From: "Menschik, David" <[redacted]>
To: "Nair, Narayan" [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Thu, 26 Oct 2023 18:28:13 -0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-update98forOS_9921.docx

We provided language to CDC for this 6-month safety review of mRNA vaccines as follows:

"Aside from previously described EB data mining limitations,[22] an additional limitation specific to the COVID vaccine era is that since most reports received involve COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID-19 vaccine reports contributing substantially to the comparator group, particularly if there is a class-effect (e.g., if both mRNA COVID-19 vaccines are associated with the same adverse event)."

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

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

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

Hi Hannah,

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

Thanks,
David

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

Sounds like a plan!

Hannah

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

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

Thanks,
David

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

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

Hannah

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

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

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

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

Thanks so very much for your continued engagement on this,
Hannah

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

Hi Hannah,

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

Best,
David

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

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

Hannah

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

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

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

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

Hi Hannah,

I agree that these are not substantive changes and will send you the authorship agreement statement shortly.
Thanks so much to you and other teammates for all the amazing work on this very impressive paper!

Congratulations on this key milestone!
David

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

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

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

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

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

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

Thanks,
David

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

Dear co-authors,

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

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

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

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

All the very best,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

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

From: "Menschik, David" [redacted]
To: "Baer, Bethany" [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke
Date: Wed, 01 Mar 2023 18:11:55 -0000
Importance: Normal
Inline-Images: image001.png; image002.png; image003.jpg; image004.jpg; image005.jpg; image006.jpg; image007.jpg

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Sounds good – thanks! 😊

From: Baer, Bethany [redacted]
Sent: Wednesday, March 1, 2023 1:10 PM
To: Menschik, David [redacted]
Subject: FW: Data Mining for Pfizer Bivalent: Ischemic Stroke

Hi David,
I am inclined to direct this specific question to Kosal and the Commonwealth team as I think they would be better at assessing all the different possible approaches to this.

I had written that first line and saw your email come through. I will respond to the string and suggest Chris email Kosal directly with us cc'ed.
Thanks!
Bethany

From: Jason, Christopher [redacted]
Sent: Wednesday, March 1, 2023 12:28 PM
To: Baer, Bethany [redacted] Menschik, David [redacted]
Cc: Bazel, Samaneh [redacted]
Subject: FW: Data Mining for Pfizer Bivalent: Ischemic Stroke

Hi Bethan and David

Quick question See email below. IS it possible to track EB05s for only certain subgroups for Pfizer monovalent and bivalent? Under the signals tab I saw the monthly tracker but I do not see a way to limit the data? Are there runs in datamining that might work? Any help would be appreciated. What I am looking for is the change in the EB05 over time by month for the PT "Ischaemic Stroke" with monovalent and bivalent Pfizer covid vaccine?

Sincerely,
Chris

From: Nair, Narayan [redacted]
Sent: Wednesday, March 1, 2023 6:51 AM
To: Thompson, Deborah [redacted] Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted]; Niu, Manette [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke

Dear Chris and Sam,
We received some follow up questions on this. Can we run the EB05 for ages 65 and older and serious? Also, my hypothesis is that some of this increase is due to stimulated reporting. The finding of a possible increase in ischemic stroke was made public on Jan 13. By my count, 31 reports came in after that date. Can you provide the EB05 for ischemic stroke prior to the public announcement and after. Perhaps give the monthly EB05's for Oct, Nov, Dec. for ages 65 and older and serious? Thanks

Narayan

From: Thompson, Deborah [redacted]
Sent: Tuesday, February 28, 2023 11:14 AM
To: Nair, Narayan [redacted] Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke

Thanks, Narayan!

Best,

Deb

From: Nair, Narayan [redacted]
Sent: Tuesday, February 28, 2023 11:12 AM
To: Thompson, Deborah [redacted] Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke

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

Please don't share the slides.

Narayan

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

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

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

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

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

Among the 41 US reports:

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

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

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

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

Thanks,

Deb

Deb Thompson, MD, MSPH, FACPM
Medical Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: "Menschik, David" [redacted]
To: "Baer, Bethany" [redacted]
Cc: "Thompson, Deborah" [redacted], "Welsh, Kerry" [redacted], "Alimchandani, Meghna" [redacted]
Bcc: "Menschik, David" [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Mon, 27 Sep 2021 11:59:18 -0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-2021-09-26_CLEAN.docx; Reactogenicity_and_Adverse_Events_duringSafety_Monitoring_of_mRNA_Vaccines_6mo_blackline.docx

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Hi Bethany,

Attached please find the revised version of the mRNA vaccine review paper that needs re-clearance. The second attachment is a black-line version I created to show differences with the prior version that was cleared.

I'm ok with the data mining portions (with one exception below) which was the focus of our contribution to this paper. Once you give the ok, we can begin the clearance process here. CDC says it's already cleared there and requesting expedited clearance here so I'm copying Deb and Kerry who cleared this last time as a heads up.

Thanks,
David

From: Menschik, David
Sent: Monday, September 27, 2021 5:54 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,

I noticed that the statement, "EB data mining has multiple limitations,[22] including that…" is missing reference #23 as discussed (i.e., should reference both 22 and 23) – can you please revise accordingly and send us back a clean copy?

Thanks,
David

From: "Menschik, David" [redacted]
To: "Baer, Bethany" [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Mon, 27 Sep 2021 09:54:59 -0000
Importance: High
Attachments: mRNA_6mo_safety_review-2021-09-26_CLEAN.docx

Bethany,

Can you please review this and advise when you are comfortable beginning the clearance process?

Thanks,
David

From: Menschik, David
Sent: Monday, September 27, 2021 5:54 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,

I noticed that the statement, "EB data mining has multiple limitations,[22] including that…" is missing reference #23 as discussed (i.e., should reference both 22 and 23) – can you please revise accordingly and send us back a clean copy?

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, September 26, 2021 9:52 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks so much for all of your work on this manuscript overall and again for finding that error in Table 3.
Please see attached clean copy for Table 3 (and associated text) corrected, and the EB language back to what you had suggested.
It has been cleared from CDC perspective- please let me know when cleared from FDA (or if there are additional edits/steps along the way to make this happen!)

Thanks so very much,
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Thursday, September 23, 2021 2:31 PM

To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thank you so so much. This is a huge mistake on my part. Table 4 is correct, but Table 3 is not- I need to get the dose denominators and recalculate those.
Thanks so very much for your attention to detail here.
Will send along an updated copy when I have it ready for you review
Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 2:19 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,

On a different note, there may be a problem with Table 3 (and may apply to Table 4 too)
Looks like the reporting rate for each of the subgroups stratified by sex or age uses the *total* number of doses administered as the denominator instead of the number of doses administered for that specific subgroup. So for example, from Table 3 we can say that for individuals aged 16-17 who received BNT162b2 the reporting rate is 6 deaths per million doses of Pfizer administered to the entire population. Since this statistic can be heavily influenced by the age distribution of the vaccinated population, output could be misleading. In this 16-17 year-old example, It may be better to use a denominator of Pfizer doses administered to 16-17 year-old individuals, instead of the entire population.

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, September 23, 2021 8:52 AM
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 so much. Thanks for your edits. I am happy to modify to your version.
I did just receive comments from CDC's office of science, so let me go ahead and look through those and send you a new version with the data mining and their changes too so that the latest goes through FDA clearance.
Thanks so much,

Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 8:22 AM
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

Good morning Hannah,

There are substantive changes and this will ultimately have to go through clearance at FDA.

Regarding the limitations section, previously accepted version said:

> EB data mining has multiple limitations[22] including that an absence of a disproportionality alert does not rule out presence of a safety problem. Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be muted by COVID-19 vaccine reports contributing substantially to the comparator group, particularly if both mRNA COVID-19 vaccines are associated with the same adverse event.

New version says:

> A limitation of EB data mining[22] is low sensitivity; that is, absence of a disproportionality alert does not rule out a possible adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

This is inadequate since there are many limitations to data mining and paper is only pointing out 'low sensitivity' which is not accurate. We recommend revising to:

> EB data mining has multiple limitations[22,23] including that the absence of a disproportionality alert does not rule out a possible corresponding adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

OK with the other data mining parts (including slimming down the results section) and deferring on non-data mining parts of the paper (for which we were not involved).

Please let us know if the proposed revision is acceptable and if so, please provide an updated clean version for our clearance process.

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 22, 2021 2:36 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 and Bethany,

I hope all is well. Please see attached for a new version of the vaccine safety 6 month manuscript. A few notes:

- One of the comments in CDC clearance was about the analysis and framing of reports of deaths in the discussion, so part of what took so long to revise and edit was that we opted to significantly change how death reports appear. (Table 4, specifically, is new and compared reports of death from a pre-print paper by CDC authors.)
- You'll also notice that we've taken out some of the details about EB mining in the results. **I hope this is okay with both of you**- as you know, there is a ton of data in this paper, and we left the information that summarized the

findings, without going into details that didn't necessarily add to the overall messages of the manuscript- welcome your thoughts about this. You'll see that I've kept everything in the methods/discussion as well as the references that you suggested.

There have been significant edits at this point, and I certainly defer to you about whether the paper should go back into formal FDA clearance. About my ideal timeline- the draft is currently back in CDC clearance- I'm hoping that it is cleared in the next few days, and then I can begin to prep for manuscript submission in the next week or so.

Let me know if it would be helpful to have a short call to go through some of these changes in more detail.

Thanks so very much,
Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 9:29 AM
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!

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:56 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

This look great- I've kept that reference in and kept all of your language.
So appreciate your work on this- and will forward on a 'clean' and 'modified' version ASAP!
All the best,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 8:46 AM
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

Hi Hannah,

Thanks! I certainly understand the desire to simplify and be economical with words. I've attached a slightly revised version which Bethany has not had a chance to review yet and copying her here in case she has further thoughts.
I think it is important to make reference to the Martin article (reference #22) which mentions several important VAERS data mining limitations so the reader does not overestimate what data mining can do (see attached for suggested placement). I changed 'driven towards the null" to "muted" and removed "if there is a class effect" and removed the immediately following parenthesis and "e.g.," to highlight main concern of potentially missing a PT that is associated with both mRNA vaccines.

Please see attached and let me know what you think.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:01 AM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks and sorry for the lack of response. I had rewritten with a similar tightening – additionally, I had deleted "particularly if there is a class-effect" or do you think that clarification is needed?
Senior authors on our team are looking through it today, so hopefully will be ready for re-clearance later this week.
Will forward on as soon as possible.
Thanks a million,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 7:59 AM
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,

Hopefully no issues with the new language provided yesterday though if so please advise.
Also wondering If you have a general estimate on when this paper will be ready for re-clearance?

Thanks,
David

From: Menschik, David
Sent: Tuesday, September 14, 2021 5:17 AM
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,

To simplify, the previously language could be replaced with:

> "Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID vaccine reports contributing

substantially to the comparator group, particularly if there is a class-effect (e.g., if multiple COVID vaccines are associated with the same adverse event)."

