Message

From: Gregory Frank [redacted]
Sent: 4/23/2021 8:52:14 PM
To: Spratling, Robin (CDC) [redacted]; Anderson, Steven [redacted]; Badgett, Kenyatta C (CDC) [redacted]; Shimabukuro, Tom (CDC) [redacted]; Walter-Garcia, Madison P (CDC) [redacted]
CC: Phyllis Arthur [redacted]; Hannah Dorsey [redacted]
Subject: [EXTERNAL] April 29 Industry FDA/CDC PV Safety Meeting Planning
Attachments: Industry Updated PV Safety Questions 042321.docx

Robin

Many thanks for the reminder to be sure we had coverage in the invitation and apologies for those we didn't include.

I wanted to circle back with this group on a few items:

- The companies took a second look at the question list and proposed to update/remove some of the questions to better reflect some of the current areas of interest for the companies. Please find these attached – we're still at 5 questions total. Please let me know if you all are able to speak to these?

- We'll plan for the format we've done in previous meetings, where after opening the meeting we'll aim for a PV/Safety point from a company be the lead discussant for each question. Hope this still works with you all!

Please let me know if you have any other questions – otherwise we look forward to the discussion next week!

Warm regards,

Greg

From: Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted]
Sent: Tuesday, April 20, 2021 10:05 AM
To: Gregory Frank [redacted]; Anderson, Steven (FDA/CBER) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted]; Hannah Dorsey [redacted]; Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]; Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Oh great, thank you! Just wanted to make sure I didn't miss it.

Robin

From: Gregory Frank [redacted]
Sent: Tuesday, April 20, 2021 10:03 AM
To: Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted] Anderson, Steven (FDA/CBER) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD)

(CTR) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Robin

It was but Tom was included – going to send out to all of you just to be safe nobody else is missing

Greg

From: Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted]
Sent: Tuesday, April 20, 2021 9:48 AM
To: Gregory Frank [redacted] Anderson, Steven (FDA/CBER) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi all—
I wanted to check in to make sure that the invitation was sent out.

Thanks!
Robin

From: Gregory Frank [redacted]
Sent: Monday, April 12, 2021 10:09 AM
To: Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted] Anderson, Steven (FDA/CBER) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Understood – sending the invitation now.

Warm regards,

Greg

From: Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted]
Sent: Monday, April 12, 2021 9:58 AM
To: Gregory Frank [redacted] Anderson, Steven (FDA/CBER) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi all,

On our end, the preference would be to stick with the 30 min QA session.

Thanks!

Robin Spratling, MPH
Vaccine Evaluation Communications Team

Vaccine Task Force/COVID-19 Response
Centers for Disease Control and Prevention
Email: [redacted]
Phone: [redacted](work)

From: Gregory Frank [redacted]
Sent: Monday, April 12, 2021 9:30 AM
To: Anderson, Steven (FDA/CBER) [redacted] Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Great. I'll go ahead and share an invitation for 2PM on April 29 – is 30 minutes still preferred, or is an hour an option?

Thanks again all,

Greg

From: Anderson, Steven [redacted]
Sent: Monday, April 12, 2021 9:25 AM
To: Spratling, Robin (CDC) [redacted] Gregory Frank [redacted] Walter-Garcia, Madison P (CDC) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta C (CDC) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Either of the times work for FDA.

Steve Anderson, Ph.D., M.P.P.
Director
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
U. S. Food & Drug Administration
10903 New Hampshire Ave.
[redacted]
Silver Spring, MD 20993

Phone: [redacted]
email: [redacted]

From: Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted]
Sent: Monday, April 12, 2021 9:04 AM
To: Gregory Frank [redacted] Walter-Garcia, Madison P (CDC) [redacted] Anderson, Steven [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Badgett, Kenyatta C (CDC) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi everyone,

Either of these dates work for Tom.

Thanks,
Robin

From: Gregory Frank [redacted]
Sent: Monday, April 12, 2021 6:32 AM
To: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison

Sorry for the delay here. From what've heard the preference is

Thursday April 29 2PM ET preferred, or Monday April 26 3PM ET.

Are these still open on your ends?

Thanks very much again,

Greg

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Sent: Thursday, April 8, 2021 10:39 AM
To: Gregory Frank [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted]; Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi Greg,

Following up to see if there has been any confirmation on the time. Thanks!

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank [redacted]
Sent: Wednesday, March 31, 2021 5:29 AM
To: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted] Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR) [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison

Many thanks for these! I'm running dates by companies now. We have a call tomorrow and hope to have confirmation afterwards.

Warm regards,

Greg

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD[redacted]
Sent: Tuesday, March 30, 2021 3:35 PM
To: Gregory Frank[redacted]Anderson, Steven (FDA/CBER)[redacted]
Cc: Phyllis Arthur[redacted] Hannah Dorsey[redacted] Spratling, Robin (CDC/DDID/NCIRD/ID) (CTR) [redacted] Badgett, Kenyatta (CDC/DDID/NCIRD/OD) (CTR)[redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi Greg,

Tom has the following availability:

- Mon April 26: 3-5pm
- Thurs April 29: 1-3pm
- Friday April 30: 1-2pm

Could we aim for a 30 minute Q&A session during one of the above slots, if that also works for Steve?

Best,

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank[redacted]
Sent: Monday, March 22, 2021 6:00 AM
To: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD)[redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur[redacted] Hannah Dorsey[redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison

Understood – some times in this window proposed below:

Tues April 20 – 12PM-4PM ET
Wed April 21 – 1-4PM ET
Thurs April 22 – 12-3PM ET
Fri April 23 – 9AM-10:30AM ET ; 12-1PM ET ; 2-4PM ET

Mon April 26 – 9-10AM ET ; 1-2PM ET ; 3-5PM ET
Thurs April 29 – 9AM-11AM ET ; 1-3PM ET
Friday April 30 – 9:30AM-11AM ET ; 12-2PM ET

Warm regards,

Greg

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Sent: Friday, March 19, 2021 4:24 PM
To: Gregory Frank [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi Greg,

Sorry for the delay! Unfortunately due to some transitions I think the 3rd or 4th week of April is the earliest we could do. Could you send over some potential times so that I can start checking on SME availability?

Best,

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank [redacted]
Sent: Saturday, March 6, 2021 6:37 AM
To: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted] Anderson, Steven (FDA/CBER)
[redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison

Many thanks – can certainly appreciate the limited bandwidth! I can stay there is a concern from our members that given how fast the issues are moving and shifting, we'll miss opportunities to understand and address some of these topics. Are there any opportunities to meet the middle here and look for the second full week of April?

Also - Steve, would FDA OBE be willing to hold an earlier meeting to discuss our FDA specific questions (attaching again here – I'll admit are most CDC-focused). In your earlier exchange, it seemed that you may be open to meeting sometime this month.

We recently held a meeting with CDC team to do a deep dive and discuss their Vaccine Effectiveness study work. The companies were very interested in having a similar discussion with FDA. If you are open to this, we could try and roll both discussions into one call?

Happy to jump on a call with either/both of you to talk through – and as always we greatly appreciate your openness to working with us on these issues!

Warm regards,

Greg

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Sent: Tuesday, March 2, 2021 12:58 PM
To: Gregory Frank [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi Greg,

Sincerest apologies. I touched base with the team again and due to limited staffing and bandwidth, they have requested this be pushed until the end of April. Would BIO be amenable to this? I did attach the slides presented at ACIP, which provide the latest update on safety information.

Best,

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank [redacted]
Sent: Friday, February 26, 2021 6:31 AM
To: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted]; Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison

Understood – we'll definitely be watching the ACIP closely and if this shakes any new topics out (or addresses any identified topics). A few options in early April to get this going:

Thurs April 1 - 9AM-12PM ET ; 1-5PM ET
Fri April 2 – 9:30-11AM ET ; 12-2PM ET ; 3-4PM ET
Mon April 5 – 9AM-10AM ET ; 12-5PM ET
Tues April 6 – 9AM-10AM ET ; 12-4PM ET
Wed April 7 – 9AM-11AM ET ; 2-4PM ET
Thurs April 8 – 9AM-3PM ET ; 4-5PM ET

Warm regards,

Greg

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Sent: Thursday, February 25, 2021 5:56 PM
To: Gregory Frank [redacted] Anderson, Steven (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi Greg,

I ran this by the team and due to the Janssen launch and several competing White House priorities, the safety team is requesting that we push this to the beginning of April. However, they will be giving a presentation at ACIP on Monday on safety that may be of interest to your membership. If you provide some options for April, I am happy to go ahead and work on getting this scheduled.

Best,

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank [redacted]
Sent: Wednesday, February 24, 2021 5:42 AM
To: Anderson, Steven (FDA/CBER) [redacted] Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Steve

Of course! To get the ball rolling here a few windows of time looking at the latter half of the week of March 8:

Wed March 10 - 9AM-11AM ET; 2-4PM ET
Thurs March 11 - 9AM-2PM ET
Fri March 12 – 9AM-11AM ET ; 12-1PM ; 2-4PM ET

Warm regards,

Greg

From: Anderson, Steven [redacted]
Sent: Tuesday, February 23, 2021 11:12 PM
To: Gregory Frank [redacted] Walter-Garcia, Madison P (CDC) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Dear Greg,

I would ask that we consider deferring until the second week of March as we are currently engaged in reviews and preparation for the FDA Vaccines and Related Biologic Products Advisory Committee meeting on Friday (February 26th) this is followed by the CDC Advisory Committee on Immunization Practice on Sunday and Monday. We have deferred several meetings to next week so next week is quite full.

Thanks in advance,

Steve

Steve Anderson, Ph.D., M.P.P.
Director

Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
U. S. Food & Drug Administration
10903 New Hampshire Ave.
[redacted]
Silver Spring, MD 20993

Phone: [redacted]
email: [redacted]

From: Gregory Frank [redacted]
Sent: Tuesday, February 23, 2021 6:16 PM
To: Anderson, Steven [redacted] Walter-Garcia, Madison P (CDC) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison, Steve

Circling back here – glad to see you both are up for the meeting. Here is a list of the topics/questions I've received from the companies so far- welcome your reactions to if/how we could walk through these.

In terms of timing, certainly we can look to March after the adcom– I can offer up some times in the first two weeks of March if that is helpful – or can work with any options on your end.

Thanks for your help and consideration again,

Greg

Greg Frank, PhD
Senior Director, Infectious Disease Policy
Biotechnology Innovation Organization (BIO)
1201 Maryland Ave SW, [redacted] Washington, DC 20024
Direct: [redacted]
Mobile: [redacted]
[redacted] | www.bio.org

From: Anderson, Steven [redacted]
Sent: Sunday, February 21, 2021 12:16 PM
To: Gregory Frank [redacted] Walter-Garcia, Madison P (CDC) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Dear Greg,

Sorry for the late response but we would be happy to participate. It could not be this week or early next week as FDA and CDC have advisory committee meetings for the next COVID-19 vaccine on Friday and subsequent days.

Regards,

Steve

Steve Anderson, Ph.D., M.P.P.
Director
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
U. S. Food & Drug Administration
10903 New Hampshire Ave.
[redacted]
Silver Spring, MD 20993

Phone: [redacted]
email: [redacted]

From: Gregory Frank [redacted]
Sent: Friday, February 19, 2021 7:43 PM
To: Walter-Garcia, Madison P (CDC) [redacted]
Cc: Anderson, Steven [redacted] Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: [EXTERNAL] RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison

Great to hear! On the topics, please stand by – I'm just waiting on some feedback from companies to be sure we've captured the questions/topics appropriately – aiming to have them over to you on Tuesday?

Enjoy your weekends,

Greg

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Sent: Thursday, February 18, 2021 11:55 AM
To: Gregory Frank [redacted]
Cc: Anderson, Steven (FDA/CBER) [redacted] Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [-EXTERNAL-] RE: Thank you from BIO!

Hi Greg,

Happy to take this back to our safety team to discuss. Can you provide the list of topics you referenced below?

Best,

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank [redacted]
Sent: Friday, February 12, 2021 6:45 AM
To: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Cc: Anderson, Steven (FDA/CBER) [redacted] Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [-EXTERNAL-] RE: Thank you from BIO!

Madison, Steve

Thanks very much again for the response to these questions last year. Our companies have been continuing to discuss our experiences with COVID-19 Vx PV/Safety, and we are interested in exploring another call to discuss several topics in this space with the CDC and FDA.

Would you be amenable to another call late this month or early March? We can pull together the topic list and share with you early next week, if that is helpful to inform your discussions.

Thanks again for your consideration, and please enjoy your weekends!

Warm regards,

Greg

Greg Frank, PhD
Senior Director, Infectious Disease Policy
Biotechnology Innovation Organization (BIO)
1201 Maryland Ave SW, [redacted] Washington, DC 20024
Direct: [redacted]
Mobile: [redacted]
[redacted] | www.bio.org

From: Walter-Garcia, Madison (CDC/DDID/NCIRD/OD) [redacted]
Sent: Friday, December 18, 2020 12:43 PM
To: Gregory Frank [redacted]
Cc: Anderson, Steven (FDA/CBER) [redacted] Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [-EXTERNAL-] RE: Thank you from BIO!

Hello Greg,

I am following up on the below questions and am happy to serve as your point of contact moving forward. Please find answers below.

- Follow-up Question: How will call center be trained to elicit the information to obtain lot#?
  - Lot number is a standard field on the VAERS report form and is documented if the reporter has this information available.

- Follow-up question for CDC/FDA– Does the de-duplication effort include all 3 sources of reports, VAERS reports from VSAFE/spontaneous VAERS reports/Industry reports?
  - The deduplication process is run on the entire VAERS database and includes any report that has been submitted to VAERS.

- Follow-up question for CDC: As more information becomes available on frequency/format/timing of exposure data from vaccination centers/states and V-safe participants, can they please share with industry? It is crucial that we understand the characteristics of who is exposed in a timely manner relative to the cases in order to contextualize the cases in as close to real time as possible
    - V-safe data will be presented at meetings of the ACIP. Also, VAERS reports generated through v-safe follow-up will be included in the weekly VAERS public data postings.

- Follow-up question for CDC: We are understanding that the identifier code will be used to differentiate a VSAFE report from a spontaneous report. We also understand that this code is not yet available. Can you provide that code to manufacturers or let us know when it will be available as we may need to do some programming to be prepared to include a new code in our surveillance systems?
    - In the HHS downloadable data, the variable that contains the v-safe code (v-safe) is called SPLTTYPE. It is found in downloadable CSV file named 'VAERS DATA' in column 'AC'. In CDC WONDER data, you can search for the v-safe code in the "Mfr/Imm Project Number" field.

- Follow-up Question for CDC: CDC has daily refresh of VAERS data so if have weekly does this mean that for the daily refresh on a Friday and if industry has their refresh on a Friday, the two will be the same or does the weekly refresh for the public data lag behind.
    - The lag for the public data is one week behind the government data. For example, public data posted on 'day 8' are the equivalent data extracts that the USG has on 'day 1.'

Best,

Madison Walter-Garcia, MPH, CHES
Partnerships Lead | Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention (CDC)
[redacted]

www.cdc.gov/COVID19

From: Gregory Frank [redacted]
Sent: Wednesday, December 16, 2020 10:03 AM
To: Painter, Elizabeth (CDC/DDID/NCIRD/OD) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: RE: [-EXTERNAL-] RE: Thank you from BIO!

Eli

Very much agree!

We were finally able to reconvene this week to recap on the meeting, which helped crystalize a number of points of follow up. Some were where Tom, Steve, and others indicated they would get back to us, and others are points that arose in our debrief.

I have listed them below, and also embedded them into the document under each of the relevant question areas for more context:

- How will VAERS call center be trained to elicit the information to obtain lot#?

- Does the de-duplication effort include all 3 sources of reports, VAERS reports from VSAFE/spontaneous VAERS reports/Industry reports?

- As more information becomes available on frequency/format/timing of exposure data from vaccination centers/states and V-safe participants, can they please share with industry? It is crucial that we understand the characteristics of who is exposed in a timely manner relative to the cases in order to contextualize the cases in as close to real time as possible.

- We understand that the identifier code will be used to differentiate a VSAFE report from a spontaneous report. We also understand that this code is not yet available. Can you provide that code to manufacturers or let us know when it will be available as we may need to do some programming to be prepared to include a new code in our surveillance systems?

- CDC has daily refresh so if have weekly does this mean that for the daily refresh on a Friday and if industry has their refresh on a Friday, the two will be the same or does the weekly refresh for the public data lag behind.

I appreciate that you are in thickest of the thick of it now, so welcome thoughts on how best to review and respond to these. Would it make sense, when the CDC and/or FDA teams are able, to review and share short written responses, or should we plan to reconnect in January to discuss how best to address these? I will follow your lead.

Once again, I can't overstate how helpful the discussion was to the members, thank you all again for taking the time to walk through these issues. I look forward to knocking out these follow up items!

Warm regards,

Greg

From: Painter, Elizabeth (CDC/DDID/NCIRD/OD) [redacted]
Sent: Saturday, December 5, 2020 8:25 AM
To: Gregory Frank [redacted]
Subject: [-EXTERNAL-] RE: Thank you from BIO!

Thanks, Greg,

It was a great discussion – I'm glad we could make it work.

All the best,
Eli

Elizabeth (Eli) Painter, PhD, MBA
Policy team and Special Assistant to the Director, Vaccine Task Force
COVID-19 Response
Centers for Disease Control and Prevention
Phone: [redacted]

From: Gregory Frank [redacted]
Sent: Saturday, December 5, 2020 7:37 AM
To: Painter, Elizabeth (CDC/DDID/NCIRD/OD) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Anderson, Steven (FDA/CBER) [redacted] Forshee, Richard (FDA/CBER) [redacted] Nair, Narayan (FDA/CBER) [redacted]
Cc: Phyllis Arthur [redacted] Hannah Dorsey [redacted]
Subject: Thank you from BIO!

Good morning all,

Just wanted to extend a note of thanks for the extraordinarily helpful conversation yesterday with the companies. I think every single question that we'd hoped to discuss was answered. We appreciate your time is extremely limited right now and it was very much appreciated.

Best of luck with the next few weeks, and we look forward to reconnecting in the future.

Warm regards,

Greg

Greg Frank, PhD
Senior Director, Infectious Disease Policy
Biotechnology Innovation Organization (BIO)
1201 Maryland Ave SW, [redacted] Washington, DC 20024
Direct: [redacted]
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Revised industry questions for FDA/CDC for discussion on April 30 2:00PM-2:30PM ET

1. Has the CDC noted any difference in the quality of V-SAFE generated VAERS reports from VAERS reports from alternative sources?
    a. Has the frequency of V-SAFE-generated VAERS reports changed from earlier presentations from the CDC?
    b. Given our understanding that V-SAFE generated VAERS reports represent a low frequency of total VAERS reports, can CDC comment on what added benefit or types of information that V-SAFE has offered to signal detection for COVID-19 vaccines through VAERS?
2. When a signal is detected by the CDC and FDA surveillance systems, what is the framework the agencies (e.g. the COVID-19 Vaccine Safety Technical (VaST)) use for decision making around the appropriate response?
    a. Are there any opportunities for industry to help facilitate this decision-making process?
3. At our December 2020 meeting, we understood the CDC will plan to make regular assessments of the V-SAFE program on how long the program will run. Can the CDC share any updates on these assessments and/or plans for continuing the V-SAFE program?
4. Can CDC share any additional thinking on whether it is seeing selection bias in VSAFE samples?
    a. How is CDC addressing scenarios where patients are nonrespondent due to hospitalization or other circumstances – do they have protocols in place to address this and quickly obtain supplementary information?
    b. How does CDC make estimates with respect to data gaps and/or non-responders?
5. Is the CDC aware of any VSAFE enrollment disparities between states?
    a. Does the CDC provide states with guidance on communicating VSAFE? If so, it is tracking communications, and is it aware of any differences in how states are communicating the program?

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 5/3/2021 4:08:17 PM
To: Anderson, Steven [redacted] Beresnev, Tatiana H (NIH) [redacted] Broder, Karen R (CDC) [redacted] Calvert, Geoffrey M (CDC) [redacted] Clark, Matthew (IHS) [redacted] Clark, Thomas A (CDC) [redacted] Cohn, Amanda C (CDC) [redacted] Collins, Limone [redacted] Cunningham, Fran [redacted] Daley, Matt [redacted] DeStefano, Frank (CDC) [redacted] Edwards, Kathy [redacted] Farizo, Karen [redacted] Forshee, Richard [redacted] Gee, Julianne M (CDC) [redacted] Helfand, Rita (CDC) [redacted] Hiers, Susan G (CDC) [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Kelman, Jeffrey A (CMS) [redacted] LaPorte, Kathleen (CDC) [redacted] Lee, Grace [redacted] MacNeil, Jessica R (CDC) [redacted] Markowitz, Lauri (CDC) [redacted] Marquez, Paige L (CDC) [redacted] Mbaeyi, Sarah A (CDC) [redacted] Myers, Tanya R (CDC) [redacted] Nair, Narayan [redacted] Oliver, Sara E (CDC) [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Rubin, Mary (HRSA) [redacted] Schechter, Robert [redacted] Schindelar, Jessica A (CDC) [redacted] Shanley, Edwin (CDC) [redacted] Shay, David K (CDC) [redacted] Shimabukuro, Tom (CDC) [redacted] Sotir, Mark J (CDC) [redacted] Steinberg, Judith L (OS) [redacted] Su, John (CDC) [redacted] Talbot, Keipp [redacted] Wasley, Annemarie (CDC) [redacted] Weintraub, Eric S (CDC) [redacted] Wharton, Melinda (CDC) [redacted] Wong, Hui-Lee [redacted] Woo, Jared M (CDC) [redacted] Young, Mardia A (CDC) [redacted]
CC: Kwan.Hui[redacted] laurie.a.aukes[redacted] belongia.edward[redacted] donahue.james[redacted] bruce.fireman[redacted] kristin.x.goddard[redacted] hanson.kayla[redacted] Nicola.Klein[redacted] ousseny.x.zerbo[redacted] Ned.Lewis[redacted] mcclure.david[redacted] ousseny.x.zerbo[redacted] kieke.burney[redacted]
Subject: [EXTERNAL] VaST - Agenda for May 3 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL
Attachments: 2021-05-03 - VaST Meeting Agenda.docx; 1_VAERS update for VaST 3 May 2021.pdf; 2_VSD RCA Covid-19 vax - update VaST - 05-03-2021 - final.pdf; 3_Department of Veterans Affairs COVID-19 RCA 05-03-21_Final VASummary_Updated.pdf; 4_FDA_RCA results_5.3.21.pdf; 5_VaST_IHS Update_5.3.21.pdf

Dear all,

This email includes the VaST agenda for today as well slides for 5 presentations.
The agenda today includes updates from VAERS, 3 RCAs (VSD, VA and FDA/CMS) and a presentation from IHS.

The VaST call link information should be on your calendars.
Reminder - all VaST documents and communications are confidential.

Lauri Markowitz and Melinda Wharton

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

VaST Agenda – May 3, 2021

Open session
1:30 - 3:00

1:30-1:35 - Announcements

1:35-1:40 - v-safe (Tom Shimabukuro, CDC)

1:40-1:50 - VAERS (John Su, CDC)

1:50-1:55 - discussion

1:55 -2:05 - VSD RCA (Nicky Klein, KPNC)

2:05-2:10 - discussion

2:10-2:20 - VA RCA (Fran Cunningham, VA)

2:20-2:25 - discussion

2:25-2:35 - FDA CMS RCA and other systems (Richard Forshee, FDA)

2:35-2:40 - discussion

2:40-2:55 - IHS (Matthew Clark, IHS)

2:55-3:00 - discussion

VAERS Update – Myopericarditis and Thrombosis with Thrombocytopenia Syndrome (TTS) after Janssen COVID-19 vaccine

May 3, 2021

John Su, MD, PhD, MPH

Update on myopericarditis

PSICOVID_0000911

Brief summary of myopericarditis after COVID-19 vaccines

- **147 reports** received as of Apr 26
- Abstraction of 48/147 completed
  - Confirmed: 27 of 48
  - Preliminary (pending confirmation): 32 of 99
  - Tentative total to date: **59 reports**
  - Crude overall reporting rate: **0.25 per 1 million doses administered***
  - Estimated background rate: **1–10 per 100,000 population****
- Continuing efforts to obtain medical records

* 236,328,940 doses administered as of Apr 26 (https://covid.cdc.gov/covid-data-tracker/#vaccination-trends)
** CDC, unpublished data

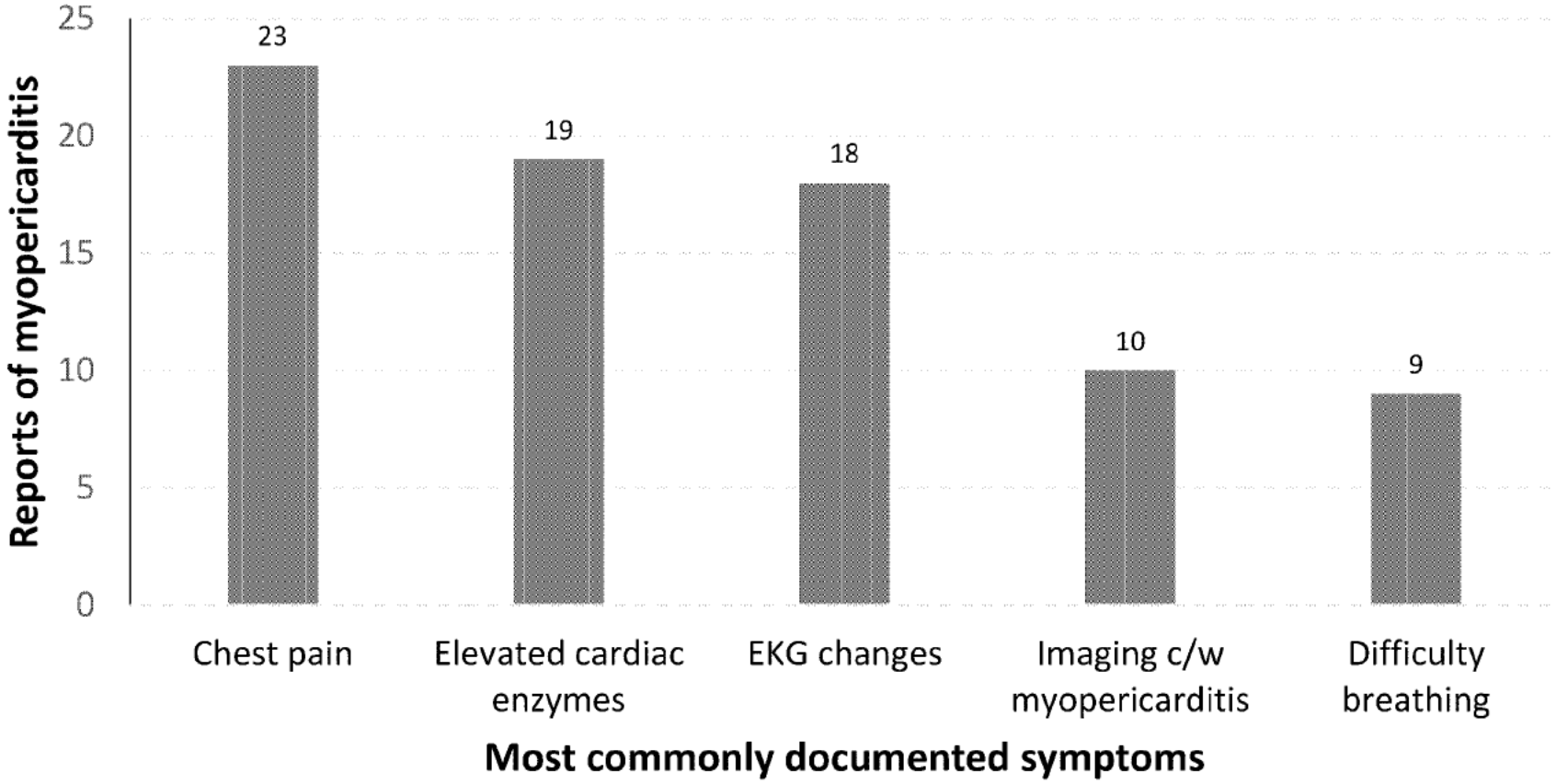
Overview of reported myopericarditis

	Pfizer-BioNTech	Moderna	Janssen	Total
Tentative case count	25	33	1	59
Median age, years (range)	41 (19, 84)	28 (18, 84)	30–39	35 (18, 84)
Median time to onset, days (range)	3 (0, 20)	3 (0, 28)	<10	3 (0, 28)
Male (%)	16 (64%)	24 (73%)	—	40 (68%)

- Estimated reporting rates*:
  - Pfizer-BioNTech: 0.20 per 1 million doses administered
  - Moderna: 0.32 per 1 million doses administered
  - Janssen: 0.12 per 1 million doses administered

* Imputed from doses administered as of May 1, 2021

Most commonly documented symptoms among reported myopericarditis (N = 27)



- 22 of 27 cases were physician-diagnosed

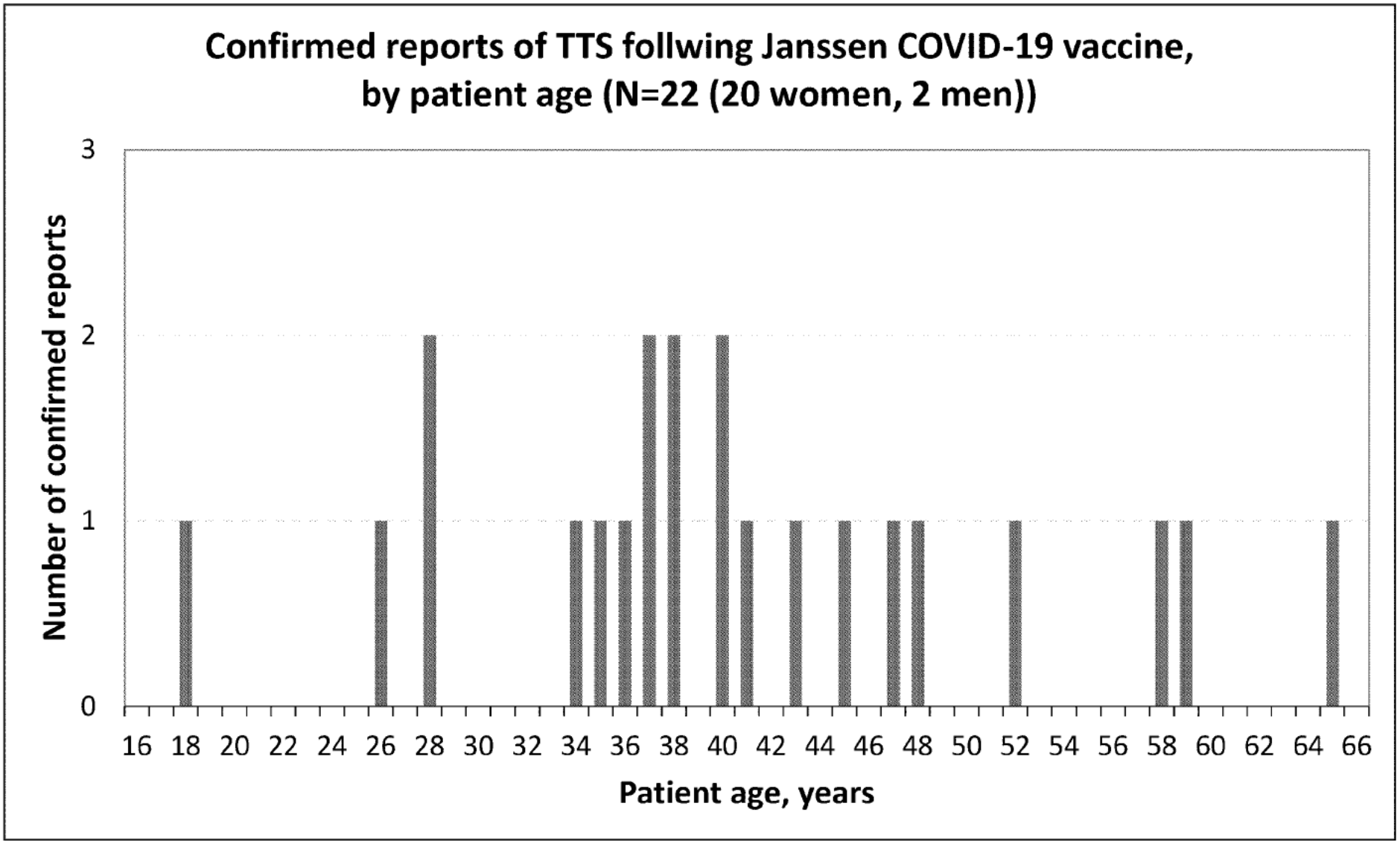
Update on TTS

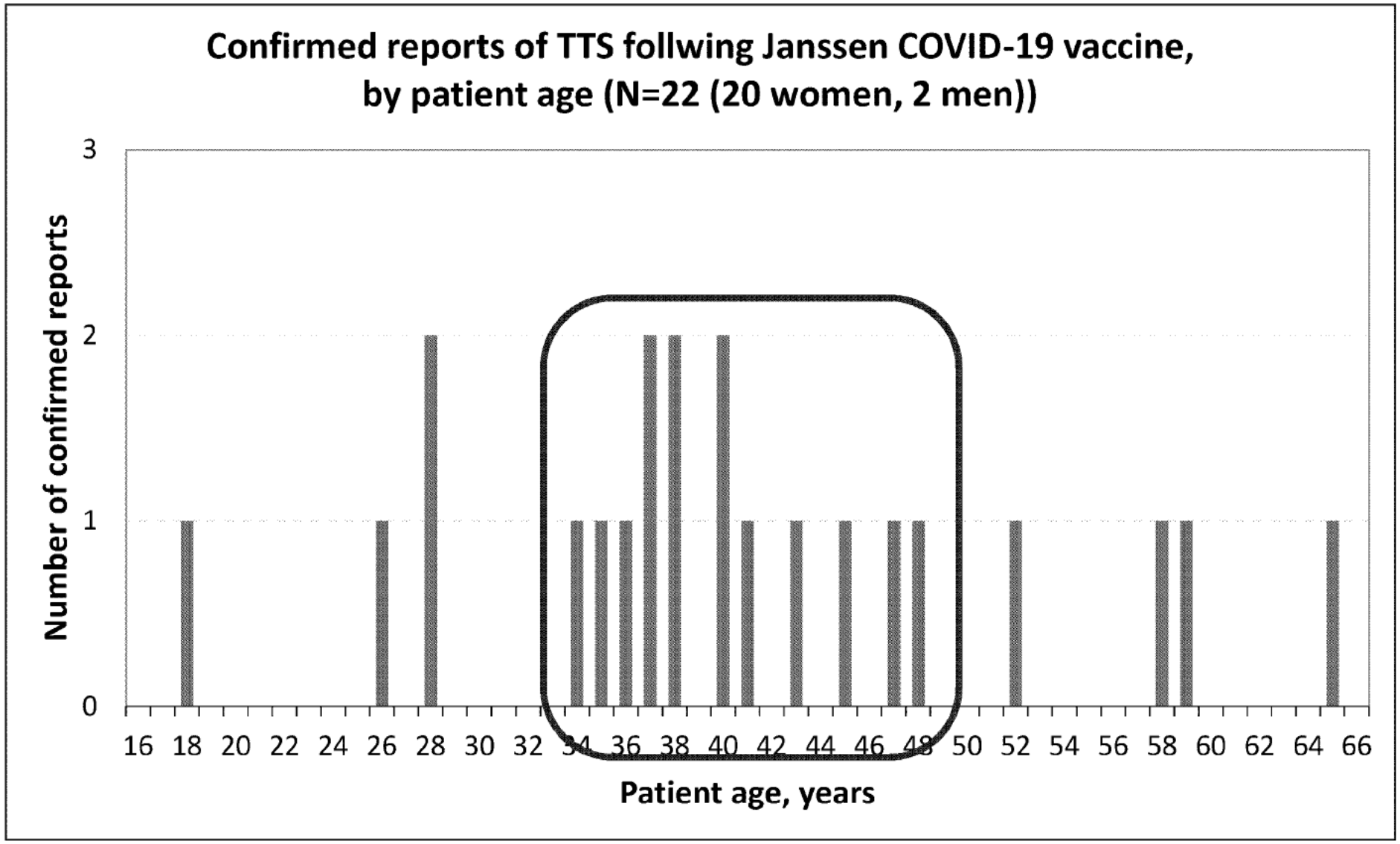
Reporting rates of TTS after Janssen COVID-19 vaccine

