIOUS		-	
Product use issue	SERIOUS			
Wrong product administered	SERIOUS			
Pulmonary embolism	SERIOUS			
Haematemesis	SERIOUS			

Device Type Suspect	Device Type Conmed
NO DATA	

2.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	10-OCT-2022 - 10-OCT-2022
INFLUENZA VACCINE INACT SPLIT 4V	Antiviral prophylaxis	10-OCT-2022 - 10-OCT-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Abstains from alcohol			NO DATA	
PATIENT	Dementia with Lewy bodies	-------2010		NO DATA	diagnosed in 2010: advanced neurodegenerative cognitive impairment, GDS 6 in follow-up.
PATIENT	Non-tobacco user			NO DATA	
PATIENT	Wheelchair user			NO DATA	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Pulmonary embolism	

Narrative

This is a spontaneous report received from a contactable reporter(s) (Other HCP) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: ES-AEMPS-[redacted]AEMPS).

A 65-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 10Oct2022 as dose 4 (booster) 0.3 ml, single (Lot number: GH9852) intramuscular for covid-19 immunisation; influenza vaccine inact split 4v (EFLUELDA), on 10Oct2022 as 0.7 ml, single (Lot number: UT505AA) intramuscular for antiviral prophylaxis. The patient's relevant medical history included: "wheelchair user" (unspecified if ongoing); "Lewy Body Disease", start date: 2010 (unspecified if ongoing), notes: diagnosed in 2010: advanced neurodegenerative cognitive impairment, GDS 6 in follow-up.; "non-smoker" (unspecified if ongoing); "no alcohol" (unspecified if ongoing). Concomitant medication(s) included: SINEMET PLUS; RIVASTIGMINE; MEMANTINE; QUETIAPINE; MIRTAZAPINE; MOTILIUM [DOMPERIDONE]. Vaccination history included: Covid-19 vaccine (dose 1, manufacturer unknown), for COVID-19 immunisation; Covid-19 vaccine (dose 2, manufacturer unknown), for COVID-19 immunisation; Covid-19 vaccine (dose 3, manufacturer unknown), for COVID-19 immunisation.
The following information was reported: PRODUCT USE ISSUE (non-serious) with onset 10Oct2022, outco

me "unknown", described as "Product use for unapproved combination"; CARDIO-RESPIRATORY ARREST (hospitalization, medically significant) with onset 11Oct2022, outcome "recovered"; PULMONARY EMBOLISM (death, hospitalization, medically significant) with onset 11Oct2022, outcome "fatal", described as "Pulmonary thromboembolism"; CYANOSIS (non-serious) with onset Oct2022, outcome "unknown", described as "Cyanosed lips"; MALAISE (non-serious) with onset Oct2022, outcome "unknown", described as "General malaise"; HICCUPS (non-serious) with onset Oct2022, outcome "unknown"; DYSPNOEA (non-serious) with onset Oct2022, outcome "unknown", described as "Sudden dyspnoea"; URINARY TRACT INFECTION (non-serious) with onset Oct2022, outcome "unknown", described as "UTI"; UNRESPONSIVE TO STIMULI (medically significant) with onset Oct2022, outcome "unknown", described as "Unresponsive"; FOAMING AT MOUTH (non-serious), PALLOR (non-serious) all with onset Oct2022, outcome "unknown" and all described as "foaming at the mouth, became pale". The patient was hospitalized for pulmonary embolism, cardio-respiratory arrest (start date: 11Oct2022). The event "pulmonary thromboembolism" required emergency room visit. The patient underwent the following laboratory tests and procedures: Abdominal X-ray: Gas in transverse and descending colon; A

2.AER Number: [redacted]

Narrative
uscultation: rhythmic without murmurs. Pale, skin coldness, notes: capillary refill more than 2"; Good air entry, preserved vesicular murmur, notes: bilateral rhonchi, no respiratory work, Sat 97%; Blood pressure measurement: 71/54 mmHg; Blood pressure measurement: 5; Coma scale: 3, notes: miotic pupils, non-reactive; Computerised tomogram: Pulmonary thromboembolism, notes: with high thrombotic load and signs of right ventricular dysfunction; Computerised tomogram head: no alterations; Electrocardiogram: sinus rhythm at 113bpm, notes: PR 105ms, electrical axis at 0°, right bundle branch hemiblock; Fraction of inspired oxygen: 1; Heart rate: 108; PS (ressure support): 5; Good air entry, MVc, bilateral rhonchi, no respira, notes: Good air entry, MVc, bilateral rhonchi, no respiratory work; Neurological examination: Glasgow 3, miotic pupils, non-reactive; Oxygen saturation: 97 %; Positive end-expiratory pressure: 5. Therapeutic measures were taken as a result of pulmonary embolism, cardio-respiratory arrest. The patient date of death was 13Oct2022. Reported cause of death: "Pulmonary thromboembolism". It was not reported if an autopsy was performed. Clinical course: Patient 65 years old. Lives with her husband, dependent for daily life basic activities, advanced neurodegenerative cognitive impairment, attends da y centre, needs a wheelchair. No known allergies. No, diabetes mellitus or dislipidemia. Hypertension. Usual treatment: Sinemet plus 1.5 tablet 9h-12h-16h-21h; Rivastigmine 13.3mg. Memantine 10mg, Quetiapine 25mg. Mirtazapine 15mg. Motilium tabl every 8h. Current illness: 11Oct2022 Brought to hospital intubated for cardio-respiratory arrest recovered at home. This afternoon she went to the outpatient clinic for general malaise and was diagnosed as UTI. Returned home, ate and then started with hiccups, sudden dyspnoea and foaming at the mouth, became pale, cyanosed lips and unresponsive. A call was made and cardiopulmonary resuscitation manoeuvres were performed 10 minutes after the call. After detection of a shockable rhythm by AED, defibrillation was performed, 1 mg of adrenaline was administered and after 1 cycle of CPR the patient presented sinus rhythm at 130bpm and was transferred to hospital. The family refers to administration of 4th dose of covid19 vaccine and flu the previous day. Evolution: poor prognosis of the patient. Sedation perfusion was started with 100ml physiological saline + 5mg haloperidol + 20mg morphine + 30mg midazolam + 1mg scopolamine. The patient was extubated, monitoring and life support were withdrawn. Admission for observation was decided. Exitus 13Oct2022. No follow-up attempts are possible. No further information is expected. Follow-up (16Nov2022): This is a spontaneous follow-up report, this is a clarification from Local Health Authority. The query response received as the patient received correctly both vaccines on the same day. Follow-up attempts are completed. No further information is expected.

Adverse Event(s) PT	Event Seriousness
Pulmonary embolism	SERIOUS
Cardio-respiratory arrest	SERIOUS
Unresponsive to stimuli	SERIOUS
Product use issue	NONSERIOUS
Malaise	NONSERIOUS
Urinary tract infection	NONSERIOUS
Hiccups	NONSERIOUS
Dyspnoea	NONSERIOUS
Foaming at mouth	NONSERIOUS
Pallor	NONSERIOUS
Cyanosis	NONSERIOUS

Concomitant Drug(s)	Therapy Date(s)	Route of Admin
CARBIDOPA MONOHYDRATE, LEVODOPA	-	NO DATA
DOMPERIDONE	-	NO DATA
MEMANTINE	-	NO DATA
MIRTAZAPINE	-	NO DATA
QUETIAPINE	-	NO DATA
RIVASTIGMINE	-	NO DATA

Device Type Suspect	Device Type Conmed

2.AER Number: [redacted]

Device Type Suspect	Device Type Conmed
NO DATA	NO DATA

3.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	21-OCT-2022 - 21-OCT-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Autism spectrum disorder			ONGOING	Autistic characteristics
PATIENT	Deaf mutism			ONGOING	
PATIENT	Epilepsy			ONGOING	Epilepsy treated with three unspecified drugs
PATIENT	Gastrointestinal carcinoma			ONGOING	Presumed gastrointestinal cancer
PATIENT	Intellectual disability			ONGOING	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Acute respiratory failure	
DEATH	PATIENT	Dyspnoea	
DEATH	PATIENT	Pulmonary embolism	

Narrative

This is a spontaneous report received from a contactable reporter(s) (Physician) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: DK-DKMA-WBS-[redacted](DKMA). Other Case identifier(s): DK-DKMA-ADR [redacted](DKMA).

A 69-year-old male patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 21Oct2022 as dose number unknown (booster), single (Lot number: GJ2552, expiration date: 31Jul2023) intramuscular for covid-19 immunisation. The patient's relevant medical history included: "Epilepsy" (ongoing), notes: Epilepsy treated with three unspecified drugs; "Severe mental retardation" (ongoing); "Deaf mutism" (ongoing); "Gastrointestinal carcinoma" (ongoing), notes: Presumed gastrointestinal cancer; "Autistic disorder" (ongoing), notes: Autistic characteristics. The patient took concomitant medications. Concomitant medication included three unspecified epileptic drugs. There was no information regarding past medication. Vaccination history included: Covid-19 vaccine (Primary Immunization series complete; unknown manufacturer), for COVID-19 immunisation.
The following information was reported: ACUTE RESPIRATORY FAILURE (death) with onset 22Oct2022, outcome "fatal", described as "Acute respiratory failure/Severely respiratory affected"; DYSPNOEA (death) with onset 22Oct2022, outcome

"fatal"; PULMONARY EMBOLISM (death) with onset 22Oct2022, outcome "fatal", described as "Suspicion of lung embolism (further diagnosing not performed)". The events "suspicion of lung embolism (further diagnosing not performed)", "acute respiratory failure/severely respiratory affected" and "dyspnoea" required emergency room visit. The patient underwent the following laboratory tests and procedures: Blood lactic acid: (22Oct2022) 8.7, notes: Unit not specified; Blood pressure systolic: (22Oct2022) 70 mmHg; Oxygen saturation: (22Oct2022) 65-70 %, notes: with 15 L oxygen; Respiratory rate: (22Oct2022) 30-40 Breaths per minute. The patient date of death was 22Oct2022. Reported cause of death: "Acute respiratory failure/Severely respiratory affected", "Dyspnoea", "Suspicion of lung embolism (further diagnosing not performed)". No autopsy was performed. The clinical course was reported as follows: The patient died on 22Oct2022 at the emergency department of a hospital. Further treatment was refrained from at the hospital.

On 18Nov2022, product quality group reported investigational results: "The complaint for "PFIZER-BIONTECH COVID-19 VACCINE" was investigated. The investigation included reviewing the involved batch records, deviation investigation, an analysis of the complaint history for the reported lot and pro

3.AER Number: [redacted]

Narrative
duct type. The final scope was determined to be the associated lot(s) of the reported lot GJ2552. A complaint sample was not returned. No related quality issues were identified during the investigation. There is no impact on product quality, regulatory, validation and stability. PGS Puurs concludes that the reported defect is not representative of the quality of the batch and the batch remains acceptable. The NTM process determined that no regulatory notification was required. The reported defect could not be confirmed. No root cause or CAPA were identified as the complaint was not confirmed." Follow-up attempts are completed. No further information is expected. Follow-up (18Nov2022): This is a follow-up spontaneous report from product quality group. Updated information included: expiration date of lot# GJ2552 and investigation results added. No follow-up attempts are possible. No further information is expected.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Pulmonary embolism	SERIOUS		-	
Acute respiratory failure	SERIOUS			
Dyspnoea	SERIOUS			

Device Type Suspect	Device Type Conmed
NO DATA	

4.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	28-OCT-2022 - 28-OCT-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Arteriosclerosis			NO DATA	
PATIENT	Arthrodesis			NO DATA	
PATIENT	Chronic obstructive pulmonary disease			NO DATA	
PATIENT	Colectomy	-------2016		NO DATA	for colon cancer
PATIENT	Femur fracture	31-MAY-2022		NO DATA	
PATIENT	Osteoarthritis			NO DATA	
PATIENT	Osteoporosis			NO DATA	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Cardiac arrest	

Narrative

This is a spontaneous report received from a contactable reporter(s) (Physician) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: IT-MINISAL02-[redacted]

An 81-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 28Oct2022 at 17:00 as dose 4 (booster), 0.3 ml single (Lot number: GH9545) intramuscular for covid-19 immunisation. The patient's relevant medical history included: "Atherosclerosis" (unspecified if ongoing); "Osteoporosis" (unspecified if ongoing); "Joint arthrodesis" (unspecified if ongoing); "COPD" (unspecified if ongoing); "Right hemicolectomy", start date: 2016 (unspecified if ongoing), notes: for colon cancer; "Fractured femur (excl neck)", start date: 31May2022 (unspecified if ongoing); "Arthrosis" (unspecified if ongoing). The patient's concomitant medications were not reported. Vaccination history included: Covid-19 vaccine (dose 1, manufacturer unknown), for covid-19 immunisation; Covid-19 vaccine (dose 2, manufacturer unknown), for covid-19 immunisation; Covid-19 vaccine (dose 3, manufacturer unknown), for covid-19 immunisation.
The following information was reported: SUDDEN DEATH (death, medically significant) with onset 29Oct2022, outcome "fatal"; PULMONARY EMBOLISM (death, medically significant) with onset 29Oct2022, out

4.AER Number: [redacted]

Narrative
come "fatal", described as "death from probable massive pulmonary embolism"; LOSS OF CONSCIOUSNESS (death, medically significant) with onset 29Oct2022, outcome "fatal", described as "subsequent loss of consciousness"; DYSPNOEA (death) with onset 29Oct2022 at 19:00, outcome "fatal", described as "Sudden and worsening dyspnea". The events "subsequent loss of consciousness", "death from probable massive pulmonary embolism", "sudden death" and "sudden and worsening dyspnea" required emergency room visit. The patient date of death was 29Oct2022. Reported cause of death: "died of cardiac arrest". Additional information: Booster dose (4th dose) of Pfizer vaccine was administered on 28Oct2022 at 5 pm. The following day, 29Oct2022 at 7 pm, sudden and worsening dyspnea appeared, brought to the emergency room of PRIVACY with 118 died of cardiac arrest. Date of last menstrual period 16Nov1991. Sender comment: The reporter (the patient's family doctor) is contacted to obtain additional information: the doctor reports that the patient had an illness at her home as a result of which she was transported to the PRIVACY emergency room where the situation worsened until the death of the patient patient, presumably for pulmonary embolism and massive pulmonary embolism. Contact the PRIVACY emergency room for a clinical repor t from the doctor and, if available, an autopsy. Waiting for a reply. Follow-up (22Nov2022): This is a follow-up report received from the same contactable Physician from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: IT-MINISAL02-[redacted]. Updated information included: The Reporter Information: Other HCP deleted and the Primary Reporter checkbox checked for the Physician.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Loss of consciousness	SERIOUS		-	
Pulmonary embolism	SERIOUS			
Sudden death	SERIOUS			
Dyspnoea	SERIOUS			

Device Type Suspect	Device Type Conmed
NO DATA	

5.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	03-NOV-2022 - 03-NOV-2022
INFLUENZA VACCINE INACT SAG 4V	Influenza immunisation	03-NOV-2022 - 03-NOV-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Benign prostatic hyperplasia			NO DATA	treatment with simvastatin
PATIENT	Dyslipidaemia			NO DATA	
PATIENT	Hyperglycaemia			NO DATA	
PATIENT	Sleep apnoea syndrome			NO DATA	with nocturnal CPAP

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
AUTOPSY	PATIENT	Cardiomegaly	
AUTOPSY	PATIENT	Left ventricular hypertrophy	
AUTOPSY	PATIENT	Pulmonary congestion	
DEATH	PATIENT	Respiratory failure	

Narrative

This is a spontaneous report received from a contactable reporter(s) (Pharmacist) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: ES-AEMPS-[redacted].