Does this help?

Thanks,
David

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 3:08 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

Hmm… you should have seen the earlier iterations of this! ☺ Yes, it should say "disproportionality" -autocorrect strikes again! Thanks for correcting that…
Our goal was to simplify as much as possible while not losing key concepts and this is where we landed after working the sentence over…
I think you've got the main point that if the comparison group is enriched with so many mRNA COVID-vaccine reports, that it becomes very difficult to exceed the EB05>2 alert threshold even for an adverse event that may be associated with mRNA vaccines – thus data mining has blind spots and this is why it's so good to have so many complimentary vaccine safety surveillance systems (e.g., VSD) that can cover different blind spots of other systems…
Happy to have a phone call if helpful to explain the importance of including specific words or anything else…

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To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

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Hi David,
Certainly will pass along the draft when ready for clearance at FDA!

In looking the additional sentence over in more detail, it seems pretty technical. If I'm understanding correctly, you're saying that the sheer volume of COVID-19 vaccine reports basically washes out the possibility of finding disproportionality (I think it should say disproportionality instead of disproportionately right?)

Do you think you can simplify the sentence so it would be understandable for the average clinician reader?

Hannah

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Cc: Baer, Bethany (FDA/CBER) [redacted]
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Thank you Hannah for all your efforts. Once you advise that paper is ready to clear at FDA, will be very helpful, if possible, to have a version with indication of where specific changes were made from prior cleared version, so that we can do our best to optimize time to re-clear here…

Wishing you an enjoyable weekend,
David

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Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Thank you David and Bethany!

Hannah

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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,
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Thanks so very much for your continued engagement on this,
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Hi Hannah,

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

Best,

David

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To: Baer, Bethany [redacted]
Cc: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

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

Hannah

From: Baer, Bethany [redacted]
Sent: Thursday, August 5, 2021 2:44 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Menschik, David (FDA/CBER) [redacted]
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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

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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

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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

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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: "Day, Brendan" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Thu, 23 Sep 2021 18:20:19 -0000
Importance: Normal

Thanks for the great catch which I'll pass on to CDC…

From: Day, Brendan [redacted]
Sent: Thursday, September 23, 2021 1:52 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Ok, got it. Thanks.

Also…

I know I'm not a reviewer for the mRNA vaccine manuscript, but I happened to notice a problem with Table 3. The reporting rate for each of the subgroups stratified by sex or age uses the *total* number of doses administered as the denominator instead of the number of doses administered for that specific subgroup. So for example, from Table 3 we can say that for individuals aged 16-17 who received BNT162b2 the reporting rate is 6 deaths per million doses of Pfizer administered to the entire population. Since this statistic can be heavily influenced by the age distribution of the vaccinated population I'm not sure how useful it is to say this. It may be more meaningful (and maybe less misleading) to use a denominator of Pfizer doses administered to 16-17 year old individuals, instead of the entire population. Lastly, I can't tell if they calculated reporting rates similarly in Table 4, but if so, then they should consider using denominators specific to each age subgroup there as well.

Brendan

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 1:47 PM
To: Day, Brendan [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Yes, we can ask them for anything we want using the attached request form.

Current CDC POCs are:
Black, Carla (CDC/DDID/NCIRD/ISD) [redacted]
Lee, Florence (CDC) [redacted]

Suggest copying them and me on the request.

Thanks,
David

From: Day, Brendan [redacted]
Sent: Thursday, September 23, 2021 1:34 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,

Based on Table 4 data, it looks like CDC has dose administration data stratified by the following age groups:
16-24
25-34
35-44
34-54
55-64
65-74
75-85
85+

I didn't see administration data stratified in these specific age groups in our Teams SCV2 folder. Do you know if we're able to ask CDC for specific age group administration data?

Brendan

From: Menschik, David [redacted]
Sent: Wednesday, September 22, 2021 2:43 PM
To: Day, Brendan [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Brendan,

Please do not share this but wanted to share with you, for the purposes of potential harmonization with CDC, this mRNA vaccine manuscript (pre-clearance draft) with an expanded section on death reports. I haven't reviewed this yet.

David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 22, 2021 2:36 PM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

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 and Bethany,

I hope all is well. Please see attached for a new version of the vaccine safety 6 month manuscript. A few notes:

- One of the comments in CDC clearance was about the analysis and framing of reports of deaths in the discussion, so part of what took so long to revise and edit was that we opted to significantly change how death reports appear. (Table 4, specifically, is new and compared reports of death from a pre-print paper by CDC authors.)
- You'll also notice that we've taken out some of the details about EB mining in the results. **I hope this is okay with both of you**- as you know, there is a ton of data in this paper, and we left the information that summarized the findings, without going into details that didn't necessarily add to the overall messages of the manuscript- welcome your thoughts about this. You'll see that I've kept everything in the methods/discussion as well as the references that you suggested.

There have been significant edits at this point, and I certainly defer to you about whether the paper should go back into formal FDA clearance. About my ideal timeline- the draft is currently back in CDC clearance- I'm hoping that it is cleared in

the next few days, and then I can begin to prep for manuscript submission in the next week or so.

Let me know if it would be helpful to have a short call to go through some of these changes in more detail.

Thanks so very much,
Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 9:29 AM
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!

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:56 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

This look great- I've kept that reference in and kept all of your language.
So appreciate your work on this- and will forward on a 'clean' and 'modified' version ASAP!
All the best,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 8:46 AM
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

Hi Hannah,

Thanks! I certainly understand the desire to simplify and be economical with words. I've attached a slightly revised version which Bethany has not had a chance to review yet and copying her here in case she has further thoughts.
I think it is important to make reference to the Martin article (reference #22) which mentions several important VAERS data mining limitations so the reader does not overestimate what data mining can do (see attached for suggested placement). I changed 'driven towards the null" to "muted" and removed "if there is a class effect" and removed the immediately following parenthesis and "e.g.," to highlight main concern of potentially missing a PT that is associated with both mRNA vaccines.

Please see attached and let me know what you think.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:01 AM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks and sorry for the lack of response. I had rewritten with a similar tightening – additionally, I had deleted "particularly if there is a class-effect" or do you think that clarification is needed?
Senior authors on our team are looking through it today, so hopefully will be ready for re-clearance later this week.
Will forward on as soon as possible.
Thanks a million,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 7:59 AM
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,

Hopefully no issues with the new language provided yesterday though if so please advise.
Also wondering If you have a general estimate on when this paper will be ready for re-clearance?

Thanks,
David

From: Menschik, David
Sent: Tuesday, September 14, 2021 5:17 AM
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,

To simplify, the previously language could be replaced with:

> "Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID vaccine reports contributing substantially to the comparator group, particularly if there is a class-effect (e.g., if multiple COVID vaccines are associated with the same adverse event)."

Does this help?

Thanks,
David

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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!

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Congratulations on this key milestone!
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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: "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
Date: Mon, 06 Dec 2021 10:55:13 -0000
Importance: Normal

Yes for me, thank you

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, December 05, 2021 6:34 PM
To: Menschik, David [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks very much David and Bethany- and for speaking on the phone about this last week.
We'd still like you acknowledge all of your work on this project—
Can we move your names to the acknowledgements (along with Jane Baumblatt, Deborah Thompson, Kerry Welsh, Narayan, Nair, Kosal Nguon who were weren't planning to remove?)

Thanks so very much and all of the best,
Hannah

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

Hi Hannah,

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

Best,
David and Bethany

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

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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If you need to retrieve password details, please go to: [redacted]

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

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

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

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

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

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- Signed consent for use of cited personal communications
- Signed patient's consent and permission to publish (if not already submitted)

Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Menschik, David (FDA/CBER)" [redacted]
Cc: "Baer, Bethany (FDA/CBER)" [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Mon, 6 Dec 2021 20:41:23 +0000
Importance: Normal

OK got it. Thank you both- and perhaps we'll work together again in the future!

Hannah

From: Menschik, David [redacted]
Sent: Monday, December 6, 2021 1:08 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Baer, Bethany (FDA/CBER) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks Hannah for your gracious offer. I feel the same as Bethany regarding it being most appropriate for me to be removed from authorship and thanks for including me in the acknowledgments.

Best,
David

From: Baer, Bethany [redacted]
Sent: Monday, December 06, 2021 12:26 PM
To: Rosenblum, Hannah (CDC) [redacted]
Cc: Menschik, David [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks, Hannah. I think it would be most appropriate for me to be removed from authorship. I appreciate the alternative offer, but I think the approach of only being included in the acknowledgements sounds best for this situation.
Thanks,
Bethany

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Monday, December 6, 2021 11:20 AM
To: Baer, Bethany [redacted]; Menschik, David [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks David and Bethany. I realize in the shuffle of writing over the weekend, I meant to also include in my note—

Since this is VAERS data and you contributed to conceptualization/revising/editing, etc., we are more than happy to keep you both included as authors (but of course it is entirely up to you! and no pressure at all)- just wanted to make sure I did offer.
All the best,
Hannah

From: Baer, Bethany [redacted]
Sent: Monday, December 6, 2021 7:16 AM
To: Menschik, David (FDA/CBER) [redacted]; Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Shay, David (CDC/DDID/NCIRD/ID) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Yes for me as well. Thank you, Hannah.

Bethany

From: Menschik, David [redacted]
Sent: Monday, December 6, 2021 5:55 AM
To: Rosenblum, Hannah (CDC) [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Yes for me, thank you

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, December 05, 2021 6:34 PM
To: Menschik, David [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks very much David and Bethany- and for speaking on the phone about this last week.
We'd still like you acknowledge all of your work on this project—
Can we move your names to the acknowledgements (along with Jane Baumblatt, Deborah Thompson, Kerry Welsh, Narayan, Nair, Kosal Nguon who were weren't planning to remove?)

Thanks so very much and all of the best,
Hannah

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

Hi Hannah,

Bethany and I have reviewed the comments from the Lancet ID Reviewers, and we agree with Reviewer #5's comment that disproportionality analysis is extremely limited when the background database has such a high proportion of reports

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

Best,
David and Bethany

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

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

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- Signed consent for use of cited personal communications
- Signed patient's consent and permission to publish (if not already submitted)

Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Baer, Bethany" [redacted]
To: "Menschik, David" [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Thu, 2 Dec 2021 15:10:49 +0000
Importance: Normal
Attachments: LancetID_comments_responses.docx
Inline-Images: image001.png

Hi David,
In case it is helpful, I have attached the reviewers' comments documents with the sections related to FDA and data mining highlighted in yellow. They are on pages 1, 4, 5, and 6. I took a little time getting back to you so that I could reread through the whole comments document again and look for any other sections that might directly relate to us. I also saw that Hannah sent us a readable version of the track-change manuscript. I looked through that and didn't see any changes that related to us.