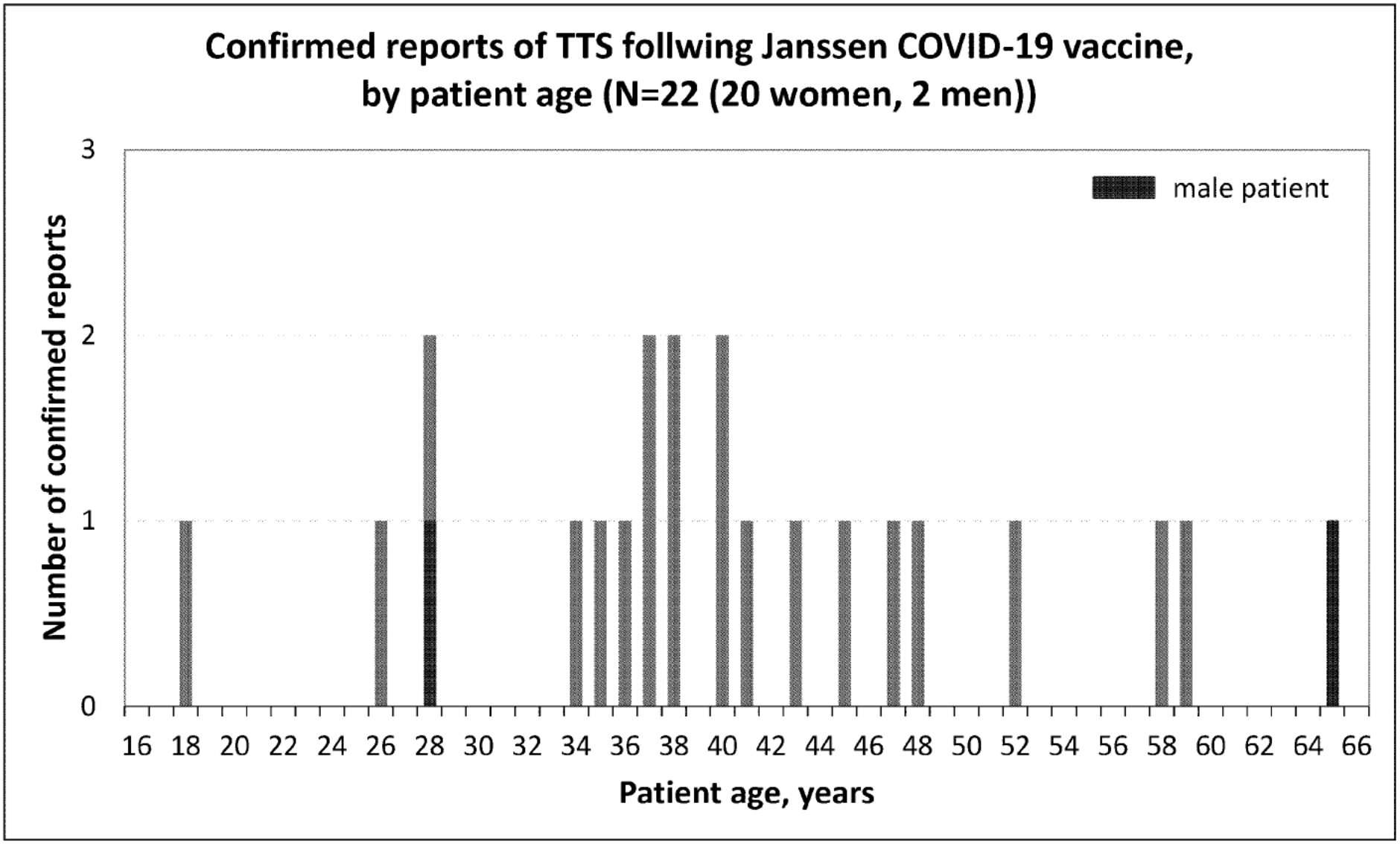
- 8.22 million vaccine doses administered* and 22 confirmed TTS cases† as of April 28, 2021
  - Some age- and sex-specific doses administered data were imputed
  - Additional potential TTS cases under review, including potential male cases
  - Of 5 additional female cases, 4 were 40–49 years of age, 1 was 50+ years of age

	Females			Males		
Age group	TTS cases	Doses admin	Reporting rate‡	TTS cases	Doses admin	Reporting rate‡
18-49 years old	**17**	1,890,270	9.0 per million	**1**	2,020,753	0.5 per million
50+ years old	**3**	2,150,667	1.4 per million	**1**	2,043,280	0.5 per million

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † One case was excluded from the final analysis: a female aged <50 years who had concurrent diagnosis of COVID-19 and TTS following receipt of Janssen vaccine; ‡ Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

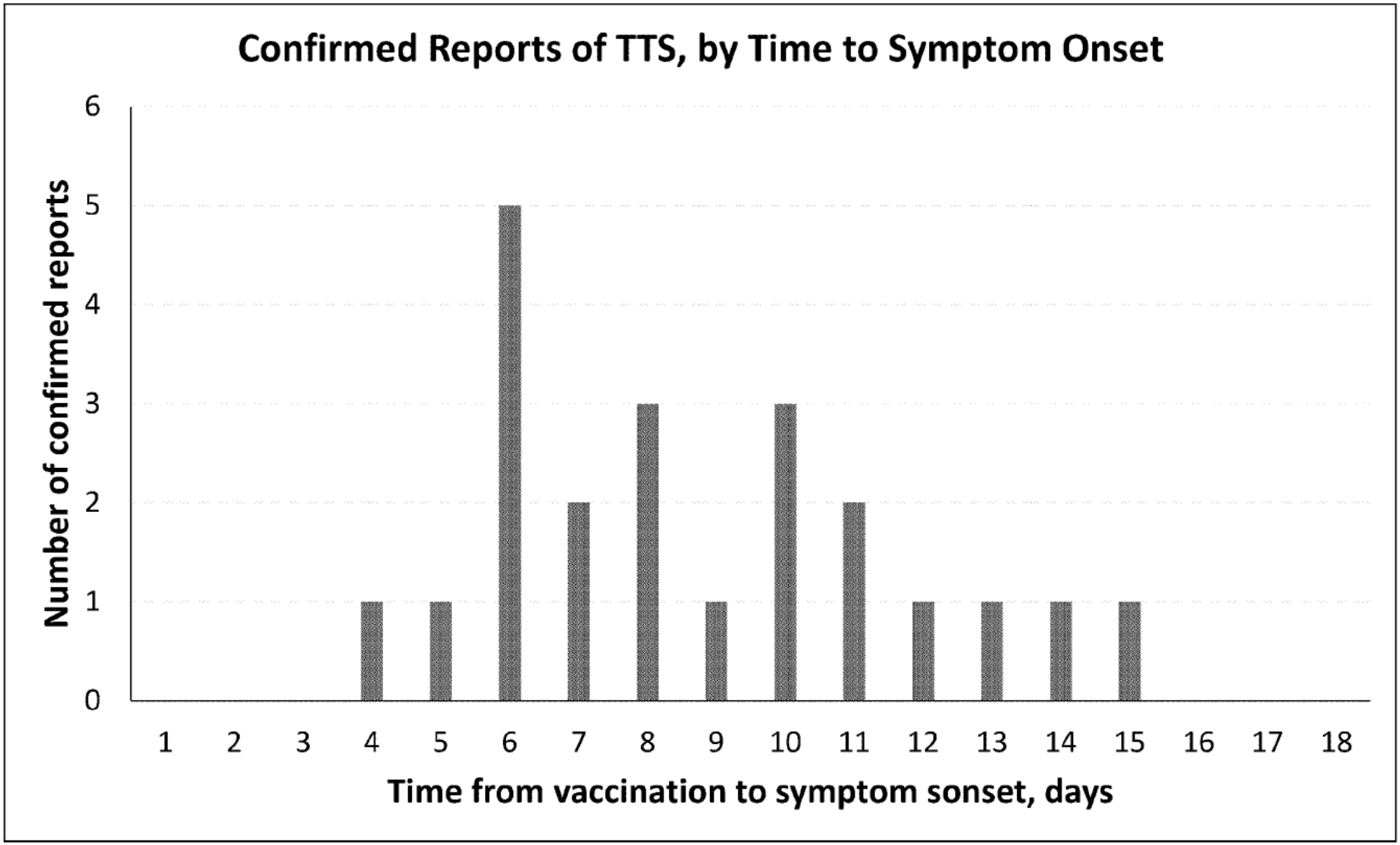

Confirmed reports of TTS follwing Janssen COVID-19 vaccine,
by patient age (N=22 (20 women, 2 men))
Number of confirmed reports
0
1
2
3
16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66
Patient age, years


Confirmed reports of TTS follwing Janssen COVID-19 vaccine,
by patient age (N=22 (20 women, 2 men))
Number of confirmed reports
0
1
2
3
16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66
Patient age, years


Confirmed reports of TTS follwing Janssen COVID-19 vaccine,
by patient age (N=22 (20 women, 2 men))
male patient
Number of confirmed reports
0
1
2
3
16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64 66
Patient age, years

Characteristics of patients with TTS after Janssen COVID-19 vaccine, N=22

- Median age 39 years (range 18–65)
- Median time to symptom onset 8 days (range 4–15 days)
- 20 cases among women, 2 among men
- 5 cases confirmed after pause on Janssen vaccine lifted on April 23, 2021
- 18/22 cases included cerebral venous sinus thrombosis (CVST)
- Other involved vessels:
  - Portal, jugular, brachial veins
  - Carotid, iliac, femoral arteries

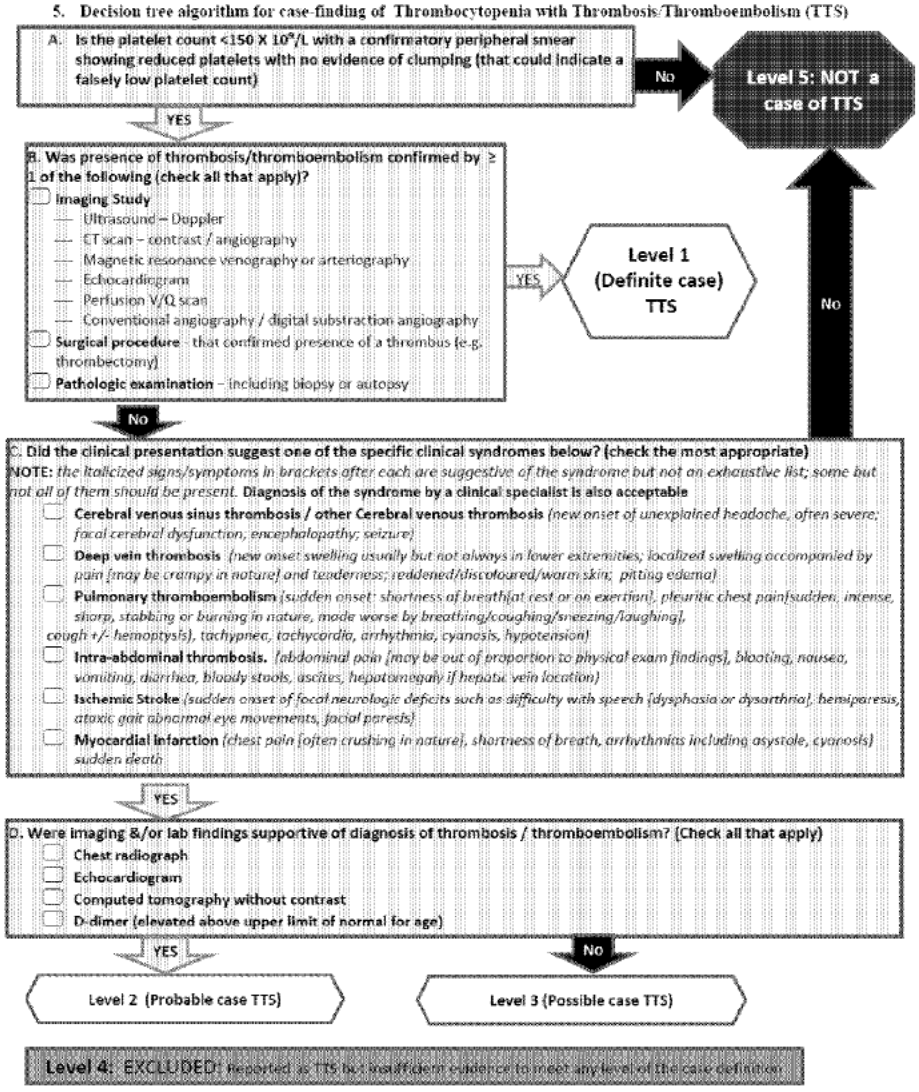

Confirmed Reports of TTS, by Time to Symptom Onset
Number of confirmed reports
0
1
2
3
4
5
6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Time from vaccination to symptom sonset, days

Summary

Summary

- **59** tentative reports of myopericarditis after COVID-19 vaccines (27 after complete abstraction, 32 still under review)
  - Median age after Pfizer (41 years) older than Moderna (28 years)
  - Males > females; Moderna somewhat more than Pfizer
  - Reporting rate (0.25 per 1M doses administered) << background rate (1–2 per 100,000K population)
- **22** reports of TTS to VAERS as April 26, 2021
  - Median age = 39 years (range: 18–65 years)
  - Median time to symptom onset 8 days (range 4–15 days)
  - No obvious patterns of risk factors detected
  - 18 of 22 reports with CVST

Extra Slides



Thrombocytopenia (<150,000 per mm^3)

AND either

Confirmation of thrombosis/embolus by imaging, surgery, or pathology

OR

Symptoms consistent with CVST, DVT, PE, intra-abdominal thrombosis, ischemic stroke, or MI

From https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-case-finding-definition/

Reports of TTS to VAERS after COVID-19 vaccines as of April 16, 2021

- Janssen COVID-19 vaccine
  - 9 confirmed reports of TTS (platelet counts <150K/mm^3) following 7.9 million doses administered
    - Reporting rate of 1.14 cases per million doses administered
- Pfizer-BioNTech COVID-19 vaccine
  - 0 reports following 107.1 million doses administered
- Moderna COVID-19 vaccine
  - 3 reports following 90,718,986 million doses administered
  - All 3 with normal platelet counts; onset 2, 6, and 12 days after vaccination

Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations

Characteristics of patients with CVST and thrombocytopenia* after Janssen COVID-19 vaccine, N=7

- Median age 37 years (range 18–59)
- Median time to symptom onset 9 days (range 6–15 days)
- 7 cases white; 1 case black (1 case without race/ethnicity data)
- Current estrogen/progesterone use (n=1)
- Pregnant or post-partum (n=0)
- Pre-existing conditions
  - Obesity (n=3)
  - Hypothyroidism (n=1)
  - Hypertension (n=2)
  - Asthma (n=1)
  - Coagulation disorders (none known)

* Note: Thrombosis usually does not occur in the presence of low platelets; these case presentations are atypical and consistent with cases observed after AstraZeneca COVID-19 vaccine

Reporting rates of TTS after Janssen COVID-19 vaccine in women

- 3.99 million vaccine doses administered to women* with 15 confirmed TTS cases† as of April 21, 2021
  - Some age-specific doses administered data were imputed

	Females		
Age group	TTS cases	Doses admin	Reporting rate‡
18-29 years old	**3**	579,709	5.2 per million
30-39 years old	**7**	594,215	11.8 per million
40-49 years old	**3**	692,370	4.3 per million
50-64 years old	**2**	1,367,529	1.5 per million
65+ years old	**0**	757,710	0 per million

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † One case was excluded from the final analysis: a female aged <50 years who had concurrent diagnosis of COVID-19 and TTS following receipt of Janssen vaccine; ‡ Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Brief description of non-CVST patients*, n=2 (patients listed in no particular order)

	Brief description
Patient 8	37 y black female, *(+) OCP use. Developed headache and L-sided paralysis 10 days after vaccine. CT = **carotid artery occlusion**; plt = **121K**, dropping to 60K first day of admission
Patient 9	59 y white female. Developed L leg swelling and bruising; confirmed as deep vein thrombosis. Next day, identified bilateral **iliac artery occlusion**; plt = **15K**.

*All were hospitalized and admitted to the intensive care unit

Locations of CVST, intracerebral hemorrhage, and other thromboses, N=9

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Location of CVST	Right transverse sinus and right sigmoid sinus	Left transverse, left sigmoid, straight, and confluence of sinuses	Superior sagittal, inferior sagittal, and straight sinuses	Right transverse and right sigmoid sinuses	Right transverse and right sigmoid sinuses	Right transverse sinus	Superior sagittal, transverse, and straight sinuses	[none]	[none]
Location of intracerebral hemorrhage	Right temporo-parietal lobe	Left temporal lobe	Bilateral frontal lobes, intra-ventricular	[none]	[none]	Occipital lobe	Right parietal, temporal lobes; basal ganglia	[none]	[none]
Locations of other thromboses	[none]	[none]	[none]	**Portal vein and right pulmonary artery**	**Bilateral lower extremity VTE, right internal jugular vein**	**Portal vein**	[none]	**Carotid artery; femoral vein; brachial, cephalic arteries**	**Left lower extremity VTE; bilateral iliac arteries**

SARS-CoV-2 test results among TTS patients, N=9

	SARS-CoV-2 viral test	SARS-CoV-2 serology
Patient 1	Negative	Not documented
Patient 2	Negative	Nucleocapsid Ab negative
Patient 3	Negative	Not documented
Patient 4	Negative	Not documented
Patient 5	Negative	Unspecified COVID Ab negative
Patient 6	Negative	Unspecified COVID Ab negative
Patient 7	h/o COVID-19 (Nov 2020)	h/o COVID-19 (Nov 2020)
Patient 8	Not documented	Not documented
Patient 9	h/o COVID-19 (Jan 2021)	h/o COVID-19 (Jan 2021)

Hematology test results among TTS patients, N=9

	Lowest platelet value (per mm^3)	PF4 HIT* antibody test result(s)
Patient 1	12,000	Not done
Patient 2	69,000	Positive
Patient 3	18,000	Positive
Patient 4	127,000	Positive
Patient 5	10,000	Positive
Patient 6	14,000	Positive
Patient 7	64,000	Positive
Patient 8	60,000	Positive
Patient 9	15,000	Pending

*Platelet factor 4 heparin induced thrombocytopenia

Treatment and outcomes among TTS patients, N=9

- Treatment
  - Heparin (n=6)
  - Nonheparin anticoagulants (n=8)*
  - Platelets (n=4)
  - Intravenous immunoglobulin (n=4)
- Outcomes
  - Death (n=1)
  - Remain hospitalized (n=5)
    - Intensive care unit (n=3)
  - Discharged home (n=3)

* 7 of these patients received argatroban; 1 received bivalirudin

Cerebral venous sinus anatomy

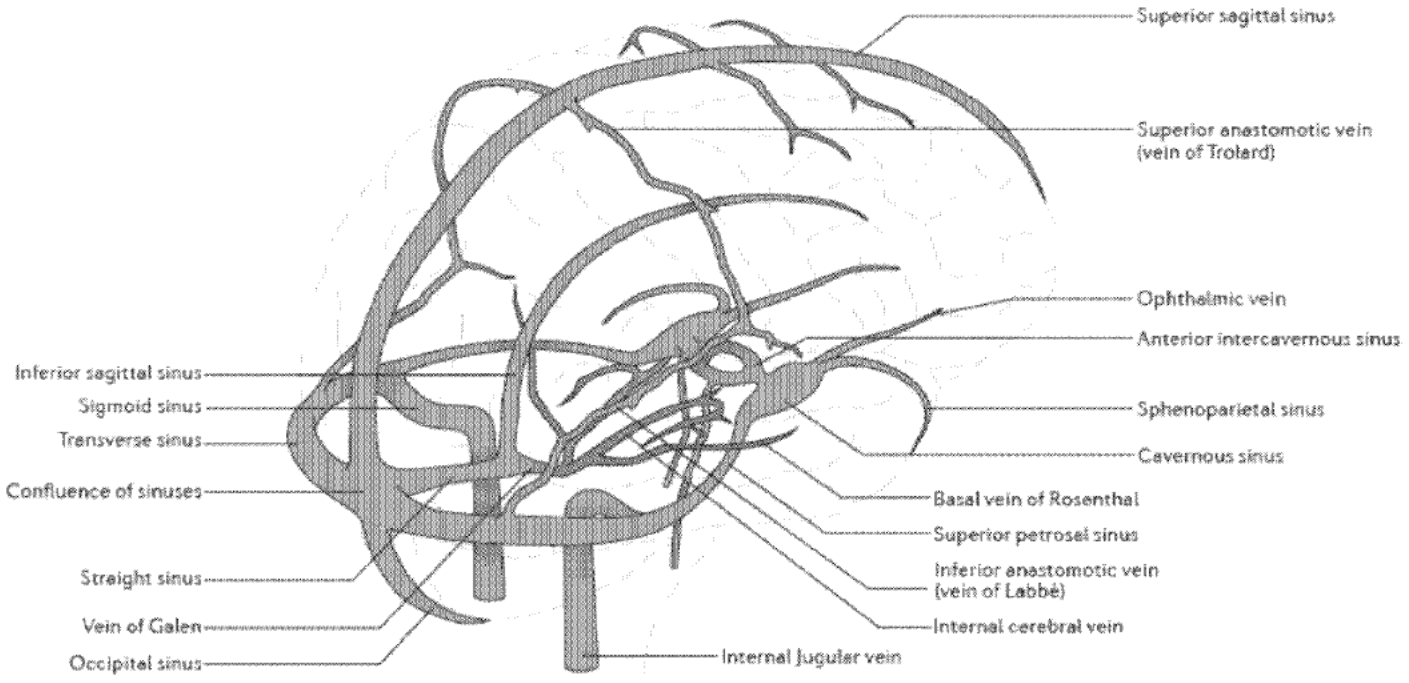


Figure 1 | **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

Silvis SM et al, Nature Reviews Neurology 13, 555-565(2017)

CVST signs and symptoms

- More common presentations
  - Isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems)
  - Focal syndrome (focal deficits, seizures, or both)
  - Encephalopathy (multifocal signs, mental status changes, stupor, or coma)

- Rare presentations
  - Cavernous sinus syndrome
  - Subarachnoid hemorrhage
  - Cranial nerve palsies

Cerebral venous sinus thrombosis (CVST)

Background epidemiology[1-3]

- Rare, 0.22–1.57 per 100,000, ~0.5-1% of all strokes
- Median age 37 years
- 8% of patients >65 years
- Female:male ratio of 3:1

Risk factors[4]

- Prothrombotic conditions (genetic or acquired)
- Oral contraceptives
- Pregnancy and the post-partum period
- Malignancy
- Infection
- Mechanical precipitants (lumbar puncture)

[1] Cerebral vein and dural sinus thrombosis in Portugal: 1980-1998. Ferro JM, Correia M, Pontes C, Baptista MV, Pita F, Cerebral Venous Thrombosis Portuguese Collaborative Study Group (Venoport) Cerebrovasc Dis. 2001;11(3):177.
[2] The incidence of cerebral venous thrombosis: a cross-sectional study. Coutinho JM, Zuurbier SM, Aramideh M, Stam J. Stroke. 2012 Dec;43(12):3375-7..
[3] Cerebral Venous Sinus Thrombosis Incidence Is Higher Than Previously Thought: A Retrospective Population-Based Study. Devasagayam S, Wyatt B, Leyden J, Kleinig T. Stroke. 2016 Sep;47(9):2180-2.
[4] Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Saposnik G, et al. 2011;42(4):1158.

Additional report of patient with non-CVST thromboses and thrombocytopenia after Janssen COVID-19 vaccine*

- 50s y/o female
- History coronary artery disease, hypertension, asthma, COPD
- Developed bruising and leg swelling 11 days after vaccination with Janssen vaccine
- Hospitalized with hematologic event that is non-CVST
  - Left lower extremity deep venous thrombosis
  - Right superficial femoral artery and bilateral iliac artery thrombosis (non-CVST)
- Thrombocytopenia of 15,000/mm^3

*Assessment based only on VAERS report; investigation in-progress including obtaining and reviewing medical records

Observed vs. expected CVST cases following Janssen COVID-19 vaccine

- Estimated annual incidence of CVST ~0.5–2 cases per 100,000 population*
- Assumed risk period of 5.6% of a calendar year: (41 days/2) ÷ 365 days
- Doses administered among women aged 20–50 years = 1,402,712 doses (as of Apr 12)

Est. annual background incidence	Obs. cases in women aged 20–50 yrs	Exp. cases in women aged 20–50 yrs	Reporting ratio, women aged 20–50 yrs
0.5 per 100K	6	0.39	**15.4**
1.0 per 100K	6	0.79	**7.6**
1.5 per 100k	6	1.18	**5.1**
2.0 per 100k	6	1.58	**3.8**

* https://www.hopkinsmedicine.org/health/conditions-and-diseases/cerebral-venous-sinus-thrombosis, http://www.med.umich.edu/1libr/Stroke/SinusVeinThrombosis.pdf, https://www.nejm.org/doi/10.1056/NEJMra042354?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub, https://www.ahajournals.org/doi/pdf/10.1161/STROKEAHA.116.013617, https://www.nature.com/articles/nrneurol.2017.104

Rapid Cycle Analysis (RCA) to Monitor the Safety of COVID-19 Vaccines in Near Real-Time within the Vaccine Safety Datalink

Kaiser Permanente Vaccine Study Center
Kaiser Permanente Northern California
Marshfield Clinic Research Institute
Vaccine Safety Datalink – Immunization Safety Office, CDC

KAISER PERMANENTE
VACCINE STUDY CENTER

Marshfield Clinic
Research Institute

VSD Rapid Cycle Analysis

The specific aims:

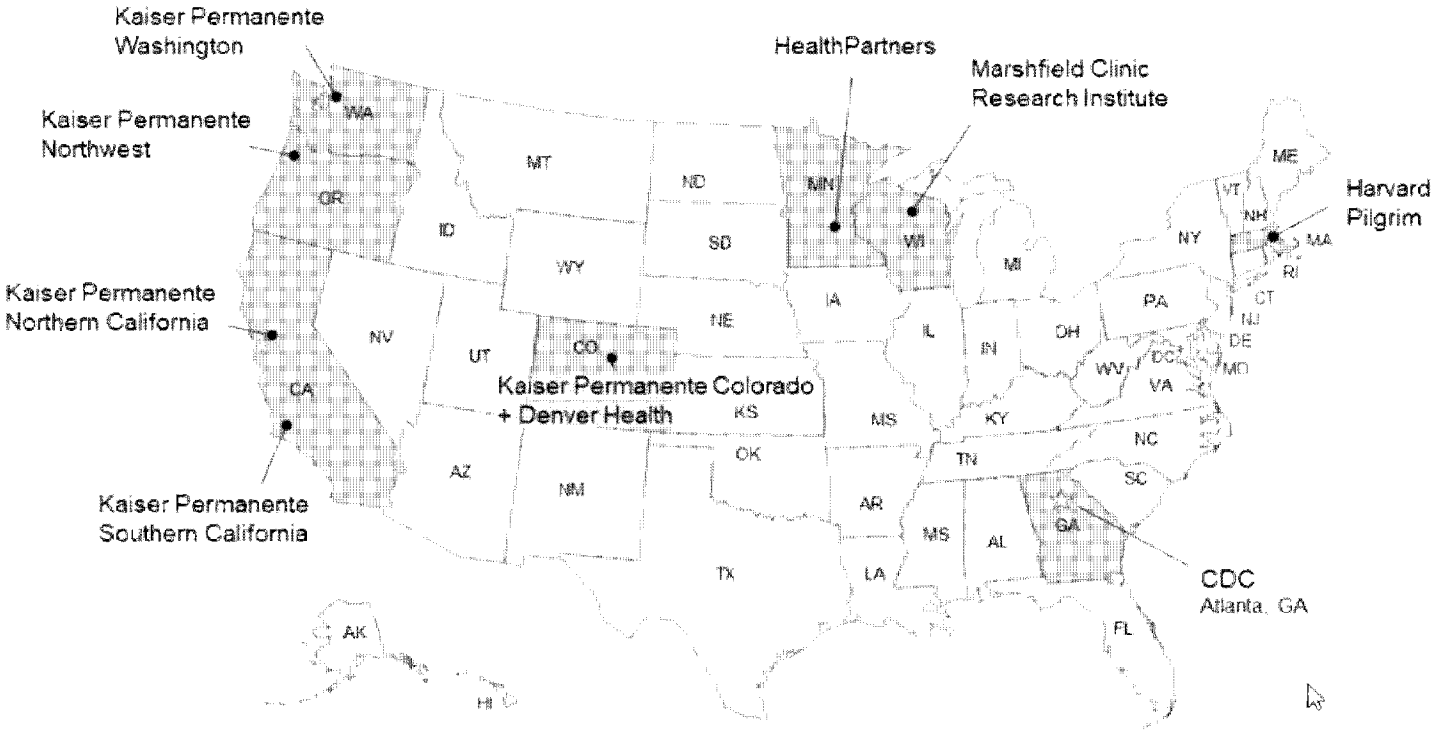
- To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

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

Project Period: Sept 2020 – August 2023 (3 years)

The Vaccine Safety Datalink (VSD)

Participating VSD Healthcare Organizations

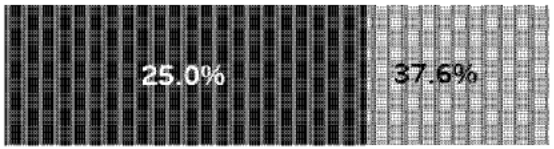


- Established in 1990
- Collaborative project between CDC and Nine Integrated Health Care Organizations

Vaccine Uptake (Data Through 4/24/21)

VSD COVID-19 Vaccine Totals

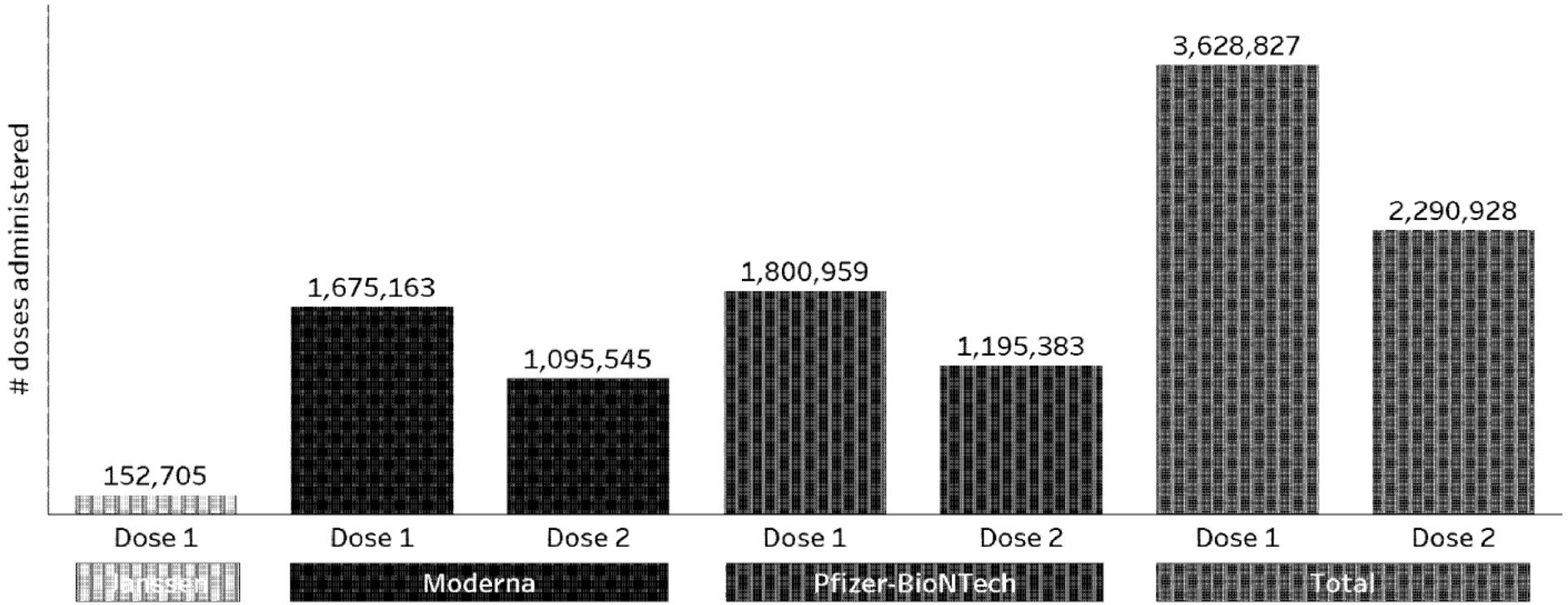
Total Doses Administered	Total Doses Admin per 100K	# People Initiating Vaccination	# People Fully Vaccinated
5,919,755	61,854	3,628,827	2,443,633
+624,838 since last week	+6,533 since last week	+305,131 since last week	+330,294 since last week