A 78-year-old male patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 03Nov2022 as dose 4 (booster), 0.3 ml single (Lot number: GH9741) intramuscular, in left deltoid for covid-19 immunisation; influenza vaccine inact sag 4v (FLUAD TETRA), on 03Nov2022 as dose number unknown, 0.5 ml single (Lot number: 501143111) intramuscular, in right deltoid for influenza immunisation. The patient's relevant medical history included: "dyslipidaemia" (unspecified if ongoing); "hyperglycaemia" (unspecified if ongoing); "benign prostatic hypertrophy" (unspecified if ongoing), notes: treatment with simvastatin; "sleep apnoea" (unspecified if ongoing), notes: with nocturnal CPAP. Concomitant medication(s) included: SIMVASTATIN taken for dyslipidaemia. Vaccination history included: Covid-19 vaccine (primary immunization series and first booster dose completed; manufacturer unknown), for COVID-19 immunisation.
The following information was reported: PRODUCT USE ISSUE (death, hospitalization) with onset 03Nov2022, outcome "fatal", described as "Product use for unapproved combination"; OFF LABEL USE (death, hospitalization) with onset

5.AER Number: [redacted]

Narrative
03Nov2022, outcome "fatal"; CARDIOMEGALY (death, hospitalization), LEFT VENTRICULAR HYPERTROPHY (death, hospitalization) all with onset 07Nov2022, outcome "fatal" and all described as "Cardiomegaly at the expense of left ventricular hypertrophy"; DYSPNOEA (death, hospitalization) with onset 07Nov2022, outcome "fatal"; PULMONARY CONGESTION (death, hospitalization) with onset 07Nov2022, outcome "fatal"; PULMONARY EMBOLISM (death, hospitalization, medically significant) with onset 07Nov2022, outcome "fatal"; RESPIRATORY FAILURE (death, hospitalization, medically significant) with onset 07Nov2022, outcome "fatal", described as "Severe respiratory insufficiency"; SYNCOPE (death, hospitalization, medically significant) with onset 07Nov2022, outcome "fatal"; CARDIO-RESPIRATORY ARREST (hospitalization, medically significant) with onset 07Nov2022, outcome "unknown", described as "cardiorespiratory arrest". The events "severe respiratory insufficiency", "syncope", "pulmonary embolism", "dyspnoea" and "cardiorespiratory arrest" required emergency room visit. The patient underwent the following laboratory tests and procedures: Activated partial thromboplastin time: 67 seconds; Autopsy: markedly congested overweight lungs, notes: markedly congested overweight lungs without evidence of massive pulmonary thromboembolism. Card iomegaly at the expense of left ventricular hypertrophy (VE: 2.5 Reference value 1.5 cm and dilation of the right ventricle. Pending subsequent results will be reviewed; Base excess: 19.7 mmol/L; 21.5 mmol/L; Blood bicarbonate: 14.2 mmol/L; Blood calcium: normal; Blood creatine phosphokinase: 182 IU/l; 69 IU/l; Blood fibrinogen: 298 mg/dl; Blood lactic acid: 122 mg/dl; Blood potassium: normal; Echocardiogram: showing severe ventricular dysfunction, notes: LVEF 5-10% with severely dilated right ventricle; Ejection fraction: 5-10 %; Fibrin D dimer: 46156 ng/ml; AG: haemogram and formula normal; Liver function test: normal; PCO2: 83 mmHg; pH body fluid: 6.84; PO2: 103 mmHg; Prothrombin index: 1.2, notes: Plasm; Prothrombin time: 1.19; Prothrombin time: 78 %; Renal function test normal: normal; SARS-CoV-2 test: negative; Troponin: 427 pg/mL. Therapeutic measures were taken as a result of respiratory failure, syncope, pulmonary embolism, dyspnoea, cardio-respiratory arrest. The patient date of death was 07Nov2022. Reported cause of death: "Severe respiratory insufficiency". The autopsy revealed "pulmonary congestion" (pulmonary congestion); "cardiomegaly at the expense of left ventricular hypertrophy" (cardiomegaly); "cardiomegaly at the expense of left ventricular hypertrophy" (left ventricular hypertrophy). The cli nical course was as follows: On 07Nov2022, emergency services came to his home for cardiorespiratory arrest. According to the family, on stretching out in bed he reported an intense sensation of suffocation with subsequent syncope. On arrival, the emergency department noted agonal respiration and pulseless electrical activity. CPR manoeuvres were started, IOT and adrenaline were administered, pulse was recovered and electrical activity without pulse returned on 5 occasions, CPR manoeuvres were maintained until arrival at the hospital emergency room after 50 minutes. On arrival at the hospital, the patient was sedated, IOT, mydriatic pupils were active and livid. Cardiology performed bedside echocardiography showing severe ventricular dysfunction LVEF 5-10% with severely dilated right ventricle. During the stay in the emergency room, cardiac rhythm was not recovered and resuscitation manoeuvres were stopped after 20 minutes, total arrest time 108 minutes. The first cause of cardiac arrest was probably massive pulmonary thromboembolism (PTE), ischaemic heart disease being less likely. Exitus was certified at 1:12 AM on 07Nov2022. The family was informed and accepted the autopsy. Pending results. As of 02Dec2022, additional autopsy information received last 23Nov2022 was reported as: markedly congested overweight l ungs without evidence of massive pulmonary thromboembolism. Cardiomegaly at the expense of left ventricular hypertrophy (VE: 2.5 Reference value 1.5 cm and dilation of the right ventricle. Pending subsequent results will be reviewed. No follow-up attempts are possible. No further information is expected. Follow-up (02Dec2022): This is a spontaneous follow-up report received from the same contactable Pharmacist. Updated information included: Patient details (Lab data), Suspect drug details (Anatomical location updated), Reaction data (New events and autopsy results: Pulmonary congestion, Cardiomegaly and Left Ventricular Hypertrophy added). No follow-up attempts are possible. No further information is expected.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Respiratory failure	SERIOUS	SIMVASTATIN	-	NO DATA
Syncope	SERIOUS			
Pulmonary embolism	SERIOUS			
Dyspnoea	SERIOUS			
Cardio-respiratory arrest	SERIOUS			
Pulmonary congestion	SERIOUS			

5.AER Number: [redacted]

Adverse Event(s) PT	Event Seriousness
Cardiomegaly	SERIOUS
Left ventricular hypertrophy	SERIOUS
Off label use	SERIOUS
Product use issue	SERIOUS

Device Type Suspect	Device Type Conmed
NO DATA	NO DATA

Narrative Line Listing

BNT162B2, BNT162B2 OMI BA.4-5
Reporting Period: All Time
Total Number of Cases: 7

1.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	03-NOV-2022 - 03-NOV-2022
INFLUENZA VACCINE INACT SAG 4V	Immunisation	03-NOV-2022 - 03-NOV-2022
TINZAPARIN SODIUM	Embolism venous	14-SEP-2022 - 02-NOV-2022
EDOXABAN TOSILATE	Embolism venous	03-NOV-2022 - 06-NOV-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Abdominal pain upper	---MAY-2022		NO DATA	Gst study since May2022 due to epigastric pain
PATIENT	Contrast media reaction			NO DATA	
PATIENT	Deep vein thrombosis	09-SEP-2022	14-SEP-2022	NO DATA	
PATIENT	Hiatus hernia			NO DATA	
PATIENT	Hypertension			NO DATA	
PATIENT	Hysterectomy			NO DATA	Hysterectomy for uterine prolapse 40ys ago
PATIENT	Lumbar spinal stenosis			NO DATA	
PATIENT	Odontogenic cyst			NO DATA	excision of a molar odontogenic cyst in 2017
PATIENT	Osteoarthritis			NO DATA	
PATIENT	Pulmonary embolism	09-SEP-2022	14-SEP-2022	NO DATA	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Cerebral infarction	
DEATH	PATIENT	Respiratory arrest	

Narrative

1.AER Number: [redacted]

Narrative

This is a spontaneous report received from a contactable reporter(s) (Physician) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: ES-AEMPS-[redacted]

An 84-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 03Nov2022 as dose 4 (booster), single (Lot number: GJ2541) intramuscular for covid-19 immunisation; influenza vaccine inact sag 4v (FLUAD TETRA), on 03Nov2022 as 1 df, single (Lot number: Unknown) intramuscular for immunisation; tinzaparin sodium (INNOHEP), from 14Sep2022 (Lot number: Unknown) to 02Nov2022 at 8000 iU 1x/day, subcutaneous for embolism venous; edoxaban tosilate (LIXIANA), from 03Nov2022 (Lot number: Unknown) to 06Nov2022 at 30 mg 1x/day, oral for embolism venous. The patient's relevant medical history included: "Thrombosis venous deep", start date: 09Sep2022, stop date: 14Sep2022; "Pulmonary thromboembolism", start date: 09Sep2022, stop date: 14Sep2022; "allergy to contrast" (unspecified if ongoing); "HTA" (unspecified if ongoing); "Polyarthrosis" (unspecified if ongoing); "Lumbar canal stenosis" (unspecified if ongoing); "Hiatal hernia" (unspecified if ongoing); "epigastric pain", start date: May2022 (unspecified if ongoing), notes: Gst study since May2022 due to epigastric pain; "Hysterectomy" (unspecified if ongoing), notes:

Hysterectomy for uterine prolapse 40ys ago; "odontogenic cyst" (unspecified if ongoing), notes: excision of a molar odontogenic cyst in 2017. The patient's concomitant medications were not reported. Past drug history included: Clexane, stop date: 14Sep2022, for Thrombosis venous deep, notes: until discharge. Vaccination history included: comirnaty (DOSE:1 BATCH: ET1831), administration date: 08Mar2021, for covid-19 immunisation; comirnaty (DOSE: 2 BATCH: EW2239), administration date: 30Mar2021, for covid-19 immunisation; comirnaty (DOSE: 3 BATCH: FG7898), administration date: 18Nov2021, for covid-19 immunisation.
The following information was reported: PRODUCT USE ISSUE (non-serious) with onset 03Nov2022, outcome "unknown", described as "Product use for unapproved combination"; OFF LABEL USE (non-serious) with onset 03Nov2022, outcome "unknown"; EMBOLIC STROKE (death, hospitalization) with onset 04Nov2022, outcome "fatal", described as "Cardioembolic stroke"; DISSEMINATED INTRAVASCULAR COAGULATION (death, hospitalization) with onset 06Nov2022, outcome "fatal"; HEPARIN-INDUCED THROMBOCYTOPENIA (death, hospitalization) with onset 06Nov2022, outcome "fatal"; PULMONARY EMBOLISM (death, hospitalization) with onset 06Nov2022, outcome "fatal", described as "Pulmonary thromboembolism"; STRESS CARDIOMYOPATHY (death, ho

spitalization) with onset 08Nov2022, outcome "fatal", described as "Tako-Tsubo cardiomyopathy"; PERIPHERAL ARTERY OCCLUSION (death, hospitalization) with onset 12Nov2022, outcome "fatal", described as "Popliteal arterial obstruction". The patient was hospitalized for stress cardiomyopathy, peripheral artery occlusion, heparin-induced thrombocytopenia, disseminated intravascular coagulation, pulmonary embolism (start date: 06Nov2022, discharge date: 13Nov2022, hospitalization duration: 8 day(s)). The events "cardioembolic stroke", "heparin-induced thrombocytopenia", "disseminated intravascular coagulation" and "pulmonary thromboembolism" required emergency room visit. The patient underwent the following laboratory tests and procedures: Activated partial thromboplastin time (25-38): (05Nov2022) 26.7 seconds; (06Nov2022) 27.9 seconds; (07Nov2022) 35.1 seconds; Alanine aminotransferase (5-33): (05Nov2022) 33 IU/l; (06Nov2022) 27 IU/l; Ammonia (11-51): (06Nov2022) 30 umol/l; Angiogram: (unspecified date) revealed a 25-mm lung tumor, notes: in the right upper lobe with adenopathies and peripheral nodules of a doubtful neoplastic versus thrombotic nature. There was also evidence of small pulmonary thromboembolism in the anterior segmental branch of the right superior pulmonary artery; (06Nov2022) Acute aortic pathology