Thanks for talking this morning. It is very helpful that we are on the same page regarding this. Based on our discussion, here is a proposed draft response to CDC:

We 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 is primarily the vaccine of interest. We acknowledged this in the limitations and understand that there is a bias toward the null when using our data mining methods in the 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. The disproportionality analysis was a very minor part of the analysis and did not affect the majority of the manuscript. As the disproportionality analysis was the only aspect of this paper that FDA was involved in, it would be most appropriate to remove the FDA employees, David Menschik and Bethany Baer, from authorship on the paper.

Thank you for discussing this with Narayan, Meghna, and Craig.

Thanks,
Bethany

From: Menschik, David [redacted]
Sent: Thursday, December 2, 2021 8:53 AM
To: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Gotcha. I haven't read it yet. I'm free to talk before 10a if helpful – then stuck in many meetings through the afternoon…

From: Baer, Bethany [redacted]
Sent: Thursday, December 02, 2021 8:51 AM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Hi David,
I can open the second document but not the first. I get the same message that you do for the first, but the second document has the reviewers' comments. I have some significant concerns and I think it is going to require some discussion on our end.
Bethany

From: Menschik, David [redacted]
Sent: Thursday, December 2, 2021 8:49 AM
To: Baer, Bethany [redacted]
Subject: FW: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Hi Bethany,

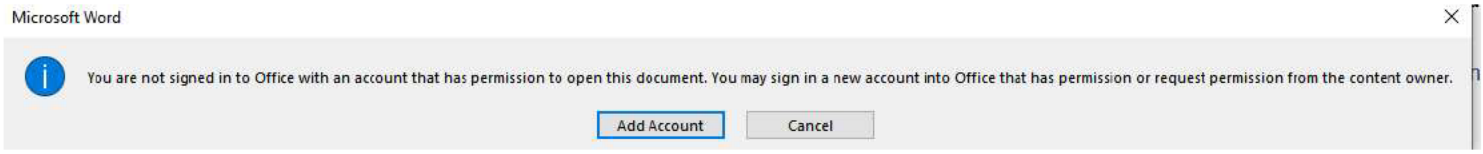
Would you be able to take first crack at this once able to access?

Thanks,
David

From: Menschik, David
Sent: Thursday, December 02, 2021 8:45 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Hi Hannah,

I cannot open the document as I get the following error:



Please advise and also please note that I'm working on a number of time sensitive tasks and out of the office tomorrow after 11:30 so likely will need more time unless straightforward...

Best,
David

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

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

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

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

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

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

All the very best,
Hannah

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

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

Dear Dr. Rosenblum,

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

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

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

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

Editorial points - IMPORTANT:

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

Authorship and reporting guidelines:

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

http://www.thelancet.com/pb/assets/raw/Lancet/authors/Rctguidelines.pdf
https://thelancet.com/pb/assets/raw/Lancet/authors/metaguidelines.pdf

Title/summary:

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

Methods:

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

Results:

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

Discussion:

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

Additional requirements:

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

Reviewers' Comments:

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

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

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

The manuscript is very well written and provides important insight to spontaneously reported adverse events following mRNA vaccination, which should be available to a

wide audience. With the broad rollout of mRNA COVID-vaccines in the US and worldwide, these results are reassuring and provide important information for the risk-benefit assessment of these vaccines.

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

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

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

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

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

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

Reviewer #5: This article provides a picture of reports of AEFI in the first six months of utilization of mRNA COVID-19 vaccines in the United States. I think that similar reports are highly desirable to reassure the population about vaccine safety and therefore priority is high. However, in the attempt of providing more information, the study goes beyond the simple description of reports from VAERS and providing a survey of data collected by v-safe. Unfortunately, the authors made this step without providing important information to the readers. With the current information I cannot establish whether and to what extent the results deserve to be discussed with more caution.
Specific comments
Introduction (page 3) "We reviewed VAERS and v-safe […] vaccines were administered". Instead of providing a simple descriptive report of the data collected in these two databases the authors 1) calculated a rate of report of death and compared that with that expected in an unspecified vaccinated population and 2) performed a disproportionality analysis. These are objectives to be declared in the and text and in the abstract.
For the above mentioned analysis the authors did not included in the methods important information.
For the disproportionality analysis we have no information on the dataset. What were the vaccines included in the dataset? What was the proportion of COVID-19 vaccines? For the latter question, the authors reported in the limitation that in the analyzed period (we know only that they included reports up to June 14th, 2021 but we have not the initial date) the great majority of reports was for the vaccines of interest. If this proportion is over 90% the possibility of identifying a signal was likely close to zero. So, why

performing such an analysis?
For the comparison of mortality rates we have not information about the comparator: does it refers to mortality following immunization with any vaccine? From the reference number 20 it seems that this rate was calculated (how?) only for COVID-19 vaccines? So what is the rationale for this comparison? Estimating the under-reporting of fatal cases? Estimating the number of reports over a mortality for any cause that was attributed to vaccines (not accidental) by reporters? What was the period in which mortality was calculated in the reference? 14 days after vaccination or longer? In summary, I think that these two rates cannot be compared or should be interpreted in a different way, at least with the details of information provided by the authors.
Page 7: "there were 4,496 reports of death…." Were all these reports from US? Did the VAERS include reports from other countries? I suppose these fatal cases have been occurred all in the US since the authors used this number to estimate the reporting rate for fatal cases using the number of doses of vaccines administered in the US. If this is the case, it should be clearly stated.
Page 8: "During the analytic period, 7,914,583 mRNA COVID-19 vaccine recipients […]". How many patients dropped out after the initial enrolment? In case the drop-out is quite high (as I suppose) the authors should compare the population included in the analysis with the population dropped out to check for a possible selection that could have had an impact on the results.
Page 10 "Analysis of deaths reported to VAERS demonstrated lower than expected reported mortality rates compared to background mortality rates". Besides my doubt about comparability given the lack of essential information, why the authors wrote "than expected"? I would have bet whatever I have that the rate was lower than that estimated for a background mortality for two reasons: 1) under-reporting and 2) background mortality include death for any cause while VAERS includes only deaths that have been somehow associated with the immunization. The authors included an interpretation similar to mine in the "limitations" section. So they likely expected this results as well.

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

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

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

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

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

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

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

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

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

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

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

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

TECHNICAL INFORMATION:

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

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

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

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

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

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

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

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

In summary, the signed statements we require are:

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

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Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Baer, Bethany" [redacted]
To: "Menschik, David" [redacted]
Subject: FW: [EXTERNAL] RE: 6 month safety review-COI form- please fill out and send back by COB 10/21
Date: Fri, 22 Oct 2021 19:22:09 +0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-2021-10-22_CLEAN_for_medRxiv.docx

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Hi David,
I wanted to let you know that this version still says that data mining is adjusted for "year of vaccination" rather than "year that the report was received" on page 5. I know you raised this point in an earlier email back in Sept. but it looks like it wasn't corrected. I am not sure if you discussed this with Hannah.
-Bethany

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, October 22, 2021 9:52 AM
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]; Markowitz, Lauri (CDC) [redacted]
Subject: [EXTERNAL] RE: 6 month safety review-COI form- please fill out and send back by COB 10/21

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

Hannah

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

Dear co-authors,

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

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

Thanks so very much,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

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

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]

To: "Gee, Julianne (CDC/DDID/NCEZID/DHQP)" [redacted], "Liu, Ruiling (CDC/NIOSH/WTCHP)" [redacted], "Marquez, Paige L. (CDC/DDID/NCEZID/DHQP)" [redacted], "Zhang, Bicheng (Tony) (CDC/DDID/NCEZID/DHQP) (CTR)" [redacted], "Strid, Penelope (CDC/DDNID/NCCDPHP/DRH)" [redacted], "Abara, Winston E. (CDC/DDID/NCHHSTP/DSTDP)" [redacted], "McNeil, Michael (CDC/DDID/NCEZID/DHQP)" [redacted], "Myers, Tanya R. (CDC/DDID/NCEZID/DHQP)" [redacted], "Hause, Anne M. (CDC/DDID/NCEZID/DHQP)" [redacted], "Menschik, David (FDA/CBER)" [redacted], "Baer, Bethany (FDA/CBER)" [redacted], "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted], "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Shay, David (CDC/DDID/NCIRD/ID)" [redacted]

Subject: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Date: Thu, 29 Jul 2021 19:21:45 +0000

Importance: High

Attachments: 6_month_safety_mRNA_COVID19_vaccine_safety_7_29.docx; 6_month_safety_mRNA_vaccine_tables_and_figures_729.docx

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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

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Menschik, David (FDA/CBER)" [redacted]
Cc: "Baer, Bethany (FDA/CBER)" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Wed, 15 Sep 2021 12:56:07 +0000
Importance: Normal

This look great- I've kept that reference in and kept all of your language.
So appreciate your work on this- and will forward on a 'clean' and 'modified' version ASAP!
All the best,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 8:46 AM
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

Hi Hannah,

Thanks! I certainly understand the desire to simplify and be economical with words. I've attached a slightly revised version which Bethany has not had a chance to review yet and copying her here in case she has further thoughts.
I think it is important to make reference to the Martin article (reference #22) which mentions several important VAERS data mining limitations so the reader does not overestimate what data mining can do (see attached for suggested placement). I changed 'driven towards the null" to "muted" and removed "if there is a class effect" and removed the immediately following parenthesis and "e.g.," to highlight main concern of potentially missing a PT that is associated with both mRNA vaccines.

Please see attached and let me know what you think.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:01 AM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks and sorry for the lack of response. I had rewritten with a similar tightening – additionally, I had deleted "particularly if there is a class-effect" or do you think that clarification is needed?
Senior authors on our team are looking through it today, so hopefully will be ready for re-clearance later this week.
Will forward on as soon as possible.
Thanks a million,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 7:59 AM
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,

Hopefully no issues with the new language provided yesterday though if so please advise.
Also wondering If you have a general estimate on when this paper will be ready for re-clearance?

Thanks,
David

From: Menschik, David
Sent: Tuesday, September 14, 2021 5:17 AM
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,

To simplify, the previously language could be replaced with:

> "Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID vaccine reports contributing substantially to the comparator group, particularly if there is a class-effect (e.g., if multiple COVID vaccines are associated with the same adverse event)."

Does this help?

Thanks,
David

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 3:08 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

Hmm… you should have seen the earlier iterations of this! ☺ Yes, it should say "disproportionality" -autocorrect strikes again! Thanks for correcting that…
Our goal was to simplify as much as possible while not losing key concepts and this is where we landed after working the sentence over…

I think you've got the main point that if the comparison group is enriched with so many mRNA COVID-vaccine reports, that it becomes very difficult to exceed the EB05>2 alert threshold even for an adverse event that may be associated with mRNA vaccines – thus data mining has blind spots and this is why it's so good to have so many complimentary vaccine safety surveillance systems (e.g., VSD) that can cover different blind spots of other systems…
Happy to have a phone call if helpful to explain the importance of including specific words or anything else…

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, September 10, 2021 2:51 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,
Certainly will pass along the draft when ready for clearance at FDA!