To date, 37.6% of VSD population initiated vaccination and 25.0% is fully vaccinated

0.0% 50.0% 100.0%

VSD COVID-19 Vaccine Totals



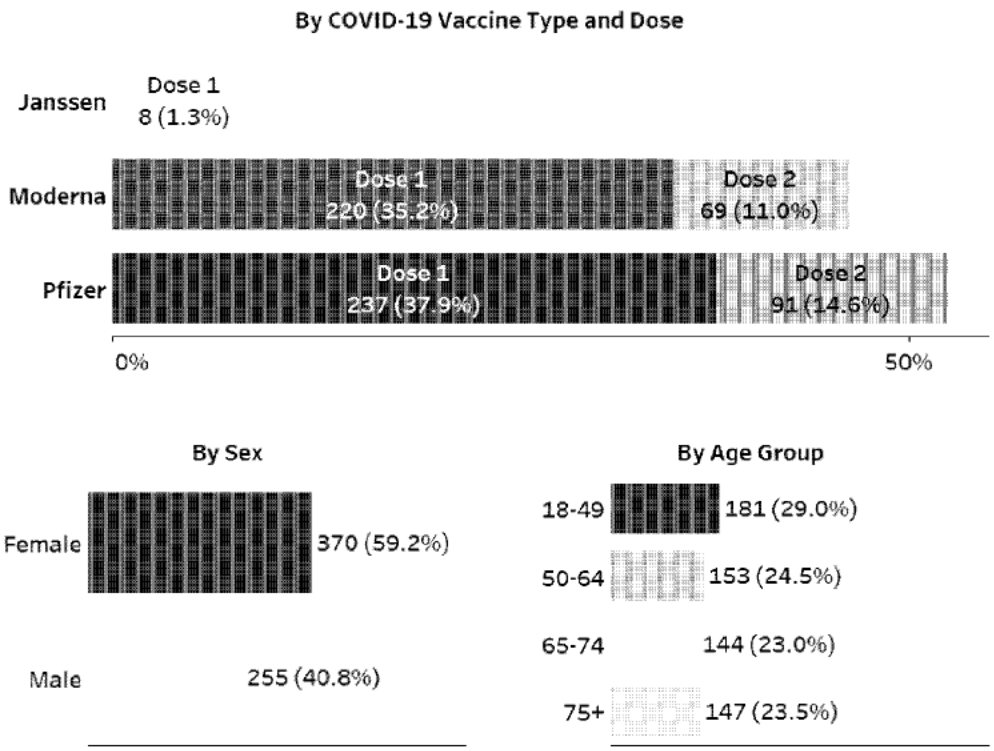
Simultaneous Vaccine Administration with COVID-19 Vaccine

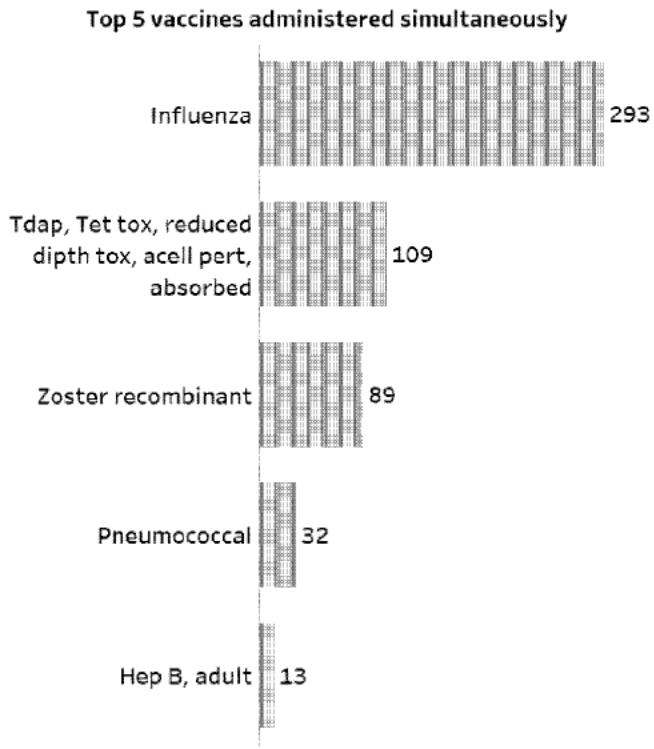
Number of COVID-19 doses admin to date:

5,919,755

Number of people who received simult vaccs:

625





Note: Individuals less than 16 years of age are excluded from all visualizations.

Analysis
(Data Through 4/24/21)

Any signal in the VSD for the 21 day risk interval? Yes or no, by outcome

#	VSD Outcomes	Abbreviation	Signal (Y/N)
1	Acute disseminated encephalomyelitis (settings = E, I)	ADEM	N
2	Acute myocardial infarction (settings = E, I)	AMI	N
3	Acute respiratory distress syndrome (settings = E, I)	ARDS	N/A
4	Anaphylaxis (settings = E, I)	ANAPH	N/A
5	Appendicitis (settings = E, I)	APPND	N
6	Bell's palsy (settings = E, I, O)	BP	N
7	Cerebral Venous Sinus Thrombosis (settings = E, I)	CVST	N
8	Convulsions / seizures (settings = E, I)	SZ	N
9	Disseminated intravascular coagulation (settings = E, I)	DIC	N
10	Encephalitis / myelitis / encephalomyelitis (settings = E, I)	ENCEPH	N
11	Guillain-Barré syndrome (settings = E, I)	GBS	N
12	Thrombotic thrombocytopenic purpura (settings = E, I)	TTP	N
13	Immune thrombocytopenia (settings = E, I, O)	ITP	N
14	Kawasaki disease (settings = E, I)	KD	N
15	Multisystem Inflammatory Syndrome in Children & Adults (MIS-C, MIS-A) (settings = E, I)	MISC	N/A
16	Myocarditis / pericarditis (settings = E, I)	MYOC	N
17	Narcolepsy and cataplexy (settings = E, I, O)	NARC	N/A
18	Stroke, hemorrhagic (settings = E, I)	HSTK	N
19	Stroke, ischemic (settings = E, I)	ISTK	N
20	Transverse myelitis (settings = E, I)	TM	N
21	Venous thromboembolism (settings = E, I, O)	VTE	N
22	Pulmonary embolism (settings = E, I)	PE	N

Abbreviations: E = ED; I = Inpt; O = Outpt

Primary Analyses: Vaccinated Concurrent Comparison "Sequential Analysis"

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute disseminated encephalomyelitis	1	.	0.01 - ne	0.800	0.800	no
Acute myocardial infarction	373	0.86	0.71 - 1.05	0.146	0.934	no
Appendicitis	280	0.82	0.66 - 1.02	0.079	0.965	no
Bell's palsy	284	1.09	0.86 - 1.39	0.495	0.267	no
CVST	7	0.78	0.21 - 3.25	0.702	0.769	no
Disseminated intravascular coagulation	15	0.46	0.18 - 1.18	0.104	0.972	no
Encephalitis / myelitis / encephalomyelitis	6	0.43	0.11 - 1.82	0.233	0.947	no
Guillain-Barré syndrome (Quick Reviewed)	5	1.49	0.18 - 39.25	0.794	0.595	no
Stroke, hemorrhagic	154	0.78	0.57 - 1.06	0.115	0.952	no
Stroke, ischemic	635	1.01	0.86 - 1.18	0.937	0.484	no
Immune thrombocytopenia	29	0.98	0.46 - 2.19	0.935	0.609	no
Myocarditis / pericarditis	31	0.70	0.37 - 1.35	0.277	0.897	no
Seizures	134	0.99	0.70 - 1.42	0.967	0.552	no
Thrombotic thrombocytopenic purpura	2	.	0.24 - .	0.260	0.260	no
Venous thromboembolism	407	1.23	1.00 - 1.53	0.047	0.027	no
Pulmonary embolism	319	0.97	0.77 - 1.21	0.752	0.645	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
[3]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[4]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
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Pulmonary embolism	**319**	**0.97**	**0.77 - 1.21**	**0.752**	**0.645**	**no**

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
[3]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[4]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Limited to ages 65+, (data through week ending March 27, 2021)

Outcome	Vaccine	Dose	Events in Risk Interval[2]	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)
Pulmonary embolism	Both mRNA	Both Doses	167	0.99	0.7 - 1.44	0.959	0.557
	Pfizer	Both Doses	87	0.91	0.52 - 1.65	0.726	0.691
	Moderna	Both Doses	78	1.08	0.67 - 1.79	0.779	0.437

[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[2]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Limited to ages 65+, (data through week ending March 27, 2021)

Outcome	Vaccine	Dose	Events in Risk Interval[2]	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)
Pulmonary embolism	Both mRNA	Both Doses	167	0.99	0.7 - 1.44	0.959	0.557
	Pfizer	Both Doses	87	0.91	0.52 - 1.65	0.726	0.691
	Moderna	Both Doses	78	1.08	0.67 - 1.79	0.779	0.437

Unvaccinated Comparison

Outcome	Vaccine	Dose	Events in Risk Interval	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value
Pulmonary embolism	Both mRNA	Both Doses	167	1.03	0.84 - 1.25	0.780
	Pfizer	Both Doses	89	1.08	0.84 - 1.38	0.524
	Moderna	Both Doses	78	1.00	0.78 - 1.29	0.965

[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[2]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute disseminated encephalomyelitis	1	.	0.01 - ne	0.800	0.800	no
Acute myocardial infarction	373	0.86	0.71 - 1.05	0.146	0.934	no
Appendicitis	280	0.82	0.66 - 1.02	0.079	0.965	no
Bell's palsy	284	1.09	0.86 - 1.39	0.495	0.267	no
CVST	7	0.78	0.21 - 3.25	0.702	0.769	no
Disseminated intravascular coagulation	15	0.46	0.18 - 1.18	0.104	0.972	no
Encephalitis / myelitis / encephalomyelitis	6	0.43	0.11 - 1.82	0.233	0.947	no
Guillain-Barré syndrome (Quick Reviewed)	5	1.49	0.18 - 39.25	0.794	0.595	no
Stroke, hemorrhagic	154	0.78	0.57 - 1.06	0.115	0.952	no
Stroke, ischemic	635	1.01	0.86 - 1.18	0.937	0.484	no
Immune thrombocytopenia	29	0.98	0.46 - 2.19	0.935	0.609	no
Myocarditis / pericarditis	**31**	**0.70**	**0.37 - 1.35**	**0.277**	**0.897**	**no**
Seizures	134	0.99	0.70 - 1.42	0.967	0.552	no
Thrombotic thrombocytopenic purpura	2	.	0.24 - .	0.260	0.260	no
Venous thromboembolism	407	1.23	1.00 - 1.53	0.047	0.027	no
Pulmonary embolism	319	0.97	0.77 - 1.21	0.752	0.645	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
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[3]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[4]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Events in Comparison Interval	Adjusted Rate Ratio[3,4]	Weekly Analysis[1] 95% Confidence Interval	Weekly Analysis[1] 2-Sided P-value	Sequential Test[2] 1-sided P-value (Fisher)	Sequential Test[2] 'Signal' 1-sided p < 0.0048
Myocarditis / pericarditis	31	16	0.70	0.37 - 1.35	0.277	0.897	no

Unvaccinated Comparison

Unvaccinated - 21-day risk interval	Events in Risk Interval	Events in Unvaccinated	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value
Myocarditis / pericarditis	**31**	**215**	**1.29**	**0.83 – 1.98**	**0.249**

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
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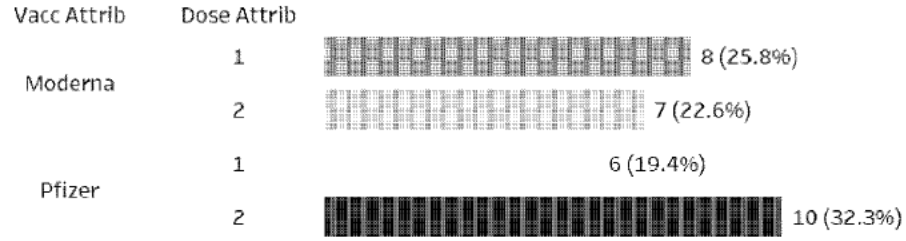
[3]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[4]**Comparison interval** is 22–42 days after either dose.

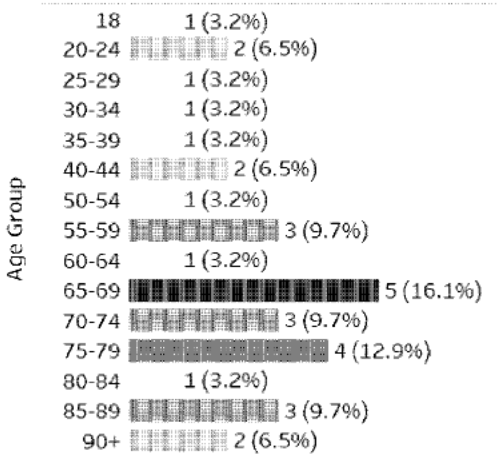
Myocarditis / Pericarditis Automated Summary: 21 day Risk Interval

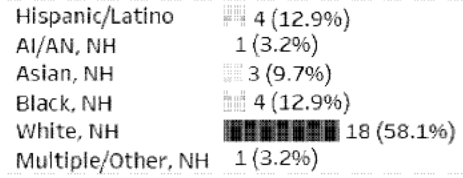
31

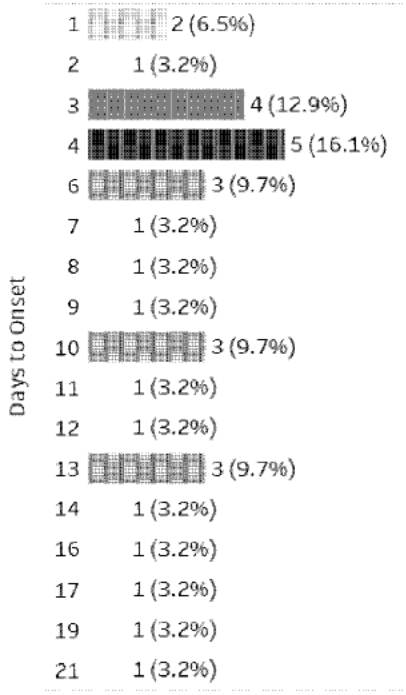
cases identified in the 1-21 day risk interval

Male	18 (58.1%)
Female	13 (41.9%)
Not Pregnant	13 (100.0%)
High Risk	23 (74.2%)
Not HR	8 (25.8%)
COVID19 HX	3 (9.7%)
No COVID19 HX	28 (90.3%)

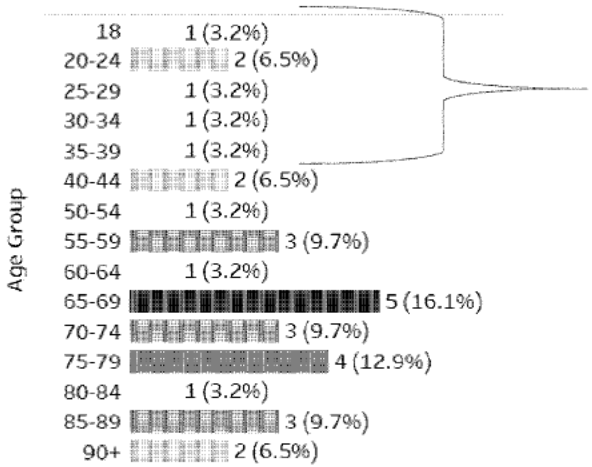








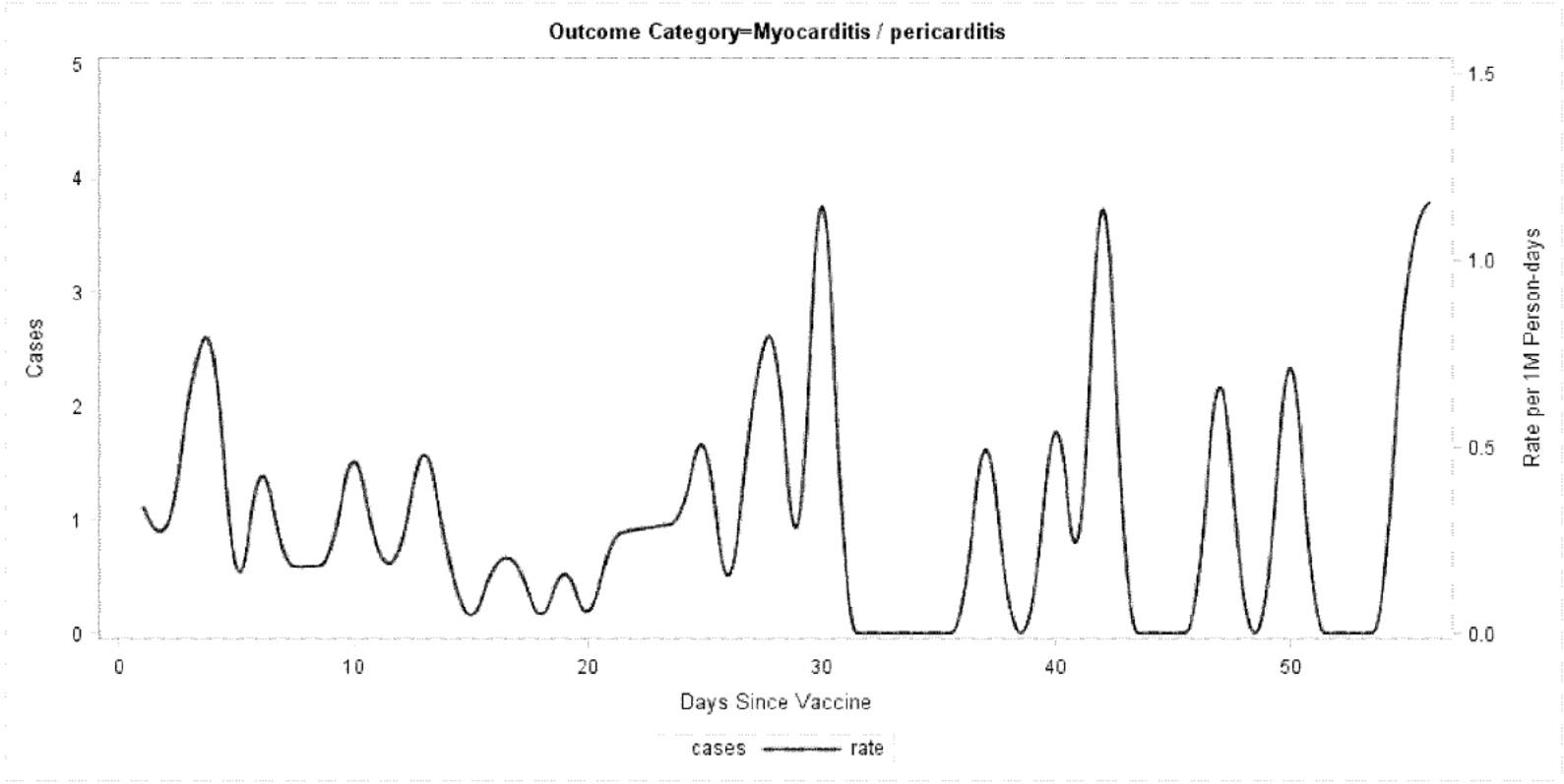
Myocarditis / Pericarditis Automated Summary: 21 day Risk Interval



For the 16 – 39 Year Age Group

6 cases were identified following 1.31 million combined mRNA doses

Myocarditis/Pericarditis -- Days since vaccination and Rate per Million Person-Days



Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute disseminated encephalomyelitis	1	.	0.01 - ne	0.800	0.800	no
Acute myocardial infarction	373	0.86	0.71 - 1.05	0.146	0.934	no
Appendicitis	280	0.82	0.66 - 1.02	0.079	0.965	no
Bell's palsy	284	1.09	0.86 - 1.39	0.495	0.267	no
CVST	**7**	**0.78**	**0.21 - 3.25**	**0.702**	**0.769**	**no**
Disseminated intravascular coagulation	15	0.46	0.18 - 1.18	0.104	0.972	no
Encephalitis / myelitis / encephalomyelitis	6	0.43	0.11 - 1.82	0.233	0.947	no
Guillain-Barré syndrome (Quick Reviewed)	5	1.49	0.18 - 39.25	0.794	0.595	no
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Thrombotic thrombocytopenic purpura	2	.	0.24 - .	0.260	0.260	no
Venous thromboembolism	407	1.23	1.00 - 1.53	0.047	0.027	no
Pulmonary embolism	319	0.97	0.77 - 1.21	0.752	0.645	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
[3]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[4]**Comparison interval** is 22–42 days after either dose.

CVST events in 21-days risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Events in Comparison Interval[3]	Adjusted Rate Ratio[4]	Weekly Analysis[1] 95% Confidence Interval	Weekly Analysis[1] 2-Sided P-value	Sequential Test[2] 1-sided P-value (Fisher)	Sequential Test[2] 'Signal' 1-sided p < 0.0048
CVST	7	4	0.78	0.21 3.25	0.702	0.769	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
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CVST events in 21-days risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Events in Comparison Interval[3]	Adjusted Rate Ratio[4]	Weekly Analysis[1] 95% Confidence Interval	Weekly Analysis[1] 2-Sided P-value	Sequential Test[2] 1-sided P-value (Fisher)	Sequential Test[2] 'Signal' 1-sided p < 0.0048
CVST	7	4	0.78	0.21 3.25	0.702	0.769	no

Unvaccinated Comparison

Outcome Event	Events in Risk Interval	Events in Unvaccinated	Weekly Analysis Adjusted Rate Ratio	Weekly Analysis 95% Confidence Interval	Weekly Analysis 2-Sided P-value
CVST	7	52	1.13	0.41 – 2.78	.782

Cerebral Venous Sinus Thrombosis (CVST): mRNA vaccines Quick Chart Review Summary

- All 11 (risk and comparison) cases have had a “informal, quick chart review”
- 5 of the 11 cases have been ruled-out
  - 2 cases were history of CVST
  - 2 cases had a head injury
  - 1 case had Chronic Cavernous Sinus Syndrome
- 6 of the 11 cases are potentially CVST cases, all ***without thrombocytopenia***

Cerebral Venous Sinus Thrombosis (CVST): mRNA vaccines Quick Chart Review Summary

#	Sex	Age group	Product	Dose	Days post vaccination to automated diagnosis date	Days post vaccination to symptom onset (chart review)	Thrombocytopenia at time of CVST	History of COVID
1	M	25-29	Moderna	1	13 days post Dose 1	3 days post Dose 1	No	No
2	F	35-39	Moderna	2	22 days post Dose 2	8 days post Dose 2	No	No
3	F	65-69	Pfizer	1 (received Dose 2)	5 days post Dose 1	Post vaccination confirmed, exact date inestimable due to other ongoing medical conditions	No	No
4	M	80-84	Moderna	2	7 days post Dose 2	Likely pre-vaccination with severe headache noted 2 weeks prior to vaccination	No	No
5	M	80-84	Pfizer	2	14 days post Dose 2	14 days post Dose 2	No	No
6	F	90+	Moderna	2	28 days post Dose 2	22 days post Dose 2	No	No

Outcome events in 21-day risk interval after Janssen vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

			Weekly Analysis[1]			Sequential Test[2]	
Outcome Event	Events in Risk Interval	Events in Comparison Interval[4]	Adjusted Rate Ratio[3]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute myocardial infarction	7	1	4.54	0.45 - 129.26	0.221	0.196	no
Appendicitis	5	5	0.78	0.19 - 3.17	0.725	0.761	no
Bell's palsy	14	3	2.02	0.54 - 9.82	0.325	0.239	no
Disseminated intravascular coagulation	1	0	.	0.07 – ne	0.427	0.427	no
Guillain-Barré syndrome	1	0	.	0.00 – ne	0.999	0.999	no
Stroke, ischemic	8	5	1.46	0.41 - 5.67	0.575	0.393	no
Immune thrombocytopenia	0	1	0.00	0.00 - 29.25	0.606	0.606	no
Seizures	1	1	0.48	0.01 - 18.70	0.646	0.896	no
Thrombotic thrombocytopenic purpura	1	0	.	0.03 - ne	0.614	0.614	no
Venous thromboembolism	8	6	0.80	0.22 - 2.87	0.732	0.749	no
Pulmonary embolism	4	6	0.35	0.05 - 1.82	0.226	0.957	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
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[4]**Comparison interval** is 22–42 days after either dose.

CVST events in 21-days risk interval after Janssen Vaccine

Compared with outcome events in unvaccinated comparators on the same calendar days

			Weekly Analysis[1]		
Outcome Event	Events in Risk Interval	Events in Unvaccinated	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value
CVST	0	12	0.1	0.00 – 83.36	0.951

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable

Outcome events in 21-day risk interval after Janssen vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Events in Comparison Interval[4]	Weekly Analysis[1] Adjusted Rate Ratio[3]	95% Confidence Interval	2-Sided P-value	Sequential Test[2] 1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute myocardial infarction	7	1	4.54	0.45 - 129.26	0.221	0.196	no
Appendicitis	5	5	0.78	0.19 - 3.17	0.725	0.761	no
Bell's palsy	14	3	2.02	0.54 - 9.82	0.325	0.239	no
Disseminated intravascular coagulation	1	0	.	0.07 – ne	0.427	0.427	no
Guillain-Barré syndrome	1	0	.	0.00 – ne	0.999	0.999	no
Stroke, ischemic	8	5	1.46	0.41 - 5.67	0.575	0.393	no
Immune thrombocytopenia	0	1	0.00	0.00 - 29.25	0.606	0.606	no
Seizures	1	1	0.48	0.01 - 18.70	0.646	0.896	no
Thrombotic thrombocytopenic purpura	1	0	.	0.03 - ne	0.614	0.614	no
Venous thromboembolism	**8**	**6**	**0.80**	**0.22 - 2.87**	**0.732**	**0.749**	**no**
Pulmonary embolism	4	6	0.35	0.05 - 1.82	0.226	0.957	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
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[4]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after Janssen vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Events in Comparison Interval[4]	Weekly Analysis[1] Adjusted Rate Ratio[3]	95% Confidence Interval	2-Sided P-value	Sequential Test[2] 1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute myocardial infarction	7	1	4.54	0.45 - 129.26	0.221	0.196	no
Appendicitis	5	5	0.78	0.19 - 3.17	0.725	0.761	no
Bell's palsy	14	3	2.02	0.54 - 9.82	0.325	0.239	no
Disseminated intravascular coagulation	1	0	.	0.07 – ne	0.427	0.427	no
Guillain-Barré syndrome	1	0	.	0.00 – ne	0.999	0.999	no
Stroke, ischemic	8	5	1.46	0.41 - 5.67	0.575	0.393	no
Immune thrombocytopenia	0	1	0.00	0.00 - 29.25	0.606	0.606	no
Seizures	1	1	0.48	0.01 - 18.70	0.646	0.896	no
Thrombotic thrombocytopenic purpura	1	0	.	0.03 - ne	0.614	0.614	no
Venous thromboembolism	8	6	0.80	0.22 - 2.87	0.732	0.749	no
Pulmonary embolism	**4**	**6**	**0.35**	**0.05 - 1.82**	**0.226**	**0.957**	**no**

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
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[4]**Comparison interval** is 22–42 days after either dose.

VTE/PE events 42 days After Janssen: Quick Chart Review Summary

- 32 VTE/PE total cases 1-42 days after Janssen
  - 3 diagnosed with both VTE and PE
- 29/32 quick reviewed to date
- 23/29 confirmed case
  - 4 symptom onset prior to vaccination, 1 indeterminant onset
- 18 with VTE/PE incidence following vaccination

Venous Thromboembolism Events 42 days After Janssen: Quick Chart Review Summary

- 9 of 18 confirmed as VTE
- None with thrombocytopenia at time of VTE

#	Dx	Sex	Age group	Days post vaccination to automated diagnosis date	Days post vaccination to symptom onset (chart review)	Thrombocytopenia at time of VTE	History of COVID-19	High risk status	Status at time of chart review
1	VTE	Female	70-74	22 days	18 days	No	No	No	Discharged
2	VTE	Male	55-59	1 day	1 day	No	No	No	Discharged
3	VTE	Male	50-54	15 days	12 days	No	No	Yes	Discharged
4	VTE	Female	70-74	9 days	7 days	No	No	Yes	Discharged
5	VTE	Male	50-54	2 days	0 days (confirmed post vaccination)	No	No	Yes	Discharged
6	VTE	Female	55-59	19 days	13 days	No	No	Yes	Discharged
7	VTE	Female	60-64	27 days	7 days	No	No	Yes	Discharged
8	VTE	Male	75-79	24 days	19 days	No	No	No	Discharged
9	VTE	Female	30-34	30 days	28 days	No	No	No	Discharged

Pulmonary Embolism Events 42 days After Janssen: Quick Chart Review Summary

- 9 of 18 confirmed as PE cases
- None with thrombocytopenia at time of PE

#	Dx	Sex	Age group	Days post vaccination to automated diagnosis date	Days post vaccination to symptom onset (chart review)	Thrombocytopenia at time of PE	History of COVID-19	High risk status	Status at time of chart review
1	PE	Male	75-79	27 days	24 days	No	No	Yes	Discharged
2	PE	Female	70-74	16 days	16 days	No, elevated platelets	No	No	Discharged
3	PE	Female	55-59	23 days	20 days	No	No	Yes	Still hospitalized (not ICU)
4	PE	Female	70-74	14 days	14 days	No	No	Yes	Discharged
5	PE	Male	45-49	36 days	5 days	No	No	Yes	Discharged
6	PE	Male	65-69	13 days	8 days	No	No	Yes	Discharged
7	PE	Male	50-54	28 days	25 days	No	No	No	Discharged
8	PE	Female	64-69	24 days	17 days	No	No	Yes	Discharged
9	PE	Female	60-64	41 days	41 days	No	No	Yes	Discharged

Anaphylaxis

Anaphylaxis Chart Review Summary

- Chart review completed for 52/55 cases through March 20, 2021*
- 25/52 (48%) cases confirmed as post-vaccination anaphylaxis

*Full review not completed until 30 days after the event

	Pfizer (n=16)	Moderna (n=8)	Janssen (n=1)
Age in years, median (range)	43 (24-74)	39 (30-67)	65
Female sex	16 (100%)	8 (100%)	1 (100%)
Minutes to symptom onset, median (range)	10 (0-300)	13 (5-30)	--
Symptom onset within 15 minutes	8 (50%)	5 (62%)	0 (0%)
Symptom onset within 30 minutes	12 (75%)	7 (87%)	0 (0%)
Prior history of allergies	14 (87%)	5 (62%)	1 (100%)
Prior history of anaphylaxis	9 (56%)	1 (13%)	1 (100%)
Dose 1	15 (94%)	7 (87%)	1 (100%)
Brighton Collaboration case definition level			
1	7 (44%)	3 (38%)	0 (0%)
2	9 (56%)	5 (62%)	1 (100%)
No. confirmed cases (95% CI) per million doses	8.6 (4.9-13.9)	4.6 (2.0-9.0)	15.1 (0.4-84.1)
No. confirmed cases (95% CI) per million female doses	14.4 (8.2-23.4)	7.7 (3.3-15.2)	28.1 (0.7-156.8)
No. confirmed cases (95% CI) per million first doses	12.6 (7.0-20.7)	5.9 (2.4-12.2)	--
No. confirmed cases (95% CI) per million female first doses	21.3 (11.9-35.1)	10.1 (4.1-20.9)	--

Summary

- No signals observed for all outcomes and all vaccines during the 21 days after vaccination, including PE and myocarditis
- There were 6 potential CVST cases ("quick-reviewed") after mRNA vaccines, none had thrombocytopenia.
- No CVST cases have been observed during the 42 days after the Janssen vaccine.
- There were 18 potential VTE and/or PE cases after Janssen, none had thrombocytopenia.

Next Steps for Thrombosis with Thrombocytopenia Syndrome (TTS)

- We will create a TTS outcome category using diagnostics codes and platelet counts according to the latest published Brighton collaboration case definition (link here) .

- Considering creating separate categories for the following outcomes with thrombocytopenia (platelet count TBD):
    - AMI
    - Ischemic Stroke
    - Pulmonary Embolisms

- In the meantime, we are continuing to chart review all cases of VTE and PE following Janssen vaccine to check for thrombocytopenia.

- Continue quick-reviews of all vaccinated CVST cases to check for thrombocytopenia.