is not seen, notes: Findings suggestive of congestive heart failure. -Pulmonary nodule of about 25 mm in right upper lobe located parahilar, with pathological right hilar and subcarinal adenopathies; Aspartate aminotransferase (4-32): (05Nov2022) 81 IU/l; (06Nov2022) 69 IU/l; Basophil count (0.1-1.41): (05Nov2022) 0.5 %; (06Nov2022) 0.5 %; (07Nov2022) 0.1 %; Basophil count (0-0.2): (05Nov2022) 0.03 x10 3/mm3; (06Nov2022) 0.03 x10 3/mm3; (07Nov2022) 0.01 x10 3/mm3; Blood alkaline phosphatase (35-105): (05Nov2022) 63 IU/l; (06Nov2022) 53 IU/l; Blood bilirubin (0-1.2): (05Nov2022) 0.60 mg/dl; (06Nov2022) 0.7 mg/dl; Blood calcium (4.6-5.3): (05Nov2022) 4.92 mg/dl; Blood creatinine (0.5-0.9): (05Nov2022) 0.75 mg/dl; (06Nov2022) 0.74 mg/dl; Blood fibrinogen (150-400): (06Nov2022) 239 mg/dl; (07Nov2022) 291 mg/dl; Blood glucose (74-106): (05Nov2022) 80 mg/dl; (06Nov2022) 81 mg/dl; Blood lactate dehydrogenase (135-214): (06Nov2022) 523 IU/l; Blood potassium (3.5-5.1): (05Nov2022) 4, notes: mEq/L; (06Nov2022) 3.5; Blood pressure measurement: (unspecified date) 100/35 mmHg; Blood sodium (136-145): (05Nov2022) 138, notes: mEq/ L; (06Nov2022) 139, notes: mEq/ L; Blood urea (16.6-48.5): (05Nov2022) 49 mg/dl; (06Nov2022) 46 mg/dl; Computerised tomogram head: (05Nov2022) Study without findings of acute intracranial patho, not

es: Brain CT is performed without intravenous contrast. No acute intracranial hemorrhage was observed. There are no signs of established acute brain ischemia; (06Nov2022) No signs of intracranial bleeding, notes: Findings compatible with multiterritorial acute ischemic infarcts of anterior and posterior circulation, of an embolic nature, in the following locations: 1. Affecting the middle and left inferior frontal gyrus, in the frontal opercular region in proximity to the pars triamgularis of the inferior frontal gyrus . 2. At the left paramedian parietal level, behind the angular fissure, subcentimeter in size. 3. Of millimeter size in the left precentral cortex, in the theoretical region of the primary motor area of the right upper limb. 4. Small patchy involvement in the cortical territory of the medial division of the right posterior renal artery. 5. Small in size in the inferomedial occipital cortical region (territory of left posterior artery). 6. In left posterior superficial border territory ACM-ACP, which is larger. Chronic ischemic infarcts of an embolic nature in the upper corticosubcortical region of the right cerebellar hemisphere. Chronic lacunar infarcts in the basal ganglia, predominantly on the left side and in the left thalamus. Lacunar infarction, probably chronic, left paramedian pontine. CON

1.AER Number: [redacted]

Narrative
CLUSION: Findings compatible with multiterritorial acute ischemic infarcts of anterior and posterior circulation, of an embolic nature, as detailed in the commentary. Chronic ischemic infarcts with a lacunar profile and an embolic nature, as detailed in the comment. multiple cerebral infarctions of embolic origin in; C-reactive protein (0-0.5): (05Nov2022) 0.29 mg/dl; (06Nov2022) 0.42 mg/dl; Echocardiogram: (unspecified date) aortic insufficiency was observed without endocard; (08Nov2022) revealed hypokinesia, notes: of all the apical segments and of the midapical interventricular septum, abundant pleural effusion and fluid. free peritoneal Cardiac catheterization compatible with stress cardiomyopathy; Electrocardiogram: (unspecified date) without apparent electrical changes; Eosinophil count (0-6.12): (05Nov2022) 0.9 %; (06Nov2022) 1.4 %; (07Nov2022) 0 %; Eosinophil count (0.2-0.5): (05Nov2022) 0.06 x10 3/mm3; (06Nov2022) 0.09 x10 3/mm3; (07Nov2022) 0.00 x10 3/mm3; Fibrin D dimer: (unspecified date) 35 g/mL; (06Nov2022) 35.62 g/mL; Gamma-glutamyltransferase (6-42): (05Nov2022) 15 IU/l; (06Nov2022) 11 IU/l; Haematocrit (36-46): (05Nov2022) 43.3 %; (06Nov2022) 36.4 %; (07Nov2022) 32.8 %; Haemoglobin (12-15): (05Nov2022) 13.8 g/dl; (06Nov2022) 12.2 g/dl; (07Nov2022) 10.6 g/dl; Immature granulocyte count (0-0.5): (05Nov2022) 0.2 %; (06Nov2022) 0.2 %; (07Nov2022) 0.2 %; International normalised ratio (0.7-1.3): (05Nov2022) 1.52; (06Nov2022) 1.48; (07Nov2022) 1.33; Lymphocyte count (20.02-52.76): (05Nov2022) 22.1 %; (06Nov2022) 31.4 %; (07Nov2022) 12.8 %; Lymphocyte count (1-4): (05Nov2022) 1.4 x10 3/mm3; (06Nov2022) 1.98 x10 3/mm3; (07Nov2022) 1.06 x10 3/mm3; Mean cell haemoglobin (27-32): (05Nov2022) 30.3; (06Nov2022) 31.6; (07Nov2022) 30.7; Mean cell haemoglobin concentration (31-34): (05Nov2022) 31.9 g/dl; (06Nov2022) 33.5 g/dl; (07Nov2022) 32.3 g/dl; Mean cell volume (78-102): (05Nov2022) 95, notes: fl; (06Nov2022) 94.3, notes: fl; (07Nov2022) 95.1, notes: fl; Monocyte count (4.7-11.72): (05Nov2022) 11 %; (06Nov2022) 9.5 %; (07Nov2022) 7.9 %; Monocyte count (0.2-0.8): (05Nov2022) 0.7 x10 3/mm3; (06Nov2022) 0.6 x10 3/mm3; (07Nov2022) 0.66 x10 3/mm3; Neutrophil count (34.76-68.25): (05Nov2022) 65.3 %; (06Nov2022) 57.2 %; (07Nov2022) 79 %; Neutrophil count (1.5-8): (05Nov2022) 4.14 x10 3/mm3; (06Nov2022) 3.60 x10 3/mm3; (07Nov2022) 6.56 x10 3/mm3; Platelet count (150-450): (05Nov2022) 114 x10 3/mm3; (06Nov2022) 53 x10 3/mm3; (07Nov2022) 35 x10 3/mm3; Prothrombin level (70-130): (05Nov2022) 55 %; (06Nov2022) 57 %; (07Nov2022) 64 %; Prothrombin time: (05Nov2022) 16.9 seconds; (06Nov2022) 16.5 seconds; (07Nov2022) 15.7 seco nds; Radioisotope scan: (14Nov2022) Numerous perfusion defects were observed, notes: predominantly in the right lung, in the following locations: anterior segment of the right upper lobe, lateral of the LM, superior of the lower right lobe, and lateral of the lower left lobe. These perfusion alterations have a triangular morphology with a peripheral base, without identifying clear parenchymal alterations in this CT (non-diagnostic); are suggestive of Thromboembolism pulmonary. CONCLUSION: Alterations in perfusion described highly suggestive of bilateral Thromboembolism pulmonary. (they predominate in the right lung); Red blood cell count (3.8-4.8): (05Nov2022) 4.56 x10 6/mm3; (06Nov2022) 3.86 x10 6/mm3; (07Nov2022) 3.45 x10 6/mm3; Red cell distribution width (11.6-14): (05Nov2022) 13.2 %; (06Nov2022) 13.5 %; (07Nov2022) 13.3 %; SARS-CoV-2 test: (unspecified date) negative; Troponin: (unspecified date) 11000; Ultrasound Doppler: (06Nov2022) Absence of atheroma, notes: burden in the carotid axes, with the left axis presenting a damping pattern. - Permeable vertebral axes with cushioning pattern in both arteries. - transcranial doppler with permeability of all the vessels observed, without data of hydrocephalus, with damping from left P2 and distal in the left middle cerebral artery territory. Due to the regular bo ne window, I cannot continue to more distal; (09Nov2022) RIGHT VENOUS LOWER EXTREMITY DOPPLER, notes: The popliteal veins and the proximal segments of the lesser saphenous vein and the twin veins are not compressible with the transducer, they have echogenic material inside and lack normal Doppler flow. Common femoral, superficial and great saphenous veins without notable alterations. Edema of subcutaneous cellular tissue in the leg. CONCLUSION: Findings related to DVT of the popliteal, lesser saphenous, and right calf veins; Vitamin B12: (07Nov2022) 557 pg/mL; White blood cell count (4-10): (05Nov2022) 6.34 x10 3/mm3; (06Nov2022) 6.30 x10 3/mm3; (07Nov2022) 8.31 x10 3/mm3. The action taken for tinzaparin sodium was dosage permanently withdrawn on 02Nov2022; for edoxaban tosilate was dosage permanently withdrawn on 06Nov2022. Therapeutic measures were taken as a result of embolic stroke, stress cardiomyopathy, peripheral artery occlusion, heparin-induced thrombocytopenia, disseminated intravascular coagulation, pulmonary embolism. The patient date of death was 13Nov2022. Reported cause of death: "Multiple cerebral infarcts of embolic etiology within systemic coagulopathy", "due to respiratory arrest as an immediate cause.". Clinical course: No known allergic drug reactions, refers eczematous allergic reaction to iodinated contrast. Toxic habits: Non-smoker or drinker. Vascular risk factor: HTA, No DM, No DL. DVT+ Pulmonary embolism in September 2022, starting anticoagulation. Polyarthrosis. Lumbar canal stenosis. Hiatal hernia. Gastrointenstinal study since May2022 due to epigastric pain. A.Qx: Hysterectomy for uterine prolapse 40 years ago, excision of a molar odontogenic cyst in 2017. As a relevant background, she was admitted to Internal Medicine from 09Sep to 14Seo due to Venous thromboembolism with superficial and deep DVT and Pulmonary embolism. (seen by scintigraphy due to doubtful allergy to IC, she only had an eczematous reaction to contrast). She has been on anticoagulation with LMWH during admission and until 03Nov, with good evolution. On 03Nov she switched from LMWH to NOACs (edoxaban correctly adjusted to the dose) and administered flu and COVID-19 vaccine (Pfizer combined with omicron). It is the next day when she presents disorientation, which is why she goes to the ER. At first (05Nov) she was assessed by the NRL team with symptoms compatible with fluctuating left hemispheric syndrome, for which a CT without contrast was performed without alterations and intravenous fluids and DZP were prescribed due to suspicion of seizure symptoms. NRL examination upon admission to the Stroke Unit: conscious. Does

1.AER Number: [redacted]

Narrative
not answer questions adequately. Hypofluent aphasia. He does not nominate, he does not repeat. Obeys simple orders, is quickly intoxicated with complex ones. Oculocephalic preference to the left without crossing the midline. Threat reflex absent in RE. Central facial paresis. Mobilizes upper and lower extremities. Hypoesthesia in the right hemibody. Bilateral indifferent CPR.), Ac Folic (Vitamin B9) 7.5 ng/ mL (3.1 - 20) on 07Nov2022. BRAIN CT (05Nov2022). COMMENT: Brain CT is performed without intravenous contrast. No acute intracranial hemorrhage was observed. There are no signs of established acute brain ischemia. Focal hypodensities in the posterior region of the right cerebellar hemisphere (PICA territory) compatible with small infarcts of indeterminate chronology given their attenuation characteristics, probably subacute/chronic. Diffuse cortico-subcortical involutional changes with ectasia to a congruent degree of the ventricular system. Patchy hypodensities in supratentorial white matter probably related to chronic small-vessel ischemic vasculopathy. Bilateral focal hypodensities in basal ganglia consistent with old lacunar infarcts and/or widened perivascular spaces. Centered midline. Atheromatous calcification of both internal carotid arteries. Scarce pneumatization of bilateral mastoid air cells, pro bably related to chronic inflammatory changes. CONCLUSION: Study without findings of acute intracranial pathology. CONTROL BRAIN CT (06Nov2022). No signs of intracranial bleeding are seen. Findings compatible with multiterritorial acute ischemic infarcts of anterior and posterior circulation, of an embolic nature, in the following locations: 1. Affecting the middle and left inferior frontal gyrus, in the frontal opercular region in proximity to the pars triamgularis of the inferior frontal gyrus . 2. At the left paramedian parietal level, behind the angular fissure, subcentimeter in size. 3. Of millimeter size in the left precentral cortex, in the theoretical region of the primary motor area of the right upper limb. 4. Small patchy involvement in the cortical territory of the medial division of the right posterior renal artery. 5. Small in size in the inferomedial occipital cortical region (territory of left posterior artery). 6. In left posterior superficial border territory ACM-ACP, which is larger. Chronic ischemic infarcts of an embolic nature in the upper corticosubcortical region of the right cerebellar hemisphere. Chronic lacunar infarcts in the basal ganglia, predominantly on the left side and in the left thalamus. Lacunar infarction, probably chronic, left paramedian pontine. CONCLUSION: Findings compat ible with multiterritorial acute ischemic infarcts of anterior and posterior circulation, of an embolic nature, as detailed in the commentary. Chronic ischemic infarcts with a lacunar profile and an embolic nature, as detailed in the comment. Doppler of supra-aortic trunks -transcranial doppler (06Nov). Given the possible allergy to iodinated contrasts to rule out coexistence of an atherothrombotic cause: - Absence of atheroma burden in the carotid axes, with the left axis presenting a damping pattern. - Permeable vertebral axes with cushioning pattern in both arteries. - transcranial doppler with permeability of all the vessels observed, without data of hydrocephalus, with damping from left P2 and distal in the left middle cerebral artery territory. Due to the regular bone window, I cannot continue to more distal. CT OF AORTA (06Nov2022). Reason for consultation: Multiple cerebral embolism. Suspect intimal flap. I request aortic CT angiography +/- PET study if possible. Exploration performed: Acute aortic syndrome protocol, with baseline thoracoabdominopelvic CT, and angiotac of the thoracic and abdominal aorta, and later abdominopelvic CT in portal phase. CONCLUSION: -Acute aortic pathology is not seen. - Findings suggestive of congestive heart failure. -Pulmonary nodule of about 25 mm in right upper lobe loca ted parahilar, with pathological right hilar and subcarinal adenopathies. To rule out lung cancer. - Probable small pulmonary thromboembolism in the anterior segmental branch of the right superior pulmonary artery. - Multiple small, ill-defined nodular opacities predominantly subpleural in both lungs (small airway infection? Follicular bronchiolitis? Vasculitis?). No follow-up attempts are possible. No further information is expected.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Embolic stroke	SERIOUS		-	
Stress cardiomyopathy	SERIOUS			
Peripheral artery occlusion	SERIOUS			
Heparin-induced thrombocytopenia	SERIOUS			
Disseminated intravascular coagulation	SERIOUS			
Pulmonary embolism	SERIOUS			
Off label use	NONSERIOUS			
Product use issue	NONSERIOUS			