In looking the additional sentence over in more detail, it seems pretty technical. If I'm understanding correctly, you're saying that the sheer volume of COVID-19 vaccine reports basically washes out the possibility of finding disproportionality (I think it should say disproportionality instead of disproportionately right?)

Do you think you can simplify the sentence so it would be understandable for the average clinician reader?

Hannah

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 10:46 AM
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

Thank you Hannah for all your efforts. Once you advise that paper is ready to clear at FDA, will be very helpful, if possible, to have a version with indication of where specific changes were made from prior cleared version, so that we can do our best to optimize time to re-clear here…

Wishing you an enjoyable weekend,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, September 10, 2021 9:21 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Thank you David and Bethany!

Hannah

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 7:53 AM
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

Hi Hannah,

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

Thanks,
David

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

Sounds like a plan!

Hannah

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

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

Thanks,
David

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

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

Hannah

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

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

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

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

Thanks so very much for your continued engagement on this,
Hannah

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

Hi Hannah,

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

Best,
David

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

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

Hannah

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

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

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

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

Hi Hannah,

I agree that these are not substantive changes and will send you the authorship agreement statement shortly.
Thanks so much to you and other teammates for all the amazing work on this very impressive paper!

Congratulations on this key milestone!
David

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

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

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

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

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

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

Thanks,
David

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

Dear co-authors,

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

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

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

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

All the very best,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

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

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Baer, Bethany (FDA/CBER)" [redacted]
Cc: "Menschik, David (FDA/CBER)" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Mon, 27 Sep 2021 20:14:35 +0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-2021-09-26_CLEANFINAL.docx

---

Hi Bethany and David,
Thanks so much. 23 should never have gotten removed – and I fixed that typo- very much appreciate you both- clean copy attached-
All the best,
Hannah

From: Baer, Bethany [redacted]
Sent: Monday, September 27, 2021 10:11 AM
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 agree with David's comment below about including both references 22 and 23 when describing the limitations.

I also wanted to mention what I think is a minor typo/missing word on pg. 11, line 7 where it says "Reports of seeking medical care after mRNA vaccine were rare; v-safe did not which symptoms prompted the participant to seek medical care."
Thanks!
Bethany

From: Menschik, David [redacted]
Sent: Monday, September 27, 2021 5:54 AM
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 noticed that the statement, "EB data mining has multiple limitations,[22] including that…" is missing reference #23 as discussed (i.e., should reference both 22 and 23) – can you please revise accordingly and send us back a clean copy?

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, September 26, 2021 9:52 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks so much for all of your work on this manuscript overall and again for finding that error in Table 3.
Please see attached clean copy for Table 3 (and associated text) corrected, and the EB language back to what you had suggested.
It has been cleared from CDC perspective- please let me know when cleared from FDA (or if there are additional edits/steps along the way to make this happen!)

Thanks so very much,
Hannah

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)
Sent: Thursday, September 23, 2021 2:31 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thank you so so much. This is a huge mistake on my part. Table 4 is correct, but Table 3 is not- I need to get the dose denominators and recalculate those.
Thanks so very much for your attention to detail here.
Will send along an updated copy when I have it ready for you review
Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 2:19 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,

On a different note, there may be a problem with Table 3 (and may apply to Table 4 too)
Looks like the reporting rate for each of the subgroups stratified by sex or age uses the *total* number of doses administered as the denominator instead of the number of doses administered for that specific subgroup. So for example, from Table 3 we can say that for individuals aged 16-17 who received BNT162b2 the reporting rate is 6 deaths per million doses of Pfizer administered to the entire population. Since this statistic can be heavily influenced by the age distribution of the vaccinated population, output could be misleading. In this 16-17 year-old example, It may be better to use a denominator of Pfizer doses administered to 16-17 year-old individuals, instead of the entire population.

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, September 23, 2021 8:52 AM
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 so much. Thanks for your edits. I am happy to modify to your version.
I did just receive comments from CDC's office of science, so let me go ahead and look through those and send you a new version with the data mining and their changes too so that the latest goes through FDA clearance.
Thanks so much,

Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 8:22 AM
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

Good morning Hannah,

There are substantive changes and this will ultimately have to go through clearance at FDA.

Regarding the limitations section, previously accepted version said:

> EB data mining has multiple limitations[22] including that an absence of a disproportionality alert does not rule out presence of a safety problem. Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be muted by COVID-19 vaccine reports contributing substantially to the comparator group, particularly if both mRNA COVID-19 vaccines are associated with the same adverse event.

New version says:

> A limitation of EB data mining[22] is low sensitivity; that is, absence of a disproportionality alert does not rule out a possible adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

This is inadequate since there are many limitations to data mining and paper is only pointing out 'low sensitivity' which is not accurate. We recommend revising to:

> EB data mining has multiple limitations[22,23] including that the absence of a disproportionality alert does not rule out a possible corresponding adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

OK with the other data mining parts (including slimming down the results section) and deferring on non-data mining parts of the paper (for which we were not involved).

Please let us know if the proposed revision is acceptable and if so, please provide an updated clean version for our clearance process.

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 22, 2021 2:36 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 and Bethany,

I hope all is well. Please see attached for a new version of the vaccine safety 6 month manuscript. A few notes:

- One of the comments in CDC clearance was about the analysis and framing of reports of deaths in the discussion, so part of what took so long to revise and edit was that we opted to significantly change how death reports appear. (Table 4, specifically, is new and compared reports of death from a pre-print paper by CDC authors.)
- You'll also notice that we've taken out some of the details about EB mining in the results. **I hope this is okay with both of you**- as you know, there is a ton of data in this paper, and we left the information that summarized the findings, without going into details that didn't necessarily add to the overall messages of the manuscript- welcome your thoughts about this. You'll see that I've kept everything in the methods/discussion as well as the references that you suggested.

There have been significant edits at this point, and I certainly defer to you about whether the paper should go back into formal FDA clearance. About my ideal timeline- the draft is currently back in CDC clearance- I'm hoping that it is cleared in the next few days, and then I can begin to prep for manuscript submission in the next week or so.

Let me know if it would be helpful to have a short call to go through some of these changes in more detail.

Thanks so very much,
Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 9:29 AM
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!

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:56 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

This look great- I've kept that reference in and kept all of your language.

So appreciate your work on this- and will forward on a 'clean' and 'modified' version ASAP!
All the best,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 8:46 AM
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

Hi Hannah,

Thanks! I certainly understand the desire to simplify and be economical with words. I've attached a slightly revised version which Bethany has not had a chance to review yet and copying her here in case she has further thoughts.
I think it is important to make reference to the Martin article (reference #22) which mentions several important VAERS data mining limitations so the reader does not overestimate what data mining can do (see attached for suggested placement). I changed 'driven towards the null" to "muted" and removed "if there is a class effect" and removed the immediately following parenthesis and "e.g.," to highlight main concern of potentially missing a PT that is associated with both mRNA vaccines.

Please see attached and let me know what you think.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:01 AM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks and sorry for the lack of response. I had rewritten with a similar tightening – additionally, I had deleted "particularly if there is a class-effect" or do you think that clarification is needed?
Senior authors on our team are looking through it today, so hopefully will be ready for re-clearance later this week.
Will forward on as soon as possible.
Thanks a million,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 7:59 AM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

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Hopefully no issues with the new language provided yesterday though if so please advise.
Also wondering If you have a general estimate on when this paper will be ready for re-clearance?

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> "Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID vaccine reports contributing substantially to the comparator group, particularly if there is a class-effect (e.g., if multiple COVID vaccines are associated with the same adverse event)."

Does this help?

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Sent: Thursday, August 05, 2021 2:48 PM
To: Baer, Bethany [redacted]
Cc: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

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

Hannah

From: Baer, Bethany [redacted]
Sent: Thursday, August 5, 2021 2:44 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Menschik, David (FDA/CBER) [redacted]
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Thank you for all of your hard work on this!
Bethany

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

Congratulations on this key milestone!
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David

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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: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Menschik, David (FDA/CBER)" [redacted]
Cc: "Baer, Bethany (FDA/CBER)" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Wed, 22 Sep 2021 18:35:57 +0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-update_92121_forclearance_clean.docx

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Hi David and Bethany,

I hope all is well. Please see attached for a new version of the vaccine safety 6 month manuscript. A few notes:

- One of the comments in CDC clearance was about the analysis and framing of reports of deaths in the discussion, so part of what took so long to revise and edit was that we opted to significantly change how death reports appear. (Table 4, specifically, is new and compared reports of death from a pre-print paper by CDC authors.)
- You'll also notice that we've taken out some of the details about EB mining in the results. **I hope this is okay with both of you**- as you know, there is a ton of data in this paper, and we left the information that summarized the findings, without going into details that didn't necessarily add to the overall messages of the manuscript- welcome your thoughts about this. You'll see that I've kept everything in the methods/discussion as well as the references that you suggested.

There have been significant edits at this point, and I certainly defer to you about whether the paper should go back into formal FDA clearance. About my ideal timeline- the draft is currently back in CDC clearance- I'm hoping that it is cleared in the next few days, and then I can begin to prep for manuscript submission in the next week or so.

Let me know if it would be helpful to have a short call to go through some of these changes in more detail.

Thanks so very much,
Hannah

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To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Baer, Bethany (FDA/CBER) [redacted]
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Thanks Hannah!

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Sent: Wednesday, September 15, 2021 8:56 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

This look great- I've kept that reference in and kept all of your language.
So appreciate your work on this- and will forward on a 'clean' and 'modified' version ASAP!
All the best,

Hannah

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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

Hi Hannah,

Thanks! I certainly understand the desire to simplify and be economical with words. I've attached a slightly revised version which Bethany has not had a chance to review yet and copying her here in case she has further thoughts.
I think it is important to make reference to the Martin article (reference #22) which mentions several important VAERS data mining limitations so the reader does not overestimate what data mining can do (see attached for suggested placement). I changed 'driven towards the null" to "muted" and removed "if there is a class effect" and removed the immediately following parenthesis and "e.g.," to highlight main concern of potentially missing a PT that is associated with both mRNA vaccines.

Please see attached and let me know what you think.

Thanks,
David

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Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Thu, 23 Sep 2021 18:30:38 +0000
Importance: Normal

Hi David,
Thank you so so much. This is a huge mistake on my part. Table 4 is correct, but Table 3 is not- I need to get the dose denominators and recalculate those.
Thanks so very much for your attention to detail here.
Will send along an updated copy when I have it ready for you review
Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 2:19 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,

On a different note, there may be a problem with Table 3 (and may apply to Table 4 too)
Looks like the reporting rate for each of the subgroups stratified by sex or age uses the *total* number of doses administered as the denominator instead of the number of doses administered for that specific subgroup. So for example, from Table 3 we can say that for individuals aged 16-17 who received BNT162b2 the reporting rate is 6 deaths per million doses of Pfizer administered to the entire population. Since this statistic can be heavily influenced by the age distribution of the vaccinated population, output could be misleading. In this 16-17 year-old example, It may be better to use a denominator of Pfizer doses administered to 16-17 year-old individuals, instead of the entire population.