Acknowledgements

- Kaiser Permanente Northern California:
  - Nicky Klein, Laurie Aukes, Berwick Chan, Bruce Fireman, Kristin Goddard, Ned Lewis, Karen Nunley, Pat Ross, Arnold Yee, Ousseny Zerbo
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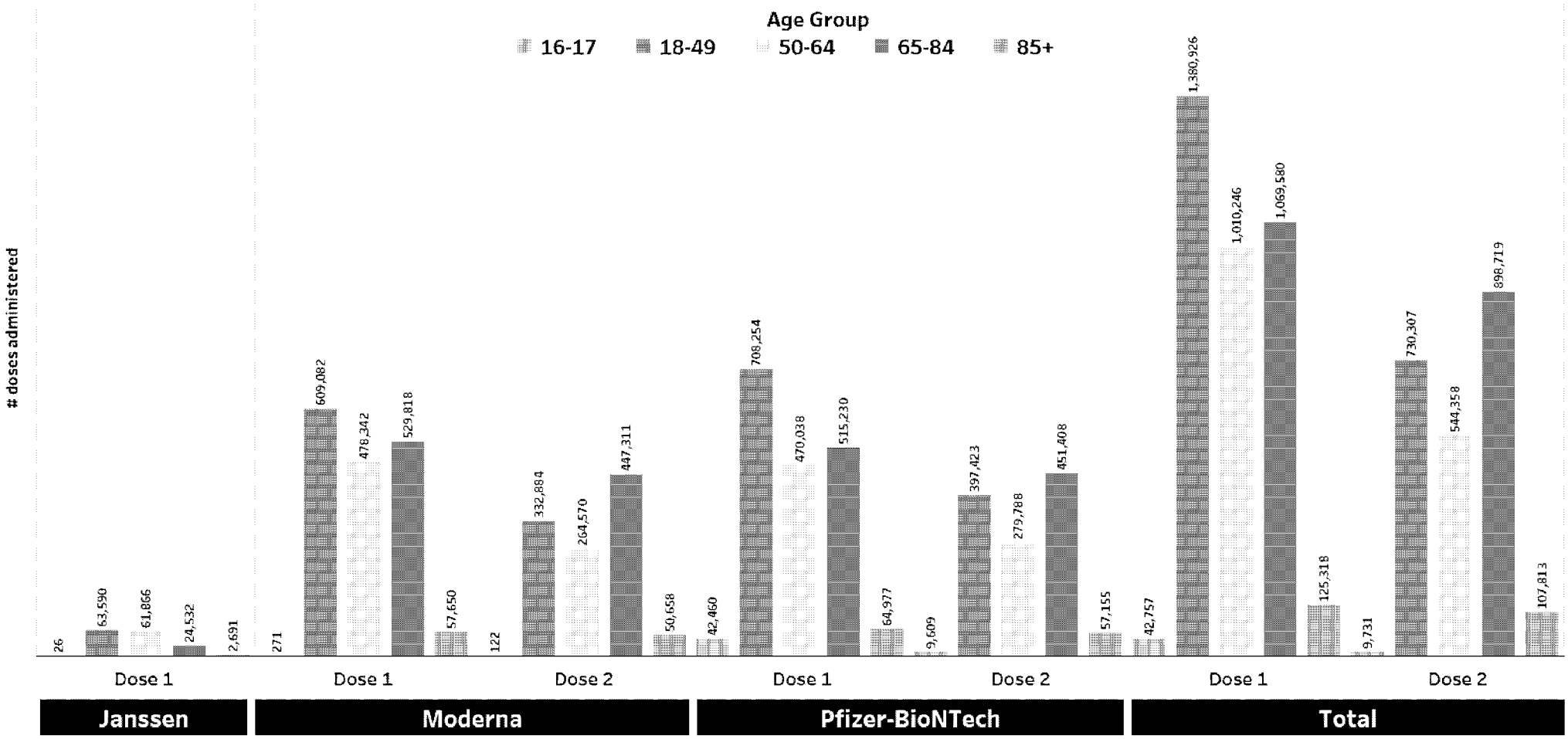
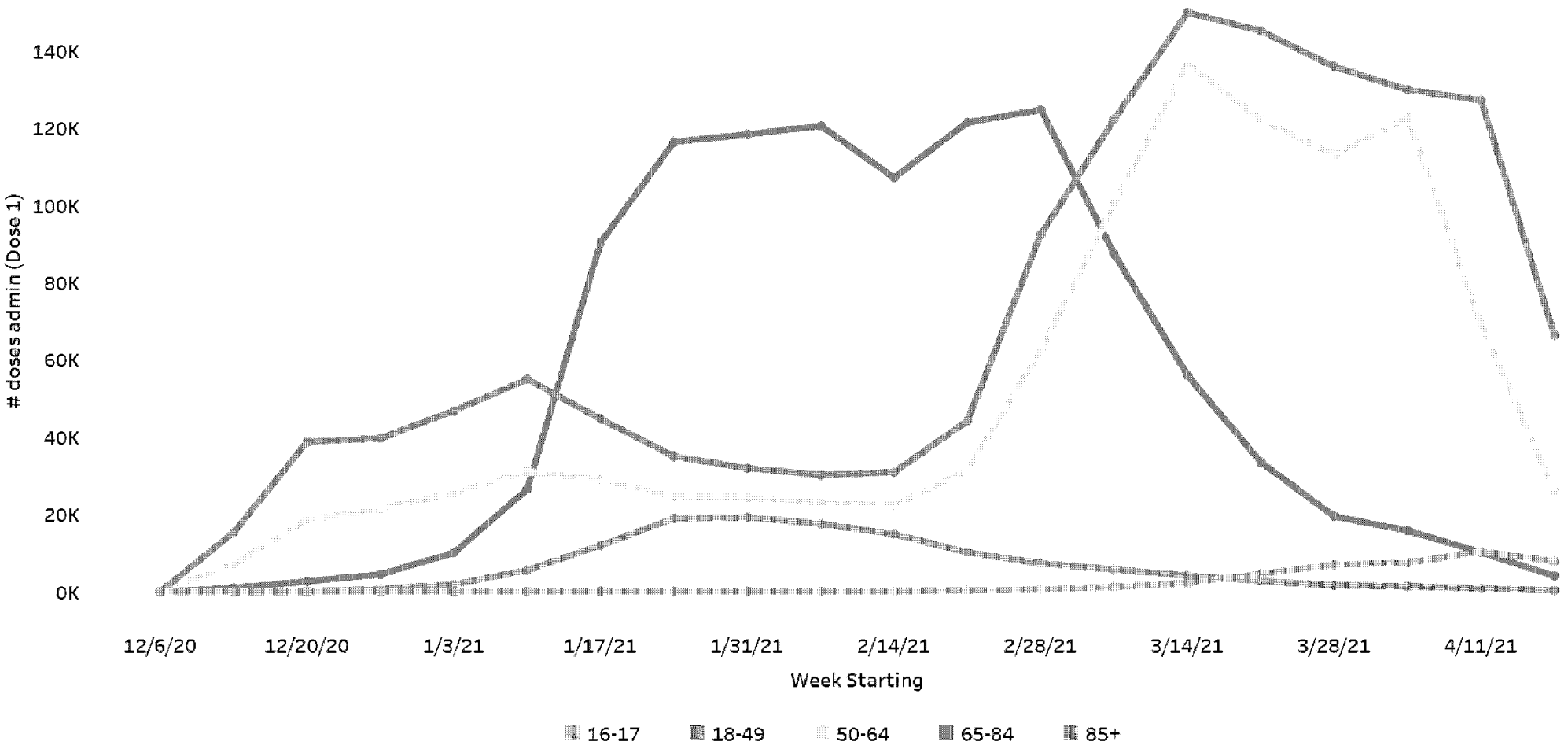
  - Jim Donahue, Ed Belongia, Kayla Hanson, Burney Kieke, Dave McClure, Erica Scotty
- CDC Immunization Safety Office:
  - Eric Weintraub, Tat'Yana Kenigsberg, Mike McNeil, Jonathan Duffy, Frank Destefano, Tanya Myers, Tom Shimabukuro
- VSD Sites
  - HealthPartners Institute, Minneapolis, Minnesota
  - Kaiser Permanente Colorado, Denver, Colorado
  - Kaiser Permanente Northwest, Portland, Oregon
  - Kaiser Permanente Southern California, Los Angeles, California
  - Kaiser Permanente Washington, Seattle, Washington
  - Denver Health, Denver, Colorado

Extra Slides

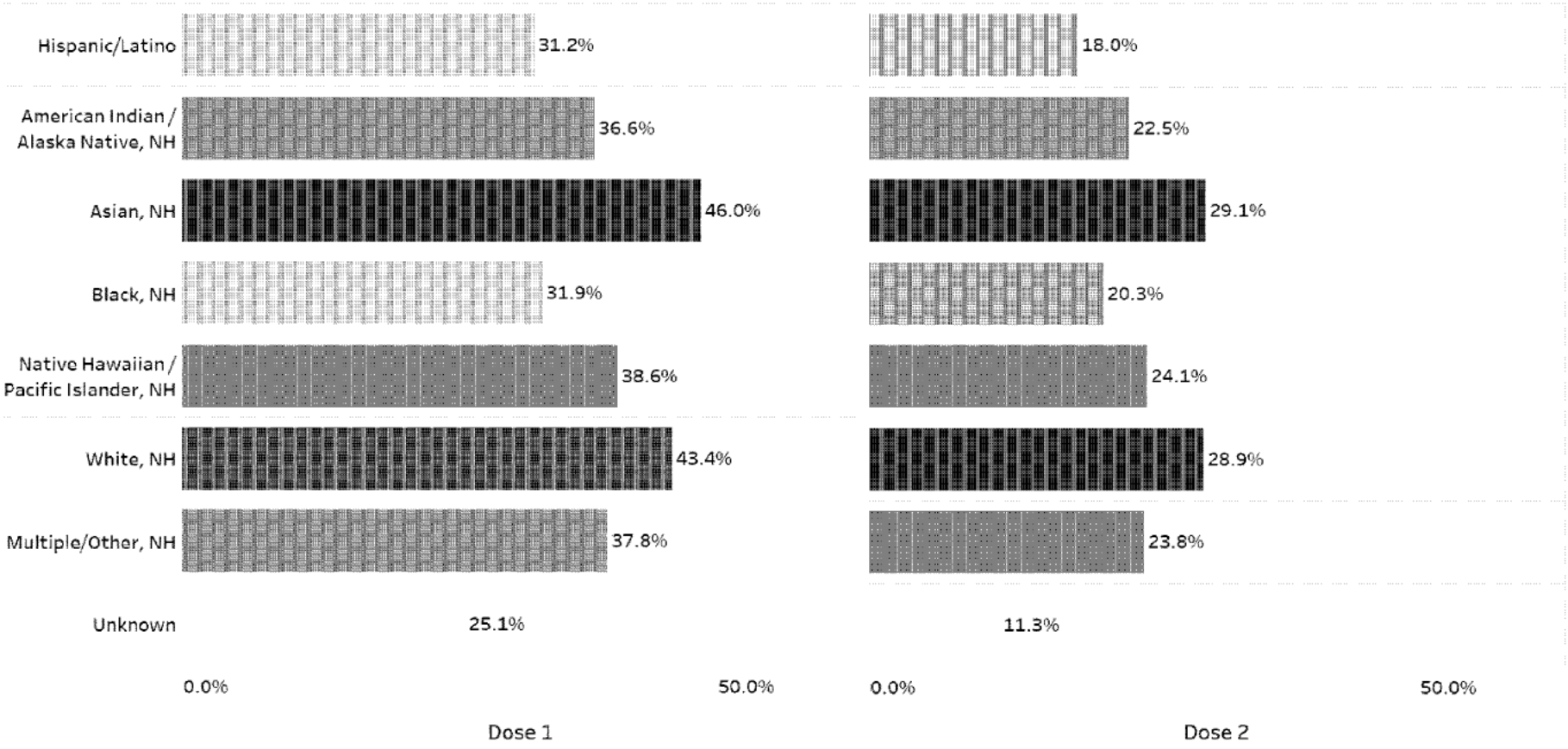
COVID-19 Vaccine Totals by Age Group



Vaccine Totals (Dose 1) by Age Group and Week



COVID-19 Vaccine Coverage by Race



Vaccine Safety Datalink (VSD) Weekly COVID-19 Vaccine Summary: April 27, 2021 *

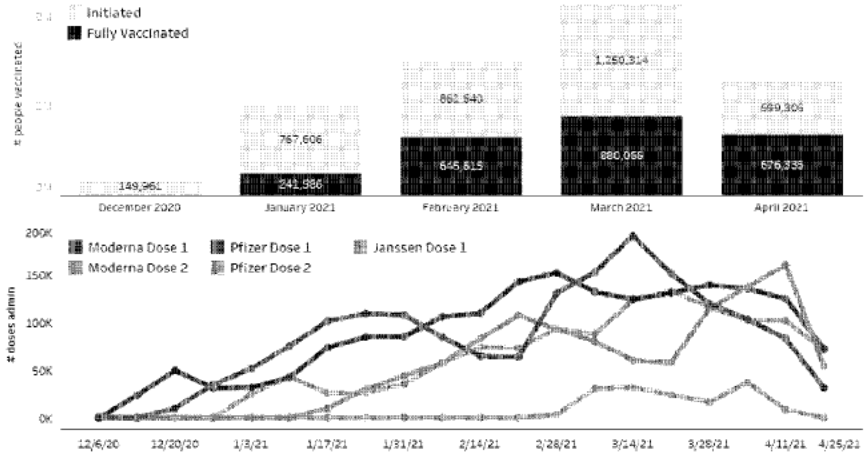
* Visualization published on April 27, 2021; data current as of previous Saturday. VSD population includes individuals 16 years of age and older.

Total # Doses Administered	Total # Doses Admin per 100K	# People Initiating Vaccination	# People Fully Vaccinated
5,919,755	61,854	3,628,827	2,443,633
+624,838 since last week	+6,533 since last week	+305,131 since last week	+330,294 since last week

To date, 37.9% of VSD population initiated vaccination and 25.0% is fully vaccinated

No signals have been observed to date.

Number of people vaccinated & doses administered over time



Number of events by outcome *

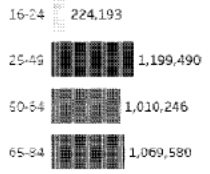
	Janssen	Moderna		Pfizer		Total
	Dose 1	Dose 1	Dose 2	Dose 1	Dose 2	
ADEM				1		1
AMI	10	98	74	115	92	389
ANAPH	4	22	12	36	7	81
ANAPH2	1	20	2	13	3	39
APPND	7	85	49	95	66	302
ARDS		2	3	1		6
BP	16	95	60	70	66	307
CVST		1	3	2	1	7
DIC	1	5	1	7	2	16
ENCEPH		2	3	2		7
GBS	2	2	3	2	2	11
HSTK	1	38	21	53	43	156
ISTK	9	187	137	183	136	652
ITP	1	4	7	12	6	30
KD						
MISC				3	1	4
MYOC		8	7	6	10	31
NARC		2	2	1	5	10
PE	6	94	67	80	80	327
SZ	1	40	22	48	25	136
TM	1	1			2	4
TTP	1	1		1		3
VTE	16	128	80	112	89	425
Total	**77**	**835**	**553**	**843**	**636**	**2,944**

* Table only displays outcomes with cases in the 1-21 day risk window (or, for anaphylaxis (ANAPH), in the 0-1 day risk window). VSD tracks 32 outcomes in total. ANAPH2 definition uses internal DX ID's to identify anaphylaxis vs. ICD-10 codes used in ANAPH. ANAPH and ANAPH2 are not mutually exclusive.

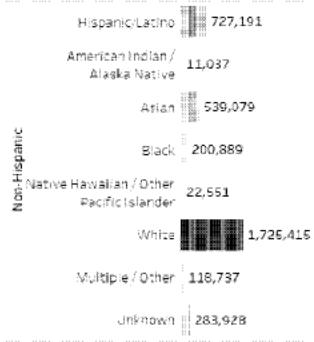
Demographic breakdown of people who initiated vaccination

By Sex

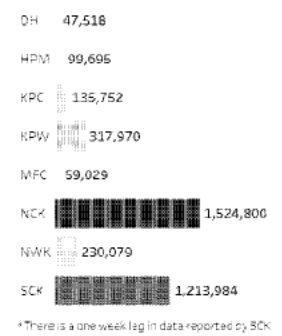
By Age Group



By Race/Ethnicity



By Site *

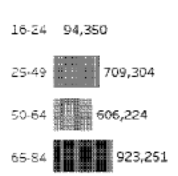


* There is a one week lag in data reported by SCK

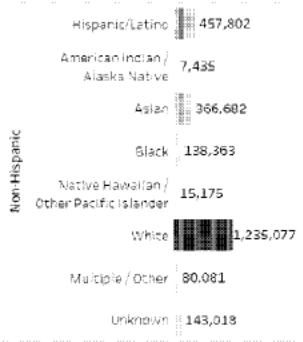
Demographic breakdown of people who are fully vaccinated

By Sex

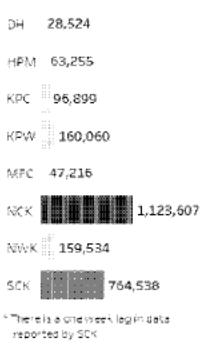
By Age Group



By Race/Ethnicity



By Site *



* There is a one week lag in data reported by SCK

Acute myocardial infarction, Venous thromboembolism, Pulmonary Embolism Additional Analyses

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute myocardial infarction	373	0.86	0.71 - 1.05	0.146	0.934	no
Venous thromboembolism	407	1.23	1.00 - 1.53	0.047	0.027	no
Pulmonary embolism	319	0.97	0.77 - 1.21	0.752	0.645	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
[3]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[4]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Limited to ages 65+, (data through week ending March 27, 2021)

Outcome	Vaccine	Dose	Events in Risk Interval[2]	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)
Acute myocardial infarction	Both mRNA	Both Doses	195	0.81	0.59 - 1.12	0.192	0.918
	Pfizer	Both Doses	115	0.76	0.48 - 1.23	0.248	0.9
	Moderna	Both Doses	78	0.74	0.47 - 1.17	0.187	0.926

[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[2]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Limited to ages 65+, (data through week ending March 27, 2021)

Outcome	Vaccine	Dose	Events in Risk Interval[2]	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)
Venous thromboembolism	Both mRNA	Both Doses	184	1.07	0.76 - 1.53	0.721	0.394
	Pfizer	Both Doses	79	0.95	0.53 - 1.76	0.832	0.642
	Moderna	Both Doses	103	1.29	0.83 - 2.04	0.271	0.159

[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
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Outcome events in 21-day risk interval after either dose of any mRNA vaccine

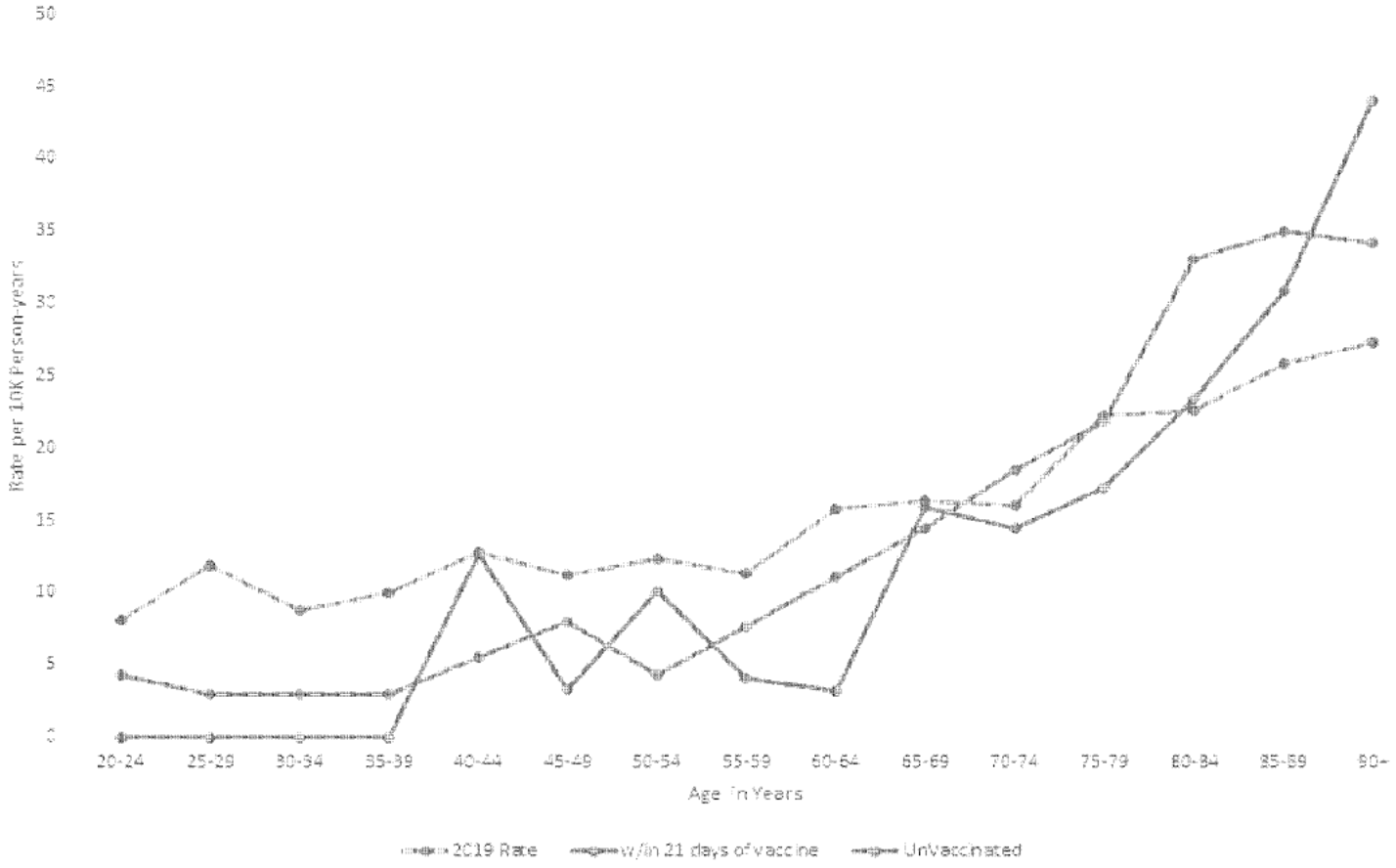
Compared with outcome events in vaccinated comparators on the same calendar days

Limited to ages 65+, (data through week ending March 27, 2021)

Outcome	Vaccine	Dose	Events in Risk Interval[2]	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)
Pulmonary embolism (subset of VTE)	Both mRNA	Both Doses	167	0.99	0.7 - 1.44	0.959	0.557
	Pfizer	Both Doses	87	0.91	0.52 - 1.65	0.726	0.691
	Moderna	Both Doses	78	1.08	0.67 - 1.79	0.779	0.437

[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[2]**Comparison interval** is 22–42 days after either dose.

Pulmonary embolism rates per 10,000 person-years by age group, among high risk individuals with no history of COVID-19 disease



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	Moderna	Both Doses	78	1.08	0.67 - 1.79	0.779	0.437

Unvaccinated Comparison

Outcome	Vaccine	Dose	Events in Risk Interval	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value
Pulmonary embolism (subset of VTE)	Both mRNA	Both Doses	167	1.03	0.84 - 1.25	0.780
	Pfizer	Both Doses	89	1.08	0.84 - 1.38	0.524
	Moderna	Both Doses	78	1.00	0.78 - 1.29	0.965

[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[2]**Comparison interval** is 22–42 days after either dose.

Outcome events in 21-day risk interval after either dose of any mRNA vaccine

Compared with outcome events in vaccinated comparators on the same calendar days

Limited to ages 65+, (data through week ending March 27, 2021)

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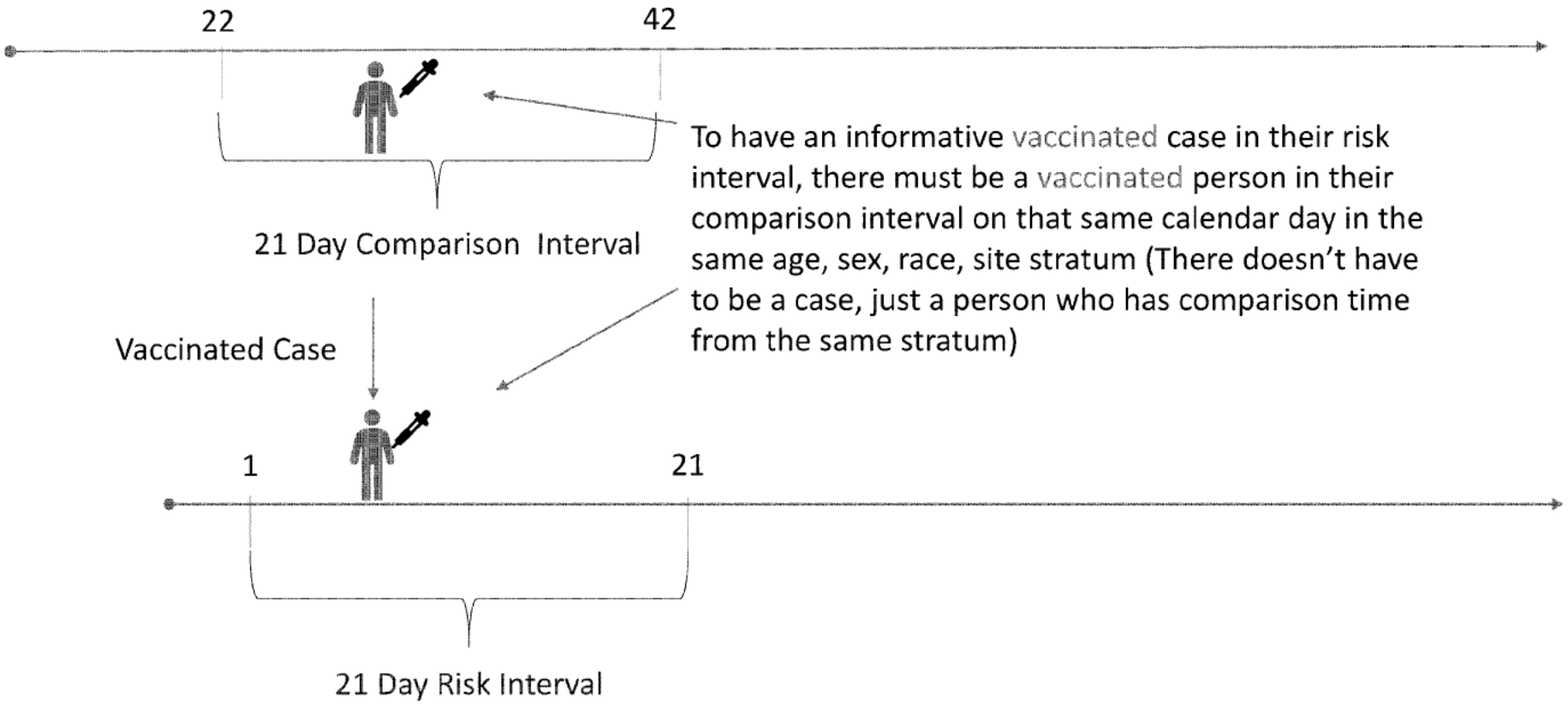
[1]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable
[2]**Comparison interval** is 22–42 days after either dose.

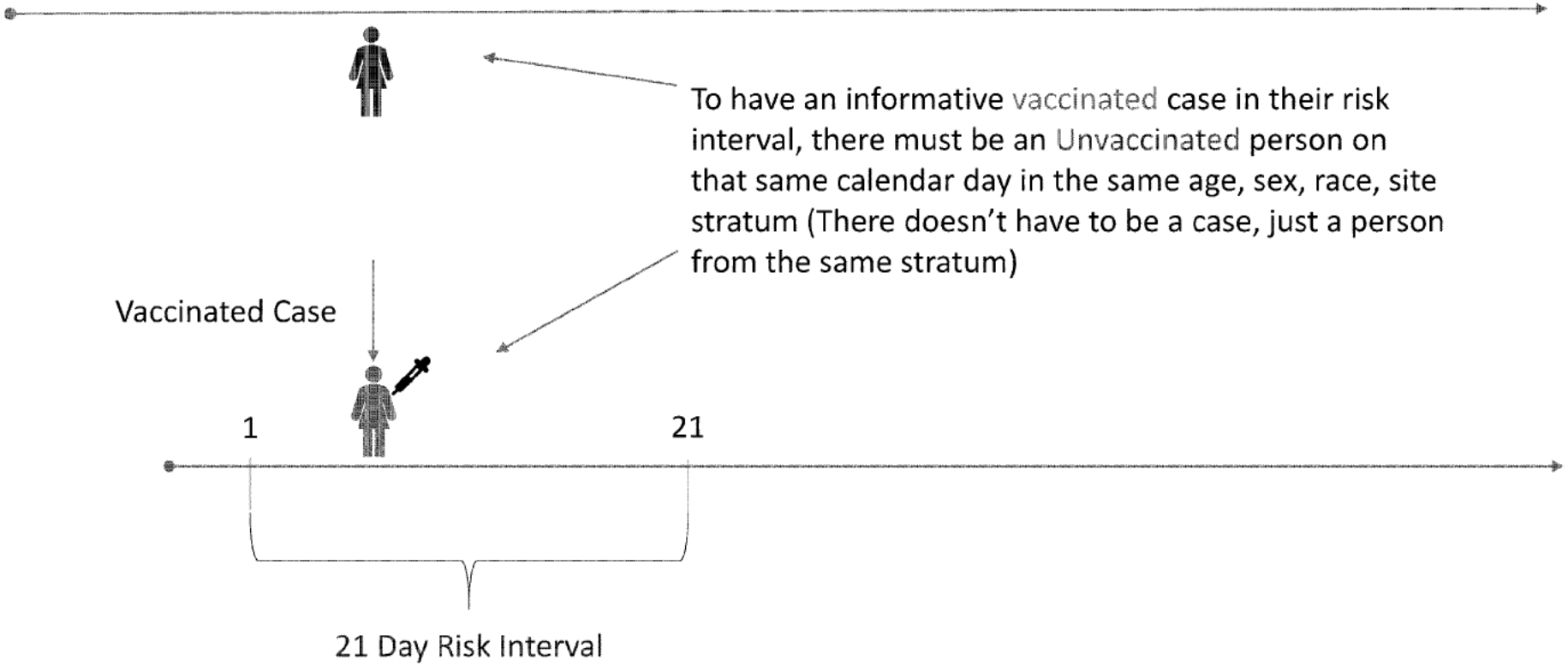
Next Steps

- Vaccinated concurrent comparators:
  - Will continue this analysis as additional informative comparator follow-up becomes available
- For each outcome
  - Dose specific analyses
  - Product specific analyses
  - Analyses for 2 risk intervals – 1-21 & 1-42 days
- Historical Comparators
  - General age comparable background rates
  - Rates following well care visits among those that received influenza vaccine in the past 18 months
  - Exploring a data evaluation lag and other methods to remove potential biases in the analysis

Vaccinated Comparison



Unvaccinated Comparison



VSD RCA COVID-19 Outcomes

#	VSD Outcomes	Abbreviation	Risk Window (days)	Chart Review	Monitoring Only	Exclude if COVID-19 in the Prior X Days
1	Acute disseminated encephalomyelitis (settings = E, I)	ADEM	1-21, 1-42	Yes		
2	Acute myocardial infarction (settings = E, I) – **First Ever**	AMI	1-21, 1-42			30 days
3	Acute respiratory distress syndrome (settings = E, I)	ARDS	1-21, 1-42		Yes	42 days
4	Anaphylaxis (settings = E, I) - **First in 7 days**	ANAPH	0-1	Yes	Yes	
5	Appendicitis (settings = E, I)	APPND	1-21, 1-42			
6	Bell's palsy (settings = E, I, O) - **First Ever**	BP	1-21, 1-42			30 days
7	Convulsions / seizures (settings = E, I)	SZ	1-21, 1-42 (day 0 included for children)			30 days
8	Disseminated intravascular coagulation (settings = E, I)	DIC	1-21, 1-42			42 days
9	Encephalitis / myelitis / encephalomyelitis (settings = E, I)	ENCEPH	1-21, 1-42			30 days
10	Guillain-Barré syndrome (settings = E, I)	GBS	1-21, 1-42	Yes		
11	Thrombotic thrombocytopenic purpura (settings = E, I)	TTP	1-21, 1-42			30 days
12	Immune thrombocytopenia (settings = E, I, O)	ITP	1-21, 1-42			30 days
13	Kawasaki disease (settings = E, I)	KD	1-21, 1-42			
14	Multisystem Inflammatory Syndrome in Children & Adults (MIS-C, MIS-A) (settings = E, I)	MISC			Yes	
15	Myocarditis / pericarditis (settings = E, I) - **First in 60 Days**	MYOC	1-21, 1-42			30 days
16	Narcolepsy and cataplexy (settings = E, I, O)	NARC			Yes	
17	Stroke, hemorrhagic (settings = E, I)	HSTK	1-21, 1-42			30 days
18	Stroke, ischemic (settings = E, I)	ISTK	1-21, 1-42			30 days
19	Transverse myelitis (settings = E, I)	TM	1-21, 1-42	Yes		
20	Venous thromboembolism (settings = E, I, O) – **First Ever**	VTE	1-21, 1-42			30 days
21	Pulmonary embolism (subset of VTE) (settings = E, I) – **First Ever**	PE	1-21, 1-42			30 days
	Notes: specific settings for code search is noted below (E = ED; I = Inpt; O = Outpt)					

Analytic Strategies: Aim 1

The number of events observed in the risk interval will be compared to the number expected, with the expected derived from 3 types of comparators, the first of which will be primary when available:

- vaccinated concurrent comparators in a comparison interval after COVID-19 vaccination.
  - On each day, outcome incidence in the vaccinees who are in their risk interval will be compared to outcome incidence in vaccinees who are concurrently—on the same calendar date—in their comparison interval.
  - Analyses will be stratified in risk sets anchored to the calendar dates of outcome events.
  - Analyses will be stratified by age group, sex, race/ethnicity, and VSD site, as well as by calendar date.