Device Type Suspect	Device Type Conmed

1.AER Number: [redacted]

Device Type Suspect	Device Type Conmed
NO DATA	

2.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	18-OCT-2022 - 18-OCT-2022
INFLUENZA VACCINE	Immunisation	18-OCT-2022 - 18-OCT-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Aortic valve disease	-------2019		NO DATA	she was evaluated in Cardiology with an echocardiogram in 2019 with a finding of an aortic valve with a degenerative appearance DLAo (Double aortic lesion) both mild, sclerotic mitral valve with mitral stenosis and mild mitral regurgitation.
PATIENT	Bundle branch block left			NO DATA	
PATIENT	COVID-19	---OCT-2020		NO DATA	
PATIENT	Hypertension			NO DATA	
PATIENT	Mitral valve incompetence			NO DATA	she was evaluated in Cardiology with an echocardiogram in 2019 with a finding of an aortic valve with a degenerative appearance DLAo (Double aortic lesion) both mild, sclerotic mitral valve with mitral stenosis and mild mitral regurgitation.
PATIENT	Mitral valve sclerosis			NO DATA	she was evaluated in Cardiology with an echocardiogram in 2019 with a finding of an aortic valve with a degenerative appearance DLAo (Double aortic lesion) both mild, sclerotic mitral valve with mitral stenosis and mild mitral regurgitation.
PATIENT	Mitral valve stenosis			NO DATA	she was evaluated in Cardiology with an echocardiogram in 2019 with a finding of an aortic valve with a degenerative appearance DLAo (Double aortic lesion) both mild, sclerotic mitral valve with mitral stenosis and mild mitral regurgitation.
PATIENT	Tobacco user			NO DATA	
PATIENT	Type 2 diabetes mellitus			NO DATA	DM (Diabetes mellitus) type 2 on treatment with Metformin with good metabolic control and up to then without known micro or macrovascular complications.(6.1% glycated in recent months)

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Embolic stroke	

Narrative

2.AER Number: [redacted]

Narrative

This is a spontaneous report received from a contactable reporter(s) (Physician) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: ES-AEMPS-[redacted].

A 65-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 18Oct2022 as dose 3 (booster), single (Lot number: GJ4535) intramuscular for covid-19 immunisation; influenza vaccine (INFLUENZA VACCINE), on 18Oct2022 as dose number unknown, single (Lot number: E37) for immunization. The patient's relevant medical history included: a history of AHT (Arterial Hypertension) on treatment with Enalapril, DM (Diabetes mellitus) type 2 on treatment with Metformin with good metabolic control and up to then without known micro or macrovascular complications. (6.1% glycated in recent months), active smoker, left bundle branch block, for which she was evaluated in Cardiology with an echocardiogram in 2019 with a finding of an aortic valve with a degenerative appearance DLAo (Double aortic lesion) both mild, sclerotic mitral valve with mitral stenosis and mild mitral regurgitation. At that time, Cardiology concluded as a diagnosis arterial hypertension, left bundle branch block and mitro-aortic sclerosis without significant repercussions, recommending control by ultrasound at 3-4 years. Concomitant medication(s) includ

ed: ENALAPRIL taken for hypertension; METFORMIN taken for type 2 diabetes mellitus. Vaccination history included: oxford astrazeneca (dose:1), administration date: 22Apr2021, for COVID-19 immunisation, reaction(s): "COVID-19", "Drug ineffective"; comirnaty (dose: 2), administration date: 20Dec2021, for COVID-19 immunisation, reaction(s): "COVID-19", "Drug ineffective", "Off label use", "Interchange of vaccine products". The following information was reported: She passed the covid-19 infection in Oct2020 confirmed by PCR SARS CoV2 positive on 10Oct2022 while being asymptomatic. In the vaccination registry, a dose of Oxford AstraZeneca was previously registered against covid on 22Apr2021, dose and Pfizer vaccine on 20Dec2021. On 18Oct2022 she received a third dose of Lot GJ4535 BioNTech/Pfizer + Seqirus flu vaccine Lot E37. Attended since 03Nov at her health center and emergency room for respiratory infection, she mentions symptoms "of 1 month with a cold", with suspicion of bilateral pneumonia and acute respiratory failure, she is referred to the emergency room, attended on 04Nov: "She refers to symptoms compatible with upper respiratory infection 1 month ago, approximately, with rhinorrhea, nasal congestion. She gave up the picture. For 2 weeks and after receiving the Covid + Influenza vaccine, she has a runny n

ose, cough, chest pain when coughing, beige phlegm and an occasional feeling of dyspnea when speaking; no fever." They are treated with salbutamol and prednisone 30 mg in a descending pattern. On 08Nov, she was treated with Formoterol/Budesonide 4.5/160, Salbutamol, Levofloxacin 500 mg and Carbocisteine 50 mg/ml (Cinfamucol) by her family doctor. It is not clear if, having already started this treatment (presumably she had already taken a dose), she was treated that same afternoon for symptoms of a stroke (cerebrovascular accident), at which time I personally attended to her for right hemiparesis and sudden onset aphasia, after being notified by part of her relatives, being referred to the emergency room due to a stroke code. In the emergency room, by Neurology, they record: "Current history: The patient presents a picture witnessed by a family member of decreased level of consciousness, right hemiparesis, right facial palsy, and conjugate gaze deviation to the left, which occurred at approximately 3:00 p.m. She is transferred to the emergency room as Stroke Code by UVI-movie. For the past 2 weeks and after receiving the Covid + Influenza vaccine, she has had a runny nose, cough, chest pain when coughing, whitish phlegm and an occasional feeling of dyspnea when speaking; no fever. In the emergency department, th

e described neurological focality is confirmed, a CT scan is requested, and angioCT of the brain that reports the following findings: AngioCT (Computerized Axial Tomography) 08Nov2022: "Conclusion: Pre-bifurcation left segment M1 (first marginal artery) occlusion with slight asymmetry in collaterality, ASPECTS 10. Floating thrombus in the posterior wall of the descending aorta. Irregularity and absence of partial opacification of a section of the right V4 segment, with a chronic atherosclerotic appearance. Artifacted study due to partial contrast extravasation and presence of technical artifact in the midline" They then conclude as a clinical judgement: Main diagnosis: left hemispheric ischemic stroke (TACI) due to pre-bifurcation M1 (first marginal artery) occlusion of probable atherothrombotic etiology. Treated with IVT (Interventricular Septum) + EVT (Extraventricular Septum) (TICI 3). Floating thrombus in the posterior wall of the descending aorta. Scans performed: Revised angioCT (computerized axial tomography). Impressive hypoechoic plaques and thrombus adhered to the aortic arch wall, descending aorta. Directed ultrasound will be performed to rule out mobile thrombus and we perform CI (chronic coronary insufficiency) to vascular surgery for study and adjustments. Echoscopy: Selective study of the aortic a

rch due to suspected floating thrombus in the proximal portion of the descending aorta by CT angiography (computerized axial tomography). The study makes it possible to identify said portion without clearly detecting a mobile thrombus at the level of the ascending aorta. Hyperechogenic plaques were identified in the left subclavian vein and in the lower face of the middle portion of the arch, <4 mm in both cases. On 11Nov, the general condition worsened due to probable aspiration pneumonia: "BP (Blood Pressure): 96/72, 80bpm, sat 99% GN (Glomerulonephritis) 3bpm. Regular general condition, bedridden, absolute diet-fluid therapy. She denies pain. General worsening compared to yesterday morning, more drowsy, neurologically worse. EF (Forced Expiration): Crackles in both bases and midfields. Answer with monosyllables. Right extremities to 2/5. - AS (subclavian artery) 10/10: 19x10^9/l, predominance of neutrophils. Sodium 148, PCR 120 (C-reactive protein), ProBNP (Natriuretic Peptide) 4618. JC (Clinical judgement): Ischemic stroke (TACI) in the territory of the ACMI (left middle cerebral artery) of probable atherothrombotic etiology. (Unstable plaques/mural thrombus in the aortic arch + intracranial stenosis of the terminal internal AC, segment M1 (first marginal artery) and branches M2 (secondary marginal artery) o

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n arteriography) Treated with IVT (Interventricular Septum) + EVT (Extraventricular Septum) (occlusion M1) AHT (arterial hypertension). DM (diabetes, ellitus) type 2. Smoking. Bilateral pneumonia, probable aspiration." Enter the same 11Nov in ICU (Intensive Care Unit): "- I. Acute hypoxemic respiratory. Septic shock of respiratory origin, SOFA 10. Aspiration pneumonia vs nosocomial. Others: Diffuse atheromatosis with floating thrombus in the proximal descending aorta and protruding thrombus in the infrarenal aorta and right primitive iliac aorta. (AngioCT (computerized axial tomography) 10Nov)" Then, as intrahospital diagnoses, they include: Bilateral pulmonary consolidation, suspicion of aspiration pneumonia. Bilateral pleural effusion. Diffuse atheromatosis with floating thrombus in the proximal descending aorta and protruding thrombus in the infrarenal aorta and right primitive iliac aorta. Diagnosis on admission to the ICU (Intensive Care Unit): Hypoxemic acute respiratory failure. Septic shock of respiratory origin, SOFA 10. Aspiration pneumonia vs nosocomial. It is evaluated by Cardiology on 11Nov after consultation from the ICU (Intensive Care Unit): "The current picture does not suggest an ischemic origin, but multiorgan involvement including cardiac level (vs stress cardiomyopathy), by ECG (Electrocar diogram) without data of ischemia, or suggestive segmental alteration and lack of correlation between excessive increase in Troponin I and low CPK (Creatine phosphokinase). No intraventricular thrombus was observed and mitral valve endocarditis cannot be ruled out with the study performed. In case of suspicion of endocarditis, request TEE (Transesophageal echocardiogram)." In the ICU (Intensive Care Unit), on 14Nov they write down: "Hematological-Immune-mediated: Serological screening of immunological etiology of systemic process. AP (Pathological History) of vaccination. Systemic thrombotic (arterial) and embolic picture. Diagnosis of diffuse atheromatosis with floating thrombus in the proximal descending aorta and protruding thrombus in the infrarenal aorta and right common iliac aorta not anticoagulated given the patient's already given coagulopathy. Thromboprophylaxis with compression stockings, antiplatelet removal given the hemorrhagic transformation. TEG (Thromboelastogram) pending. Mild stable anemia without signs of hemorrhagic shock (Hb - Heamoglobin 12.1/Hto (Hematocrit) 37%). Multifactorial thrombocytopenia in recovery (88000 ->114000) extrinsic coagulopathy despite treatment with vitK and mild intrinsic, significant increase in D-dimer 115300, thrombopenia, decreasing fibrinogen...high suspicion o f DIC (Disseminated intravascular coagulation). Complete study and Ab (antibody) antiFP4 pending, immunological treatment (Igev/TPE) has been temporized for the moment." Serology was performed with anti-Heparin/F4pl Ab (antibody) on 14Nov with a negative result. A cervical study was performed: <50% stenosis of the left internal carotid artery associated with plaque with instability data (plaque without significant stenosis but with irregular edges). Transcranial study: 50 - 80% stenosis MCA (middle cerebral artery) M2 (second marginal artery) right. Proximal right vertebral V4 stenosis probably > 80%. Through the suprasternal window, no image compatible with a mobile thrombus at the beginning of the descending Ao was identified, although the spatial resolution of this technique is limited. The patient died on 16Nov2022. The outcome of the events PRODUCT USE ISSUE, OFF LABEL USE, EMBOLIC STROKE was fata, for the events THROMBOCYTOPENIA, DISSEMINATED INTRAVASCULAR COAGULATION, ANAEMIA, COAGULOPATHY, FIBRIN D DIMER INCREASED, BLOOD FIBRINOGEN DECREASED was recovering; for all other events was unknown. The patient was hospitalized for respiratory tract infection, pneumonia, acute respiratory failure, cough, rhinorrhoea, nasal congestion, productive cough, chest pain, dyspnoea (start date: 03Nov2022). The events "res piratory infection", "bilateral pneumonia", "hypoxemic acute respiratory failure", "cough", "rhinorrhea", "nasal congestion", "beige phlegm", "chest pain when coughing", "occasional feeling of dyspnea when speaking", "right hemiparesis", "right facial palsy", "conjugate gaze deviation to the left" and "sudden onset aphasia" required emergency room visit. Therapeutic measures were taken as a result of embolic stroke, respiratory tract infection, pneumonia, acute respiratory failure, cough, rhinorrhoea, nasal congestion, productive cough, chest pain, dyspnoea, thrombocytopenia, hemiparesis, facial paralysis, pneumonia aspiration, disseminated intravascular coagulation, gaze palsy, aphasia, pleural effusion, anaemia, coagulopathy, fibrin d dimer increased, blood fibrinogen decreased. The patient date of death was 16Nov2022. Reported cause of death: "Thromboembolic stroke". It was not reported if an autopsy was performed. Follow-up attempts are completed. No further information is expected.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Off label use	SERIOUS	ENALAPRIL	-	NO DATA
Product use issue	SERIOUS	METFORMIN	-	NO DATA
Embolic stroke	SERIOUS			
Respiratory tract infection	SERIOUS			
Pneumonia	SERIOUS			
Acute respiratory failure	SERIOUS			

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Adverse Event(s) PT	Event Seriousness
Cough	SERIOUS
Rhinorrhoea	SERIOUS
Nasal congestion	SERIOUS
Productive cough	SERIOUS
Chest pain	SERIOUS
Dyspnoea	SERIOUS
Septic shock	SERIOUS
Thrombocytopenia	SERIOUS
Hemiparesis	SERIOUS
Facial paralysis	SERIOUS
Hypoxia	SERIOUS
Pneumonia aspiration	SERIOUS
Disseminated intravascular coagulation	SERIOUS
Gaze palsy	SERIOUS
Aphasia	NONSERIOUS
General physical health deterioration	NONSERIOUS
Speech disorder	NONSERIOUS
Movement disorder	NONSERIOUS
Arteriosclerosis	NONSERIOUS
Pleural effusion	NONSERIOUS
Anaemia	NONSERIOUS
Coagulopathy	NONSERIOUS
Fibrin D dimer increased	NONSERIOUS
Blood fibrinogen decreased	NONSERIOUS

Device Type Suspect	Device Type Conmed
NO DATA	NO DATA

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Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	06-OCT-2022 - 06-OCT-2022
INFLUENZA VACCINE INACT SPLIT 4V	Immunisation	12-OCT-2022 - 12-OCT-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Hypertension			NO DATA	
PATIENT	Type 2 diabetes mellitus			NO DATA	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Multiple organ dysfunction syndrome	

Narrative

This is a spontaneous report received from a non-contactable reporter(s) (Physician) from the European Medicines Agency (EMA) EudraVigilance-WEB. Regulatory number: DE-PEI-[redacted].