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, September 23, 2021 8:52 AM
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 so much. Thanks for your edits. I am happy to modify to your version.
I did just receive comments from CDC's office of science, so let me go ahead and look through those and send you a new version with the data mining and their changes too so that the latest goes through FDA clearance.
Thanks so much,

Hannah

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 8:22 AM
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

Good morning Hannah,

There are substantive changes and this will ultimately have to go through clearance at FDA.

Regarding the limitations section, previously accepted version said:

> EB data mining has multiple limitations[22] including that an absence of a disproportionality alert does not rule out presence of a safety problem. Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be muted by COVID-19 vaccine reports contributing substantially to the comparator group, particularly if both mRNA COVID-19 vaccines are associated with the same adverse event.

New version says:

> A limitation of EB data mining[22] is low sensitivity; that is, absence of a disproportionality alert does not rule out a possible adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

This is inadequate since there are many limitations to data mining and paper is only pointing out 'low sensitivity' which is not accurate. We recommend revising to:

> EB data mining has multiple limitations[22,23] including that the absence of a disproportionality alert does not rule out a possible corresponding adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

OK with the other data mining parts (including slimming down the results section) and deferring on non-data mining parts of the paper (for which we were not involved).

Please let us know if the proposed revision is acceptable and if so, please provide an updated clean version for our clearance process.

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 22, 2021 2:36 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 and Bethany,

I hope all is well. Please see attached for a new version of the vaccine safety 6 month manuscript. A few notes:

- One of the comments in CDC clearance was about the analysis and framing of reports of deaths in the discussion, so part of what took so long to revise and edit was that we opted to significantly change how death reports appear. (Table 4, specifically, is new and compared reports of death from a pre-print paper by CDC authors.)
- You'll also notice that we've taken out some of the details about EB mining in the results. **I hope this is okay with both of you**- as you know, there is a ton of data in this paper, and we left the information that summarized the findings, without going into details that didn't necessarily add to the overall messages of the manuscript- welcome your thoughts about this. You'll see that I've kept everything in the methods/discussion as well as the references that you suggested.

There have been significant edits at this point, and I certainly defer to you about whether the paper should go back into formal FDA clearance. About my ideal timeline- the draft is currently back in CDC clearance- I'm hoping that it is cleared in the next few days, and then I can begin to prep for manuscript submission in the next week or so.

Let me know if it would be helpful to have a short call to go through some of these changes in more detail.

Thanks so very much,
Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 9:29 AM
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!

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:56 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

This look great- I've kept that reference in and kept all of your language.
So appreciate your work on this- and will forward on a 'clean' and 'modified' version ASAP!
All the best,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 8:46 AM
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

Hi Hannah,

Thanks! I certainly understand the desire to simplify and be economical with words. I've attached a slightly revised version which Bethany has not had a chance to review yet and copying her here in case she has further thoughts.
I think it is important to make reference to the Martin article (reference #22) which mentions several important VAERS data mining limitations so the reader does not overestimate what data mining can do (see attached for suggested placement). I changed 'driven towards the null" to "muted" and removed "if there is a class effect" and removed the immediately following parenthesis and "e.g.," to highlight main concern of potentially missing a PT that is associated with both mRNA vaccines.

Please see attached and let me know what you think.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 15, 2021 8:01 AM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi David,
Thanks and sorry for the lack of response. I had rewritten with a similar tightening – additionally, I had deleted "particularly if there is a class-effect" or do you think that clarification is needed?
Senior authors on our team are looking through it today, so hopefully will be ready for re-clearance later this week.
Will forward on as soon as possible.
Thanks a million,

Hannah

From: Menschik, David [redacted]
Sent: Wednesday, September 15, 2021 7:59 AM
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,

Hopefully no issues with the new language provided yesterday though if so please advise.
Also wondering If you have a general estimate on when this paper will be ready for re-clearance?

Thanks,
David

From: Menschik, David
Sent: Tuesday, September 14, 2021 5:17 AM

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,

To simplify, the previously language could be replaced with:

> "Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be driven towards the null by COVID vaccine reports contributing substantially to the comparator group, particularly if there is a class-effect (e.g., if multiple COVID vaccines are associated with the same adverse event)."

Does this help?

Thanks,
David

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 3:08 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

Hmm… you should have seen the earlier iterations of this! ☺ Yes, it should say "disproportionality" -autocorrect strikes again! Thanks for correcting that…
Our goal was to simplify as much as possible while not losing key concepts and this is where we landed after working the sentence over…
I think you've got the main point that if the comparison group is enriched with so many mRNA COVID-vaccine reports, that it becomes very difficult to exceed the EB05>2 alert threshold even for an adverse event that may be associated with mRNA vaccines – thus data mining has blind spots and this is why it's so good to have so many complimentary vaccine safety surveillance systems (e.g., VSD) that can cover different blind spots of other systems…
Happy to have a phone call if helpful to explain the importance of including specific words or anything else…

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, September 10, 2021 2:51 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,
Certainly will pass along the draft when ready for clearance at FDA!

In looking the additional sentence over in more detail, it seems pretty technical. If I'm understanding correctly, you're saying that the sheer volume of COVID-19 vaccine reports basically washes out the possibility of finding disproportionality (I think it should say disproportionality instead of disproportionately right?)

Do you think you can simplify the sentence so it would be understandable for the average clinician reader?

Hannah

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 10:46 AM
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

Thank you Hannah for all your efforts. Once you advise that paper is ready to clear at FDA, will be very helpful, if possible, to have a version with indication of where specific changes were made from prior cleared version, so that we can do our best to optimize time to re-clear here…

Wishing you an enjoyable weekend,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, September 10, 2021 9:21 AM
To: Menschik, David [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Thank you David and Bethany!

Hannah

From: Menschik, David [redacted]
Sent: Friday, September 10, 2021 7:53 AM
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

Hi Hannah,

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

Thanks,
David

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

Sounds like a plan!

Hannah

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

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

Thanks,
David

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

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

Hannah

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

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

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

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

Thanks so very much for your continued engagement on this,
Hannah

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

Hi Hannah,

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

Best,
David

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

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

Hannah

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

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

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

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

Hi Hannah,

I agree that these are not substantive changes and will send you the authorship agreement statement shortly.
Thanks so much to you and other teammates for all the amazing work on this very impressive paper!

Congratulations on this key milestone!
David

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

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

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

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

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

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

Thanks,
David

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

Dear co-authors,

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

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

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

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

All the very best,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

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

From: "Baer, Bethany" [redacted]
To: "Menschik, David" [redacted], "Rosenblum, Hannah (CDC)" [redacted]
Cc: "Shay, David K (CDC)" [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Mon, 6 Dec 2021 12:16:12 +0000
Importance: Normal

Yes for me as well. Thank you, Hannah.

Bethany

From: Menschik, David [redacted]
Sent: Monday, December 6, 2021 5:55 AM
To: Rosenblum, Hannah (CDC) [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Yes for me, thank you

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, December 05, 2021 6:34 PM
To: Menschik, David [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks very much David and Bethany- and for speaking on the phone about this last week.
We'd still like you acknowledge all of your work on this project—
Can we move your names to the acknowledgements (along with Jane Baumblatt, Deborah Thompson, Kerry Welsh, Narayan, Nair, Kosal Nguon who were weren't planning to remove?)

Thanks so very much and all of the best,
Hannah

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

Hi Hannah,

Bethany and I have reviewed the comments from the Lancet ID Reviewers, and we agree with Reviewer #5's comment that disproportionality analysis is extremely limited when the background database has such a high proportion of reports

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

Best,
David and Bethany

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

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).

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

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- Signed patient's consent and permission to publish (if not already submitted)

Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Zinderman, Craig E" [redacted]
To: "Menschik, David" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Thu, 9 Sep 2021 19:32:18 +0000
Importance: Normal

Thanks. That's a good addition. If it needs to go through Clearance again, might want to let her know that.

Thanks,
Craig

From: Menschik, David [redacted]
Sent: Thursday, September 09, 2021 3:31 PM
To: Zinderman, Craig E [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Yes -though understand we will get a chance to review it after CDC makes this round of changes…
I also asked Hannah if we can add a limitation for data mining about class effects in the COVID vaccine era due to COVID vaccine reports overwhelming the comparator group…

From: Zinderman, Craig E [redacted]
Sent: Thursday, September 09, 2021 3:25 PM
To: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Has it already been through FDA Clearance?

Thanks,
Craig

From: Menschik, David [redacted]
Sent: Thursday, September 09, 2021 3:18 PM
To: Nair, Narayan [redacted]; Alimchandani, Meghna [redacted]; Zinderman, Craig E [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

FYI

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

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

Thanks so very much for your continued engagement on this,
Hannah

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

Hi Hannah,

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

Best,
David

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

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

Hannah

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

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

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

From: Menschik, David [redacted]
Sent: Thursday, July 29, 2021 3:37 PM
To: Rosenblum, Hannah (CDC) [redacted]

Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

Hi Hannah,

I agree that these are not substantive changes and will send you the authorship agreement statement shortly.
Thanks so much to you and other teammates for all the amazing work on this very impressive paper!

Congratulations on this key milestone!
David

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

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

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

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

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

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

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Thursday, July 29, 2021 3:22 PM
To: Gee, Julianne M (CDC) [redacted]; Liu, Ruiling (CDC) [redacted]; Marquez, Paige L (CDC) [redacted]; Zhang, Bi C (CDC) [redacted]; Strid, Penelope (CDC) [redacted]; Abara, Winston E (CDC) [redacted]; Mcneil, Michael M (CDC) [redacted]; Myers, Tanya R (CDC) [redacted]; Hause, Anne M (CDC) [redacted]; Menschik, David [redacted]; Baer, Bethany [redacted]; Su, John (CDC) [redacted]; Shimabukuro, Tom (CDC) [redacted]; Shay, David K (CDC) [redacted]

Subject: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Importance: High

Dear co-authors,

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

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

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

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

All the very best,
Hannah

Hannah G. Rosenblum, MD
Epidemic Intelligence Service Officer

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

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Menschik, David (FDA/CBER)" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Thu, 9 Sep 2021 19:33:12 +0000
Importance: Normal
Attachments: mRNA_6mo_safety_review-update98forOS_9921.docx

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

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Cc: Menschik, David [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond

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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: "Baer, Bethany" [redacted]
To: "Menschik, David" [redacted]
Subject: FW: Data Mining for Pfizer Bivalent: Ischemic Stroke
Date: Wed, 1 Mar 2023 18:10:07 +0000
Importance: Normal
Inline-Images: image001.png; image002.png; image003.jpg; image004.jpg; image005.jpg; image006.jpg; image007.jpg

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Hi David,
I am inclined to direct this specific question to Kosal and the Commonwealth team as I think they would be better at assessing all the different possible approaches to this.