- Unvaccinated concurrent comparators in a comparison interval after COVID-19 vaccination.
  - On each day, outcome incidence in the vaccinees who are in their risk interval will be compared to outcome incidence in Unvaccinated individuals who are concurrently—on the same calendar date—at risk.
  - Analyses will be stratified in risk sets anchored to the calendar dates of outcome events.
  - Analyses will be stratified by age group, sex, race/ethnicity, and VSD site, as well as by calendar date.

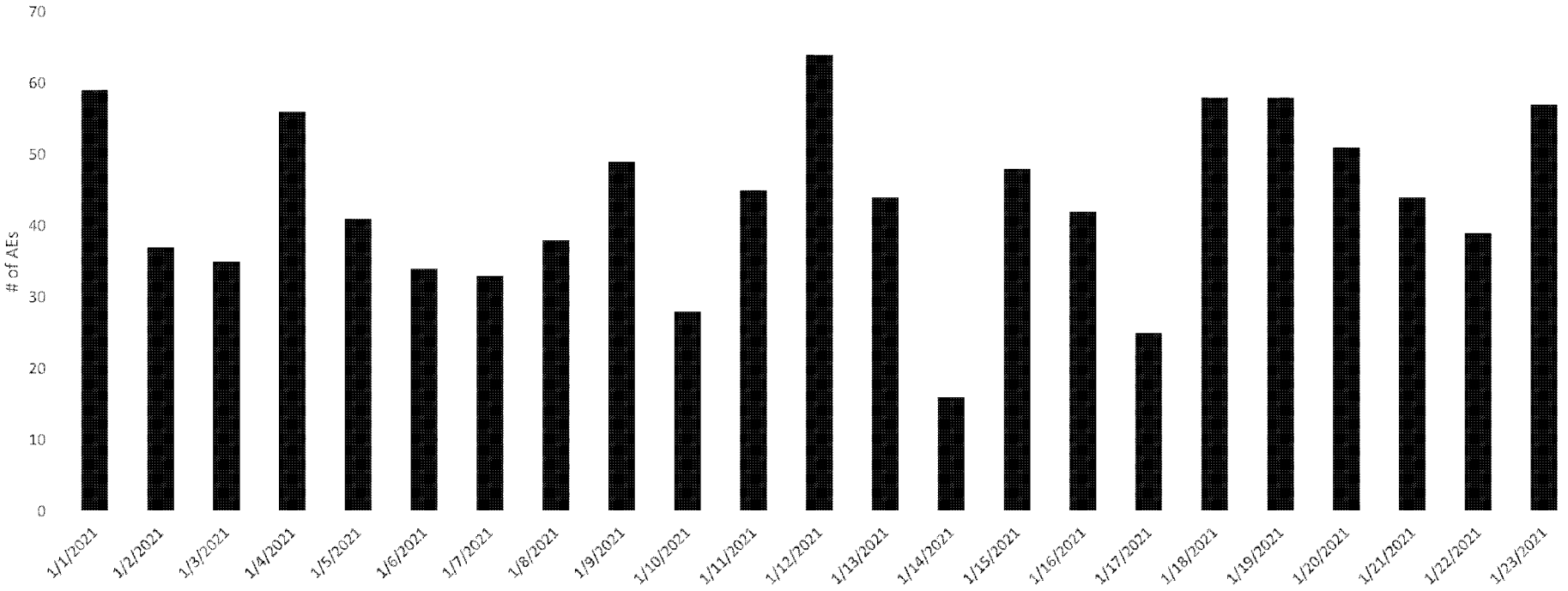
- self-controls in a comparison interval after COVID-19 vaccination.
  - Among the vaccinees who had an outcome event in either the risk interval or the comparison interval, we compare outcome incidence in the risk interval with outcome incidence in the comparison interval.

Analytic Strategies: Aim 1

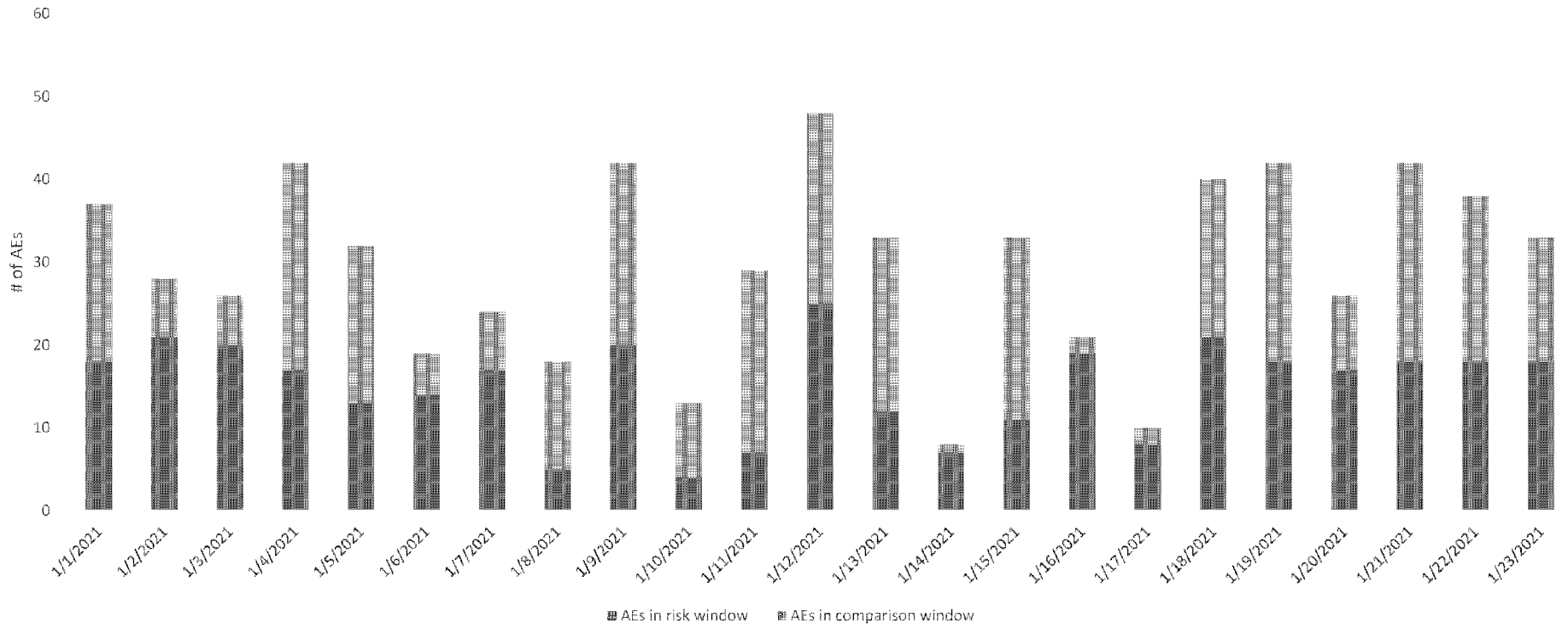
Design	Advantages	Limitations
Primary		
Concurrent Vaccinated	- Not confounded by time-stable co-morbidities, propensities to use health services, or demographics - Follow-up in the comparison interval is on the same calendar dates as follow-up time in the risk interval - Avoids bias that can arise from day-to-day variation in health services - Reduces bias that can arise from data lags	- Transient difficulty finding appropriate comparators soon after a new risk group becomes eligible for vaccine
Unvaccinated concurrent	- Well-adjusted for calendar time	- Bias from comorbidities, demographics, and propensities that may be associated with both the outcome and vaccination status
Supplemental		
Self-Control	- Not confounded by time-stable co-morbidities, propensities to use health services, or demographics as the same vaccinees are contributing person time to both the risk and the comparison intervals	- Bias from differences between risk and comparison intervals in calendar time - Analyses are less timely and can only include vaccinees for whom the control window is complete and for whom the data have settled

- Primary design will be vaccinated concurrent comparators
- If vaccinated concurrent comparators are unavailable, the primary analyses will use Unvaccinated concurrent comparators

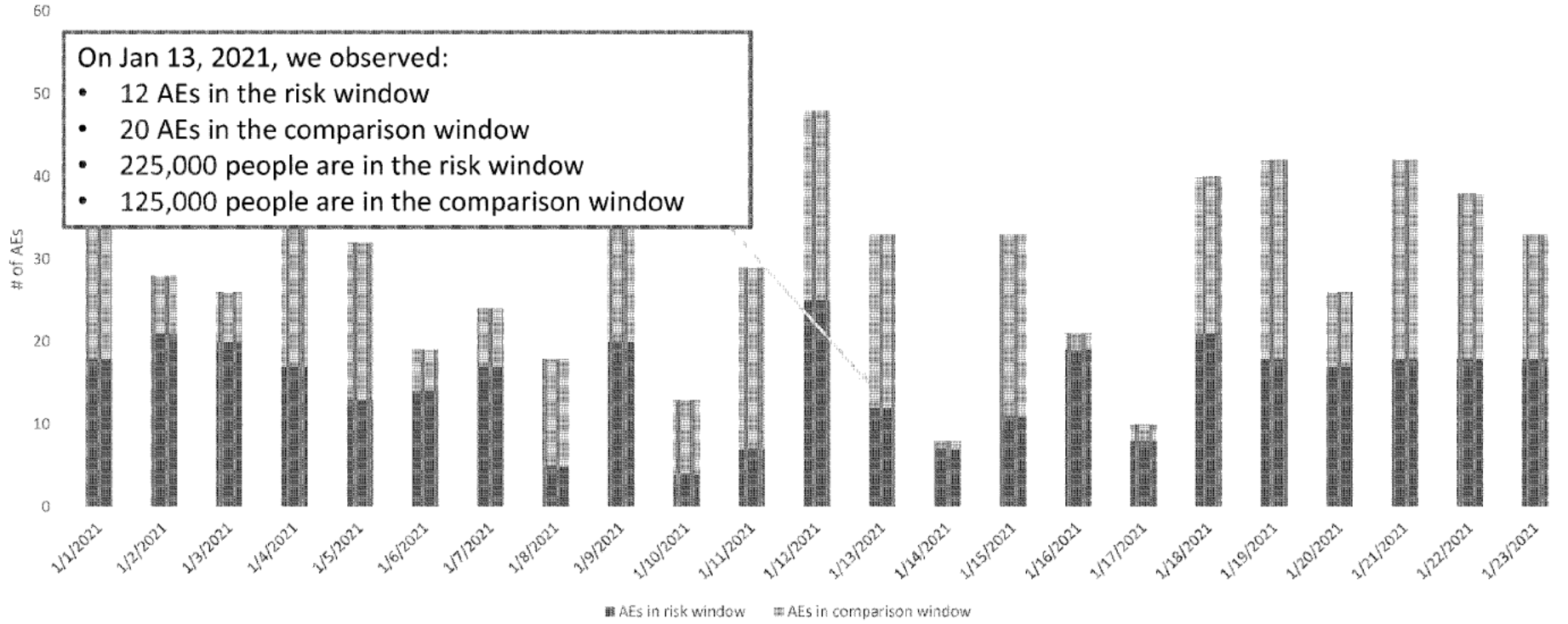
Total # of Events on Each Day



Did the event occur in a risk or comparison interval?



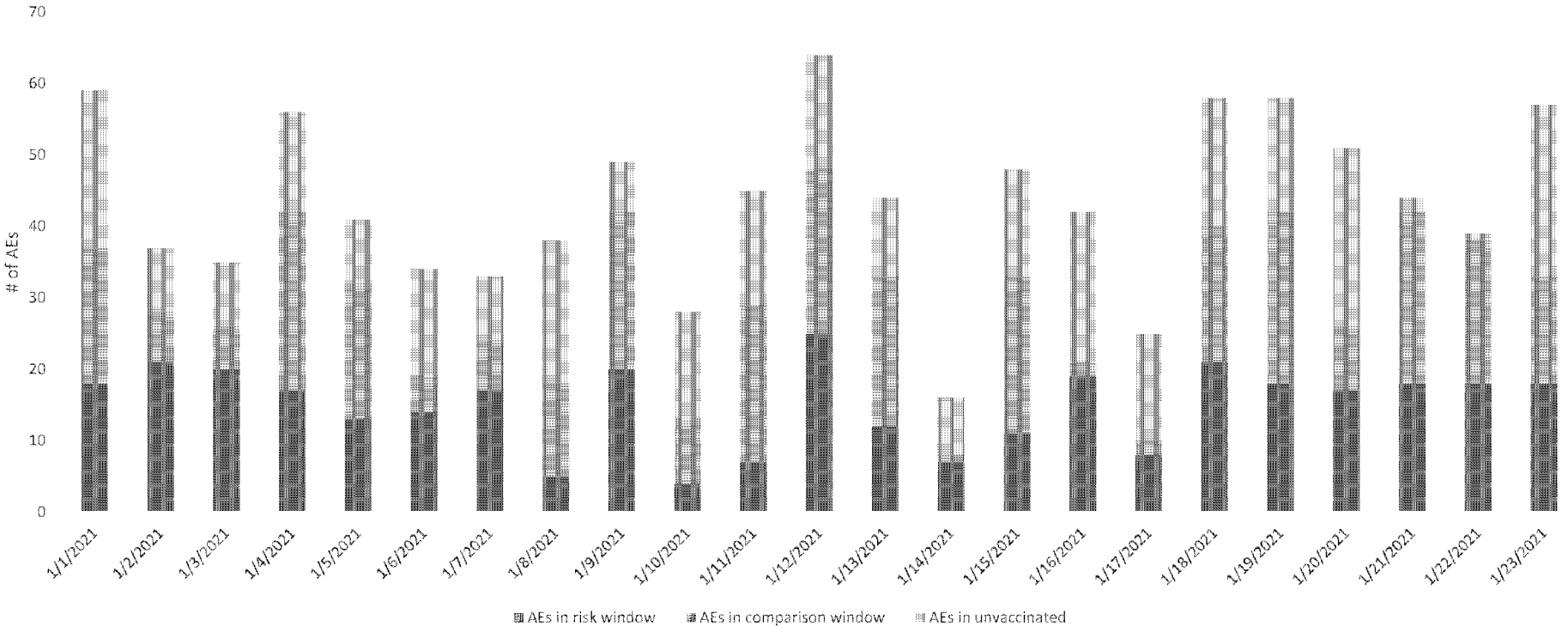
Vaccinated Concurrent Comparator Analyses



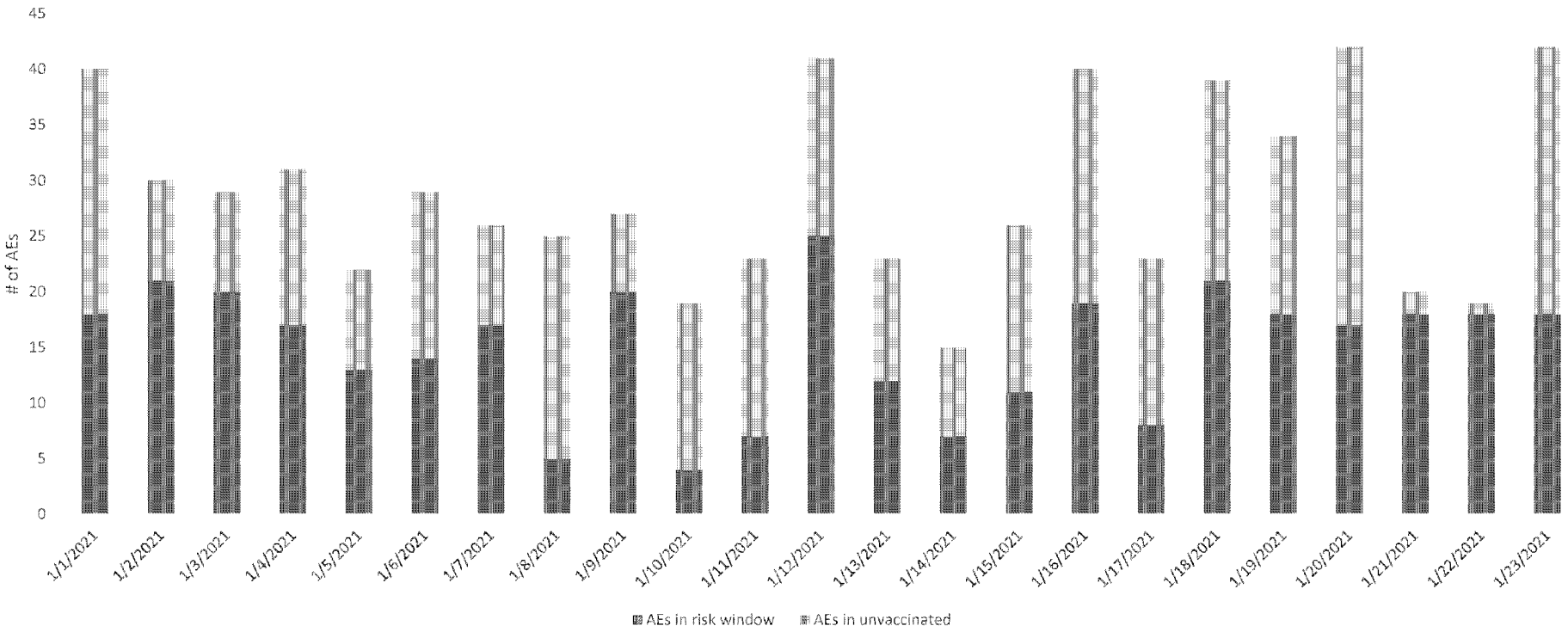
Looking at the data each day in this way, we inherently adjust for variations that occur on different days (e.g., a holiday, every Monday, or a weekend).

At each analysis, we compute a summary rate ratio (risk vs comparison) with all the data available to date. This rate ratio is adjusted for calendar time by day.

Did the event occur in a risk or comparison interval or Unvaccinated?



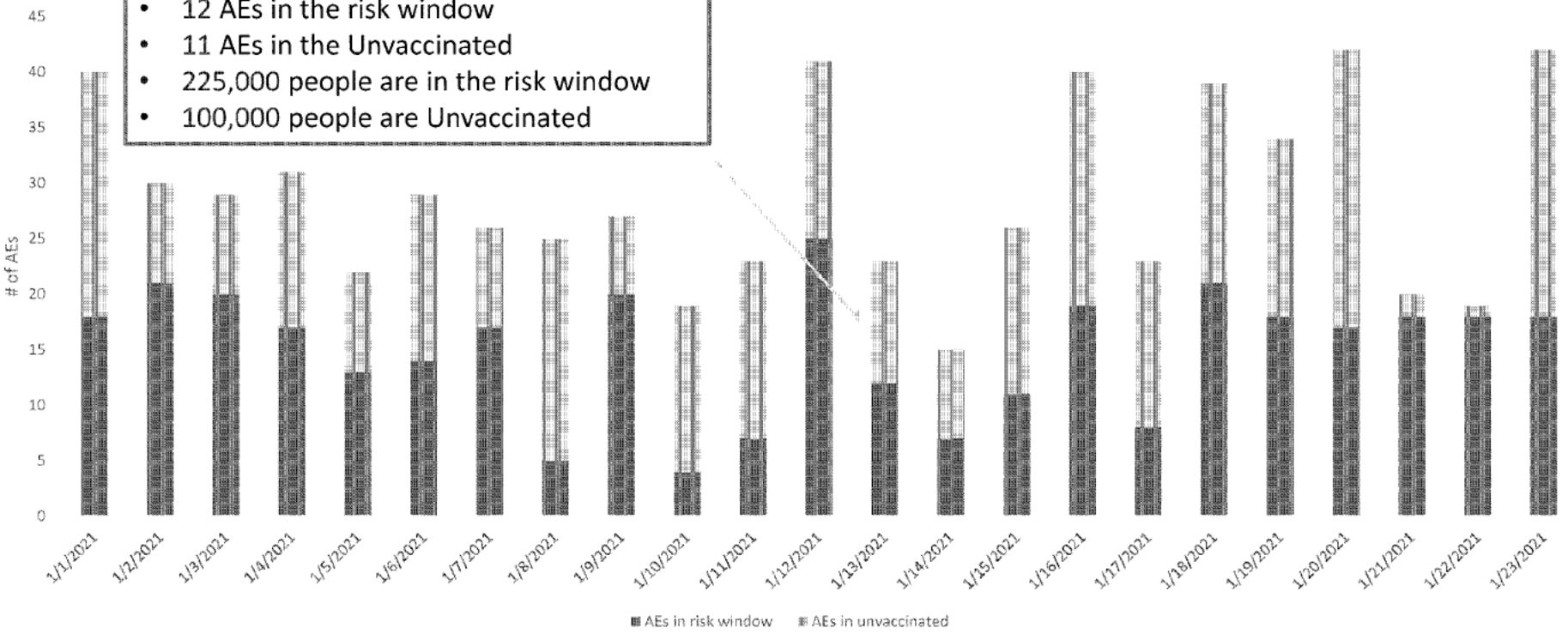
Did the event occur in a risk interval or in the Unvaccinated?



Unvaccinated Concurrent Comparator Analyses

On Jan 13, 2021, we observed:

- 12 AEs in the risk window
- 11 AEs in the Unvaccinated
- 225,000 people are in the risk window
- 100,000 people are Unvaccinated

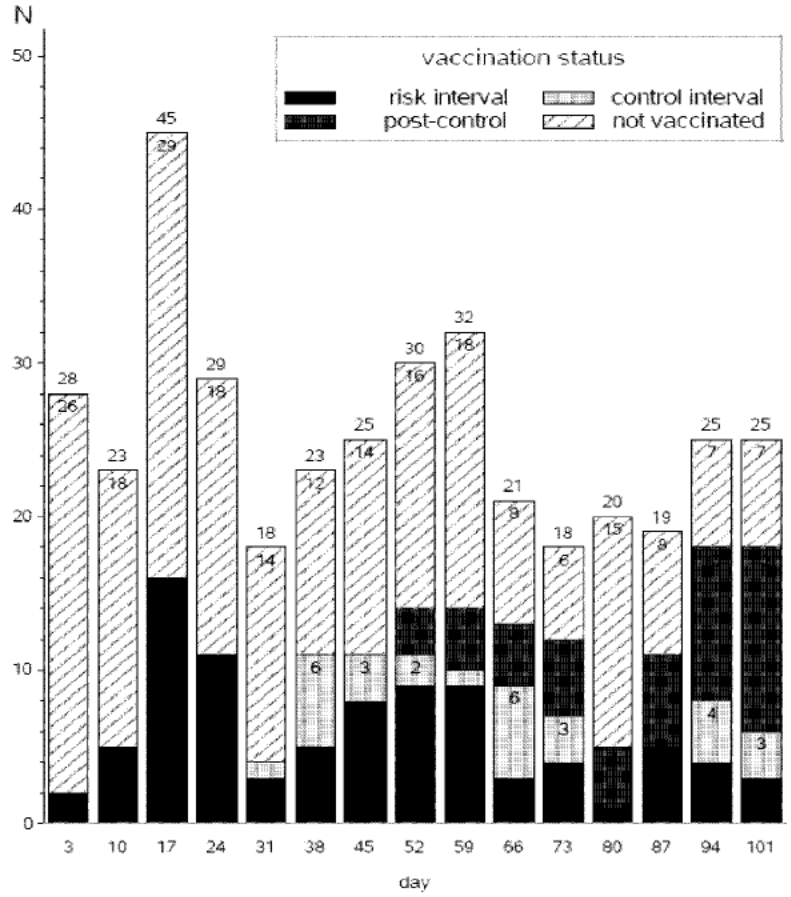


At each analysis, we compute a summary rate ratio (risk vs Unvaccinated) with all the data available to date. This rate ratio is adjusted for calendar time by day

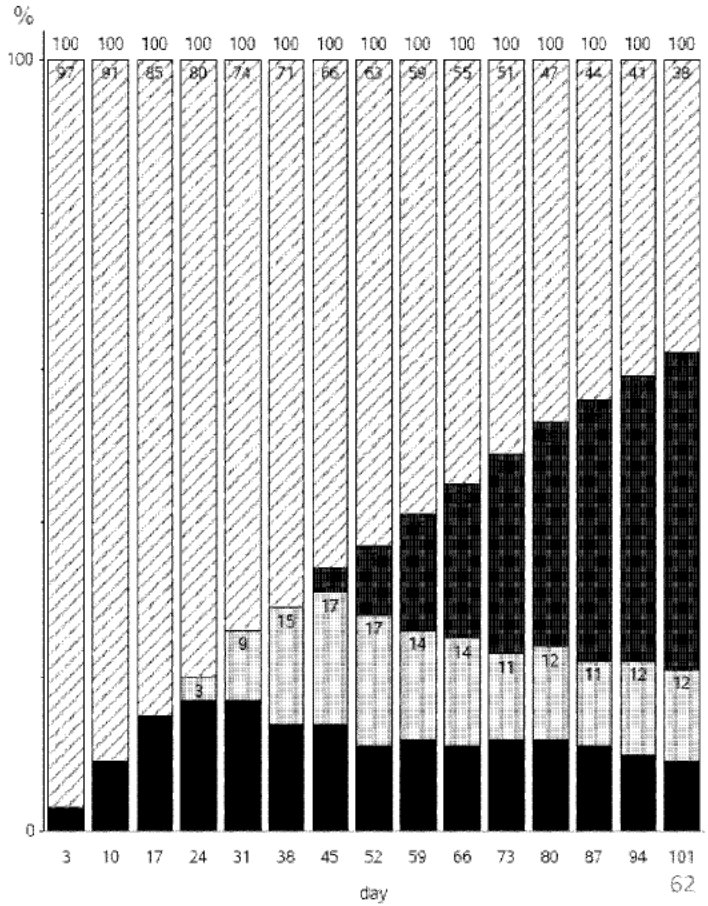
Looking at the data each day in this way, we inherently adjust for variations that occur on different days (e.g., a holiday, every Monday, or a weekend).

All AEs and follow-up in the population by vaccination status and day

All AEs in the population on selected days by vaccination status



Distribution of the population on selected days by vaccination status



PSICOVID_00009205

Analysis

- Poisson regression will be used to model outcome incidence observed during the risk interval in comparison with incidence expected (under H0)

- Sequential Analysis is the Vaccinated Comparator
  - Significant Threshold is a 1-Sided P-Value < 0.0048

- Models are adjusted for:
  - —Calendar day
  - —Age in categories
  - —Race
  - —Site
  - —Sex

Rate Ratio Estimates

Poisson regression will be used to model outcome incidence observed during the risk interval in comparison with incidence expected (under H_0)

- Estimates of the rate ratio (RR) will be reported with nominal 95% confidence intervals rather than confidence intervals that are widened to correspond with the threshold of the sequential tests.
- Trends in outcome incidence over calendar time and time-since-vaccination, and heterogeneity across subgroups will be tracked.
- Supplementary analyses will disaggregate the risk interval (days 1-7, days 8-15, etc.), comparing risk interval weeks with each other and with the incidence expected (under H_0) from our primary comparator. We'll also look at whether incidence varies across the weeks of the comparison interval.

Sequential Tests

- For each outcome, the primary analysis each week will include a sequential test of the one-sided null hypothesis that the vaccine does not increase risk in the risk interval.

- The threshold for a signal is pre-specified by an alpha-spending plan that keeps the overall chance of a Type 1 error below 0.05 for 2 years (104 weekly analyses).
  - With a Pocock style plan, the 2-sided p-value required for a signal at a weekly analysis is 0.0096, amounting to a 1-sided p-value of 0.0048.

- The criteria for signaling are not criteria for "stopping".
  - After a signal, weekly updates will continue as we add analyses to evaluate the signal.

- The multiplicity of different hypotheses tested will be taken into consideration informally.
  - Our sequential testing adjusts for the multiplicity of weekly looks at each hypothesis, but we will not adjust formally for the multiplicity of hypotheses.

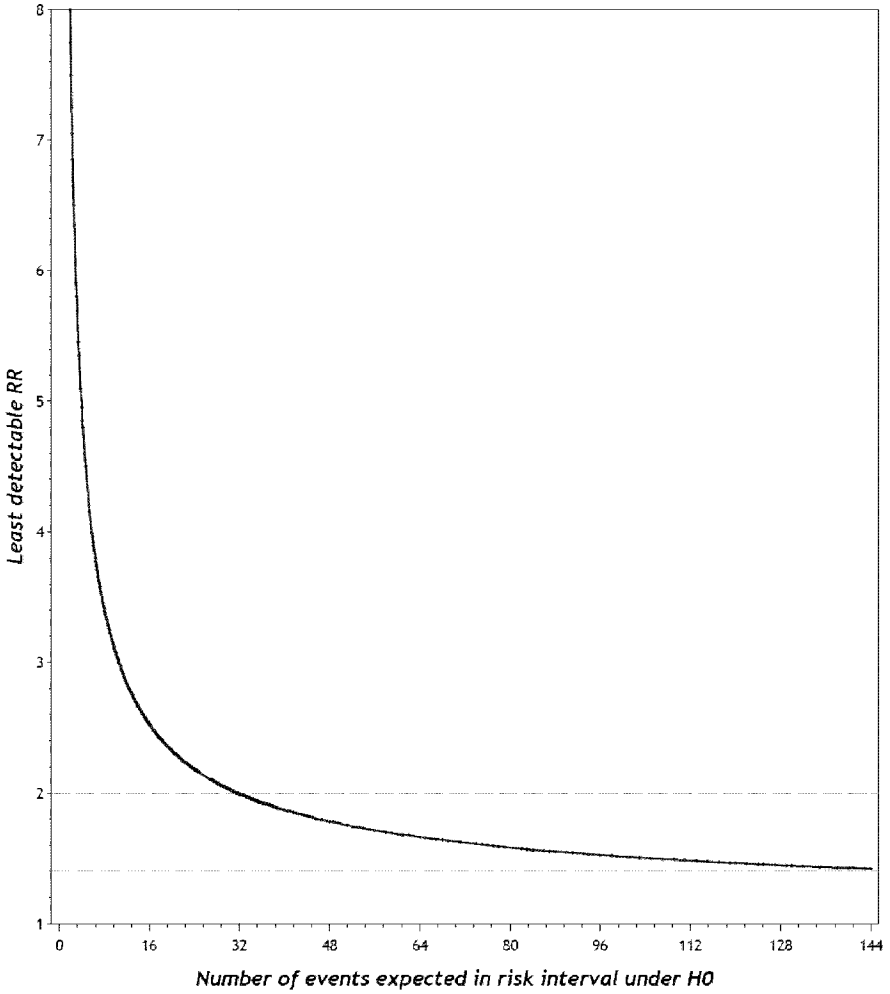
Power (Aim 1)

Power of planned analyses comparing observed outcomes vs expected outcomes in a risk interval—where the expected is based on vaccinees in a comparison interval.

- The magnitude of the rate ratio (RR) detectable with 80% power will decrease as the number of outcomes expected in the risk interval (under H_0) increases.
- If our alpha-spending plan sets the threshold for a signal at 2-sided p=0.0096 (amounting to 1-sided p=0.0048) then RR = **2.0** is detectable when **32** outcomes are expected in the risk interval.
  - RRs of 5, 4, 3, and 1.5 are detectable when 4, 6, 11, and 110 AEs, respectively, are expected in risk interval.
- If E denotes the background rate (outcomes expected per 100,000 person-years under H0) then an RR of 2.0 is detectable when the number of person-days in the risk interval is:

$$32/E \times 365{,}000$$

  - For example, if the background rate is 32 per 100,000 person years, then an RR of 2 is detectable when 365,000 person days are in the risk interval, which we'd have if 1.74 million vaccinees are each observed 21 days.



Relative risk detectable with 80% power, comparing AEs in risk v. comparison intervals of equal length, By the N of events expected in risk interval under the H0 that the vaccine is safe.

Time-to-signal by the rate ratio and the N of events expected weekly under H0

- This table reports on the time-to-signal in 5 million simulations of safety surveillance in each of 12 scenarios, defined by:
  - 3 levels of the rate ratio: 1.5, 2, and 3, and
  - 4 levels of outcome incidence expected under H0: 1, 5, 20, or 100 outcome events per week.
- The top row of each panel indicates when the chance of detecting the panel's RR exceeds 50, 80 and 95% for an AE with expected incidence of only 1 per week
  - The top row of the top panel shows time-to-signal if the true RR=1.5 for an outcome so rare that under H0 we expect only 1 AE per week. (An example of such an outcome would be TTP if we have about 500,000 VSD vaccinees per week)
  - For this infrequent outcome (1 AE/week), the chance of detecting RR=1.5 exceeds 50% by the 55th week and exceeds 80% by the 101st week. It won't ever exceed 95%.
  - For this infrequent outcome, the chance of detecting RR=3.0 exceeds 50% by week 7, 80% by week 11, 95% by week 17.
- Similarly, the 2nd row of each panel indicates when the chance of detecting the RR exceeds 50, 80 and 95% for an AE with expected incidence of 5/week (perhaps Bell's Palsy). The chance of detecting RR=2 passes 50% by week 4, 80% by week 7, 95% by week 11.

For simplicity, expected incidence (under H0) was constant in each scenario.

		Week when chance of signl passes:		
		50%	80%	95%
Rate Ratio	AEs/week expected in risk intervl			
1.5	1 (TTP)	55	101	
	5 (Bells P.)	12	22	33
	20 (seizure)	4	6	9
	100 (AMI)	1	2	2
2	1 (TTP)	19	32	49
	5 (Bells P.)	4	7	11
	20 (seizure)	2	2	3
	100 (AMI)	1	1	1
3	1 (TTP)	7	11	17
	5 (Bells P.)	2	3	4
	20 (seizure)	1	1	1
	100 (AMI)	1	1	1

Signal Follow-up

- If the criteria for a signal are met, we will already have the supplemental comparators (i.e., Unvaccinated concurrent and self-control) available for context and interpretation of results.

- Further analyses of the potential vaccine-outcome association may be undertaken, such as:
  - —Chart review (especially of outcomes during the risk interval)
  - —Evaluate for clustering of outcomes if they appear during brief sub-intervals within the risk interval
  - —Evaluate for clustering in subgroups defined by:
    - age
    - sex
    - race/ethnicity
    - VSD site
    - prior COVID-19 disease

Chart Review

- We will conduct routine chart review for selected rare outcomes (e.g., GBS, ADEM, TM, anaphylaxis) shortly after a case is detected and prior to analysis.

