From: CDC IMS 2019 NCOV Response VTF ACIP WG[eocevent400@cdc.gov]

Attendees: [redacted]; [redacted]; [redacted]; [redacted]; 'keipp.talbot [redacted]; 'keipp.talbot [redacted]; 'matthew.f.daley [redacted]; 'kathryn.edwards [redacted]; [redacted]; 'Lisa.A.Jackson [redacted]; 'martin_kulldorff [redacted]; [redacted]; [redacted]; [redacted]; 'robert.schechter [redacted]; 'whitlepr [redacted] Anderson, Steven; Beresnev, Tatiana H (NIH); Clark, Matthew (IHS); [redacted]; 'Fran.Cunningham [redacted]; Farizo, Karen; Forshee, Richard; Kelman, Jeffrey A (CMS); Nair, Narayan; Rubin, Mary (HRSA); Steinberg, Judith L (OS); Wong, Hui-Lee; Markowitz, Lauri (CDC); Wharton, Melinda (CDC); Hiers, Susan G (CDC); Shanley, Edwin (CDC); Shimabukuro, Tom (CDC); Woo, Jared M (CDC); Broder, Karen R (CDC); Calvert, Geoffrey M (CDC); Clark, Thomas A (CDC); Cohn, Amanda C (CDC); DeStefano, Frank (CDC); Dooling, Kathleen L (CDC); Gee, Julianne M (CDC); Hamburger, Tanya (CDC); Helfand, Rita (CDC); Lindsey, Nicole P (CDC); MacNeil, Jessica R (CDC); Marquez, Paige L (CDC); Mbaeyi, Sarah A (CDC); Mcneil, Michael M (CDC); Myers, Tanya R (CDC); Oliver, Sara E (CDC); Panagiotakopoulos, Lakshmi (CDC); Sotir, Mark J (CDC); Su, John (CDC); Wasley, Annemarie (CDC); Weintraub, Eric S (CDC); Young, Mardia A (CDC); Shay, David K (CDC); LaPorte, Kathleen (CDC); Bretthauer-mueller, Rosemary (CDC); Mullen, Jennifer (CDC); 'hadas.rotem [redacted]; 'EMILIA.ANIS [redacted]; 'BOAZ.LEV [redacted]; 'dana.arac [redacted] 'sharon.alroy [redacted] 'mevoracho [redacted]; 'yaron.niv [redacted]; 'sharon.olsha [redacted]; 'deniz.ainbinder [redacted] 'michal.hirsch [redacted]; 'noa.cedar [redacted]; 'roee.singer [redacted]; 'eric.haas [redacted]; 'Lital.Keinan2 [redacted]'

Location: Zoom; https://cdc.zoomgov.com/j/1601235749?pwd=NU83YmtqMXVSN0xPMzY1ZGxrc1pTQT09

Subject: [EXTERNAL] ACIP COVID-19 VaST Workgroup Meeting (Open Session)

Importance: Normal

Start Time: Mon 4/5/2021 5:30:00 PM (UTC)

End Time: Mon 4/5/2021 7:00:00 PM (UTC)

Required Attendees: [redacted]; [redacted]; [redacted]; [redacted]; 'keipp.talbot [redacted]; 'keipp.talbot [redacted]; 'matthew.f.daley [redacted]; 'kathryn.edwards [redacted]; [redacted]; 'Lisa.A.Jackson [redacted]; 'martin_kulldorff [redacted]; [redacted]; [redacted]; [redacted]; 'robert.schechter [redacted]; 'whitlepr [redacted]; Anderson, Steven; Beresnev, Tatiana H (NIH); Clark, Matthew (IHS); [redacted]; 'Fran.Cunningham [redacted]; Farizo, Karen; Forshee, Richard; Kelman, Jeffrey A (CMS); Nair, Narayan; Rubin, Mary (HRSA); Steinberg, Judith L (OS); Wong, Hui-Lee; Markowitz, Lauri (CDC); Wharton, Melinda (CDC); Hiers, Susan G (CDC); Shanley, Edwin (CDC); Shimabukuro, Tom (CDC); Woo, Jared M (CDC); Broder, Karen R (CDC); Calvert, Geoffrey M (CDC); Clark, Thomas A (CDC); Cohn, Amanda C (CDC); DeStefano, Frank (CDC); Dooling, Kathleen L (CDC); Gee, Julianne M (CDC);

Hamburger, Tanya (CDC); Helfand, Rita (CDC); Lindsey, Nicole P (CDC); MacNeil, Jessica R (CDC); Marquez, Paige L (CDC); Mbaeyi, Sarah A (CDC); Mcneil, Michael M (CDC); Myers, Tanya R (CDC); Oliver, Sara E (CDC); Panagiotakopoulos, Lakshmi (CDC); Sotir, Mark J (CDC); Su, John (CDC); Wasley, Annemarie (CDC); Weintraub, Eric S (CDC); Young, Mardia A (CDC); Shay, David K (CDC)

Topic: ACIP COVID-19 VaST Workgroup Meeting (Open Session)
Date: April 5, 2021
Time: 01:30-03:00 PM Eastern Time (US and Canada)