A 76-year-old male patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY), on 06Oct2022 as dose number unknown, single (Lot number: GH9715) at the age of 76 years for covid-19 immunisation; influenza vaccine inact split 4v (VAXIGRIP TETRA), on 12Oct2022 as single (Lot number: W3E121V) for immunisation. The patient's relevant medical history included: "Type II diabetes mellitus" (unspecified if ongoing); "Arterial hypertension" (unspecified if ongoing). The patient's concomitant medications were not reported. The following information was reported: PARAPARESIS (death, hospitalization, life threatening) with onset 22Oct2022, outcome "fatal", described as "Flaccid paraparesis of the legs"; HYPONATRAEMIA (death, hospitalization, life threatening) with onset 22Oct2022, outcome "fatal", described as "Hyponatremia"; HYPOKALAEMIA (death, hospitalization, life threatening) with onset 22Oct2022, outcome "fatal", described as "Hypopotassaemia"; MYOSITIS (death, hospitalization, life threatening), RHABDOMYOLYSIS (death, hospitalization, life threatening) all with onset 22Oct2022, outcome "fatal" and all described as "Postvaccin

al myositis with rhabdomyolysis"; GUILLAIN-BARRE SYNDROME (death, hospitalization, life threatening) with onset 22Oct2022, outcome "fatal", described as "Suspected Guillain Barre Syndrome"; RENAL FAILURE (death, hospitalization, life threatening) with onset 25Oct2022, outcome "fatal", described as "kidney failure"; HEPATIC FAILURE (death, hospitalization, life threatening) with onset 25Oct2022, outcome "fatal", described as "liver failure"; MULTIPLE ORGAN DYSFUNCTION SYNDROME (death, hospitalization, life threatening) with onset 27Oct2022, outcome "fatal", described as "multiple organ failure". The patient underwent the following laboratory tests and procedures: Blood bilirubin: 13.11 mg/dl; Blood creatine phosphokinase: 31340 IU/l; Blood creatine phosphokinase MB: 478 IU/l; Chest X-ray: unremarkable; C-reactive protein: 268.34 mg/l; Troponin T: 0.038; Urine analysis: unremarkable. Therapeutic measures were taken as a result of hyponatraemia, myositis, rhabdomyolysis, hypokalaemia, guillain-barre syndrome, paraparesis. The patient date of death was 28Oct2022. Reported cause of death: "Multiple organ failure". It was not reported if an autopsy was performed. The patient was admitted to the hospital for clarification of a painful, flaccid paraparesis of the legs. Laboratory tests showed a clear increase in creatin

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e kinase as well as increased infection, liver and kidney values. There was no fever at any time, and the patient was not clinically septic. A focus of infection could not initially be found with an unremarkable urine status and chest X-ray. Assuming a possibly autoimmunologically mediated (possibly postvaccinal) myositis, 500 mg prednisolone was administered intravenously once. This did not lead to an improvement in the symptoms, but there was a dramatic further deterioration in the laboratory values with the development of acute kidney failure in crushed kidneys with significant rhabdomyolysis and liver failure with the development of generalized jaundice, so that further intensive care treatment was required unfortunately could not take place in the local clinic due to a lack of bed capacities. At the current time, the clinical picture is unclear, there is an acute inflammatory process of unclear etiology, whether there is a connection with the previous vaccinations cannot be assessed at the moment. PEI assessment for all events and Comirnaty is D. Unclassifiable. PEI assessment for all events and Vaxigrip Tetra is D. Unclassifiable. No follow-up attempts are possible. No further information is expected.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Multiple organ dysfunction syndrome	SERIOUS		-	
Hyponatraemia	SERIOUS			
Myositis	SERIOUS			
Rhabdomyolysis	SERIOUS			
Hypokalaemia	SERIOUS			
Renal failure	SERIOUS			
Guillain-Barre syndrome	SERIOUS			
Paraparesis	SERIOUS			
Hepatic failure	SERIOUS			

Device Type Suspect	Device Type Conmed
NO DATA	

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Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	01-NOV-2022 - 01-NOV-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Atrial fibrillation			NO DATA	ONSET DATE: UNKNOWN
PATIENT	Cerebral infarction	26-JUL-2018		NO DATA	
PATIENT	COVID-19	19-AUG-2022		NO DATA	which was cured owing to administration of LAGEVRIO.
PATIENT	Dementia			NO DATA	ONSET DATE: UNKNOWN
PATIENT	Diabetes mellitus			NO DATA	ONSET DATE: UNKNOWN
PATIENT	Gastrostomy	13-AUG-2018		NO DATA	
PATIENT	Glycosuria			NO DATA	
PATIENT	Hypertension			NO DATA	
PATIENT	Loss of personal independence in daily activities			NO DATA	ONSET DATE: UNKNOWN Nursing Care Level was 4; ADL Independence Measure was C-2 Total assistance;
PATIENT	Neurogenic bladder			NO DATA	
PATIENT	Parkinson's disease			NO DATA	ONSET DATE: UNKNOWN

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Cardiovascular disorder	
DEATH	PATIENT	Cerebrovascular disorder	
DEATH	PATIENT	Respiratory arrest	
DEATH	PATIENT	Sudden death	

Narrative

This is a spontaneous report received from contactable reporter(s) (Physician) from product quality group and Regulatory Authority. Regulatory number: [redacted](PMDA).

An 87-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY RTU FOR BA.4-5), on 01Nov2022 at 14:17 as dose 4 (booster), single (Lot number: GJ1842, Expiration Date: 31Jul2023) at the age of 87 years intramuscular for covid-19 immunisation. The patient's relevant medical history included: "Diabetes mellitus" (unspecified if ongoing), notes: ONSET DATE: UNKNOWN; "Parkinson's disease" (unspecified if ongoing), notes: ONSET DATE: UNKNOWN; "Late effects of cerebral infarction", start date: 26Jul2018 (unspecified if ongoing); "Atrial fibrillation" (unspecified if ongoing), notes: ONSET DATE: UNKNOWN; "dementia" (unspecified if ongoing), notes: ONSET DATE: UNKNOWN; "COVID-19 infection", start date: 19Aug2022 (unspecified if ongoing), notes: which was cured owing to administration of LAGEVRIO.; "had a gastrostoma", start date: 13Aug2018 (unspecified if ongoing); "receiving total assistance for Activities of daily living" (unspecified if ongoing), notes: ONSET DATE: UNKNOWN, Nursing Care Level was 4; ADL Independence Measure was C-2 Total assistance;; "Glycosuria" (unspecified if ongoing); "Hypertension" (unspecified if ongoing);

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Narrative
"Neurogenic bladder" (unspecified if ongoing). Concomitant medication(s) included: JANUVIA taken for glycosuria, start date: 16Jul2020; EBRANTIL [URAPIDIL] taken for neurogenic bladder, start date: 04Sep2020; AMLODIPINE taken for hypertension, start date: 02Aug2022. Past drug history included: Lagevrio for COVID-19 infection; Insulin, notes: She received insulin, which stabilized the HbA1c at around 7.0. Vaccination history included: comirnaty (dose 1, single, Batch/lot number:FC5947, Expiration date: 30Sep2021, Route of Administration: Intramuscular , Administration time: 12:10), administration date: 22Jun2021, for COVID-19 immunisation, reaction(s): "COVID-19 infection", "COVID-19 infection"; comirnaty (dose 2, single, Batch/lot number:FC8736, Expiration date: 30Sep2021, Route of Administration: Intramuscular , Administration time: 12:20), administration date: 13Jul2021, for COVID-19 immunisation, reaction(s): "COVID-19 infection", "COVID-19 infection"; moderna (dose 3, single, Batch/lot number: 3005786, Route of Administration: Intramuscular , Administration time: 14:14), administration date: 16Feb2022, for COVID-19 immunisation, reaction(s): "COVID-19 infection", "COVID-19 infection", "Hypothermia", "pancreatitis"; Influenza vaccination, for immunisation. The following information was reported: HYPOTH ERMIA (medically significant) with onset 02Nov2022 at 09:00, outcome "unknown", described as "the course which descended into hypothermia was similar to that of the 3rd inoculation."; PRODUCTIVE COUGH (non-serious) with onset 02Nov2022 at 21:00, outcome "unknown"; SPUTUM INCREASED (non-serious) with onset 03Nov2022, outcome "unknown", described as "The amount of aspirated sputum slightly increased"; SUDDEN DEATH (death, medically significant) with onset 04Nov2022 at 04:00, outcome "fatal"; RESPIRATORY ARREST (death, medically significant) with onset 04Nov2022 at 04:00, outcome "fatal", described as "state of respiratory arrest"; CARDIOVASCULAR DISORDER (death), outcome "fatal", described as "cardiovascular diseases"; CEREBROVASCULAR DISORDER (death), outcome "fatal", described as "cerebrovascular diseases". The patient underwent the following laboratory tests and procedures: Blood pressure measurement: (01Nov2022) 131/56, notes: at 09:30; Body temperature: (01Nov2022) 36.0 Centigrade, notes: before vaccination; (01Nov2022) 35.8 Centigrade, notes: at night; (01Nov2022) 36.0 Centigrade, notes: at 09:30; (01Nov2022) 35.8 Centigrade, notes: at 18:00; (01Nov2022) 35.8 Centigrade, notes: at 21:00; (02Nov2022) 34.5 Centigrade, notes: at 09:00; (02Nov2022) 34.5 Centigrade, notes: at 21:00; (02Nov2022) 35.4 Centigrade, n otes: at:06:00; (02Nov2022) 34.5 Centigrade, notes: at 09:30; (02Nov2022) 34.9 Centigrade, notes: at 14:00; (03Nov2022) 33.9 Centigrade, notes: at 00:00; (03Nov2022) 35.5 Centigrade, notes: at 21:00; (03Nov2022) 34.7 Centigrade, notes: at 06:00; (03Nov2022) 33.9 Centigrade, notes: at 09:30; (03Nov2022) 34.0 Centigrade, notes: at 14:30; (04Nov2022) 36.1 Centigrade, notes: at 00:00; Heart rate: (01Nov2022) 72, notes: at night; (01Nov2022) 74, notes: at 09:30; (01Nov2022) 68, notes: at 18:00; (01Nov2022) 72, notes: at 21:00; (02Nov2022) 66, notes: at 09:00; (02Nov2022) 58, notes: at 21:00; (02Nov2022) 66, notes: at:06:00; (02Nov2022) 66, notes: at 09:30; (02Nov2022) 60, notes: at 14:00; (03Nov2022) 70, notes: at 00:00; (03Nov2022) 63, notes: at 21:00; (03Nov2022) 57, notes: at 06:00; (03Nov2022) 70, notes: at 09:30; (03Nov2022) 68, notes: at 14:30; (04Nov2022) 74, notes: at 02:00; (04Nov2022) 74, notes: at 00:00; Oxygen saturation: (01Nov2022) 98 %, notes: at night; (01Nov2022) 97 %, notes: at 09:30; (01Nov2022) 98 %, notes: at 18:00; (01Nov2022) 98 %, notes: at 21:00; (02Nov2022) 99 %, notes: at 09:00; (02Nov2022) 98 %, notes: at 21:00; (02Nov2022) 97 %, notes: at:06:00; (02Nov2022) 99 %, notes: at 09:30; (02Nov2022) 99 %, notes: at 14:00; (03Nov2022) 94 %, notes: at 00:00; (03Nov2022) 98 %, notes: at 21:00; (03No v2022) 96 %, notes: at 06:00; (03Nov2022) 98 %, notes: at 09:30; (03Nov2022) 97 %, notes: at 14:30; (04Nov2022) 98 %, notes: at 02:00; (04Nov2022) 97 %, notes: at 00:00. Therapeutic measures were not taken as a result of sudden death. The patient date of death was 04Nov2022. Reported cause of death: "Sudden death", "state of respiratory arrest", "cardiovascular diseases", "cerebrovascular diseases". No autopsy was performed. Clinical course: The patient was an 87-year and 8-month-old female. On 01Nov2022, before vaccination, Body temperature 36.0 Centigrade. On 01Nov2022, she received the vaccination. At night: Body temperature (BT), 35.8 Centigrade; Pulse rate (PR), 72; and Oxygen saturation (SpO2), 98%. On 02Nov2022 at 09:00, although she did not have pyrexia but had body temperature decreased (BT, 34.5 Centigrade; PR, 66; and SpO2, 99%). The communication was as usual. At 21:00, BT, 34.5 Centigrade; PR, 58; and DpO2, 08% (as reported). Productive cough was observed. On 03Nov2022 at 0:00, BT, 33.9 Centigrade; PR, 70; and SpO2, 94%. Her response was favourable. The amount of aspirated sputum slightly increased. At 21:00, BT, 35.5 Centigrade; PR, 63; and SpO2, 98%. The amount of aspirated sputum was small. On 04Nov2022 at 02:00, PR, 74; and SpO2, 98%. The amount of aspirated sputum was large. Her response was f avourable. At 04:00, she was found in a state of respiratory arrest. On 04Nov2022 at 04:00 (2 days 13 hours 43 minutes after the vaccination), the patient experienced sudden death. On 04Nov2022 (3 days after the vaccination), the outcome of the event was fatal. The reporting physician classified the event as serious (death) and assessed that the causality between the event and BNT162b2 as un-assessable. Other possible causes of the event such as any other diseases were cardiovascular diseases and cerebrovascular diseases. The reporting physician commented as follows: She did not undergo a blood test or an imaging test this time. However, the course which descended into hypothermia was similar to that of the 3rd inoculation. Therefore, it was thought the event was possibly an adverse reaction. Conclusion: The complaint for PFIZER-BIONTECH COVID-19 VACCINE was investigated. The investigation included reviewing the involved batch records, deviation investigation, an analysis of the complaint history for the reported lot and product type. The final scope was determined to be the associated lot(s) of the reported lot GJ1842. A complaint sample was not returned. No related quality issues were identified during the investigation. There is no impact on product quality, regulatory, validation and stability. PGS Puurs con