I had written that first line and saw your email come through. I will respond to the string and suggest Chris email Kosal directly with us cc'ed.
Thanks!
Bethany

From: Jason, Christopher [redacted]
Sent: Wednesday, March 1, 2023 12:28 PM
To: Baer, Bethany [redacted] Menschik, David [redacted]
Cc: Bazel, Samaneh [redacted]
Subject: FW: Data Mining for Pfizer Bivalent: Ischemic Stroke

Hi Bethan and David

Quick question See email below. IS it possible to track EB05s for only certain subgroups for Pfizer monovalent and bivalent? Under the signals tab I saw the monthly tracker but I do not see a way to limit the data? Are there runs in datamining that might work? Any help would be appreciated. What I am looking for is the change in the EB05 over time by month for the PT "Ischaemic Stroke" with monovalent and bivalent Pfizer covid vaccine?

Sincerely,
Chris

From: Nair, Narayan [redacted]
Sent: Wednesday, March 1, 2023 6:51 AM
To: Thompson, Deborah [redacted] Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted] Niu, Manette [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke

Dear Chris and Sam,
We received some follow up questions on this. Can we run the EBO5 for ages 65 and older and serious? Also, my hypothesis is that some of this increase is due to stimulated reporting. The finding of a possible increase in ischemic stroke was made public on Jan 13. By my count, 31 reports came in after that date. Can you provide the EB05 for ischemic stroke prior to the public announcement and after. Perhaps give the monthly EB05's for Oct, Nov, Dec. for ages 65 and older and serious? Thanks

Narayan

From: Thompson, Deborah [redacted]
Sent: Tuesday, February 28, 2023 11:14 AM
To: Nair, Narayan [redacted] Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke

Thanks, Narayan!

Best,

Deb

From: Nair, Narayan [redacted]
Sent: Tuesday, February 28, 2023 11:12 AM
To: Thompson, Deborah [redacted]; Alimchandani, Meghna [redacted] Welsh, Kerry [redacted] Jason, Christopher [redacted] Bazel, Samaneh [redacted]
Subject: RE: Data Mining for Pfizer Bivalent: Ischemic Stroke

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

Please don't share the slides.

Narayan

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

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

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

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

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

Among the 41 US reports:

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

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

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

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

Thanks,

Deb
Deb Thompson, MD, MSPH, FACPM
Medical Officer

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: "Su, John (CDC/DDID/NCEZID/DHQP)" [redacted]
To: "Menschik, David (FDA/CBER)" [redacted]
Subject: [EXTERNAL] RE: data mining limitations
Date: Wed, 22 Sep 2021 16:43:32 +0000
Importance: Normal

Hi David,

Signal detection with VAERS data has always been tricky business. I think we're always looking for any quantitative tools to help make sense of what we're seeing. That said, FDA has always made clear the limitations of data mining. Those of us who work with VAERS data frequently are mindful of those limitations; I just figured I share those limitations with folks who aren't as familiar with VAERS (e.g., CISA).

Appreciate the below language. Thanks!

- John

From: Menschik, David [redacted]
Sent: Wednesday, September 22, 2021 12:33 PM
To: Su, John (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: data mining limitations

Hi John,

In the mRNA vaccine review article that we're co-authors on, we recently expanded data mining limitations section as per attached work-in-progress draft (Hannah indicated acceptance of the language) and excerpt below for convenience:

> EB data mining has multiple limitations[22] including that an absence of a disproportionality alert does not rule out presence of a safety problem. Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be muted by COVID-19 vaccine reports contributing substantially to the comparator group, particularly if both mRNA COVID-19 vaccines are associated with the same adverse event.

Thought it might be helpful to share this manuscript update with you, especially if folks on your end may be placing excess value on data mining alerts (EB05>2) or the absence of specific data mining alerts.

Best,
David

PS: If you'd like to discuss more, happy to do so by phone (better suited than email…)

From: "Rosenblum, Hannah (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Menschik, David (FDA/CBER)" [redacted], "Baer, Bethany (FDA/CBER)" [redacted]
Cc: "Shay, David (CDC/DDID/NCIRD/ID)" [redacted]
Subject: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Wed, 1 Dec 2021 21:24:28 +0000
Importance: High
Attachments: 11_30_21_mRNA_6mo_safety_review_tracked_changes_LancetID_comment_response.docx; LancetID_comments_responses.docx

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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).

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

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

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

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

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

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

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

In summary, the signed statements we require are:

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

Please also check whether you need to provide the following:

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

Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Baer, Bethany" [redacted]
To: "Menschik, David" [redacted]
Subject: RE: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Date: Thu, 23 Sep 2021 12:00:41 +0000
Importance: Normal

Hi David,
I agree with your comments below. I was surprised by the extent of the change in the data mining discussion/limitations part (especially without discussion with us). I think your proposed edit below is a significant improvement without too radical of a change from what they had landed on. I think it is a good balance. I am also okay with the grouping of the data mining results for the results section as I don't think the detailed info was clinically important and their summary statement is still accurate.

I agree that it has to go through clearance again. I wish we could avoid that hassle for the reviewers but there are a lot of changes. Thank you for doing the blackline comparison version and for proposing the change to the data mining limitations section.
Bethany

From: Menschik, David [redacted]
Sent: Thursday, September 23, 2021 6:48 AM
To: Baer, Bethany [redacted]
Subject: FW: [EXTERNAL] 6 month safety review- approval for CDC clearance- please review and respond
Importance: High

Hi Bethany,

Attached is the new clean manuscript and there is no redline version per below. I created a "blackline version" of the manuscript (comparing previous clean version with this clean version; attached) and it appears that there are substantive changes that will require re-clearance.
I'm not satisfied with the late changes to the data mining limitation section. Recent version said:

> EB data mining has multiple limitations[22] including that an absence of a disproportionality alert does not rule out presence of a safety problem. Additionally, since most reports received during this surveillance period involved COVID-19 vaccines, disproportionately scores (which are adjusted by year to control for time-dependent, potentially confounding, exposure and outcome variables) can be muted by COVID-19 vaccine reports contributing substantially to the comparator group, particularly if both mRNA COVID-19 vaccines are associated with the same adverse event.

New version says:

> A limitation of EB data mining[22] is low sensitivity; that is, absence of a disproportionality alert does not rule out a possible adverse event. A new concern with disproportionality scores, which are adjusted by year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

This is inadequate since there are many limitations to data mining and they are only pointing out 'low sensitivity' which is not accurate. If you agree, would advise revising to:

> EB data mining has multiple limitations[22,23] including that the absence of a disproportionality alert does not rule out a possible corresponding adverse event. A new concern with disproportionality scores, which are adjusted by

year to control for time-dependent confounders, is that during the study period most VAERS reports were for COVID-19 vaccinations. As all VAERS reports are used for vaccine-event comparisons in EB data mining, potential associations with mRNA COVID-19 vaccines plausibly could be missed.

I'm ok with the other data mining parts (including slimming down the results section) and deferring on non-data mining parts of the paper (for which we were not involved).

Any additional edits or thoughts welcome.

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, September 22, 2021 2:36 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 and Bethany,

I hope all is well. Please see attached for a new version of the vaccine safety 6 month manuscript. A few notes:

- One of the comments in CDC clearance was about the analysis and framing of reports of deaths in the discussion, so part of what took so long to revise and edit was that we opted to significantly change how death reports appear. (Table 4, specifically, is new and compared reports of death from a pre-print paper by CDC authors.)
- You'll also notice that we've taken out some of the details about EB mining in the results. **I hope this is okay with both of you**- as you know, there is a ton of data in this paper, and we left the information that summarized the findings, without going into details that didn't necessarily add to the overall messages of the manuscript- welcome your thoughts about this. You'll see that I've kept everything in the methods/discussion as well as the references that you suggested.

There have been significant edits at this point, and I certainly defer to you about whether the paper should go back into formal FDA clearance. About my ideal timeline- the draft is currently back in CDC clearance- I'm hoping that it is cleared in the next few days, and then I can begin to prep for manuscript submission in the next week or so.

Let me know if it would be helpful to have a short call to go through some of these changes in more detail.

Thanks so very much,
Hannah

From: "Baer, Bethany" [redacted]
To: "Menschik, David" [redacted], "Rosenblum, Hannah (CDC)" [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703
Date: Fri, 14 Jan 2022 18:46:18 +0000
Importance: Normal

Great job, Hannah.
I, Bethany Baer, agree to be acknowledged in the paper "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.
Thanks,
Bethany

From: Menschik, David [redacted]
Sent: Friday, January 14, 2022 1:17 PM
To: Rosenblum, Hannah (CDC) [redacted]
Cc: Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Congratulations Hannah!

I, David Menschik, agree to be acknowledged in the paper "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

Best,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Friday, January 14, 2022 12:34 PM
To: Menschik, David [redacted]; Baer, Bethany [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Dear David and Bethany,
Happy 2022! This manuscript was just accepted for publication at Lancet ID. (In addition to removing the disproportionality analysis, we were actually asked on a second revision to remove the comparison of expected rates of death).

Could you each send a formal statement such as the following that I can submit to them?

"I, [First, Last Name], agree to be acknowledged in the paper "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"

Thank you so much and all of the very best,
Hannah

From: Menschik, David [redacted]
Sent: Monday, December 6, 2021 1:08 PM
To: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Baer, Bethany (FDA/CBER) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks Hannah for your gracious offer. I feel the same as Bethany regarding it being most appropriate for me to be removed from authorship and thanks for including me in the acknowledgments.

Best,
David

From: Baer, Bethany [redacted]
Sent: Monday, December 06, 2021 12:26 PM
To: Rosenblum, Hannah (CDC) [redacted]
Cc: Menschik, David [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks, Hannah. I think it would be most appropriate for me to be removed from authorship. I appreciate the alternative offer, but I think the approach of only being included in the acknowledgements sounds best for this situation.
Thanks,
Bethany

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Monday, December 6, 2021 11:20 AM
To: Baer, Bethany [redacted]; Menschik, David [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

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 and Bethany. I realize in the shuffle of writing over the weekend, I meant to also include in my note—
Since this is VAERS data and you contributed to conceptualization/revising/editing, etc., we are more than happy to keep you both included as authors (but of course it is entirely up to you! and no pressure at all)- just wanted to make sure I did offer.
All the best,
Hannah

From: Baer, Bethany [redacted]
Sent: Monday, December 6, 2021 7:16 AM
To: Menschik, David (FDA/CBER) [redacted]; Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Cc: Shay, David (CDC/DDID/NCIRD/ID) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Yes for me as well. Thank you, Hannah.

Bethany

From: Menschik, David [redacted]
Sent: Monday, December 6, 2021 5:55 AM
To: Rosenblum, Hannah (CDC) [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Yes for me, thank you

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Sunday, December 05, 2021 6:34 PM
To: Menschik, David [redacted]; Baer, Bethany [redacted]
Cc: Shay, David K (CDC) [redacted]
Subject: RE: [EXTERNAL] [WARNING : MESSAGE ENCRYPTED] FW: Your Submission THELANCETID-D-21-02703

Thanks very much David and Bethany- and for speaking on the phone about this last week.
We'd still like you acknowledge all of your work on this project—
Can we move your names to the acknowledgements (along with Jane Baumblatt, Deborah Thompson, Kerry Welsh, Narayan, Nair, Kosal Nguon who were weren't planning to remove?)