- If the criteria for a signal are met, further analyses of the potential vaccine-outcome association may be undertaken through chart review.

- In collaboration with MCRI and CDC, with feedback from participating VSD sites, we will design, test, validate, and manage all chart reviews across the participating sites.

Study Design: Aim 2

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

- After a COVID-19 vaccine becomes routinely available in the VSD, we will monitor vaccine coverage overall, and in strata defined by age group, sex, race/ethnicity, and VSD site.

- Surveillance of vaccine coverage will be updated weekly.
  - —For each week during the study period, we will tabulate the number of doses delivered, the cumulative number of doses, and vaccine coverage.
  - —If different vaccines are in use in the VSD population, we will monitor vaccine coverage separately for each type of vaccine, and for all COVID-19 vaccines combined.

Vaccine Safety Datalink (VSD)

- VSD consists of electronic health data from each participating site
  - —Demographic data: sex, age, race, and service area
  - —Vaccine data: type of vaccine, vaccination date, and vaccination site
  - —Medical record: includes all healthcare utilization (outpatient, emergency department, and hospitalizations)

- The total 2020 VSD population is ~12.4 million people (3.8% of the total U.S. population).
  - —2,483,518 children (<18 YOA)
  - —9,916,888 adults (18+ YOA)
  - —2019 birth cohort was 105,586

Vaccine Safety Datalink

- Active surveillance: newly licensed vaccines
- Evaluate vaccine safety:
  - —of new recommendations for existing vaccines
  - —for vaccines in high-risk populations, particularly pregnant women (+ other groups)
  - —changes to the vaccine schedule
- Develop new methodologies for vaccine safety assessment
- Test hypotheses noted by signals from VAERS, clinical trials, and other platforms

Importance of Rapid Cycle Analysis in Vaccine Safety

- Rare adverse events may be impossible to detect in pre-licensure studies
- Reports to passive surveillance systems (e.g., the Vaccine Adverse Event Reporting System) often need rapid surveillance/follow-up
- Traditional cohort or case control studies are not well suited for rapid signal detection
  - —Studies can take months to years using traditional approaches

Rapid Cycle Analysis in VSD

- Rapid Cycle Analysis (RCA) allows VSD to detect adverse events following vaccination in near real-time so the public can be informed quickly of possible risks.
- VSD has used RCA to monitor safety of many vaccines including:
  - DTaP-IPV/Hib
  - DTaP-IPV
  - Human papillomavirus (4 valent and 9 valent)
  - Influenza
  - Rotavirus
  - Meningococcal conjugate
  - Measles, mumps, rubella, and varicella (MMRV)
  - Tetanus, Diphtheria, Pertussis (Tdap)
  - Recombinant zoster vaccine

Data

- Sites that participate in VSD produce weekly dynamic data files (DDF) that capture information on demographics, immunizations, and ICD-coded diagnoses assigned by health care providers in outpatient, emergency, or hospital encounters.

- The DDF will be used as the primary data source for both Aims 1 and 2, including identifying and following vaccine recipients for outcomes of interest.

Covariates

- Selected covariates including age, sex, site, race/ethnicity and calendar time will be considered *a priori* and will be used as stratification variables.

- Additional covariates may be considered with CDC and the VSD RCA working group as appropriate.

Historical Comparator Analysis

General Analytic Approach

- MFC will use historical comparators
- Most appropriate for infrequent or rare outcomes
- Using historical data accumulated over multiple years provides more stable estimates and greater statistical power, which potentially leads to earlier detection of a safety signal
- Ideally, the historical period starts October 1, 2015 (the start of ICD-10 coding) and ends December 31, 2019 to avoid the influence of the pandemic in the early part of 2020
- Limitation: Secular trends in disease or in diagnostic or coding practices may lead to either false signaling or failure to identify a true signal

Sequential Analysis using MaxSPRT and CMaxSPRT

- Near real-time surveillance based on weekly aggregate data
- Sequential analysis to detect signals, but maintaining a pre-defined type I error rate
- Poisson-based MaxSPRT, developed by VSD researchers (Kulldorff, et al.)
- Compare observed number of events to expected number based on the historical background rates
  - Expected counts based on the incidence rate expected during the risk window multiplied by the number of vaccines administered
  - Reject H_0 of no excess risk if log-likelihood ratio exceeds a critical value → **statistical signal**
- Critical values based on probability of a false positive (e.g. α=0.05) and planned length of surveillance, defined in terms of expected counts under the null hypothesis
- Use conditional MaxSPRT (CMaxSPRT) when the number of historical cases is small and background rates are unstable

Historical Comparator Groups

- General VSD population (age comparable)
  - Used to estimate general background person-time rates
  - Rates multiplied by vaccine counts to produce expected (prorated to length of post-vax window)
- Other comparator group(s) defined by care-seeking behavior and/or comparator vaccine visits*
  - Well visits (e.g., ICD10: Z00.00, Z00.01)
  - Non-COVID vaccination (e.g., Td, Tdap, pneumococcal, influenza)
  - Compute number events in post-visit risk windows
- Some combination of well visits and vaccination visits in the historical period?
  - For example, well visit and a flu vaccine in the previous 18 months
- Compare different groups to vaccinated group using baseline covariates

Analyses for Days 1-21 & 1-42 Risk Intervals

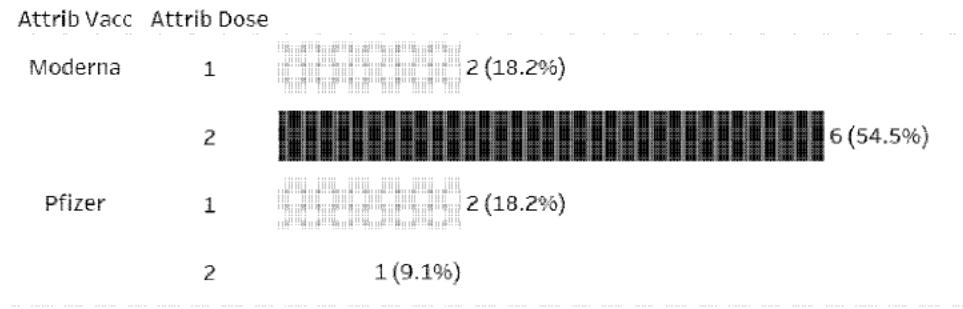
Analytic Methods	*Moderna*			*Pfizer*			*mRNA-Vaccines Combined*			*Janssen*
	Dose 1	Dose 2	Dose 1 & Dose 2 Combined	Dose 1	Dose 2	Dose 1 & Dose 2 Combined	Dose 1	Dose 2	Dose 1 & Dose 2 Combined	Dose 1
Vaccinated Concurrent Comparators	√	√	√	√	√	√	√	√	✓	✓
Unvaccinated Concurrent Comparators	√	√	√	√	√	√	√	√	√	√
Historical Background rates	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Historical Well care visits	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

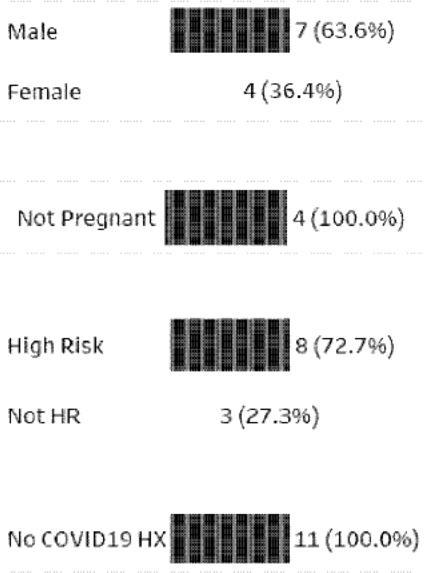
√ = featured
√ = available (not featured)
√ = planned

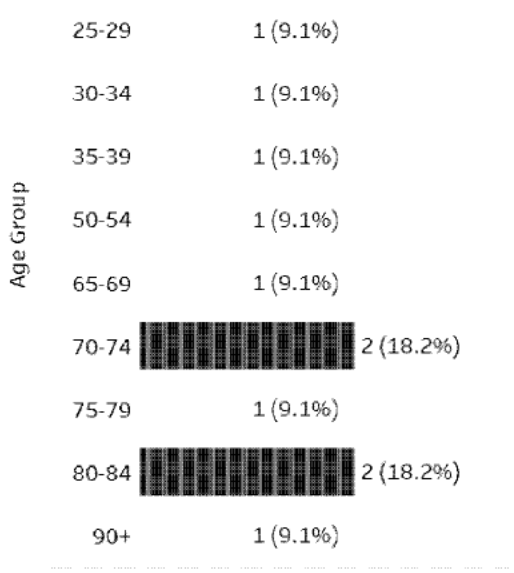
Cerebral Venous Sinus Thrombosis (CVST): mRNA vaccines Automated Summary

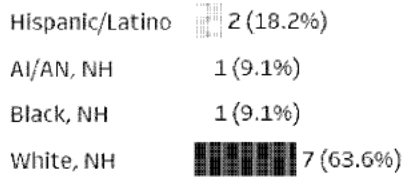
11

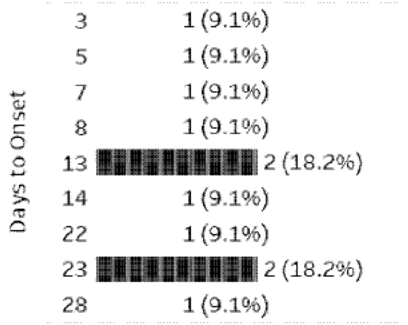
automated cases identified in the 1-84 day risk interval





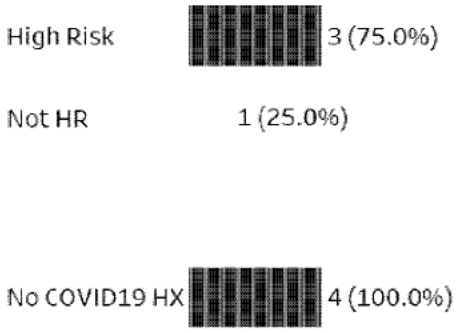


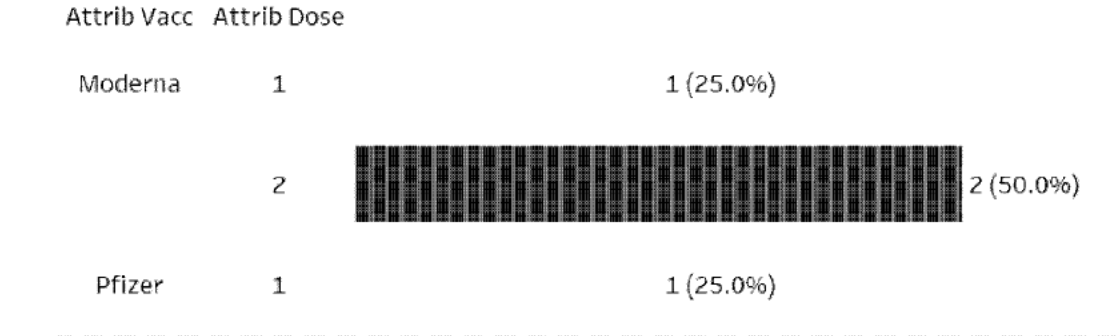


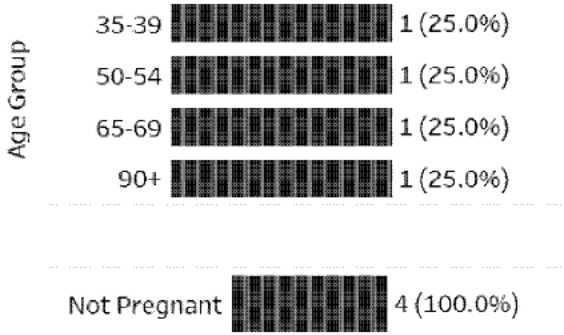


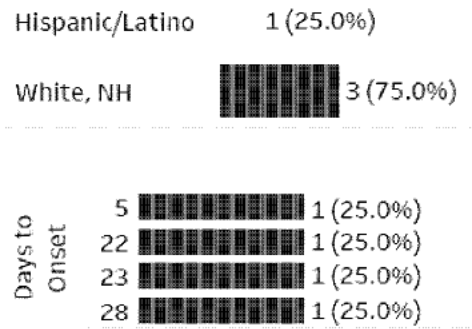
Cerebral Venous Sinus Thrombosis (CVST): mRNA vaccines Automated Summary among Women

automated cases identified in the 1-84 day risk interval among women (N=11 among both sexes)







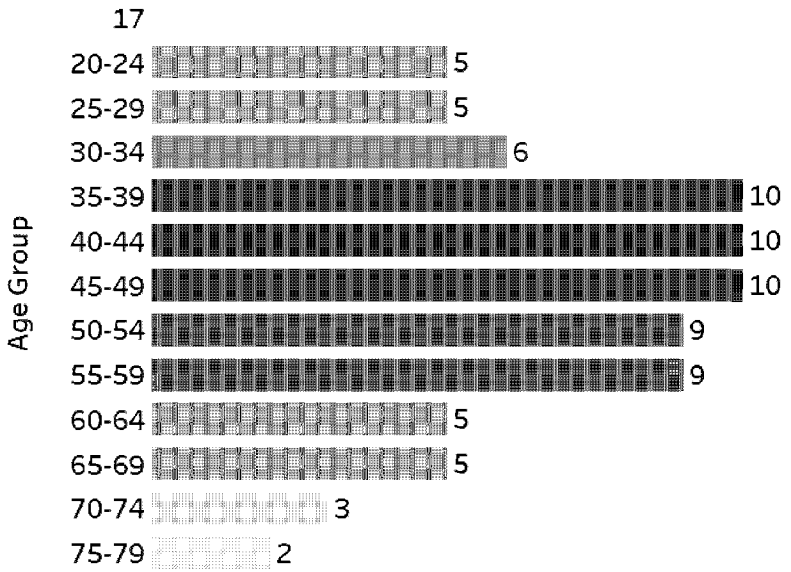


Anaphylaxis Automated Summary

80

Automated cases identified on days 0-1

Age in years ranged from 20-79, with 51 of the cases between ages 25-54



GBS Summary

Outcome	No. Automated Cases	No. Completed Chart Review	No. Chart Confirmed Cases
GBS	15	5	1

- Chart review completed for 5 cases, only 1 was confirmed
  - 3 cases not confirmed (1 history of GBS, 1 rule out, 1 miscode)
  - 1 confirmed case classified as Brighton Level 2, 88 year-old male with onset of symptoms 1 day after Moderna dose 1; noted as recovered with neurologic sequelae as of last follow-up visit and also received Moderna dose 2
  - 1 case classified as Brighton Level 4, no alterative diagnosis but does not fulfill the minimal case criteria (no documentation of diminished or absent reflexes)
- Chart review in progress for 10 cases
  - Quick reviews completed for 7 cases suggest incident GBS following vaccination

ADEM & TM Summary

Outcome	No. Automated Cases	No. Completed Chart Review	No. Chart Confirmed Cases
ADEM	1	0	0
TM	4	1	0

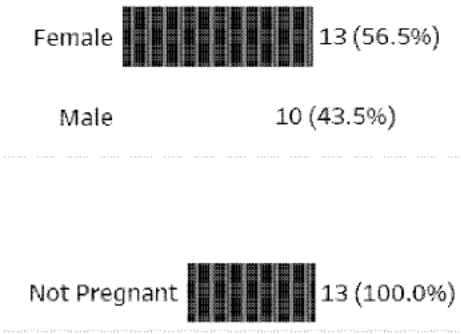
- 4 automated cases of TM identified, chart review in progress for 3 cases and 1 not confirmed
  - Quick reviews completed for 2 cases suggest incident TM following vaccination
  - 1 case not confirmed as incident by chart review (symptom onset documented prior to COVID-19 vaccination)
- 1 automated case of ADEM identified, chart review in progress
  - Quick review completed suggests incident case of ADEM following vaccination

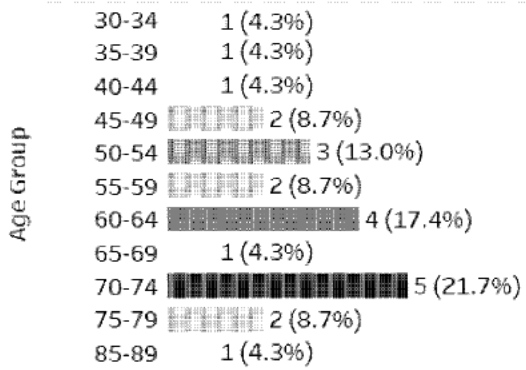
VTE/PE events 42 days After Janssen: Quick Chart Review Summary

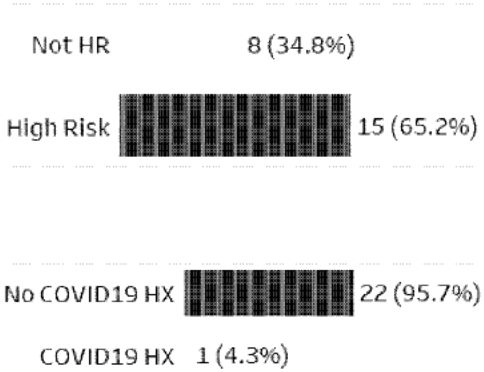
- 32 VTE/PE cases (including 3 cases diagnosed with both VTE and PE) in 1-42 days
- 29 have been quick reviewed to date, 3 are in progress
  - 6/29 were ruled out as not VTE
  - 23/29 were confirmed VTE/PE cases
    - 4/23 were determined to have symptom onset prior to vaccination
      - Including 2 cases with thrombocytopenia documented prior to vaccination
    - 1/23 had an indeterminate symptom onset
    - 18/23 are potential VTE/PE cases with incidence following vaccination
      - 10 female (5 PE, 5 VTE), 8 males (4 PE, 4 VTE)
      - Ages ranged from 30-79
      - None with history of COVID-19 infection or thrombocytopenia noted at time of VTE/PE

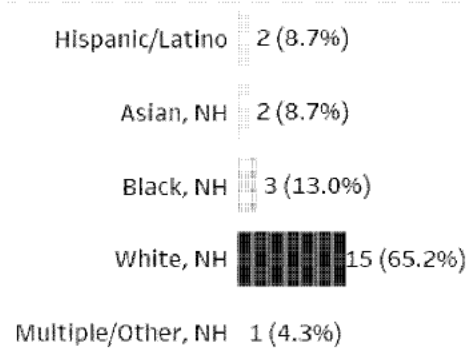
Venous thromboembolism automated summary: Cases after Janssen vaccine during the 42 days after vaccination

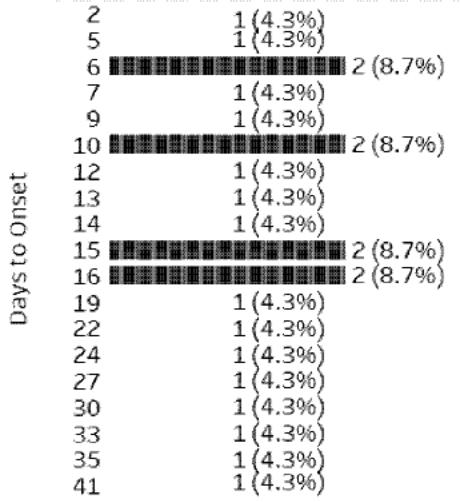
automated cases identified in the 1-42 day risk interval after Janssen vaccine





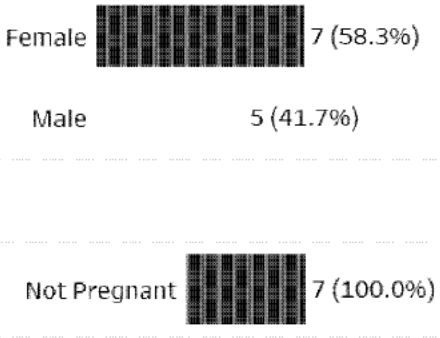


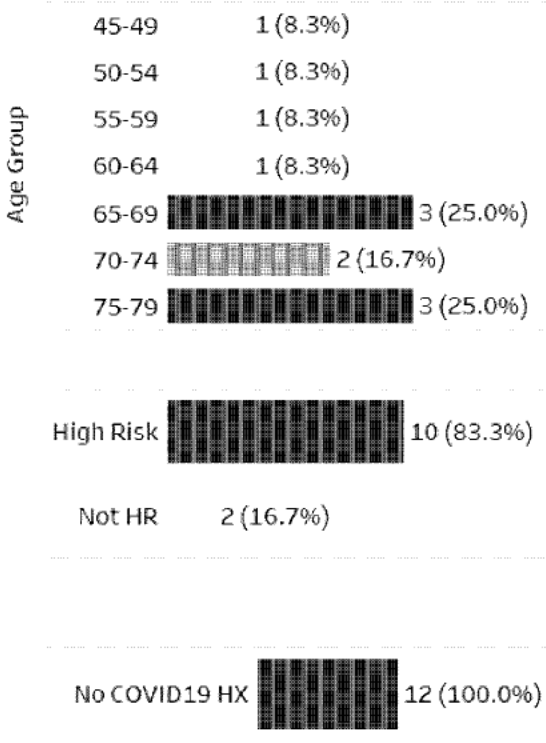


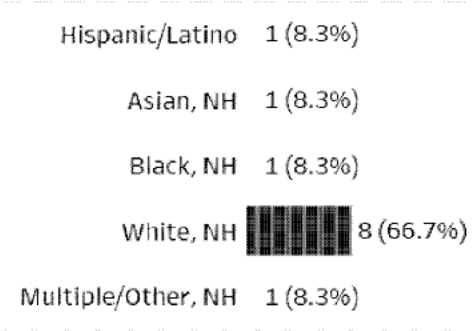


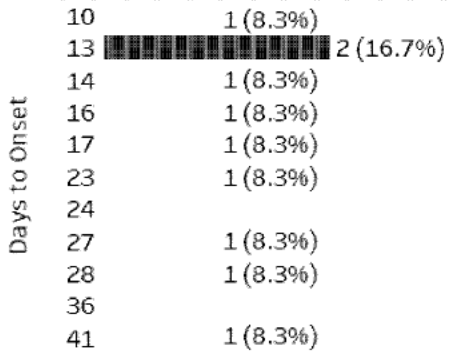
Pulmonary embolism (PE) automated Summary: Cases after Janssen vaccine during the 42 days after vaccination

automated cases identified in the 1-42 day risk interval after Janssen vaccine









U.S. FOOD & DRUG ADMINISTRATION

An Update of CBER Active Monitoring of COVID-19 Vaccine Safety

Office of Biostatistics & Epidemiology, CBER

Last Updated: April 29, 2021

Rapid-cycle analyses (RCA) or "Near real-time surveillance"

- 15 possible Adverse Events of Special Interest (AESI)
- By brand, by dose, by health insurance system, and by age
- Test at sequential cuts of data as data accrues for rapid signal detection

FDA Rapid Cycle Analysis of COVID-19 Vaccines : Working list of 15 possible adverse events of special interest (AESI)

Acute myocardial infarction	Bell's Palsy	Narcolepsy
Anaphylaxis	Encephalomyelitis	Non-hemorrhagic Stroke
Appendicitis	Guillain-Barré syndrome	Pulmonary Embolism (PE)
Disseminated intravascular coagulation (DIC)	Hemorrhagic Stroke	Transverse Myelitis
Deep Vein Thrombosis (DVT)	Myocarditis/Pericarditis	Immune thrombocytopenia (ITP)

FDA-CMS
(Center for Medicare & Medicaid Services)

Rapid Cycle Analysis
(Near-Real Time Surveillance)

Rapid-cycle analyses (RCA) or "Near real-time surveillance"

- Compare the observed incidence rate (IR) of 15 AESIs among COVID-19 vaccinees versus the "Expected" IR
- "Expected" IRs
  - Background rates had there been no COVID-19 vaccinations
  - Annual IR in adults aged 65+ years during 2017-2019
  - Selection: IRs for AESIs returned to historical rates (2017-2019) after a dip March-June 2020.
- Background rates standardized to the distribution of COVID-19 vaccinees for nursing home, age, sex, race

AMI, PE, and DIC

AESI	Care setting	Clean Window	Risk Window	Clinical Margin of Significance
Acute myocardial infarction (AMI)	IP	365 days	1-28 days	1.25
Pulmonary Embolism (PE)	IP, OP/PB	365 days	1-28 days	1.25
Disseminated Intravascular Coagulation (DIC)	IP, OP-ED	365 days	1-28 days	1.25

IP refers to inpatient facility claims.
OP/PB refers to all outpatient facility claims, and professional/provider claims except those professional/provider claims with a laboratory place of service.
OP-ED refers to the subset of outpatient facility claims that occur in the emergency department

Crude RR for PE elevated from baseline rates

- Acute Myocardial Infarction (Pfizer)
  - Association met threshold for further QC and sensitivity analyses
  - After seasonality adjustment, relative risk reduced from 1.22 to 1.10 and the association was not statistically significant.

- Pulmonary Embolism (Pfizer)
  - Association met threshold for further QC and sensitivity analyses
  - After seasonality adjustment, relative risk reduced from 1.44 to 1.31 and remained statistically significant.

- Disseminated Intravascular Coagulation (Pfizer)
  - Association met threshold for further QC and sensitivity analyses
  - After seasonality adjustment, relative risk reduced from 1.52 to 1.31 and the association was not statistically significant.

***Data through observation week 17, 4/3/2021**

Quality Assurance and Signal Characterization

Signal Assessment Summary

Category	Tasks	AMI	PE	DIC
Data Quality Assurance	1. Check for duplication of vaccines/outcomes	Done	Done	Done
	2. Check for unusual variability in claims accrual	Done	Done	Done
	3. Check for issues with dose number identification	Done	Done	Done
	4. Check number of individuals with multiple outcomes (i.e., overlap between outcome populations)	Done	Done	Done
	5. Check frequency of individual codes and claim settings used to flag outcomes in the historical and observation periods	Done	Done	Done
Billing / Event Identification	6. Changes in diagnosis criteria or guidelines in detecting outcomes or vaccines	Done	Done	Done
	7. Assess changes in payment policy or claims submission	Done	Done	Done
Signal Characterization	8. Run PMaxSPRT with seasonality adjustment (i.e., use Jan-Mar exp rates)	Done / Continuing	Done / Continuing	Done / Continuing
	9. Summarize demographic and covariate distributions of cases and vaccines compared to the general age 65+ pop	Preliminary Summary Done	Preliminary Summary Done	Preliminary Summary Done
	10. Create patient profiles and review with clinicial experts	Done	Done	Done
	11. Create temporal scan statistics to identify case clusters	Done	Done	Done
	12. Check frequency of prior COVID diagnosis	Done	Done	Done
	13. Run PMaxSPRT with alternative expected rates population (e.g., flu vaccinated pop)	In Progress	In Progress	In Progress
	14. Characterize RRs by patient strata (NH residency, sex, age, race) to assess possible sources of confounding	Done	Done	Done

Quality Assurance

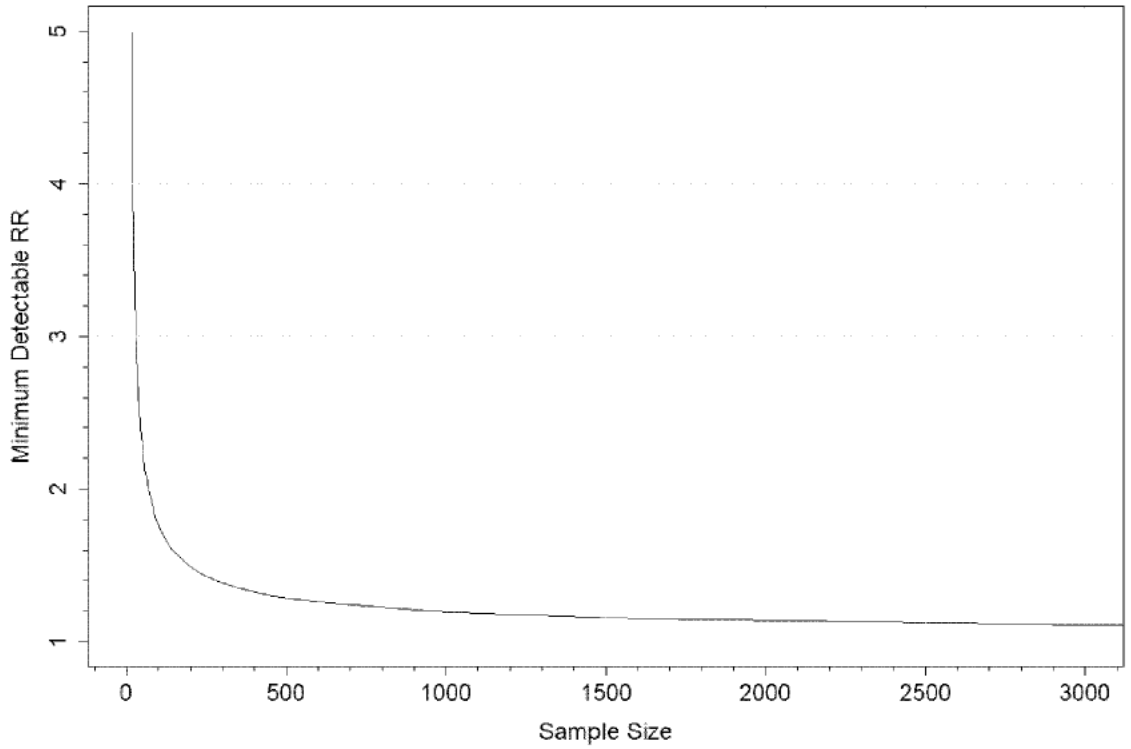
- Several analyses were performed to evaluate data quality, including:
  - Seasonality through stratification
    - PMaxSPRT sensitivity analysis using Jan-Mar background rates resulted in no statistically significant association for AMI and DIC and delayed observed association for PE post-Pfizer.
  - Potential duplication of vaccines, persons, and AESIs
    - No evidence of concern
  - Discrepancies in dose assignment
    - No evidence of concern
  - Variability in claims accrual
    - No evidence of concern
  - Changes in payment, coding, and claims submission policies
    - No evidence of concern

Signal Characterization

- Analyses were performed to verify findings from the RCA, including:
  - Outcome definitions
    - Proportion of specific claims-based codes to identify AMI and PE events were lower in COVID-19 vaccinees in RCA ('observed') than in historical period used to calculate background rates ('expected'). This was not seen for DIC.
  - Temporal scan statistics
    - Temporal scan statistic did not identify significant clustering for AMI, DIC, or PE post Pfizer first dose
  - Patient claim profiles
    - Majority of AMI cases were NSTEMI or Type 2 AMI, and approximately 25-40% were deemed unlikely to be true cases. For PE, 40-50% of cases were considered unlikely to be true cases due to use of anticoagulants or lack of diagnostic scans or treatment
    - As DIC is best validated using laboratory data, there was insufficient granularity in claims data to assess the likelihood of true DIC with confidence. Nonetheless, 15% of cases appear more likely to be true DIC cases (i.e., inpatient and patient evaluation claims recorded); 63% had limited diagnostic coding for DIC (e.g., only one institutional claim but no evaluation claims).
  - Prior COVID Diagnosis
    - Proportion of AMI, PE, and DIC cases post Pfizer vaccination that had a prior COVID diagnosis was 18%, 19%, and 24%, respectively
  - Risk Ratios by Strata
    - RRs estimated by strata indicate larger relative risk for AMI, PE, and DIC in the nursing home population compared to the non-nursing home population

Next steps: Inferential Studies

- Minimum detectable risk ratios (RRs) a Self-Control Risk Interval (SCRI) study



- Hypothetical number of AESIs
- 80% power
- Risk window = 28 days

Next steps: Inferential Studies

- Study designs under consideration:
  - Primary analyses: SCRI or SCCS using post-vaccination control interval after Dose 2
  - Secondary analyses: SCRI or Self-Controlled Case Series (SCCS) using pre-vaccination control interval as comparator and only Dose 1
  - Cohort analyses if a reference source for vaccine capture and quantitative bias analyses for recalibration of RR is available

Conclusions

- Rates are elevated but below RR > 1.5

Questions to VaST members

- How do we communicate these RCA results to the public?
- How do address the trade-off of the uncertainty of self-controlled studies using pre-vaccination intervals versus a more timely analyses?
- Any suggestions for adjustment of risk factors for cardiovascular events during PMaxRT runs? We currently are standardizing the expected rates to nursing home status, age, sex, race/ethnicity.
- Should we consider incorporating severity of the AESIs in determination of our clinical margin and if so, how do we do that? The clinical margins are currently selected based on whether the AESIs are common (signal faster) or rare.