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Narrative
cludes that the reported defect is not representative of the quality of the batch and the batch remains acceptable. The NTM process determined that no regulatory notification was required. The reported defect could not be confirmed. No root cause or CAPA were identified as the complaint was not confirmed. As of 28Nov2022, it was reported that on 04Nov2022 patient had event "Sudden death", Resulted in death. Causality with drug was Unassessable. Date of Death was 04Nov2022. The patient had not received treatment for the event and no autopsy was performed. It was further reported that patient was admitted to a facility for medical and long-term care; Nursing Care Level was 4; ADL Independence Measure was C-2 Total assistance; If the Patient Could Swallow/Ingest or Not: gastrostomy state; No abnormality before/after Inoculation. On 04Nov2022, at 04:00, the patient was found in unusual when the nurse visited the room, the patient was in the cardio-respiratory state. No Emergency Service was Requested.No Autopsy Imaging was Performed. Consideration of and Physician's Comment on Cause(s) of Death (including Judgement Rationale) : The patient was an elderly and had a medical history of atrial fibrillation and cerebral infarction, but the condition was stable until just before the event. The low body temperature had bee n observed at times, and it was also noted after the third vaccination. It is highly likely to be an acute deterioration due to cerebrovascular/ cardiovascular diseases. Physician's Consideration of Causality between Vaccination and Death (including Judgement Rationale): As written above, it is thought that the causality cannot be ruled out. Follow-up (22Nov2022): This is a follow-up report from Pfizer Product Quality Group providing investigation results. Updated information included: Batch and lot tested and found within specifications was ticked. Conclusion was updated. Follow-up (28Nov2022): This is a spontaneous follow-up report from the same contactable physician, response of follow up letter. Updated information include: patient details (patient information, historical vaccine, other relevant medical history and lab data were updated), product details (route of administration was updated and concomitant medication was added), and event details (treatment and autopsy details were updated). Follow-up attempts are completed. No further information is expected.

Adverse Event(s) PT	Event Seriousness
Sudden death	SERIOUS
Respiratory arrest	SERIOUS
Cardiovascular disorder	SERIOUS
Cerebrovascular disorder	SERIOUS
Hypothermia	SERIOUS
Productive cough	NONSERIOUS
Sputum increased	NONSERIOUS

Concomitant Drug(s)	Therapy Date(s)	Route of Admin
AMLODIPINE	02-AUG-2022 -	NO DATA
SITAGLIPTIN PHOSPHATE	16-JUL-2020 -	NO DATA
URAPIDIL	04-SEP-2020 -	NO DATA

Device Type Suspect	Device Type Conmed
NO DATA	NO DATA

5.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	20-NOV-2022 - 20-NOV-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Breast cancer			NO DATA	discovered 20 years ago
PATIENT	Cellulitis			NO DATA	discovered from after breast cancer operation
PATIENT	Hypertension			NO DATA	discovered date unknown
PATIENT	Lumbar spinal stenosis			NO DATA	discovered date unknown
PATIENT	Lymphadenectomy			NO DATA	discovered 20 years ago
PATIENT	Spinal osteoarthritis			NO DATA	discovered date unknown

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Acute kidney injury	
DEATH	PATIENT	Bacteraemia	
DEATH	PATIENT	Blood lactic acid increased	
DEATH	PATIENT	Disseminated intravascular coagulation	
DEATH	PATIENT	Hyperkalaemia	
DEATH	PATIENT	Multiple organ dysfunction syndrome	
DEATH	PATIENT	Platelet count decreased	
DEATH	PATIENT	Rhabdomyolysis	
DEATH	PATIENT	Sepsis	
DEATH	PATIENT	Severe invasive streptococcal infection	
DEATH	PATIENT	Streptococcal sepsis	
DEATH	PATIENT	Vaccination site cellulitis	

Narrative

5.AER Number: [redacted]

Narrative

This is a spontaneous report received from a contactable reporter(s) (Nurse) from Regulatory Authority. Regulatory number: [redacted] (PMDA).

A 79-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY RTU FOR BA.4-5), on 20Nov2022 as dose 5 (booster), single (Lot number: GJ1836, Expiration Date: 31Jul2023) at the age of 79 years, in left arm for covid-19 immunisation. The patient's relevant medical history included: "Postoperative of left breast cancer(With Lymph node excision)" (unspecified if ongoing), notes: discovered 20 years ago; "Postoperative of left breast cancer(With Lymph node excision)" (unspecified if ongoing), notes: discovered 20 years ago; "Recurrent left upper extremity cellulitis" (unspecified if ongoing), notes: discovered from after breast cancer operation; "hypertension" (unspecified if ongoing), notes: discovered date unknown; "Osteoarthritis of cervical spine" (unspecified if ongoing), notes: discovered date unknown; "Lumbar spinal stenosis" (unspecified if ongoing), notes: discovered date unknown. The patient's concomitant medications were not reported. Vaccination history included: Covid-19 vaccine (dose 1, single; manufacturer unknown), for COVID-19 immunisation; Covid-19 vaccine (dose 2, single; manufacturer unknown), for COVID-19 immunisation; Covid-19 vaccine

(dose 3 (booster), single; manufacturer unknown), for COVID-19 immunisation; Covid-19 vaccine (dose 4 (booster), single; manufacturer unknown), for COVID-19 immunisation, reaction(s): "no adverse effect".
The following information was reported: SEVERE INVASIVE STREPTOCOCCAL INFECTION (death, hospitalization) with onset 20Nov2022, outcome "fatal", described as "Fulminant G group hemolytic streptococcal infection/Severe invasive streptococcal infection"; VACCINATION SITE PAIN (non-serious) with onset 21Nov2022, outcome "unknown", described as "Developed painful L arm, redness, and swelling/ injection site pain"; VACCINATION SITE ERYTHEMA (non-serious) with onset 21Nov2022, outcome "unknown", described as "Developed painful L arm, redness, and swelling/ injection site redness"; VACCINATION SITE SWELLING (non-serious) with onset 21Nov2022, outcome "unknown", described as "Developed painful L arm, redness, and swelling/injection site swelling"; RHABDOMYOLYSIS (death, hospitalization, medically significant) with onset 21Nov2022, outcome "fatal", described as "Rhabdomyolysis/rapidly progressive rhabdomyolysis and hyperkalaemia"; MALAISE (non-serious) with onset 21Nov2022, outcome "unknown"; BLOOD LACTIC ACID INCREASED (death) with onset 22Nov2022, outcome "fatal", described as "Abnormal elevation of lactate"; CYANOSI

S (non-serious) with onset 22Nov2022, outcome "unknown", described as "Cyanosis peripheral"; DISSEMINATED INTRAVASCULAR COAGULATION (death, hospitalization, medically significant) with onset 22Nov2022, outcome "fatal", described as "DIC"; MOVEMENT DISORDER (non-serious) with onset 22Nov2022, outcome "unknown", described as "Difficulty moving her body"; ENDOTRACHEAL INTUBATION COMPLICATION (medically significant) with onset 22Nov2022, outcome "unknown", described as "Difficulty with intubation"; JOINT STIFFNESS (non-serious) with onset 22Nov2022, outcome "unknown", described as "Mandibular rigidity/had abnormal rigidity of mandible and neck and could not open her mouth at all even by muscle relaxant"; PLATELET COUNT DECREASED (death, hospitalization) with onset 22Nov2022, outcome "fatal", described as "Platelets decreased"; HYPERKALAEMIA (death, medically significant) with onset 22Nov2022, outcome "fatal", described as "Rapidly progressive rhabdomyolysis and hyperkalaemia/continued to have hyperkalaemia/Hyperkalaemia"; VACCINATION SITE HAEMORRHAGE (non-serious) with onset 22Nov2022, outcome "unknown", described as "Redness, swelling, and haemorrhage subcutaneous on her left upper arm"; SEPSIS (death, hospitalization, medically significant) with onset 22Nov2022, outcome "fatal"; CONDITION AGGRAVATED (non-serious)

with onset 22Nov2022, outcome "unknown", described as "The symptoms worsened"; MUSCULAR WEAKNESS (non-serious) with onset 22Nov2022, outcome "unknown", described as "lower extremities weakness of"; MOBILITY DECREASED (non-serious) with onset 22Nov2022, outcome "unknown", described as "movement difficulty"; PURPURA (non-serious) with onset 22Nov2022, outcome "unknown", described as "purpura at the vaccination site on her left upper arm"; ERYTHEMA (non-serious) with onset 22Nov2022, outcome "unknown", described as "redness spreading to the trunk/Strong redness in the left side of abdomen."; FEELING HOT (non-serious) with onset 22Nov2022, outcome "unknown", described as "warmth of the left upper limb"; BLOOD PRESSURE DECREASED (non-serious) with onset 23Nov2022, outcome "unknown"; DEPRESSED LEVEL OF CONSCIOUSNESS (medically significant) with onset 23Nov2022, outcome "unknown", described as "The level of consciousness gradually decreased"; MUSCULOSKELETAL STIFFNESS (non-serious) with onset 23Nov2022, outcome "unknown", described as "had abnormal rigidity of mandible and neck and could not open her mouth at all even by muscle relaxant"; BACTERAEMIA (death), outcome "fatal"; MULTIPLE ORGAN DYSFUNCTION SYNDROME (death), outcome "fatal", described as "Multi-organ failure"; VACCINATION SITE CELLULITIS (death), outcome "f

atal", described as "Cellulitis at the vaccination site"; STREPTOCOCCAL SEPSIS (death, medically significant), outcome "fatal", described as "Fulminant streptococcal sepsis"; ACUTE KIDNEY INJURY (death, medically significant), outcome "fatal", described as "Acute renal failure". The patient was hospitalized for rhabdomyolysis, disseminated intravascular coagulation, severe invasive streptococcal infection, platelet count decreased (start date: 22Nov2022, discharge date: 23Nov2022, hospitalization duration: 2 day(s)); for sepsis (start date: 22Nov2022). The events "rhabdomyolysis/rapidly progressive rhabdomyolysis and hyperkalaemia", "rapidly progressive rhabdomyolysis and hyperkalaemia/continued to have hyperkalaemia/hyperkalaemia", "dic", "abnormal elevation of lactate", "sepsis", "difficulty with intubation", "developed painful l arm, redness, and swelling/ injection site pain", "developed painful l arm, redness, and swelling/ injection site redness", "developed painful l arm, redness, and swelling/injection site swelling", "redness, swelling, and haemorrhage subcutaneous on her left upper arm", "the symptoms worsened", "difficulty moving her body", "mandibular rigidity/had abnormal rigidity of mandible and neck and could not open her mouth at all even by muscle relaxant", "cricothyrotomy", "tracheostomy", "lo