Thanks so very much and all of the best,
Hannah

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

Hi Hannah,

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

Best,
David and Bethany

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

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.

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2. One copy where your changes are highlighted (tracked changes).
3. A separate, point by point response to the editorial and referee comments typed immediately following each specific point above. Please do not use boxes for responses.
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Yours sincerely,

Phoebe Hall
Senior Editor
The Lancet Infectious Diseases

From: "Helfand, Rita (CDC/DDID/NCEZID/OD)" [redacted]
To: "Jernigan, Daniel B. (CDC/DDPHSS/OD)" [redacted], "Lubar, Debra (CDC/DDID/NCEZID/OD)" [redacted], "Kuhnert, Wendi (CDC/DDID/OD)" [redacted]
Cc: "Braden, Chris (CDC/DDID/NCEZID/OD)" [redacted]
Subject: FW: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older
Date: Fri, 13 Jan 2023 19:02:00 +0000
Importance: Normal
Attachments: Tough_QA_Preliminary_COVID-19_Vaccine_Safety_Signal_for_65+.pdf

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FYI

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

Good afternoon,

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

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

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

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

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

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

Thank you for your continued partnership.

CDC's Division of Healthcare Quality Promotion Strategic Partnership Team

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

TOUGH QUESTIONS AND ANSWERS

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

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

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

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

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

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

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

- Scientists are working to determine if this is a true association.
- Our analyses become more stable with more data. We're hopeful to have a clearer picture from the assessment and more data in the coming weeks.

- In January, CDC and FDA will share updates to the assessment in planned upcoming vaccine safety meetings, including with ACIP's COVID-19 Vaccine Working Group and FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). CDC and FDA have already briefed the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST).

When did CDC first notice this signal?

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

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

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

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

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

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

- Please see the above answer.
- CDC hopes to assess all factors listed above by mid-February 2023.
- Signal assessment analyses and supplementary analyses in the data system where the signal was detected are underway. The timeline for these assessments will take weeks. The timeline for formal epidemiologic studies in other data systems will take months.

- Additional expected data will make the assessment stronger. CDC will continue to update on its assessment of whether a causal association between bivalent booster vaccine and ischemic stroke exists.

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

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

Has stroke and COVID-19 vaccinations been studied previously?

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

Should people with a family history of stroke be concerned?

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

What is CDC doing about this?

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

What is FDA doing about this?

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

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

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

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

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

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

- CDC evaluates the benefits of COVID-19 vaccines through multiple methodologies, employing various methods and using information collected through different surveillance platforms or electronic health records, among other avenues. In addition, COVID-19 vaccines continue to undergo the most comprehensive and intense safety monitoring in U.S. history. These data are presented and discussed through ongoing benefit-risk analyses to both the ACIP COVID-19 vaccines Work Group and the public ACIP meetings. These analyses have

continued to demonstrate that COVID-19 vaccination is the single best way to protect people from serious COVID-19 illness and the benefits continue to outweigh the risks. As with all emerging data for the vaccines, CDC and ACIP will continue to evaluate the balance of benefits and risks for COVID-19 vaccines.

What is an ischemic stroke?

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

From: "Fitter, David L. (CDC/DDPHSIS/CGH/GID)" [redacted]
To: "Dahl, Benjamin A. (CDC/DDPHSIS/CGH/GID)" [redacted]
Subject: FW: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older
Date: Fri, 13 Jan 2023 19:23:24 -0000
Importance: Normal
Attachments: Tough_QA_Preliminary_COVID-19_Vaccine_Safety_Signal_for_65+.pdf

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FYI. Rita is likely going to send to WHO via GACVS (Global Advisory Committee on Vaccine Safety).

From: Helfand, Rita (CDC/DDID/NCEZID/OD) [redacted]
Sent: Friday, January 13, 2023 2:06 PM
To: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Fitter, David L. (CDC/DDPHSIS/CGH/GID) [redacted]
Subject: FW: CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older

I'm assuming you've seen this but just in case…

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

Good afternoon,

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

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

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

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

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

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

Thank you for your continued partnership.

CDC's Division of Healthcare Quality Promotion Strategic Partnership Team

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

TOUGH QUESTIONS AND ANSWERS

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

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

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

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

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

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

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

- Scientists are working to determine if this is a true association.
- Our analyses become more stable with more data. We're hopeful to have a clearer picture from the assessment and more data in the coming weeks.

- In January, CDC and FDA will share updates to the assessment in planned upcoming vaccine safety meetings, including with ACIP's COVID-19 Vaccine Working Group and FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC). CDC and FDA have already briefed the ACIP COVID-19 Vaccine Safety Technical Sub-Group (VaST).

When did CDC first notice this signal?

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

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

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

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

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

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

- Please see the above answer.
- CDC hopes to assess all factors listed above by mid-February 2023.
- Signal assessment analyses and supplementary analyses in the data system where the signal was detected are underway. The timeline for these assessments will take weeks. The timeline for formal epidemiologic studies in other data systems will take months.

- Additional expected data will make the assessment stronger. CDC will continue to update on its assessment of whether a causal association between bivalent booster vaccine and ischemic stroke exists.

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

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

Has stroke and COVID-19 vaccinations been studied previously?

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

Should people with a family history of stroke be concerned?

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

What is CDC doing about this?

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

What is FDA doing about this?

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

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

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

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

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

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

- CDC evaluates the benefits of COVID-19 vaccines through multiple methodologies, employing various methods and using information collected through different surveillance platforms or electronic health records, among other avenues. In addition, COVID-19 vaccines continue to undergo the most comprehensive and intense safety monitoring in U.S. history. These data are presented and discussed through ongoing benefit-risk analyses to both the ACIP COVID-19 vaccines Work Group and the public ACIP meetings. These analyses have

continued to demonstrate that COVID-19 vaccination is the single best way to protect people from serious COVID-19 illness and the benefits continue to outweigh the risks. As with all emerging data for the vaccines, CDC and ACIP will continue to evaluate the balance of benefits and risks for COVID-19 vaccines.

What is an ischemic stroke?

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

From: "Markowitz, Lauri (CDC/DDID/NCIRD/DVD)" [redacted]
To: "Weintraub, Eric (CDC/DDID/NCEZID/DHQP)" [redacted]
Cc: "Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP)" [redacted], "Woo, Jared (CDC/DDID/NCEZID/DHQP)" [redacted]
Subject: RE: VaST minutes
Date: Thu, 30 Mar 2023 19:08:43 -0000
Importance: Normal
Attachments: 2023-03-27_-_VaST_minutes_draft_confidential_lm.docx

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Eric,

It was difficult to easily convert Nicky's presentation into minutes. We (Jared and I), took some liberty for the sequence in which the data were presented to make the information easier to convey.
Can you check and see if the VSD section of the minute is correct?

Lauri

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Thursday, March 30, 2023 2:47 PM
To: Weintraub, Eric (CDC/DDID/NCEZID/DHQP) [redacted]
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]; Woo, Jared (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: VaST minutes

Hi Eric,
I usually don't ask you to review minutes for VaST, but because of the importance of the presentation this week. I'd like you to look over the draft to see if we got this right. I'll send them to you before COB.
Lauri

VaST meeting notes
March 27, 2023
Confidential - DRAFT

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

Participants

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

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

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

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

Technical SMEs: Ed Belongia (VSD), James Donahue (VSD), Bruce Fireman (VSD), Rich Forshee (FDA), Kristin Goddard (VSD), Kayla Hanson (VSD), Nicky Klein (VSD), Ned Lewis (VSD), Yun Lu (FDA), Chip Walter (Duke)

Agenda

VSD RCA transition presentation, Dr. Nicola Klein, VSD
CISA: Clinical Research Study Update, Dr. Karen Broder, CDC
Note – summary slides were distributed from VA studies of bivalent vaccine, including a brief overview of rapid cycle analysis and a full list of evaluations underway

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

- Reminders about COI and confidentiality
- Last planned VaST meeting is on 4/3
- Doses distributed: 971,469,075; Doses administered: 673,465,377 (last updated: March 23)
  - Doses distributed: Pfizer-BioNTech: 586,424,075; Pfizer-BioNTech(bivalent): 83,131,360; Moderna: 352,247,700; Moderna (bivalent): 39,006,980; Janssen/J&J: 31,552,000; Novavax: 1,245,300; Other: N/A
  - Doses administered: Pfizer-BioNTech: 401,685,954; Pfizer-BioNTech(bivalent): 35,171,689; Moderna: 251,852,502; Moderna (bivalent): 19,888,687 Janssen/J&J: 18,991,177; Novavax: 83,047; Other: 852,697
  - At least one dose: 269,835,963; Primary series: 230,283,056; Bivalent booster dose: 54,579,043
  - 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).

VSD RCA transition presentation – Dr. Nicky Klein (VSD)
Dr. Klein presented an overview of VSD and the processes, methods for the RCA, serious outcomes monitored, analytic strategies, and timeline of the RCA signals for all COVID-19 vaccines.

Primary series
Anaphylaxis
The rate of anaphylaxis was ~ 5 cases/million doses for the mRNA primary series and did not change over time. The rate of anaphylaxis was <5 cases/million doses for mRNA booster doses.

Myocarditis/pericarditis
In data through June 2021, there were no safety signals for any outcome in the 21-day window after both mRNA doses in persons aged 12+ years in VSD. In a subgroup analysis of persons aged 12–39 years, there were elevated rates of myocarditis/pericarditis in the 0-7- and 0-21-day windows.

In August 2021, there was a signal for myocarditis/pericarditis in the 1-21-day risk window. Following this, VSD investigated myocarditis/pericarditis by mRNA product. In August 2022, VSD published a study on the risk of myocarditis and pericarditis following mRNA vaccination (https://doi.org/10.1016/j.vaccine.2022.07.007) which showed an increased risk of myocarditis and pericarditis in persons aged 12–39 years following mRNA vaccination. The risk estimates were slightly higher following Moderna than after Pfizer-BioNTech mRNA COVID-19 vaccines.

Final RCA findings for persons ≥12 years
Final RCA findings, using data through May 2022, showed signals for acute myocarditis infarction (AMI), myocarditis/pericarditis, and venous thromboembolism (VTE). The AMI signal was following dose 2 of Pfizer-BioNTech and dose 2 of both mRNA vaccines. The myocarditis/pericarditis signal was following dose 2 and both doses of Pfizer-BioNTech and both mRNA vaccines. The VTE signal was following dose 2 and both doses of Pfizer-BioNTech and both mRNA vaccines.