Acknowledgments

- Steven Anderson
- Richard Forshee
- Azadeh Shoaibi
- Hui-Lee Wong
- CBER Surveillance Team: Cindy Zhou, Patricia Lloyd, Joyce Obidi, Kristin Sepulveda
- Manette Niu
- CBER OBE Colleagues
- Federal Colleagues: CMS, VA, CDC
- FDA Partners: Acumen, IBM Watson – and new partners in FY2021

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 5/10/2021 5:05:26 PM
To: Anderson, Steven [redacted] Beresnev, Tatiana H (NIH) [redacted] Broder, Karen R (CDC) [redacted] Calvert, Geoffrey M (CDC) [redacted] Clark, Matthew (IHS) [redacted] Clark, Thomas A (CDC) [redacted] Cohn, Amanda C (CDC) [redacted] Collins, Limone [redacted] Cunningham, Fran [redacted] Daley, Matt [redacted] DeStefano, Frank (CDC) [redacted]; Edwards, Kathy [redacted] Farizo, Karen [redacted] Forshee, Richard [redacted] Gee, Julianne M (CDC) [redacted] Hause, Anne M (CDC) [redacted] Helfand, Rita (CDC) [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted] Kelman, Jeffrey A (CMS) [redacted] LaPorte, Kathleen (CDC) [redacted] Lee, Grace [redacted] MacNeil, Jessica R (CDC) [redacted] Marquez, Paige L (CDC) [redacted] Mbaeyi, Sarah A (CDC) [redacted] Myers, Tanya R (CDC) [redacted] Nair, Narayan [redacted] Oliver, Sara E (CDC) [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Rubin, Mary (HRSA) [redacted] Schechter, Robert [redacted] Schindelar, Jessica A (CDC) [redacted] Shanley, Edwin (CDC) [redacted] Shay, David K (CDC) [redacted] Shimabukuro, Tom (CDC) [redacted] Sotir, Mark J (CDC) [redacted] Steinberg, Judith L (OS) [redacted] Su, John (CDC) [redacted] Talbot, Keipp [redacted] Wasley, Annemarie (CDC) [redacted] Weintraub, Eric S (CDC) [redacted] Wharton, Melinda (CDC) [redacted] Wong, Hui-Lee [redacted] Woo, Jared M (CDC) [redacted] Young, Mardia A (CDC) [redacted]
CC: Markowitz, Lauri (CDC) [redacted]
Subject: [EXTERNAL] VaST - Agenda for May 10 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL
Attachments: ACIP_VaxSafety_Shimabukuro_5-12-2021_v8.pdf; ACIP 05-12-2021_Lee VaST draft-V3.pdf; VaST planning_5_10_2021.pdf; 2021-05-10 - VaST Meeting Agenda.docx

Dear all,

Attached are the presentations for today. The first two are the draft ACIP presentations for May 12. The VaST presentation will be updated based on the data presented today by Tom Shimabukuro. I am also resending the agenda.

The VaST call information should be on your calendars.
Reminder - all VaST documents and communications are confidential.

Lauri

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

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: Monday, May 10, 2021 12:11 PM
To: Anderson, Steven (FDA/CBER) [redacted] Beresnev, Tatiana (NIH) [C] [redacted] Broder, Karen (CDC/DDID/NCEZID/DHQP) [redacted]; Calvert, Geoffrey M. (CDC/NIOSH/WTCHP) [redacted] Clark, Matthew (IHS/ALB) [redacted] Clark, Thomas A. (CDC/DDID/NCIRD/DVD) <tnc4@cdc.gov>; Cohn, Amanda (CDC/DDID/NCIRD/OD) [redacted] Collins, Limone

[redacted] Cunningham, Fran [redacted] Daley, Matt [redacted] Destefano, Frank (CDC/DDID/NCEZID/DHQP) [redacted] Edwards, Kathy [redacted] Farizo, Karen (FDA/CBER) [redacted] Forshee, Richard (FDA/CBER) [redacted] Gee, Julianne (CDC/DDID/NCEZID/DHQP) [redacted] Hause, Anne M. (CDC/DDID/NCEZID/DHQP) [redacted] Helfand, Rita (CDC/DDID/NCEZID/OD) [redacted] Hopkins, Bob [redacted] Jackson, Lisa [redacted] Jennifer Nelson [redacted] Kelman, Jeffrey A. (CMS/CM) [redacted] LaPorte, Kathleen (CDC/DDID/NCIRD/ID) [redacted] Lee, Grace [redacted] MacNeil, Jessica R. (CDC/DDID/NCIRD/OD) [redacted] Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted] Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) [redacted] Mbaeyi, Sarah (CDC/DDID/NCIRD/OD) [redacted] Myers, Tanya R. (CDC/DDID/NCEZID/DHQP) [redacted] Nair, Narayan (FDA/CBER) [redacted] Oliver, Sara Elizabeth (CDC/DDID/NCIRD/DVD) [redacted] Patricia Whitley-Williams [redacted] Riley, Laura [redacted] Rubin, Mary (HRSA) [redacted] Schechter, Robert [redacted] Schindelar, Jessica (CDC/DDID/NCEZID/DHQP) [redacted] Shanley, Edwin (CDC/DDID/NCIRD/OD) [redacted] Shay, David (CDC/DDID/NCIRD/ID) [redacted] Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) [redacted] Sotir, Mark (CDC/DDID/NCIRD/DVD) [redacted] Steinberg, Judith (HHS/OASH) [redacted] Su, John (CDC/DDID/NCEZID/DHQP) [redacted] Talbot, Keipp [redacted] Wasley, Annemarie (CDC/DDPHSIS/CGH/GID) [redacted] Weintraub, Eric (CDC/DDID/NCEZID/DHQP) [redacted] Wharton, Melinda (CDC/DDID/NCIRD/ISD) [redacted] Wong, Hui-Lee (FDA/CBER) [redacted] Woo, Jared (CDC/DDID/NCEZID/DHQP) [redacted] Young, Mardia (CDC/DDID/NCEZID/DHQP) (CTR) [redacted]
Subject: VaST - Agenda for May 10 (1:30 - 3 pm ET) - CONFIDENTIAL

Dear all,

This email includes the VaST agenda for today. Presentations will be sent before the call in a subsequent email.

The VaST call information should be on your calendars.
Reminder - all VaST documents and communications are confidential.

Lauri Markowitz and Melinda Wharton

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

Update: thrombosis with thrombocytopenia syndrome (TTS) following U.S. COVID-19 vaccines

Advisory Committee on Immunization Practices (ACIP)
May 12, 2021

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Task Force
Vaccine Safety Team

Disclaimer

- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) or the U.S. Food and Drug Administration (FDA)
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC or FDA

Topics

- Background
- Thrombosis with thrombocytopenia syndrome (TTS) following COVID-19 vaccine
- Summary

Background

Thrombosis*

- Thrombosis occurs when blood clots block blood vessels
  - Thromboses can be venous or arterial
  - Complications include heart attack, stroke, infarctions
- Causes and risk factors include:
  - Trauma, immobility, inherited disorders (genetic), autoimmune disease, obesity, hormone therapy or birth control pills, pregnancy, smoking, cancer, older age, etc.
- Symptoms may include:
  - Pain and swelling in an extremity, chest pain, numbness or weakness on one side of the body, sudden change in mental status
- Diagnosed mainly through imaging (e.g., CT, MRI, ultrasound) and blood tests

* Source: https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis

Platelets and thrombocytopenia (low platelets)*

- Platelets (thrombocytes) are colorless blood cells that help blood clot; normal platelet count is 150,000–450,000 per microliter
- Platelets stop bleeding by clumping and forming plugs in blood vessel injuries
- Thrombocytopenia is a condition in which you have a low blood platelet count (<150,000 per microliter)
- Dangerous internal bleeding can occur when your platelet count falls below 10,000 per microliter
- Though rare, severe thrombocytopenia can cause bleeding into the brain, which can be fatal

* Source: https://www.mayoclinic.org/diseases-conditions/thrombocytopenia/symptoms-causes/syc-20378293

This is an official

CDC HEALTH ALERT

Distributed via the CDC Health Alert Network
April 13, 2021, 1:00 PM ET
CDCHAN-00442

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

Summary
As of April 12, 2021, approximately 6.85 million doses of the Johnson & Johnson (J&J) COVID-19 vaccine (Janssen) have been administered in the United States. The Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) are reviewing data involving six U.S. cases of a rare type of blood clot in individuals after receiving the J&J COVID-19 vaccine that were reported to the Vaccine Adverse Events Reporting System (VAERS). In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women aged 18–48 years. The interval from vaccine receipt to symptom onset ranged from 6–13 days. One patient died. Providers should maintain a high index of suspension for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine. When these specific type of blood clots are observed following J&J COVID-19 vaccination, treatment is different from the treatment that might typically be administered for blood clots. Based on studies conducted among the patients diagnosed with immune thrombotic thrombocytopenia after the AstraZeneca COVID-19 vaccine in Europe, the pathogenesis of these rare and unusual adverse events after vaccination may be associated with platelet-activating antibodies against platelet factor-4 (PF4), a type of protein. Usually, the anticoagulant drug called heparin is used to treat blood clots. In this setting, the use of heparin may be harmful, and alternative treatments need to be given.

CDC will convene an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on Wednesday, April 14, 2021, to further review these cases and assess potential implications on vaccine policy. FDA will review that analysis as it also investigates these cases. Until that process is complete, CDC and FDA are recommending a pause in the use of the J&J COVID-19 vaccine out of an abundance of caution. The purpose of this Health Alert is, in part, to ensure that the healthcare provider community is aware of the potential for these adverse events and can provide proper management due to the unique treatment required with this type of blood clot.

Background
VAERS is a national passive surveillance system jointly managed by CDC and FDA that monitors adverse events after vaccinations. The six patients (after 6.85 million vaccine doses administered) described in these VAERS reports came to attention in the latter half of March and early April of 2021 and developed symptoms a median of 9 days (range = 6–13 days) after receiving the J&J COVID-19 vaccine. Initial presenting symptoms were notable for headache in five of six patients, and back pain in the sixth who subsequently developed a headache. One patient also had abdominal pain, nausea, and vomiting. Four developed focal neurological symptoms (focal weakness, aphasia, visual disturbance) prompting presentation for emergency care. The median days from vaccination to hospital admission was 15 days (range = 10–17 days). All were eventually diagnosed with

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AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets

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News 07/04/2021

EMA confirms overall benefit-risk remains p

EMA's safety committee (PRAC) has concluded to
be listed as very rare side effects of Vaxzevria (f

In reaching its conclusion, the committee took in
advice from an ad hoc expert group.

Research

JAMA | Original Investigation

US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021

Isaac See, MD; John R. Su, MD, PhD, MPH; Allison Lale, MD, MPH; Emily Jane Woo, MD, MPH; Alice Y. Guh, MD, MPH; Tom T. Shimabukuro, MD, MPH, MBA; Michael B. Streiff, MD; Agam K. Rao, MD; Allison P. Wheeler, MD, MSCI; Suzanne F. Beavers, MD; Anna P. Durbin, MD; Kathryn Edwards, MD; Elaine Miller, RN, MPH; Theresa A. Harrington, MD, MPH&TM; Adamma Mba-Jonas, MD, MPH; Narayan
Duong T. Nguyen, DO; Kawsar R. Talaat, MD; Victor C. Urrutia, MD; Shannon C. Walker, MD; C. Buddy Cre
Thomas A. Clark, MD, MPH; Frank DeStefano, MD, MPH; Karen R. Broder, MD

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
April 30, 2021

Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine — United States, March–April 2021

David K. Shay, MD[1]; Julianne Gee, MPH[1]; John R. Su, MD, PhD[1]; Tanya R. Myers, PhD[1]; Paige Marquez, MSPH[1]; Ruiling Liu, PhD[1]; Bicheng Zhang, MS[1]; Charles Licata, PhD[1]; Thomas A. Clark, MD[1]; Tom T. Shimabukuro, MD[1]

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Janssen (Ad.26.COV2.S) COVID-19 vaccine (Janssen Biotech, Inc., a Janssen Pharmaceutical company, Johnson

VAERS reports reviewed, 97% were classified as nonserious and 3% as serious,† including three reports among women of cases of thrombosis in large arteries or veins accompanied by thrombocytopenia during the second week after vaccination.

https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
https://jamanetwork.com/journals/jama/fullarticle/2779731
https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e2.htm?s_cid=mm7018e2_w

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
April 27, 2021

Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021

Jessica R. MacNeil, MPH[1]; John R. Su, MD, PhD[1]; Karen R. Broder, MD[1]; Alice Y. Guh, MD[1]; Julia W. Gargano, [illegible]
Stephen C. Hadler, MD[1]; Heather M. Scobie, PhD[1]; Amy E. Blain, MPH[1]; Danielle Moulia, MPH[1]; Matthew F. Dale
José R. Romero, MD[4]; H. Keipp Talbot, MD[5]; Grace M. Lee, MD[6]; Beth P. Bell, MD[7]; Sara E.

Summary

What is already known about this topic?

On April 13, 2021, CDC and the Food and Drug Administration (FDA) recommended pausing use of the Janssen COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome (TTS) among vaccine recipients.

What is added by this report?

On April 23, the Advisory Committee on Immunization Practices concluded that the benefits of resuming Janssen COVID-19 vaccination among persons aged ≥18 years outweighed the risks and reaffirmed its interim recommendation under FDA's Emergency Use Authorization, which includes a new warning for rare clotting events among women aged 18–49 years.

What are the implications for public health practice?

Resuming use of the Janssen COVID-19 vaccine will ensure flexibility, choice, and improved access. Education about TTS risk with Janssen COVID-19 vaccine is critical.

https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7017e4-H.pdf

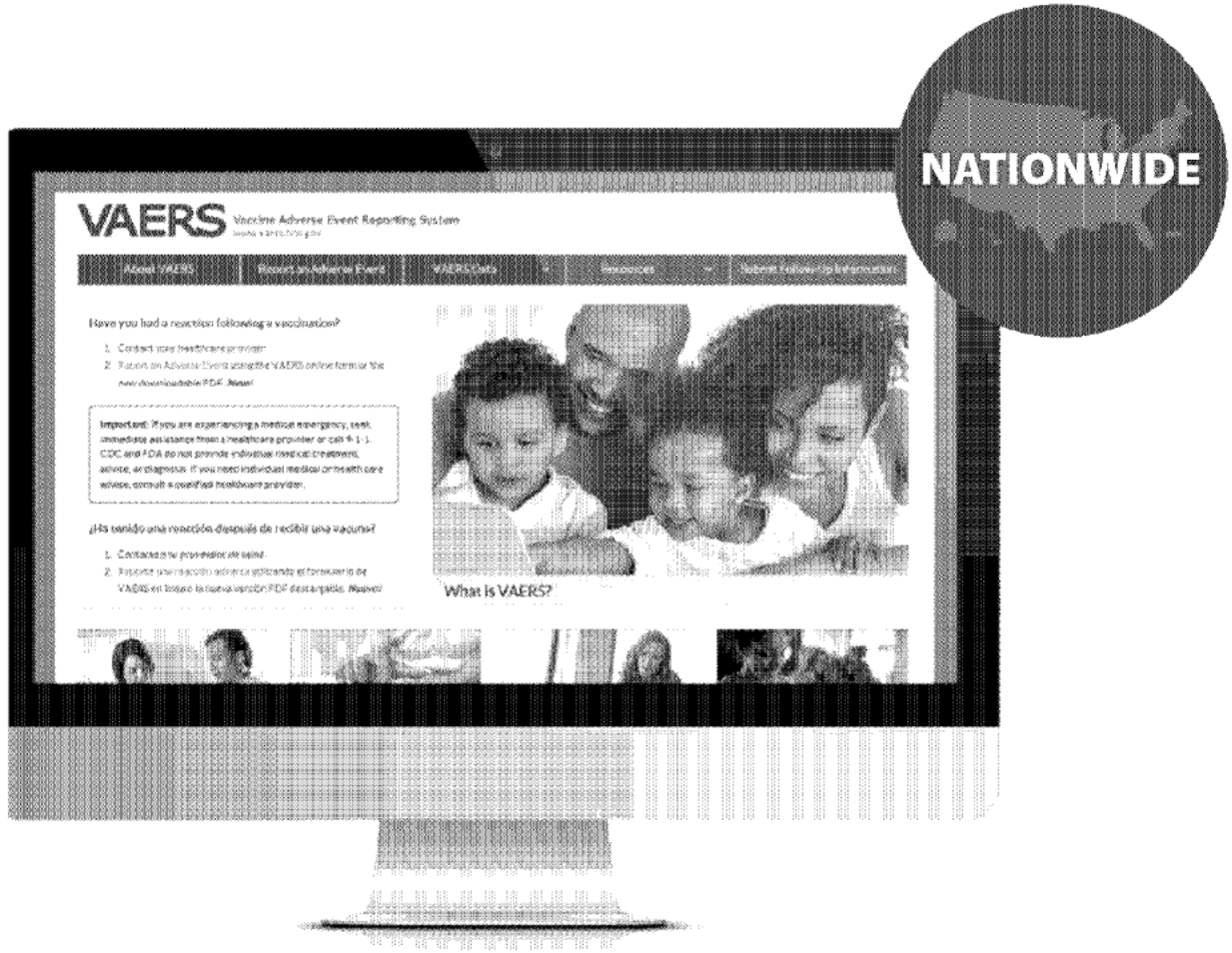
Update on TTS cases

VAERS is the nation's early warning system for vaccine safety

CDC + FDA

VAERS

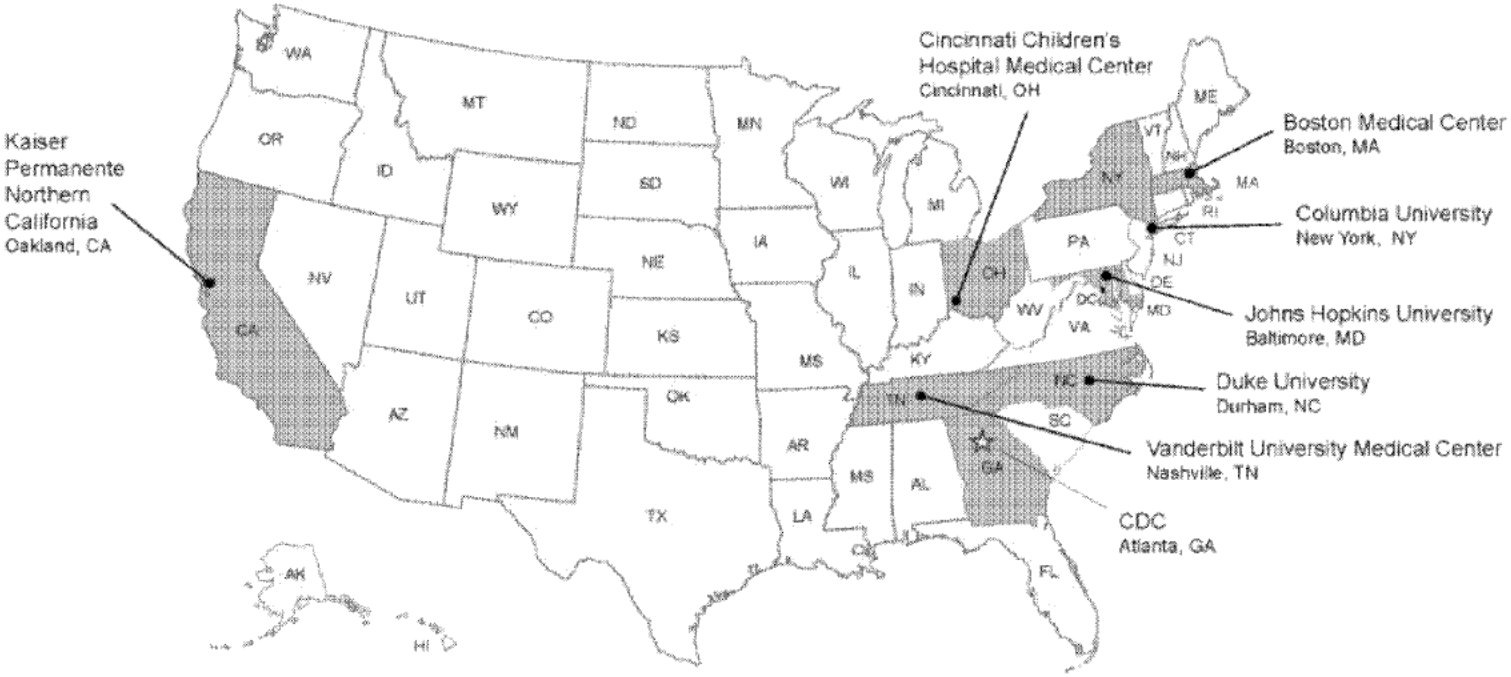
Vaccine Adverse Event Reporting System



http://vaers.hhs.gov

CISA

Clinical Immunization Safety Assessment (CISA) Project



7 participating medical research centers with vaccine safety experts

- clinical consult services*
- clinical research

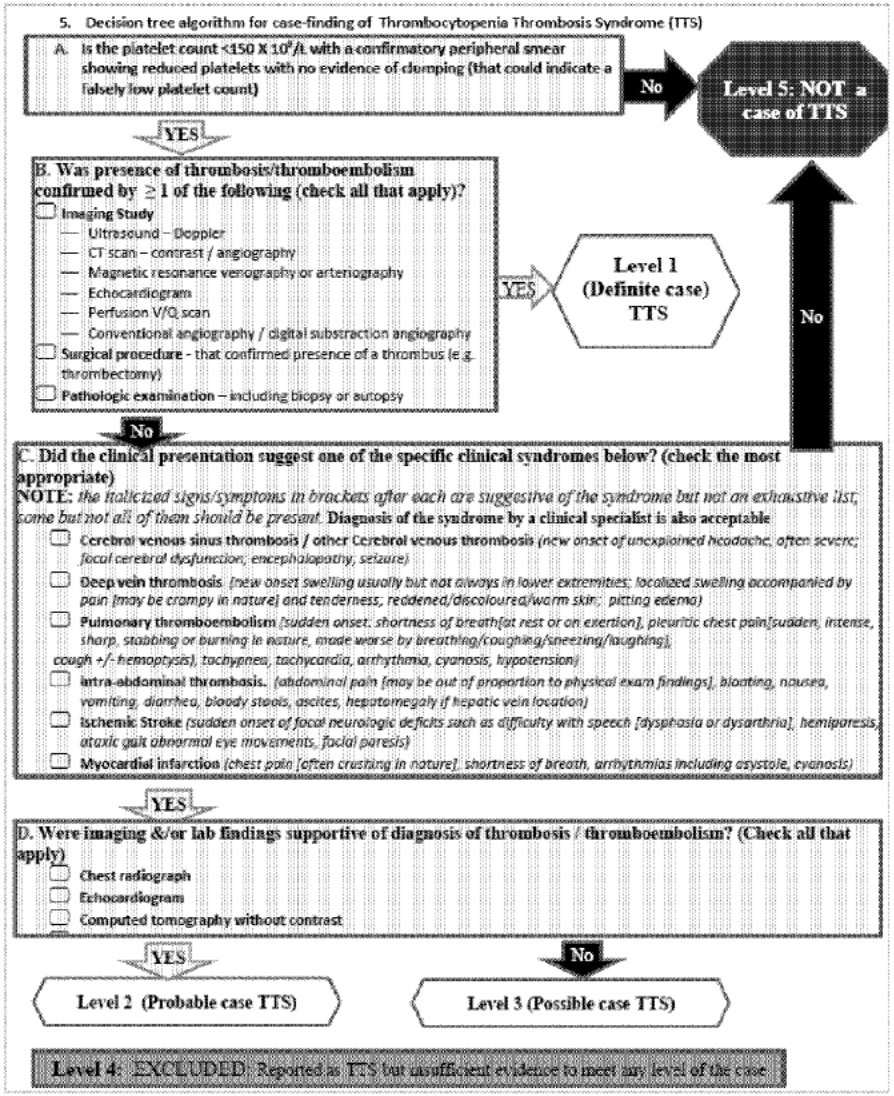
*More information about clinical consults available at http://www.cdc.gov/vaccinesafety/Activities/CISA.html

Case finding in VAERS for TTS following COVID-19 vaccines

- Healthcare providers directly contact CDC with potential TTS cases
  - CDC initiates an investigation and facilitates submission of a VAERS report
- FDA physicians review incoming VAERS reports daily to identify potential TTS cases
- VAERS database search conducted daily for possible TTS reports
- Medical records requested for all potential TTS case reports to confirm thrombosis with laboratory evidence of thrombocytopenia, using working case definition
- CDC and FDA medical officers review TTS case reports and available medical records; CISA experts including hematologists consulted

Interim Brighton Collaboration case definition for thrombosis with thrombocytopenia syndrome (TTS)

- New onset thrombocytopenia: platelet count <150,000 per microliter*
- No known recent exposure to heparin
- Presence of venous or arterial thrombosis
  - In addition to rare thromboses (e.g., cerebral venous thrombosis), currently includes more common thromboses (e.g., as deep vein thrombosis, pulmonary thromboembolism, ischemic stroke, and myocardial infarction)



https://brightoncollaboration.us/wp-content/uploads/2021/04/TTS-Interim-Case-Definition-v9.2-April22-202116538.docx

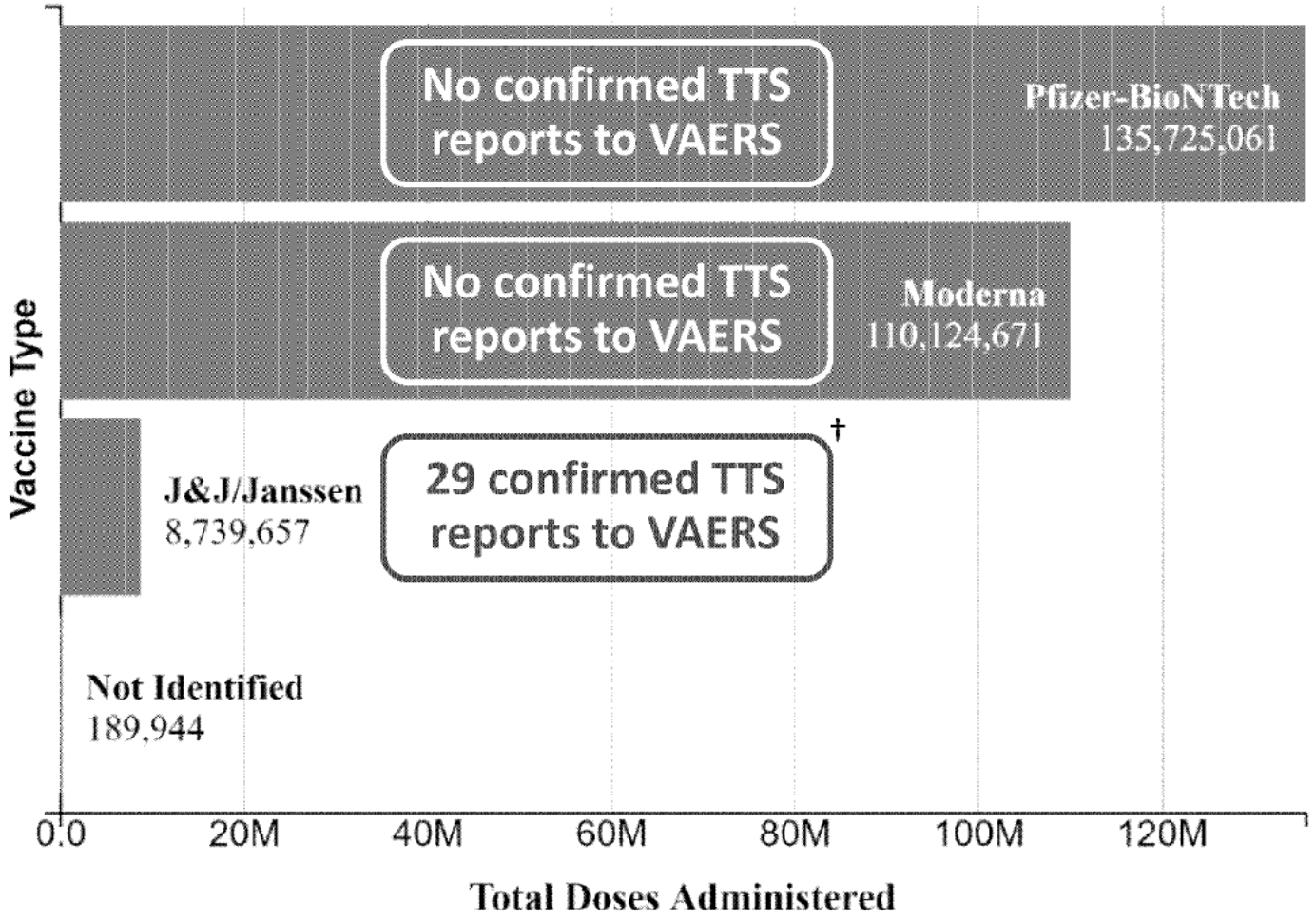
* A blood smear should be evaluated to rule out platelet clumping that could indicate a falsely low platelet count

CDC working case definition for TTS following COVID-19 vaccine

- Tier 1 TTS case
  - Thrombosis in an unusual location, including cerebral venous sinuses, portal vein, splenic vein, and other rare venous and arterial thromboses
    - May also concurrently have thrombosis in more common locations (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, etc.)
  - Platelet count <150,000 per microliter
  - Positive (+) heparin-PF4 ELISA HIT antibody* result is supportive, but not required
- Tier 2 TTS case
  - Thrombosis in a common location only (e.g., venous thromboembolism, axillary vein thrombosis, deep vein thrombosis, pulmonary embolism, etc.)
    - Does not include only acute myocardial infarction or ischemic stroke
  - Platelet count <150,000 per microliter
  - Positive (+) heparin-PF4 ELISA HIT antibody* result is required

* Heparin platelet factor 4 enzyme-linked immunosorbent assay heparin-induced thrombocytopenia antibody test

U.S. COVID-19 Vaccine Administration by Vaccine Type*



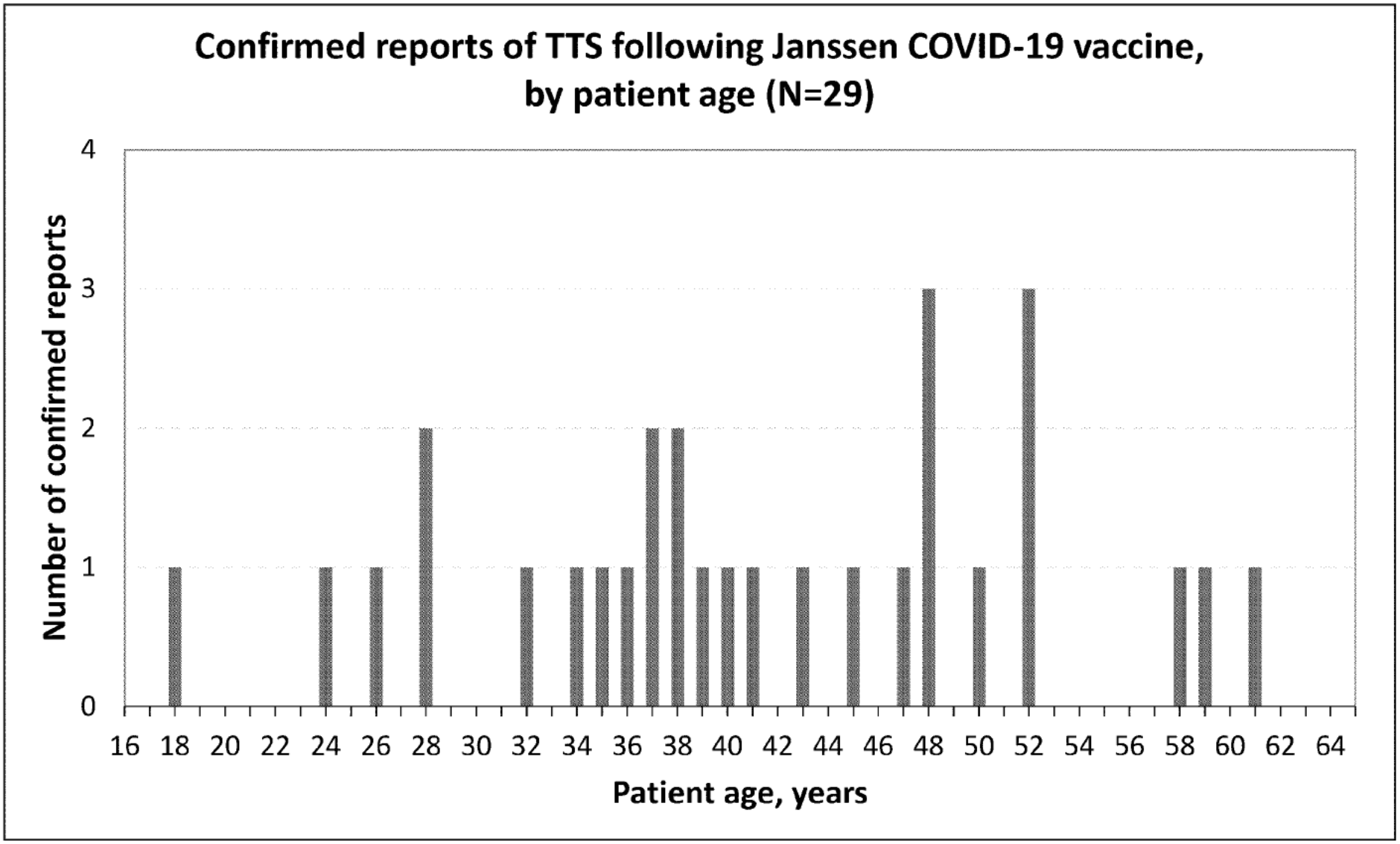
* data source: https://covid.cdc.gov/covid-data-tracker/#vaccinations, as of May 7, 2021