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Narrative
wer extremities weakness of" and "movement difficulty" required physician office visit. The event "fulminant g group hemolytic streptococcal infection/severe invasive streptococcal infection" required emergency room visit. The patient underwent the following laboratory tests and procedures: Blood creatine phosphokinase (41-153): (22Nov2022) 1338 IU/l; (23Nov2022) 46957 IU/l, notes: at 16:00; (23Nov2022) 6775 IU/l, notes: At 04:00 the patient's condition was aggravated; Blood creatinine (0.46-0.79): (22Nov2022) 1.34 mg/dl; (23Nov2022) 2.36 mg/dl, notes: At 04:00 the patient's condition was aggravated; Blood culture: (unspecified date) could be multi-organ failure, notes: due to sepsis and bacteraemia caused by Streptococcus; (22Nov2022) positive, notes: Strept ococcus dysgalactiae ssp equisiviris. Based on all tests, fungus after death was identified; (23Nov2022) Positive, notes: Strept ococcus dysgalactiae ssp equisiviris. Based on all tests, fungus after death was identified; (24Nov2022) treptococcus was detected through Gram staining.; Blood lactate dehydrogenase (124-222): (23Nov2022) 2267 IU/l; Blood lactic acid: (22Nov2022) abnormal elevation; (23Nov2022) 30 mmol/L, notes: at 16:00; Blood potassium (3.6-4.8): (23Nov2022) 9.5 mmol/L, notes: at 16:00; (23Nov2022) 6.4 mmol/L, notes: At 04:00 the patient's c ondition was aggravated; Blood pressure measurement: (22Nov2022) began to decrease to the range of, notes: 80s; (23Nov2022) decreased started, notes: at 16:00; Blood urea (8-20): (22Nov2022) 36.2 mg/dl; (23Nov2022) 47.1 mg/dl; Computerised tomogram: (unspecified date) unknown results; C-reactive protein: (22Nov2022) high levels; (22Nov2022) 24.13 mg/dl, notes: Normal Low was Below 0.14; (22Nov2022) 24 mg/dl; Electrocardiogram: (unspecified date) unknown results; Fibrin D dimer: (22Nov2022) 176 ug/ml; (23Nov2022) 473.6 ug/ml, notes: Normal High was below 1.0; (23Nov2022) 473 ug/ml, notes: At 04:00 . the patient's condition was aggravated; Fibrin degradation products: (22Nov2022) 247.4 ug/ml; Gram stain: (unspecified date) Positive for streptococci; Haemoglobin (11.6-14.8): (23Nov2022) 6.6 g/dl, notes: at 16:00; infection: (unspecified date) unknown results; Lactic acidosis: (22Nov2022) 10 mmol/L; (23Nov2022) 30 mmol/L; Platelet count (15.8-34.8): (22Nov2022) 7.2 x10 4/mm3; (23Nov2022) 1.9, notes: unit: x 10 4/UL at 16:00; (23Nov2022) 3.7, notes: unit: x10 4/uL At 04:00 the patient's condition was aggravated; Procalcitonin: (22Nov2022) 44.58 ng/ml; (22Nov2022) 44.53 ng/ml, notes: Normal Low was Below 0.05; Prothrombin time ratio (0.85-1.15): (23Nov2022) 2.75, notes: unit: x 10 4/UL; (23Nov2022) 2.28, notes: At 04 :00 the patient's condition was aggravated; SARS-CoV-2 test: (unspecified date) unknown results; Urine analysis: (unspecified date) unknown results; X-ray: (unspecified date) unknown results. Therapeutic measures were taken as a result of rhabdomyolysis, hyperkalaemia, disseminated intravascular coagulation, sepsis, severe invasive streptococcal infection, platelet count decreased, depressed level of consciousness, malaise, purpura, erythema, musculoskeletal stiffness, blood pressure decreased. The patient date of death was 23Nov2022. Reported cause of death: "Rhabdomyolysis/rapidly progressive rhabdomyolysis and hyperkalaemia", "cellulitis at the vaccination site", "fulminant streptococcal sepsis", "DIC", "Acute renal failure", "rapidly progressive rhabdomyolysis and hyperkalaemia/continued to have hyperkalaemia/Hyperkalaemia", "abnormal elevation of lactate", "Multi-organ failure", "bacteraemia", "sepsis", "Fulminant G group hemolytic streptococcal infection/Severe invasive streptococcal infection", "Platelets decreased". No autopsy was performed. The patient received the fifth dose of Comirnaty RTU for BA.4-5(Lot number GJ1836, Expiration date 31Jul2023) as a single dose for COVID-19 immunization. Whether the patient received any other vaccines within 4 weeks prior to the COVID vaccine was unknown. Concomita nt drugs taken within two weeks before the event onset was unknown. Family medical history relevant to AE(s) was unknown. On 20Nov2022 or 21Nov2022 (Presumed), the patient experienced Severe G group invasive streptococcal infection. The AE required visit to Emergency Room and Intensive Care Unit. ICU duration of stay was from 22Nov2022 23:10 to 23Nov2022 23:43. The outcome of event was fatal with treatment including antibiotics, catecholamine, continuous dialysis, artificial respiration, blood transfusion etc.. The reporter classified the event as serious(death) and assessed that the event was related to BNT162b2. (There is a high possibility that phlegmonous developed from vaccination site.) The Duration of stay in hospital was from 22Nov2022 20:00 to 23Nov2022 23:43. On 22Nov2022, the patient experienced Rhabdomyolysis. The AE required visit to Emergency Room and Intensive Care Unit. ICU duration of stay was from 22Nov2022 23:10 to 23Nov2022 23:43. Treatment including antibiotics, catecholamine, continuous dialysis, artificial respiration, blood transfusion etc.. The reporter assessed that the causality between the event and BNT162b2 as unassessable. (There is a high possibility that phlegmonous developed from vaccination site.) On 22Nov2022, the patient experienced Platelets decreased, ICU Duration of stay w as from 22Nov2022 23:10 to 23Nov2022 23:43. treatment including antibiotics, catecholamine, continuous dialysis, artificial respiration, blood transfusion etc.. Date of Death was23Nov2022. The reporter classified the event as serious(death) and assessed that the causality between the event and BNT162b2 as unassessable (There is a high possibility that phlegmonous developed from vaccination site). The Duration of stay in hospital was from 22Nov2022 20:00 to 23Nov2022 23:43. On 22Nov2022, the patient experienced Disseminated intravascular coagulation. The Duration of stay in hospital was from 22Nov2022 20:00 to 23Nov2022 23:43. ICU Duration of stay was from 22Nov2022 23:10 to 23Nov2022 23:43. Teatment including antibiotics, catecholamine, continuous dialysis, artificial respiration, blood transfusion etc.. The reporter classified the event as serious (death) and assessed that the causality between the event and BNT162b2 as unassessable (There is a high possibility that phlegmonous developed from vaccination site). Autopsy was not performed due to Willingness of bereaved family. The course of the event was as follows: The patient had a past medical history of Postoperative of left breast cancer, post Lymph node excision and cellulitis of left arm. On 20Nov2022, the patient received the fifth dose of COVID-19 vac

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Narrative

cine to the left upper limb. On the 21Nov2022, the next day, she developed injection site redness, pain and swelling as well as malaise. On the 22Nov2022, the symptoms were aggravated, and she had lower extremities weakness of and movement difficulty. She presented to her local hospital and then presented to ER at our hospital at 20:00 on the 22nd. She had a clear consciousness, but had cyanosis peripheral with severe redness, oedema, and warmth of the left upper limb. Her CRP was 24 mg/dL, CK 1338 u/l, BUN 36.2 mg/dL, Cr 1.34 mg/dL, platelet count 7.2 x10 4/uL, Procalcitonin 44.53 and D-dimer 176ug/mL, showing DIC, sepsis from cellulitis and rhabdomyolysis. At 23:10, she entered ICU. She had purpura at the vaccination site on her left upper arm and redness spreading to the trunk. CV A line was secured, and fluid infusion of meropenem and RECOMODULIN Injection was initiated. The blood pressure began to decrease to the range of 80s. And thus, NAD and DOA were initiated. Acidosis progressed (BE-8) with Lactic acidosis at 10 mmol/L, and hence MEYLON was used. Since she did not respond to LASIX, at 04:00 on 23Nov2022, CHDF (continuous hemodiafiltration) was initiated. The level of consciousness gradually decreased. Her respiration was assisted with NPPV. At 04:00. on 23Nov2022, the patient's condition was aggravat

ed with Cr of 2.36 mg/dl, K 6.4 mmol/L, D-dimer 473 mg/l, platelet count 3.7 x10 4/uL, CK 6775 u/l and PT-INR 2.28. At 8:00 on 23Nov2022, she had respiration aggravated, and intubation was tried by the judgement that ventilator would be needed. Mask ventilation went well, but she had abnormal rigidity of mandible and neck and could not open her mouth at all even by muscle relaxant. She underwent urgent tracheostomy and was managed under artificial ventilator thereafter. From the clinical course, severe streptococcal infection was suspected, and VICCILLIN, DALACIN and TOGLOBULIN were also added. CHDF was continued, but the symptoms were aggravated so fast, and it was impossible to control K. On 23Nov2022, at 16:00, CK 46957 u/L, K 9.5 mmol/L, Hb6.6 g/dl, platelet 1.9 x 10 4/uL, Lactate(reported as Lac) 30mmol/L were noted. Blood pressure decreased started. BOSMIN was used, but she could not hold, and from 23Nov2022 23:29, she became in a state of CPA, thus cardiac massage, BOSMIN was administered, but spontaneous circulation could not be obtained, and she passed away at 23:43. From blood culture performed on 24Nov2022, Streptococcus was detected through Gram staining. On 29Nov2022, definitive diagnosis of Streptococcus dysgalactiae ssp equisiuilis, G group invasive streptococcal was made. During the course, blood

transfusion (RBC FFP), many drugs including infusion etc. were used. Abnormal rigidity was observed in the whole body.
Investigation Items: The patient lived with her husband at home. The patient was in state of ADL independent. The patient could swallow/ingest. On 21Nov2022, abnormalities was found. Situations of abnormalities found: pain, swelling and malaise in left upper limb (vaccination site). On the following day, 22Nov2022, the patient experienced difficulty in moving her body, and she visited a nearby medical institution. CRP high. The patient was referred to our hospital for suspected cellulitis of vaccination site.
Emergency service was not requested. The patient visited our hospital (Emergency Outpatient) accompanied by her family. The patient arrived at hospital at 20:00 on 22Nov2022.
Physical findings of the patient upon arrival: Oedema, strong hot feeling and haemorrhage subcutaneous in left upper limb. Strong redness in the left side of abdomen. Treatment details: Insertion of catheters into central vein and artery. Blood access catheter. Mechanical ventilation. CHDF (continuous hemodiafiltration). Antihypertensive (MEROPEN, Ampicillin and CLINDAMYCIN). Tracheostomy (7.5 tube). Nasogastric tube. NAD, AD, DOA, Midazolam, MEYLON, albumin, Gamma-globulin, FENTANYL, ROCURONIUM and many other inf

usion solutions, etc. Blood transfusion. Performed test including: Blood test (peripheral blood, biochemical, coagulation and blood gas), CT of chest through pelvis, Electrocardiogram, chest/abdominal Xp, blood culture, infection, COVID-19 and urine analysis. Autopsy imaging was not performed.
Consideration of and physician's comment on cause(s) of death (including judgement rationale): It was multi-organ failure (including rhabdomyolysis and DIC) due to severe invasive streptococcal infection, and its progression speed was very fast and was in a state that was beyond treatment limit.
Physician's consideration of causality between vaccination and death (including judgement rationale): Infection spread from vaccination site. A relation was considered that vaccination site was on the side of lymph node excision. Hemolytic streptococcus can have fast speed such as this (as reported), but if possible, physician wish that investigation should be conducted on its interaction with the vaccine or its relation with abnormal muscle stiffness, etc. (Blood collection sample and fungus have been conserved).

Follow-up (30Nov2022): This is a spontaneous follow-up report from the same contactable nurse updated information includes: lab (added blood culture), event (added bacteraemia and multi-organ failure), and clinical c

ourse.

Follow-up (14Dec2022): This is a spontaneous follow-up report from the same contactable nurse
Updated information: relevant medical history, lab data, suspect vaccine data (Lot number and Expiration Dat), reactions data (severe invasive streptococcal infection, platelets decreased, malaise, muscular weakness, mobility decreased , cyanosis, feeling hot, purpura, erythema, depressed level of consciousness, musculoskeletal stiffness, blood pressure decreased added as events; hospitalized of Rhabdomyolysis; Hospitalization end time of 'Disseminated intravascular coagulation' added; description of 'Vaccination site erythema, Vaccination site pain, Vaccination site swelling, Jaw joint rigid state of ' updated; Autopsy Done updated to no; Cause of Death added) and clinical course of the events.

Follow-up attempts are completed. No further information is expected.

5.AER Number: [redacted]

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Rhabdomyolysis	SERIOUS		-	
Hyperkalaemia	SERIOUS			
Disseminated intravascular coagulation	SERIOUS			
Blood lactic acid increased	SERIOUS			
Sepsis	SERIOUS			
Severe invasive streptococcal infection	SERIOUS			
Platelet count decreased	SERIOUS			
Bacteraemia	SERIOUS			
Multiple organ dysfunction syndrome	SERIOUS			
Vaccination site cellulitis	SERIOUS			
Streptococcal sepsis	SERIOUS			
Acute kidney injury	SERIOUS			
Endotracheal intubation complication	SERIOUS			
Depressed level of consciousness	SERIOUS			
Vaccination site pain	NONSERIOUS			
Vaccination site erythema	NONSERIOUS			
Vaccination site swelling	NONSERIOUS			
Vaccination site haemorrhage	NONSERIOUS			
Condition aggravated	NONSERIOUS			
Movement disorder	NONSERIOUS			
Joint stiffness	NONSERIOUS			
Malaise	NONSERIOUS			
Muscular weakness	NONSERIOUS			
Mobility decreased	NONSERIOUS			
Cyanosis	NONSERIOUS			
Feeling hot	NONSERIOUS			
Purpura	NONSERIOUS			
Erythema	NONSERIOUS			

5.AER Number: [redacted]

Adverse Event(s) PT	Event Seriousness
Musculoskeletal stiffness	NONSERIOUS
Blood pressure decreased	NONSERIOUS

Device Type Suspect	Device Type Conmed
NO DATA	

6.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	02-DEC-2022 - 02-DEC-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Angina pectoris			NO DATA	
PATIENT	Arthralgia			NO DATA	
PATIENT	Constipation			NO DATA	
PATIENT	Diabetes mellitus			NO DATA	For 40 years
PATIENT	Gastritis			NO DATA	
PATIENT	Hypertension			NO DATA	
PATIENT	Lung neoplasm malignant	---MAR-2022		NO DATA	Found with metastases to bone.
PATIENT	Metastases to bone			NO DATA	
PATIENT	Pleural effusion	14-NOV-2022		NO DATA	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Apnoea	
DEATH	PATIENT	Arrhythmia	
DEATH	PATIENT	Cerebral haemorrhage	
DEATH	PATIENT	Cerebral infarction	
DEATH	PATIENT	Dyspnoea exertional	
DEATH	PATIENT	Myocardial infarction	
DEATH	PATIENT	Pulmonary embolism	
DEATH	PATIENT	Respiratory arrest	
DEATH	PATIENT	Thrombosis	

Narrative

6.AER Number: [redacted]