Children
Through January 2023, there were no safety signals detected in the weekly surveillance monitoring in children aged 5–11 years following Pfizer-BioNTech vaccination. Through February 2023, there were no outcomes that met signaling criteria in the 21 days after mRNA COVID-19 primary series in children aged 6 months-4/5 years, although vaccine uptake was low.

Guillain Barre Syndrome (GBS) Following Janssen Vaccine
There was never a signal in VSD routine weekly surveillance, but unadjusted rates confirmed a significantly higher incidence compared to background rates. Incidence after Janssen vaccine was 21 times higher than after mRNA vaccines. VSD findings were consistent with an association between increased risk of GBS and Janssen COVID-19 vaccine. There was no evidence of an association between GBS and mRNA COVID-19 vaccines.

Monovalent booster
Following mRNA primary series and monovalent booster, only myocarditis/pericarditis met the signaling criteria in the 21 days after vaccination among ages ≥12 years in the VSD population. There was also a signal for Bell's palsy following Janssen and Pfizer-BioNTech monovalent booster in the 21-day window in persons aged 12+ years.

There were no safety signals detected in the weekly surveillance monitoring in children aged 5–11 years following mRNA monovalent booster vaccination. However, vaccine uptake was low.

Bivalent booster
There were no outcomes that met signaling criteria in the 21 days after mRNA COVID-19 bivalent booster in persons aged 5–64 years.

The rate ratio for ischemic stroke among persons aged 65+ years met signaling criteria consistently for 8 weeks but slowly attenuated and now does not meet signaling criteria.

Discussion and questions
1. Are there additional data on the signal for Bell's palsy presented?
   - The only information readily available is for individuals who had Bell's palsy within a month after Janssen vaccine.
2. Were VTE or AMI rates increased given the higher risk of stroke?
   - There are rates that compared events in risk interval and comparison interval following dose 2, monovalent booster, and bivalent booster on the additional slides (105 and 106).
   - For the AMI signal following Pfizer-BioNTech dose 2, it did signal during surveillance but unlike VTE, AMI no longer met signaling criteria at the end of surveillance for the primary series. However, in the RCA, once something signals it is always considered having signaled.
   - In the FDA follow-up self-controlled study on outcomes after the primary series, there was no increased risk for AMI, ITP, DIC, or myocarditis/pericarditis; the results were not consistent for PE; and there was a small elevated risk of Bell's Palsy after exposure to COVID-19 mRNA vaccines. These results support the favorable safety profile of COVID-19 mRNA vaccines administered in the elderly. (https://www.medrxiv.org/content/10.1101/2023.01.19.23284803v1)
3. There was no signal for myocarditis when looking at all ages?
   - It did signal for the primary series, it just took a couple of months to do so.
   - Does this mean that age stratification should always be considered; there is no way to pre-determine an age-specific risk prior to administration.
4. Are there any additional hypotheses on the stroke signal attenuating?
   - It is still possible that it is a high flu dose or it is confounding. VSD will need more data from future seasons.
5. For the elevated rate of myopericarditis after the monovalent Pfizer booster dose in persons aged 16–17 years, do you recall the average interval before the dose, and whether this was similar or different to the intervals before dose 2 of the primary series or before the bivalent booster dose?
   - VSD does not have average timing from primary -> monovalent boosters or monovalent-> bivalent boosters readily available. Most people in VSD did get their primary series on the original 21/28 day schedule between dose 1 and dose 2.

CISA: Clinical Research Study Update – Dr. Karen Broder (CDC)
Dr. Broder presented an update of the current CISA clinical research studies regarding COVID-19 vaccines.

- RCT of simultaneous vs sequential mRNA COVID-19 and IIV4 vaccines: Lead, Chip Walter at Duke
  - Study has enrolled 349 people and are enrolling for a 2nd season with a target goal of 450.
  - Safety results will be submitted by February 2024

  - Simultaneous mRNA COVID-19 and IIV4 Vaccination Study - Full Text View - ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT05028361)
- Observational pediatric study of 5–15-year-olds: Lead, Mike Smith at Duke
  - Study has enrolled 280 children enrolled with a target of 320 children.
  - Safety of Pediatric COVID-19 Vaccination - Full Text View - ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT05157191) (protocol is posted) – enrolling
- RCT of simultaneous vs sequential mRNA COVID-19 vaccine w/ other pediatric vaccines in children 6 months-4 years
  - Study will begin enrollment in the 3rd quarter of 2023 with a target goal of 600 children
  - Protocol is currently in development and subject to change
- Observational maternal vaccination study: Lead, Gita Swami at Duke
  - Study has enrolled 149 pregnant women and has a target goal of 350.
  - Preliminary safety results anticipated by the second quarter of 2024
  - Study 1: Observational Maternal COVID-19 Vaccination Study - Full Text View - ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04826640) – enrolling
- Simultaneous mRNA COVID-19 and IIV4 vaccination in pregnancy study (concept, not yet implemented)*
  - PIs will implement the study in the third quarter of 2023 and will develop the protocol and enroll participants during the 2024-2025 influenza season.
  - Preliminary results are expected to be available during the fourth quarter of 2026

From:	Menschik, David
To:	Su, John (CDC); Shimabukuro, Tom (CDC)
Cc:	Nair, Narayan; Zinderman, Craig E; Alimchandani, Meghna; Marquez, Paige L (CDC); Broder, Karen R (CDC); Harrington, Theresa (CDC)
Subject:	Weekly data mining
Date:	Tuesday, March 16, 2021 7:13:14 AM
Attachments:	USST 20210311.xls DE VAERS data mining methods and limitations_2021_03_DRAFT.pptx

Hi 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 'US Signals Summary Table' ('as of date' 3/11/21) along with 3 slides providing contextual information including caveats and limitations. 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

Drug	Event	US EB06 20210311	US Serious EB06 20210311	US Fatal EB06 20210311	US Infant EB06 20210311	US Child EB06 20210311	US Teen EB06 20210311	US Adult EB06 20210311	US Adult2 EB06 20210311	US Adult3 EB06 20210311	US Female EB06 20210311	US Male EB06 20210311
COVID19 (COVID19 (JANSSEN))	Chills	2.297					0.571	2.002	1.651	1.572	2.184	1.697

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 EBGM CI (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:	Zinderman, Craig E
To:	Menschik, David; Su, John (CDC); Shimabukuro, Tom (CDC)
Cc:	Nair, Narayan; Alimchandani, Meghna; Marquez, Paige L (CDC); Broder, Karen R (CDC); Harrington, Theresa (CDC)
Subject:	RE: Weekly data mining
Date:	Tuesday, March 23, 2021 2:00:03 PM
Attachments:	USST 2021_0319.xls DE VAERS data mining methods and limitations_2021_03_DRAFT.pptx

Hi John and Tom,

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Thanks,
Craig

Drug	Event	US EB05 20210319	US Serious EB05 20210319	US Fatal EB05 20210319	US Infant EB05 20210319	US Child EB05 20210319	US Teen EB05 20210319	US Adult1 EB05 20210319	US Adult2 EB05 20210319	US Adult3 EB05 20210319	US Female EB05 20210319	US Male EB05 20210319	Comment
COVID19 (COVID19 (JANSSEN))	Chills	2.26	0.935	0.892			1.012	2.074	2.085	1.965	2.363	1.742	
COVID19 (COVID19 (JANSSEN))	Feeling cold	2.47						2.822	1.257	1.048	2.595	0.938	
COVID19 (COVID19 (JANSSEN))	Hyperhidrosis	1.898	0.873				0.567	2.04	1.369	0.554	1.615	1.687	
COVID19 (COVID19 (JANSSEN))	Pyrexia	2.041	0.928	0.892			0.971	1.95	1.845	1.559	2.098	1.651	
COVID19 (COVID19 (JANSSEN))	Tremor	2.074	0.693					1.825	1.553	0.997	1.942	1.276	

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- Can be useful for screening and hypothesis generating only
  - Evaluate findings in clinical and epidemiological context (e.g., unexpected?)
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DE VAERS Data Mining Methods

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    - adjusted by age, gender and year received
- Vaccine-PT pairs ranked by lower 5% bound of EBGM CI (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)

Message

From: Menschik, David [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0407D7354456470CAB9BC2D3F98D6D3C-MENSCHIK]
Sent: 7/22/2021 11:49:49 AM
To: Alimchandani, Meghna [redacted]; Zinderman, Craig E [redacted]
CC: Nair, Narayan [redacted]; Baer, Bethany [redacted]
Subject: FW: [EXTERNAL] 6 month safety review
Attachments: mRNA COVID19 vaccine safety 6 mo draft_721_clean.docx; mRNA COIVD19 vaccine six month safety review_Clearance Form.pdf; mrna vaccine 6 mo- tables and figures_714.docx

Importance: High
Flag: Follow up

Hi Meghna,

We just received this manuscript on COVID-19 mRNA vaccine 6-month safety review. **CDC is seeking a very rapid turnaround time (tomorrow) for clearance**. Bethany is on leave through 8/3 though the data mining sections have no substantive changes (other than a single sentence which was added to the end of the results section by CDC, addressed in my comment. Please note that Bethany and I had not received any version of any part of the manuscript, aside from the data mining methods and results paragraphs prior to the email below. Bethany's and my only interactions to date with CDC regarding this paper involved data mining. After reading the entire paper once, nothing jumped out as problematic though I have not been as close to the other data and issues as others here at FDA. For clearance, I understand I need two SMEs prior to division and office level clearance. Can you please advise regarding who should review at each level of clearance? I was thinking of asking Jane Baumblatt and Deb Thompson (though Kerry was primary for the Pfizer vaccine for initial period).

Thanks,
David

From: Rosenblum, Hannah (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Wednesday, July 21, 2021 5:59 PM
To: Menschik, David [redacted]; Baer, Bethany [redacted]
Subject: [EXTERNAL] 6 month safety review

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

Dear David & Bethany:
I hope you're both well.

Thank you so much for all of your work so far on the 6 month vaccine safety manuscript.
I'm writing because the draft: "Reactogenicity and Adverse Events during the First Six Months of mRNA COVID-19 Vaccination in the United States: A Prospective Observation Study of Reports in Vaccine Adverse Events Reporting System (VAERS) & v-safe" is ready for your review.

The manuscript and tables/figure drafts are attached- please let me know if you have any issues accessing the files.

If possible, I would appreciate your feedback by **COB Friday July 23**- but I realize this is a bit of a tight turnaround, so let me know if that won't be possible for you.

In addition to general feedback, comments and edits, I'm specifically looking for your feedback about the EB data mining methods and results sections. It has gone through some rounds of CDC edits, but I'd really appreciate your edits and modifications, and also if there are any references I should be including.

Also—what is the process for manuscript clearance at FDA? As you know, this paper was originally supposed to be a 3 month and then 4 month review, and so I'm hoping to get this 6 month version into CDC clearance this weekend or as early next week as possible, and wondering if the two agencies would be able to clear content simultaneously.

I look forward to your comments and thanks so much again.
Warm regards,
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