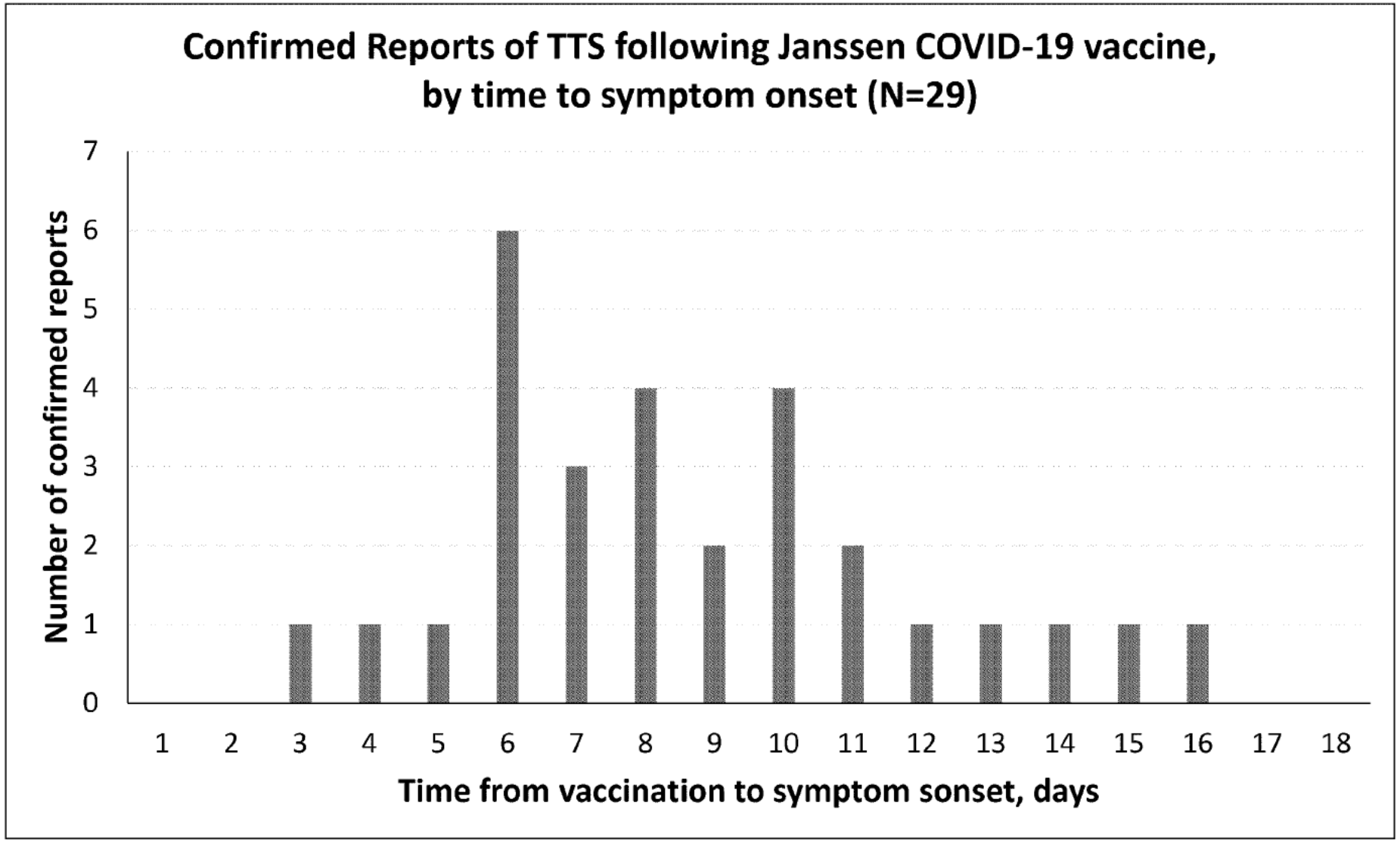
† One CVST with thrombocytopenia case was observed in Janssen COVID-19 vaccine pre-authorization clinical trials in a 25-year-old male; this case is not included in the VAERS post-authorization confirmed case count

Characteristics of patients with TTS after Janssen COVID-19 vaccine, N=29 (Tier 1 = 25; Tier 2 = 4)

- Median age 40 years (range 18–61)
- Median time to symptom onset 9 days (range 3–15 days)
- All received Janssen COVID-19 vaccine before the pause
- Female (n=23), male (n=6)
- 19 cases were cerebral venous sinus thrombosis (CVST) with thrombocytopenia
- Pregnant or post-partum* (n=0)
- Past SARS-CoV-2 infection (n=5); 3 by history, 2 by nucleocapsid serology testing only
- Risk factors for thrombosis†
  - Systemic estrogen/progesterone‡ (n=4)
  - Obesity (n=12)
  - Hypertension (n= 6)
  - Hypothyroidism (n=3)
  - Diabetes (n=3)
  - Current cigarette smoking (n=2)
  - Malignancy (n=1)
  - Coagulation disorders (n=0)

* Within 12 weeks of delivery; † Reference source: https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis;
‡ 2 patients were taking oral contraceptive pills (OCP), 1 patient was on hormone replacement therapy (HRT) patch, 1 was undergoing fertility treatment


Confirmed reports of TTS following Janssen COVID-19 vaccine, by patient age (N=29)
Number of confirmed reports
0
1
2
3
4
16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54 56 58 60 62 64
Patient age, years


Confirmed Reports of TTS following Janssen COVID-19 vaccine, by time to symptom onset (N=29)
Number of confirmed reports
0
1
2
3
4
5
6
7
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Time from vaccination to symptom sonset, days

Reporting rates of TTS after Janssen COVID-19 vaccine

8.73 million total Janssen COVID-19 vaccine doses administered*

	Females			Males		
Age group	TTS cases	Doses admin	Reporting rate† (per million)	TTS cases	Doses admin	Reporting rate† (per million)
18-29 yrs old	**3**	641,510	4.7	**2**	714,458	2.8
30-39 yrs old	**8**	642,745	12.4	**1**	728,699	1.4
40-49 yrs old	**7**	743,256	9.4	**1**	775,390	1.3
50-64 yrs old	**5**	1,463,416	3.4	**2**	1,505,505	1.3
65+ yrs old	**0**	814,947	0	**0**	697,925	0

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

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Locations of thromboses in TTS patients following Janssen COVID-19 vaccine, N=29 (not mutually exclusive)

- Cerebral venous sinuses*
- Anterior cerebral artery
- Carotid artery (internal and external)
- Femoral vein and artery
- Hepatic vein
- Iliac artery
- Internal jugular vein
- Lower extremity veins
- Portal vein
- Pulmonary artery
- Superior mesenteric vein and artery
- Splenic vein
- Upper extremity veins

*10 of 19 patients with cerebral venous sinus thrombosis experienced an intracerebral hemorrhage: temporo-parietal junction, temporal lobe, frontal lobe, occipital lobe, cerebellum, intraventricular, subarachnoid

Selected laboratory findings in TTS patients following Janssen COVID-19 vaccine, N=29

- **Platelet nadir levels (normal levels: 150,000–450,000 per microliter)***
  - <50,000 (n=18)
  - 50–<100,000 (n=7)
  - 100,000–149,000 (n=4)

- **Heparin-PF4 ELISA HIT antibody results**
  - Positive (+) (n=25)†
  - Negative (-) (n=2)
  - Not available (n=2)

* Platelet nadir range: 9,000-127,000 per microliter

† Tier 2 TTS required a positive (+) heparin-PF4 ELISA antibody test as part of definition

SARS-CoV-2 testing results in TTS patients, N=29

- **SARS-CoV-2 nucleic acid or antigen viral assay**
  - Negative (n=26)
  - Positive (n=0)
  - Not available (n=3)
- **SARS-CoV-2 serology by nucleocapsid antibody**
  - Negative (n=4)
  - Positive (n=2)*
  - Not available/not specified (n=23)†

* Neither of these patients reported a history of COVID-19.

† Three had a negative serology, the report did not specify whether nucleocapsid or spike protein antibody

Treatment and outcomes among TTS patients following Janssen COVID-19 vaccine, N=29

- **Treatment**
  - Heparin (n=13)
    - 10/12 (83%) admitted before HAN ‡
    - 3/17 (18%) admitted after HAN ‡
  - Non-heparin anticoagulants (n=27)
  - Platelet transfusion (n=7)
  - Intravenous immunoglobulin (n=18)

- **Outcomes†**
  - Death (n=3)§
  - Remain hospitalized (n=4)
    - Intensive care unit (n=1)
  - Discharged to post-acute care facility (n=2)
  - Discharged home (n=19)

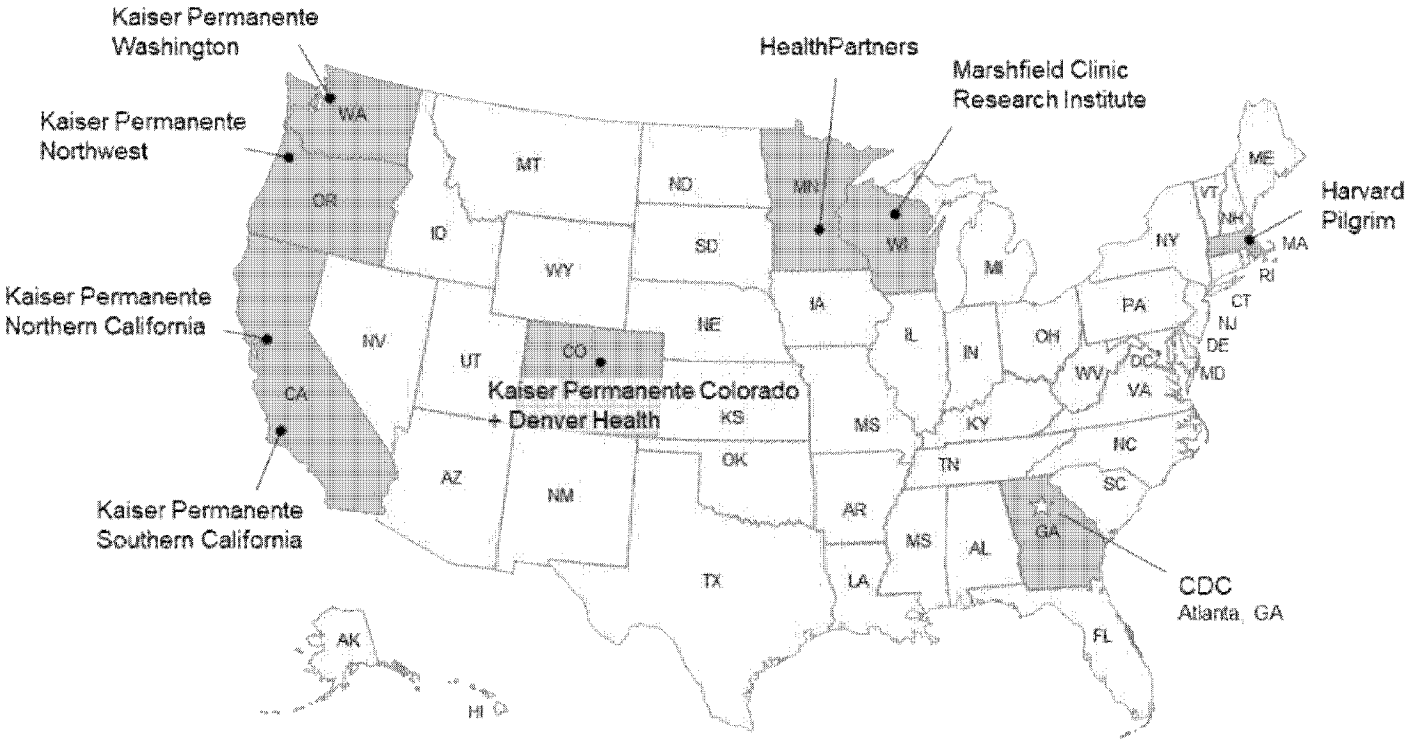
† As of May 7, 2021. Outcome is unknown for 1 patient.

‡ HAN released on April 13, 2021

§ None of the patients who died received heparin; all had signs of severe CVST (hemorrhage + mass effect) on initial imaging and died within 2 days of presentation.

VSD

Vaccine Safety Datalink



- 9 participating integrated healthcare organizations
- Data on over 12 million persons per year

VSD: Cerebral venous sinus thrombosis (CVST) after mRNA COVID-19 vaccines

- 3.3 million doses of Pfizer-BioNTech and 3.0 million doses of Moderna COVID-19 vaccine doses administered in VSD as of April 24, 2021
  - 11 total cases of CVST identified following mRNA vaccines
    - 3 after Pfizer-BioNTech and 8 after Moderna COVID-19 vaccines
    - 5 cases ruled out (historical n=2, history of head injury n=2, chronic cavernous sinus syndrome n=1)
    - 6 cases potentially CVST, but all <u>without</u> thrombocytopenia
- <u>No confirmed cases</u> of incident CVST with thrombocytopenia after 6.3 million doses of mRNA COVID-19 vaccines administered in VSD

VSD: Thrombosis events after Janssen COVID-19 vaccine

- 159,885 Janssen COVID-19 vaccine doses administered in VSD through April 24, 2021
  - No statistical signals detected for any prespecified Rapid Cycle Analysis outcomes
  - No CVST cases identified
- 32 VTE/PE cases identified in the 1-42 days following vaccination (including 3 cases diagnosed with both VTE and PE)
  - 29 of the cases have been quick reviewed to date (3 in progress)
    - 6 were ruled out as not VTE/PE
    - 23 were confirmed VTE/PE cases
      - 4 were determined to have symptom onset prior to vaccination
        - » Including 2 cases with thrombocytopenia documented prior to vaccination
      - 1 had an indeterminate symptom onset
      - 18 are potential VTE/PE cases with incidence following vaccination
        - » 10 female (5 PE, 5 VTE), 8 males (4 PE, 4 VTE)
        - » Ages ranged from 30-79
        - » None with history of COVID-19 infection
        - » None with thrombocytopenia noted at time of VTE/PE

VTE = venous thromboembolism

PE = pulmonary embolism

Summary and next steps

Summary

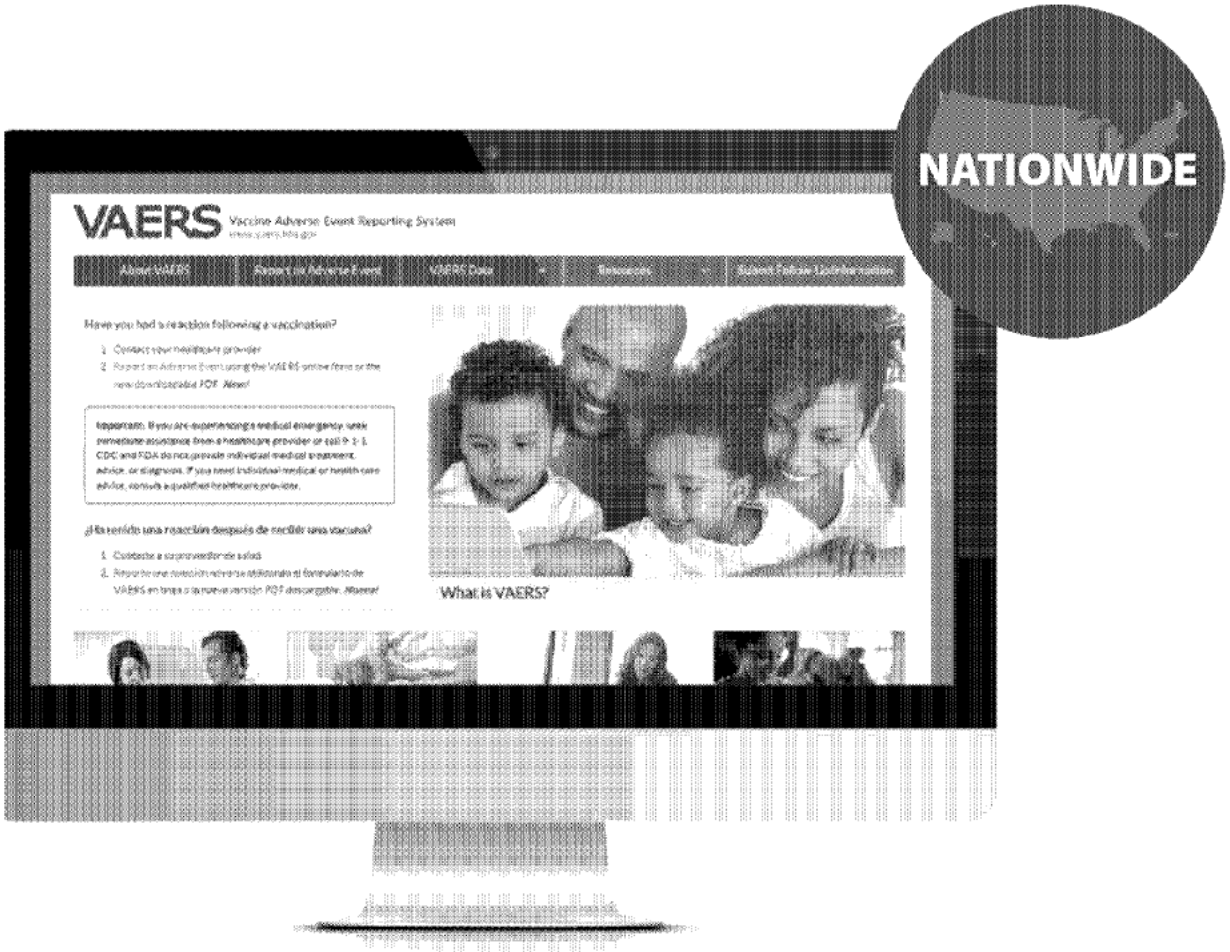
- TTS is a rare, clinically serious and potentially life-threatening condition; current evidence suggests a potential causal association with the Janssen COVID-19 vaccine
- Symptom onset appears to occur at least several days after vaccination, typically around 1–2 weeks after vaccination; most cases are in women, with most aged 18-49 years old
- The clinical features of TTS following Janssen COVID-19 vaccine appear similar to what is being observed following the AstraZeneca COVID-19 vaccine in Europe
- It is important to recognize TTS early and initiate appropriate treatment
  - Do not treat thrombosis with thrombocytopenia cases with heparin unless heparin-PF4 ELISA HIT antibody testing is negative
- TTS does not appear to be associated with mRNA COVID-19 vaccines
- The U.S. vaccine safety monitoring system is able to rapidly detect rare adverse events following immunization and quickly assess safety signals
- Safety surveillance and research on TTS continues
- CDC is committed to open and transparent communication of vaccine safety information

Next steps

- Continue enhanced monitoring in VAERS and conduct surveillance in other vaccine safety systems (e.g., VSD, CMS, VA electronic health record)
- Update ACIP and the public as addition information becomes available

How to report an adverse event to VAERS

- Go to vaers.hhs.gov
- Submit a report online
- For help:
  - Call [redacted]
  - Email info[redacted]
  - video instructions https://youtu.be/sbCWhcQADFE



- Please send records to VAERS ASAP if contacted and asked
  - HIPAA permits reporting of protected health information to public health authorities including CDC and FDA

Adolescent vaccination and v-safe enrollment

Smartphone-based **active safety monitoring**

v-safe[SM]
after vaccination
health checker

http://cdc.gov/vsafe

PSICOVID_00009286

Use of v-safe for adolescent COVID-19 vaccination

- CDC encourages parents and guardians to enroll their vaccinated adolescents into v-safe
- Parents and guardians can complete health surveys on behalf of their adolescents, describing symptoms and health events after vaccination
  - CDC encourages completing health surveys even if vaccinated persons are feeling well and have no side effects
- Participation in v-safe will help CDC continue to monitor the safety of COVID-19 vaccines as use is expanded into younger populations
- Promote v-safe participation at vaccination locations
  - Take advantage of the post-vaccination observation period to encourage v-safe participation

Acknowledgments

We wish to acknowledge the contributions of investigators from the following organizations:

Centers for Disease Control and Prevention

COVID-19 Vaccine Task Force

Vaccine Safety Team

Immunization Safety Office

Division of Healthcare Quality Promotion

Clinical Immunization Safety Assessment Project

Vaccine Safety Datalink

Food and Drug Administration

Center for Biologics Evaluation and Research

Questions

Back-up Slides

Proposed VAERS MedDRA PT and text string search terms for TTS

- **MedDRA PTs for large vessel thrombosis and embolism in unusual locations**
  - Aortic embolus, aortic thrombosis, aseptic cavernous sinus thrombosis, brain stem embolism, brain stem thrombosis, carotid arterial embolus, carotid artery thrombosis, cavernous sinus thrombosis, cerebral artery thrombosis, cerebral venous sinus thrombosis, cerebral venous thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, mesenteric artery embolism, mesenteric artery thrombosis, mesenteric vein thrombosis, splenic artery thrombosis, splenic embolism, splenic thrombosis, thrombosis mesenteric vessel, visceral venous thrombosis, hepatic artery embolism, hepatic artery thrombosis, hepatic vein embolism, hepatic vein thrombosis, portal vein embolism, portal vein thrombosis, portosplenomesenteric venous thrombosis, splenic vein thrombosis, spontaneous heparin-induced thrombocytopenia syndrome, femoral artery embolism, iliac artery embolism, jugular vein embolism, jugular vein thrombosis, subclavian artery embolism, subclavian vein thrombosis, obstetrical pulmonary embolism, pulmonary artery thrombosis, pulmonary thrombosis, pulmonary venous thrombosis, renal artery thrombosis, renal embolism, renal vein embolism, renal vein thrombosis, brachiocephalic vein thrombosis, vena cava embolism, vena cava thrombosis, truncus coeliacus thrombosis
- **MedDRA PTs for more common thrombotic events**
  - Axillary vein thrombosis, deep vein thrombosis, pulmonary embolism
- **MedDRA PTs for thrombocytopenia**
  - Autoimmune heparin-induced thrombocytopenia, Heparin-induced thrombocytopenia, Immune thrombocytopenia, Non-immune heparin associated thrombocytopenia, Spontaneous heparin-induced thrombocytopenia syndrome, Thrombocytopenia, Thrombocytopenic purpura
- **Text string for**
  - "thrombocytopenia" or "low platelets" in symptom text

COVID-19 Vaccine Safety Technical (VaST) Work Group

Assessment

Grace M. Lee, MD MPH

Advisory Committee on Immunization Practices

May 12, 2021

COVID-19 Vaccine Safety Technical (VaST) Work Group

Objectives

- Review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data
- Serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring
- Advise on analyses, interpretation, and data presentation
- Provide updates to the ACIP COVID-19 Vaccines Work Group and the ACIP on COVID-19 vaccine safety

VaST Activities

Pre-authorization

Jun-Dec 2020

- 14 meetings to prepare for vaccine safety surveillance in the U.S.

ACIP Recommendations

- Dec 12 – Pfizer/BioNTech
- Dec 14 – 1st dose administered in U.S.
- Dec 19 – Moderna
- Feb 28 – Janssen

Post-authorization

Dec 21-present

- 19 independent meetings to review vaccine safety data across multiple surveillance systems

VaST Meeting - April 12
CVST with thrombocytopenia

- 6 cases of CVST with thrombocytopenia identified as a rare, but serious adverse event following Janssen vaccine
- Risk factors for CVST with thrombocytopenia not well understood
- Timely and transparent communication with healthcare providers and the public is crucial to maintain confidence in the vaccination program

Janssen vaccine - Thrombosis with Thrombocytopenia Syndrome (TTS)

CDC and FDA
April 13

- CDC and the FDA recommended pausing use of the Janssen COVID-19 vaccine after reports of TTS among vaccine recipients
- HAN issued

ACIP meeting
April 14

- Review of reported cases of TTS
- Need for additional information to support evidence-based decision making, including

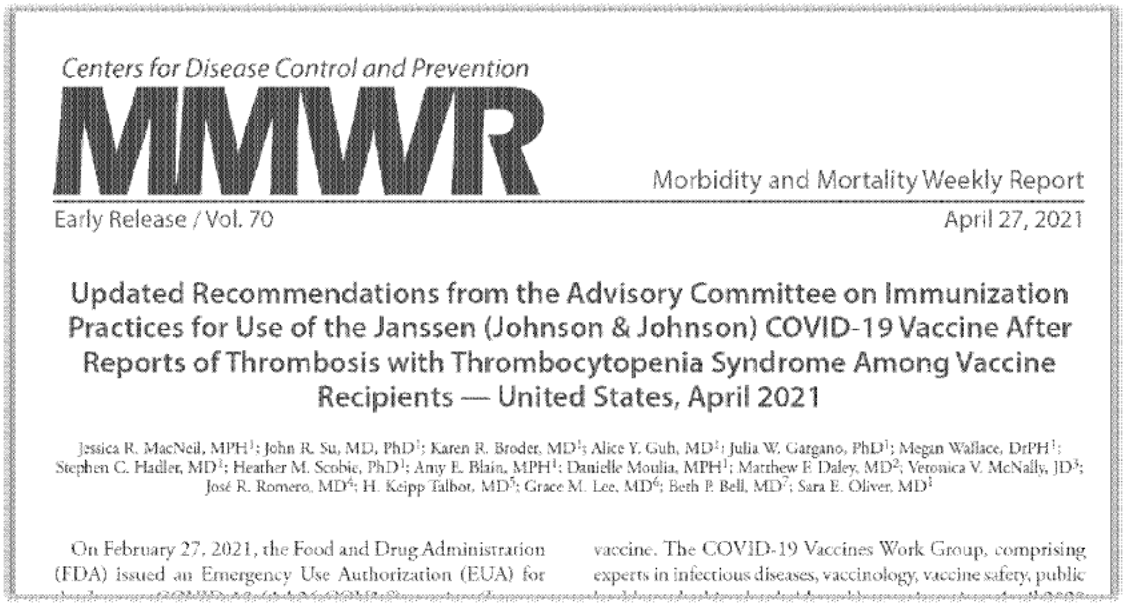
VaST Meetings - April 19th and 22nd Thrombosis with Thrombocytopenia Syndrome (TTS)

- Risk for TTS following Janssen vaccine (VAERS)
  - 7 per million doses in females <50 years* (highest in 30-39 years)
  - <1 per million doses in female 50+ and males*
- No signals identified for CVST, other thromboembolic disease, or thrombocytopenia following Janssen vaccine in VSD RCA and VA RCA (>200,000 doses)
- Update from Global Advisory Committee on Vaccine Safety (GACVS) on TTS cases following AstraZeneca vaccine

**Includes all doses (not adjusted for follow-up time)*

ACIP meeting – April 23

- ACIP concluded that the benefits of resuming Janssen COVID-19 vaccination among persons aged ≥18 years outweighed the risks and reaffirmed its interim recommendation under FDA's EUA
- New warning for rare clotting events among women aged 18–49 years



Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Early Release / Vol. 70 April 27, 2021

Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021

Jessica R. MacNeil, MPH[1]; John R. Su, MD, PhD[1]; Karen R. Broder, MD[1]; Alice Y. Guh, MD[1]; Julia W. Gargano, PhD[1]; Megan Wallace, DrPH[1]; Stephen C. Hadler, MD[1]; Heather M. Scobie, PhD[1]; Amy E. Blain, MPH[1]; Danielle Moulia, MPH[1]; Matthew F. Daley, MD[2]; Veronica V. McNally, JD[3]; José R. Romero, MD[4]; H. Keipp Talbot, MD[5]; Grace M. Lee, MD[6]; Beth P. Bell, MD[7]; Sara E. Oliver, MD[1]

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for vaccine. The COVID-19 Vaccines Work Group, comprising experts in infectious diseases, vaccinology, vaccine safety, public

VaST Meetings - April 26, May 3, May 10

- Reviewed updated data on TTS from VAERS
  - April 26 – 8.1 million received Janssen vaccine, 18 cases of TTS
  - May 3 – 8.3 million received Janssen vaccine, 21 cases of TTS (20 female, 1 male)
    - TTS rate of 9 per million doses administered in women 18-49 years
- VSD and VA RCA – 152,705 and 117,162 received Janssen vaccine, no cases of CVST following Janssen; implementing TTS definition

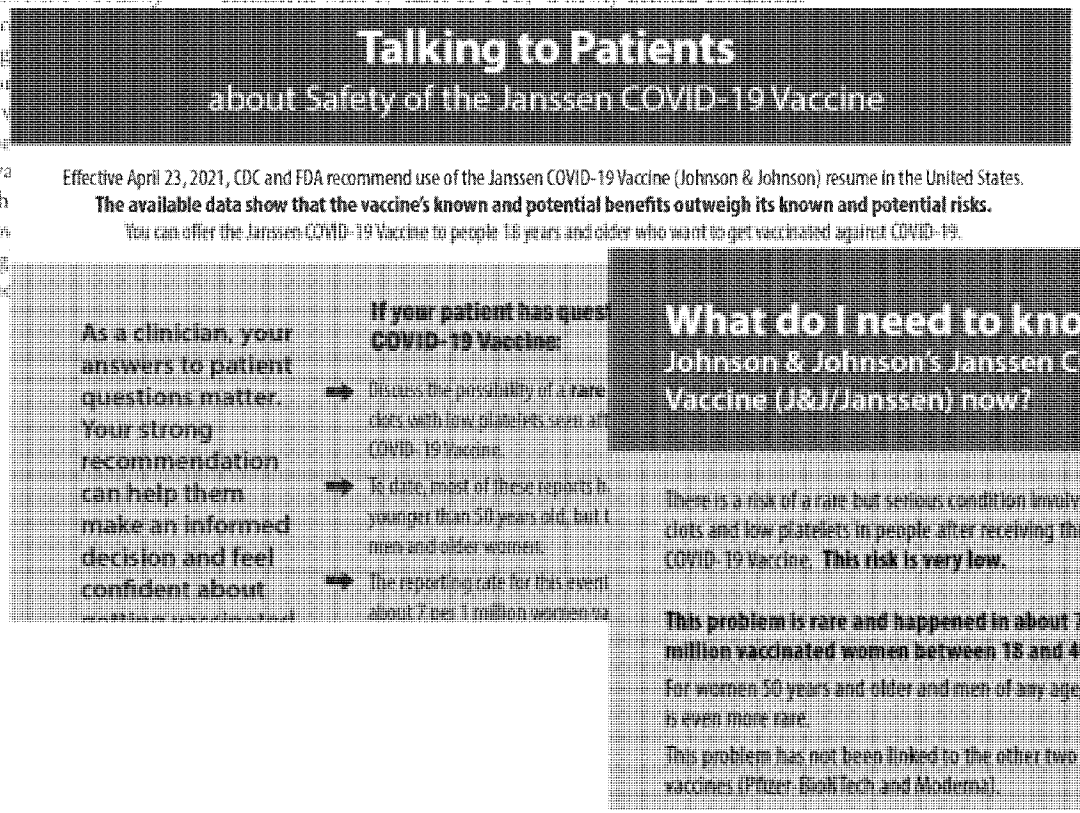
Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine — United States, March–April 2021

David K. Shay, MD[1]; Julianne Gee, MPH[1]; John R. Su, MD, PhD[1]; Tanya R. Myers, PhD[1]; Paige Marquez, MSPH[1]; Ruiling Liu, PhD[1]; Bicheng Zhang, MS[1]; Charles Licata, PhD[1]; Thomas A. Clark, MD[1]; Tom T. Shimabukuro, MD[1]

On April 30, 2021, this report was posted as an MMWR *Early Release on the* MMWR *website (https://www.*

On February 27, 2021, the Food and Drug (FDA) issued an Emergency Use Author for Janssen (Ad.26.COV2.S) COVID-19 Biotech, Inc., a Janssen Pharmaceutical co & Johnson) (*1*). The Janssen COVID-19 va COVID-19 vaccine authorized for use in th uses a replication-incompetent human adenov tor platform* (*2*) and is administered as a sing dose, whereas the first two authorized vaccine

consistent with 17 cases of TTS,[§] a newly defined condition.



VaST Summary (need to update this)

- Risk of TTS highest in female <50 years
  - Other risk factors for TTS not well established yet
- Risk mitigation strategies
  - Educate patients about benefits and risks of available vaccines
  - Increase awareness & ensure timely diagnosis and management of TTS
- VaST will continue to monitor TTS, thromboembolic disease, and thrombocytopenia in all available vaccine safety surveillance systems
- VaST will update the ACIP COVID-19 vaccines workgroup, ACIP secretariat and ACIP on a regular basis

VaST Members

VaST Members
Grace Lee (ACIP)
Robert Hopkins (NVAC)
Matt Daley
Veronica McNally
Keipp Talbot
Kathy Edwards
Lisa Jackson
Jennifer Nelson
Laura Riley
Robert Schechter
Patricia Whitley-Williams

CDC Co-Leads
Lauri Markowitz
Melinda Wharton

Ex Officio and Liaison Representatives
Tatiana Beresnev (NIH)
Karen Farizo; Hui Lee Wong (FDA)
Judith Steinberg (OIDP)
Jeffrey Kelman (CMS)
Matthew Clark (IHS)
Mary Rubin (HRSA)
Fran Cunningham (VA)
Limone Collins (DoD)

Administrative Support
Jared Woo

HAN Communication – April 13

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

- Recommendations for Clinicians: diagnosis and treatment
  - Evaluate patients with a screening PF4 enzyme-linked immunosorbent (ELISA) assay as would be performed for autoimmune HIT. Consultation with a hematologist is strongly recommended.
  - Do not treat with heparin, unless HIT testing is negative
- Recommendations for Public Health: case reporting through VAERS
  - Encourage healthcare providers and the public to report all serious and life-threatening adverse events and deaths following receipt of COVID-19 vaccines to VAERS
- Recommendations for the Public: clinical signs and symptoms to monitor
  - Contact healthcare provider, or seek medical care if you develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination with the J&J COVID-19 vaccine

HAN Archive- 00442 | Health Alert Network (HAN) (cdc.gov)

VaST planning

May 10, 2021

Landscape awareness

- VaST meeting weekly since 12/2020 when first COVID-19 vaccine authorized
- Maternal immunization focused calls started monthly in 3/2021
- Should VaST meetings be continued weekly?
  - Consider revised schedule with other meetings scheduled as needed.

- Upcoming issues for awareness
  - Adolescent EUAs (Pfizer this week, Moderna in June)
  - Other vaccines (Novavax, AZ) - timeline unclear
  - Booster doses - timeline unclear
  - BLAs (Pfizer, Moderna, J&J)

Some outstanding issues

- TTS
- Janssen J&J
- Maternal immunization
- CMS RCA signal
- Myocarditis

VaST calls – possible schedule

DATE	POSSIBLE AGENDA
May 10	Prepare for May 13 ACIP meeting and other updates
May 17	Updated data on TTS (VAERS) and RCAs
May 24	Maternal immunization focused session and early adolescent data
May 31	Memorial Day
June 7	Adolescent data, and updates VAERS and RCAs
June 14	no call
June 21	Adolescent data, and updates from VAERS and RCAs
June 28	Maternal immunization focused session and other updates
July 5	no call
July 12	Adolescent data, and updates from VAERS and RCAs
July 19	no call
July 26	Maternal immunization focused session and other updates

VaST Agenda – May 10, 2021

Open session
1:30 - 3:00

1:30-1:35 - Announcements

1:35-1:40 - v-safe and adolescents (Tanya Myers, CDC)

1:40-1:50 - discussion

1:50-2:05 - ACIP presentation - ISO (Tom Shimabukuro, CDC)

2:05-2:15 - discussion

2:15-2:25 - ACIP presentation - VaST comment (Grace Lee, VaST)

2:25-2:35 - discussion

2:35-2:45 - VaST cadence