Narrative
This is a spontaneous report received from a contactable reporter(s) (Physician) from Regulatory Authority. Regulatory number: [redacted](PMDA). An 82-year-old male patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY RTU FOR BA.4-5), on 02Dec2022 at 10:30 as dose 5 (booster), single (Lot number: GJ5751, Expiration Date: 31Jul2023) at the age of 82 years for covid-19 immunisation. The patient's relevant medical history included: "left lung cancer/ lung cancer" (unspecified if ongoing); "Pleural effusion" (unspecified if ongoing); "Diabetes mellitus" (unspecified if ongoing). The patient's concomitant medications were not reported. Vaccination history included: Covid-19 vaccine (1st single dose, MANUFACTURER UNKNOWN), for COVID-19 immunisation; Covid-19 vaccine (2nd single dose, MANUFACTURER UNKNOWN), for COVID-19 immunisation; Covid-19 vaccine (3rd single dose, MANUFACTURER UNKNOWN), for COVID-19 immunisation; Covid-19 vaccine (4th single dose, MANUFACTURER UNKNOWN), for COVID-19 immunisation. The following information was reported: DYSPNOEA EXERTIONAL (death) with onset 02Dec2022, outcome "fatal", described as "shortness of breath on exertion"; RESPIRATORY ARREST (death, medically significant) with onset 03Dec2022 at 09:20, outcome "fatal". The patient underwent the following laboratory tests and pro cedures: Body temperature: (02Dec2022) 36.5 Centigrade, notes: before vaccination. The patient date of death was 03Dec2022. Reported cause of death: "Respiratory arrest", "shortness of breath on exertion". No autopsy was performed. Clinical course: The patient was a 82-year and 1 months-old male. On 03Dec2022 at 09:20 (22 hours 50 minutes after vaccination), the patient experienced respiratory arrest. On 03Dec2022 (1 day after vaccination), the outcome of the event was fatal. The course of the event was as follows: at vaccination (02Dec2022), although the patient had shortness of breath on exertion, he was able to walk by himself. On the morning of the following day, the patient's family member found him in a state of respiratory arrest. The reporting physician classified the event as serious(death) and the causality between the event and BNT162B2 as unassessable. Other possible cause of the event such as any other diseases was lung cancer. The reporting physician commented as follows: The patient was considered to have 1-2 months to live, but his condition suddenly changed on the following day of the coronavirus vaccination. The relation was suspected, but his family member did not wish autopsy. Follow-up (19Dec2022): This is a spontaneous follow-up report from the same contactable physician, response of follow up letter. New information included as per source verbatim: Updated information: Patient's initial updated; Historical Vaccine of dose 4 (CMT, note) updated, adverse events of dose 4 was added; Medical histories (Arthralgia, Angina pectoris, Hypertension, Gastritis, metastases to bone, Constipation) added. Lab data (Pleural effusion biopsy) added; Detail of product (Route of administration) was updated; Concomitant drugs added. Description and onset time of event "Respiratory arrest" and Cause of death was updated. New events and Causes of Death(Apnoea, Thrombosis, Myocardial infarction, Cerebral infarction, Pulmonary embolism, Cerebral haemorrhage, Arrhythmia) were added; Additional information: On 01Aug2022 at 15:30, the patient received the fourth single dose of BNT162b2 (COMIRNATY, Solution for injection, Lot number FR1790, Expiration date 30Nov2022) intramuscular in left shoulder for COVID-19 immunisation. After the 4th vaccination, the patient developed pyrexia of 38 degrees Centigrade on the following day. The patient received the fifth single dose of BNT162b2, intramuscular in left shoulder for COVID-19 immunisation. Weakened immune system If the reason for a booster dose (3rd dose) is a weakened immune system, please select one of the conditions below: Current or recent cancer (includ ing blood cancers such as Hodgkin's disease, leukemias, and myelomas) The patient did not receive any other vaccines within 4 weeks prior to the COVID vaccine. Concomitant drugs as follows: LOXONIN 60 mg 2T 2x for left shoulder pain by oral, start on 01Dec2022. TAKECAB 20 mg 1T 1X for gastritis by oral, start on 24Mar2022. AMLODIPINE OD 2.5 mg 1T 1x for Hypertension by oral, start on 24Mar2022. JANUVIA 50 mg 1T for Diabetes mellitus by oral, start on 24Mar2022. ISOSORBIDE MONONITRATE 20 mg 2T 2x for Angina pectoris by oral, start on 24Mar2022. MAGNESIUM OXIDE 250 mg 2T 2x for Constipation by oral, start on 24Mar2022. Patient's medical histories including left lung cancer, onset date was on Mar2022 and found with metastases to bone. Pleural effusion onset date was on 14Nov2022. Diabetes

6.AER Number: [redacted]

Narrative
mellitus was for 40 years. Relevant tests including pleural effusion biopsy on 24Nov2022, result was cancer cell. On 03Dec2022 at 09:15, the patient experienced Apnoea. On 03Dec2022, the outcome of event was fatal without treatment. The reporting physician classified the event as serious(death) and assessed that the causality between the event and BNT162b2 as unassessable. The autopsy was not performed. Intention of the patient's family. Abnormalities before/after inoculation was none. Time and date of abnormaliti es found was at 09:15 on 03Dec2022. The patient was found stopped breathing. The emergency service was not performed. Time and date of confirmation of death was at 10:05 on 03Dec2022. The autopsy imaging was not performed. Consideration of and physician's comment on cause(s) of death (including judgement rationale) as follows: There is a possibility that acute thrombosis (myocardial infarction, cerebral infarction or pulmonary embolism) became the cause of death. Cerebral haemorrhage, lethal arrhythmia, etc. can be considered as other cause of death. Physician's consideration of causality between vaccination and death (including judgement rationale) as follows: A possibility can be considered that lethal thrombosis was caused by the vaccination, but causality is unassessable.

Adverse Event(s) PT	Event Seriousness
Respiratory arrest	SERIOUS
Dyspnoea exertional	SERIOUS
Apnoea	SERIOUS
Thrombosis	SERIOUS
Myocardial infarction	SERIOUS
Cerebral infarction	SERIOUS
Pulmonary embolism	SERIOUS
Cerebral haemorrhage	SERIOUS
Arrhythmia	SERIOUS

Concomitant Drug(s)	Therapy Date(s)	Route of Admin
AMLODIPINE	24-MAR-2022 -	ORAL
ISOSORBIDE MONONITRATE	24-MAR-2022 -	ORAL
LOXOPROFEN SODIUM	01-DEC-2022 -	ORAL
MAGNESIUM OXIDE	24-MAR-2022 -	ORAL
SITAGLIPTIN PHOSPHATE	24-MAR-2022 -	ORAL
VONOPRAZAN FUMARATE	24-MAR-2022 -	ORAL

Device Type Suspect	Device Type Conmed
NO DATA	NO DATA

7.AER Number: [redacted]

Suspect Drug(s)	Indication(s) PT	Therapy Dates
BNT162B2, BNT162B2 OMI BA.4-5	COVID-19 immunisation	07-DEC-2022 - 07-DEC-2022

Medical History

Patient/Parent Indicator	Coded Condition	Start Date	Stop Date	Ongoing	Notes
PATIENT	Cerebral infarction	09-JUN-2022		NO DATA	hospitalized
PATIENT	Hypertension			NO DATA	

Patient Notes

Cause of Death/Autopsy

Type	Patient/Parent Indicator	Coded Condition	Notes
DEATH	PATIENT	Agonal respiration	
DEATH	PATIENT	Cerebral haemorrhage	
DEATH	PATIENT	Cerebral infarction	
DEATH	PATIENT	Cerebral ventricular rupture	
DEATH	PATIENT	Hydrocephalus	
DEATH	PATIENT	Hypertension	
DEATH	PATIENT	Thalamus haemorrhage	

Narrative

This is a spontaneous report received from a contactable reporter(s) (Physician) from Regulatory Authority. Regulatory number: [redacted] (PMDA).

A 66-year-old female patient received BNT162b2, BNT162b2 omi ba.4-5 (COMIRNATY RTU FOR BA.4-5), on 07Dec2022 at 10:00 as dose 5 (booster), single (Lot number: Unknown) at the age of 66 years for covid-19 immunisation. The patient's relevant medical history included: "cerebral infarction (left frontal lobe deep white matter infarction)", start date: 09Jun2022 (unspecified if ongoing), notes: hospitalized; "hypertension" (unspecified if ongoing). The patient took concomitant medications. Vaccination history included: Covid-19 vaccine (Primary immunization series complete, MANUFACTURER UNKNOWN), for COVID-19 immunisation; Covid-19 vaccine (DOSE 3 (BOOSTER), SINGLE, MANUFACTURER UNKNOWN), for COVID-19 immunisation; Covid-19 vaccine (DOSE 4 (BOOSTER), SINGLE, MANUFACTURER UNKNOWN), for COVID-19 immunisation. The following information was reported: BLOOD PRESSURE DECREASED (non-serious) with onset 07Dec2022, outcome "unknown"; MYDRIASIS (non-serious) with onset 07Dec2022, outcome "unknown", described as "pupils dilated"; FALL (non-serious), CONTUSION (non-serious) all with onset 07Dec2022 at 12:00, outcome "unknown" and all described as "lied on a sofa from which she fe

ll off once and bruised the side of the head"; DEPRESSED LEVEL OF CONSCIOUSNESS (medically significant) with onset 07Dec2022 at 15:15, outcome "unknown", described as "JCS 200"; AGONAL RESPIRATION (death, medically significant) with onset 07Dec2022 at 15:15, outcome "fatal"; HYPERTENSION (death) with onset 07Dec2022 at 15:15, outcome "fatal", described as "blood pressure of 172/133 mmHg/Hypertension"; PYREXIA (non-serious) with onset 07Dec2022 at 15:15, outcome "unknown", described as "body temperature of 40.7 degrees Centigrade"; CEREBRAL VENTRICULAR RUPTURE (death, medically significant) with onset 07Dec2022 at 15:15, outcome "fatal", described as "cerebral intraventricular rupture"; ALTERED STATE OF CONSCIOUSNESS (medically significant) with onset 07Dec2022 at 15:15, outcome "unknown", described as "consciousness disturbed"; HYDROCEPHALUS (death, medically significant) with onset 07Dec2022 at 15:15, outcome "fatal", described as "obstructive hydrocephalus"; THALAMUS HAEMORRHAGE (death, medically significant) with onset 07Dec2022 at 15:15, outcome "fatal", described as "right thalamus haemorrhage/thalamus haemorrhage"; CEREBRAL INFARCTION (death, medically significant), outcome "fatal"; CEREBRAL HAEMORRHAGE (death, medically significant), outcome "fatal". The event "consciousness disturbed" required emergency

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Narrative

room visit. The patient underwent the following laboratory tests and procedures: Blood pressure measurement: (07Dec2022) 172/133 mmHg; (07Dec2022) decreased; Body temperature: (07Dec2022) 40.7 Centigrade; Coma scale: (07Dec2022) 200; Computerised tomogram head: (07Dec2022) a state of right thalamus haemorrhage, notes: cerebral intraventricular rupture, and obstructive hydrocephalus. The patient date of death was 07Dec2022. Reported cause of death: "right thalamus haemorrhage/thalamus haemorrhage", "cerebral intraventricular rupture", "obstructive hydrocephalus", "agonal respiration", "cerebral infarction", "blood pressure of 172/133 mmHg/Hypertension", "Cerebral haemorrhage". It was not reported if an autopsy was performed.

Clinical course of the events: The patient was a 66-year and 11-month-old female. On 07Dec2022 at around 10:00, the patient received the fifth single dose of BNT162b2 (COMIRNATY, Solution for injection, Lot number Unknown). On 07Dec2022 at 15:15(about 5 hours 15 minutes after the vaccination), the patient experienced events. The course of the event was as follows: On 09Jun2022, the patient developed cerebral infarction (left frontal lobe deep white matter infarction) and was hospitalized. The patient underwent rehabilitation, and after the discharge from the hospital, the patient was orall

y receiving anticoagulant drugs. At around 10:00 on 07Dec2022, the patient received the vaccination of a novel coronavirus vaccine (the 5th dose; manufactured by Pfizer) at another hospital/clinic and returned home at around 10:30. After having lunch at 12:00, the patient lied on a sofa from which she fell off once and bruised the side of the head. At 12:40, when her live-in husband went outside, there was nothing unusual about her. At 15:15, when her husband came back home, as consciousness disturbed was noted, the patient was transferred by ambulance to the reporting hospital. Her consciousness level at the time of presentation to the hospital was Japan Coma Scale (reported as JCS) 200 with a body temperature of 40.7 degrees Centigrade and blood pressure of 172/133 mmHg. Head Computerised tomogram(CT) that was immediately taken confirmed a state of right thalamus haemorrhage, cerebral intraventricular rupture, and obstructive hydrocephalus. The patient ended up in a state of difficulty with lifesaving, presenting with blood pressure decreased, pupils dilated, and agonal respiration in a short period of time after taking a CT. At 16:43, the patient's death was confirmed in the presence of her husband. Other possible causes of the event such as any other diseases were the patient had a medical history of hyperte

nsion. In addition, due to status post cerebral infarction, the patient was orally receiving antiplatelet drug.

The reporting physician classified the event as serious(death) and assessed that the causality between the event and BNT162b2 as unassessable.

The reporting physician commented as follows: Since the patient received the vaccination at another hospital/clinic, details at the time of the vaccination are unknown. The name of drug product was also unknown because the patient received the vaccination at another facility. The patient had a medical history of cerebral infarction and hypertension. While a causality with the vaccination is unknown, given that this was a case in which the patient developed thalamus haemorrhage several hours after the vaccination and died, this was reported.

The information on the batch/lot number for BNT162b2, BNT162b2 omi ba.4-5 has been requested and will be submitted if and when received.

Follow-up (13Dec2022): This is a spontaneous follow-up report from the same contactable physician via a Pfizer colleague. Updated information: New event "Cerebral haemorrhage" added; Cause of death "Cerebral haemorrhage" added; unknown if autopsy was done.

The information on the batch/lot number for BNT162b2, BNT162b2 omi ba.4-5 has been requested and will be submitted if and

when received.

Adverse Event(s) PT	Event Seriousness	Concomitant Drug(s)	Therapy Date(s)	Route of Admin
Thalamus haemorrhage	SERIOUS		-	
Cerebral ventricular rupture	SERIOUS			
Hydrocephalus	SERIOUS			
Agonal respiration	SERIOUS			
Cerebral infarction	SERIOUS			
Hypertension	SERIOUS			

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Adverse Event(s) PT	Event Seriousness
Cerebral haemorrhage	SERIOUS
Altered state of consciousness	SERIOUS
Depressed level of consciousness	SERIOUS
Fall	NONSERIOUS
Contusion	NONSERIOUS
Blood pressure decreased	NONSERIOUS
Mydriasis	NONSERIOUS
Pyrexia	NONSERIOUS

Device Type Suspect	Device Type Conmed
NO DATA	