Identify yourself when signing in

1. If joining by Zoom, enter your First and Last Name, and after your last name, enter your position/role in ( ). For example, either (ACIP Member), (Liaison), (Consultant), or (CDC Staff)
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Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/2/2021 8:54:44 PM
To: Anderson, Steven [redacted]; Bell, Beth [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]; Dooling, Kathleen L (CDC) [redacted]; Edwards, Kathy [redacted]; Farizo, Karen [redacted]; Forshee, Richard [redacted]; Gee, Julianne M (CDC) [redacted]; Hamburger, Tanya (CDC) [redacted]; Helfand, Rita (CDC) [redacted]; Hiers, Susan G (CDC) [redacted]; Hopkins, Bob [redacted]; Jackson, Lisa [redacted]; Kelman, Jeffrey A (CMS) [redacted]; Kulldorf, Martin [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]; 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]
Subject: [EXTERNAL] VaST - Draft minutes and report from March 29 (CONFIDENTIAL)
Attachments: 2021-02-01 VaST Meeting Minutes Draftv4.docx; 2021-03-29 - VaST Report Data Table DRAFT.docx

Dear VaST members and attendees,

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

The next VaST call is April 5, 1:30 – 3:00 pm EDT.

Draft agenda:
- Israel's Covid-19 vaccine safety monitoring
- FDA methods for data mining
- FDA CMS Rapid Cycle Analysis (RCA)
- VSD and VA RCA and overview of plans

Thanks to all,
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 meeting notes - DRAFT

March 29, 2021

Confidential

Presentation slides were distributed; presentations are only briefly summarized in meeting notes. Chat notes not answered verbally on the call are available but have not been incorporated into the minutes.

Participants

Expert consultant members: Kathy Edwards, Mat Daley, Bob Hopkins (Co-Chair), Lisa Jackson, Grace Lee (Co-Chair), Veronica McNally, Laura Riley, Rob Schechter, Patricia Whitley-Williams

Ex officio and liaison members: Tatiana Beresnev, Matthew Clark, Limone Collins, Karen Farizo, Jeff Kelman, Martin Kulldorf, Judith Steinberg, Hui Lee Wong

CDC: Johanna Chapin Bardales, Karen Broder, Frank DeStefano, Kathleen Dooling, Julianne Gee, Tanya Hamburger, Rita Helfand, Kwan Hur, Susan Hiers, Nicole Lindsey, Lauri Markowitz (CDC Co-lead), Paige L. Marquez, Michael McNeil, Sara Oliver, Eddie Shanley, David Shay, Tom Shimabukuro, John Su, Melinda Wharton (CDC Co-lead), Jared Woo

Technical SMEs: Steve Anderson, Bethany Baer, Barbara Bardenheier, Fran Cunningham, Sungching Glenn, Runxin Huang, Amelia Jazwa, David Menschik, Kerresa Morrissette, Lei Qian, Denison Ryan, Lina Sy, Stan Xu, Craig Zinderman

Agenda

- Administrative issues and announcements
- Processes and procedures for evaluating death reports to VAERS
- VAERS, with focus on death reports
- Updates: data available on deaths in VA ADERS, DoD, VSD, Genesis
- FDA methods for data mining*
- Communications and media relations*

*Not discussed; presentation moved to a future meeting due to time constraints.

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

- Reminders about COI and confidentiality
- Doses distributed: 180,646,465; Doses administered: 143,462,691 (last updated: March 28)
  - Pfizer-BioNTech: 90,301,965; Moderna: 85,398,200; J&J/Janssen 4,946,300
  - Doses administered: Pfizer-BioNTech: 72,981,111; Moderna: 67,249,447; J&J/Janssen: 3,090,712; Unknown: 141,421
  - First doses 93,631,163; Fully vaccinated: 51,593,564

These data are posted on the CDC website and are updated regularly ([HYPERLINK "https://covid.cdc.gov/covid-data-tracker/" \l "vaccinations).%E2%80%AF" \h]

Processes and procedures for evaluating reports of death to VAERS following COVID-19 vaccination – Dr. Tom Shimabukuro (CDC)

Dr. Shimabukuro presented on the processes and procedures for evaluating death reports submitted to VAERS. The registration of deaths is a state function determined by a physician, coroner, or medical examiner. Deaths can be reported to CDC and evaluated through two routes: 1) 'top-down' evaluations that occurs when VAERS receives a death report after COVID-19 vaccination; 2) 'bottom-up' evaluations occur when CDC is notified by an official about death after COVID-19 vaccination. Dr. Shimabukuro reviewed some differences between these two. The vast majority of deaths reports and evaluations are 'top-down.' Once received, the Immunization Safety Office (ISO) assigns the review to a clinician. Reports are processed the day of receipt. Dr. Shimabukuro also reviewed the range of analyses done on surveillance data and for individual cases (for the 'bottom up' evaluations).

Questions and discussion

1. What proportion of reports have a final determination as 'unusual'? Dr. Shimabukuro indicated that the proportion is small.
2. For acute MI and stroke reports to VAERS, is there follow-up to determine if these resulted in death? Yes, at two time points, 60 days and 1 year, for reports that do not indicate the patient had recovered at time of report.
3. How frequently does the cause of death change after investigation or consultation? This question is best answered by people working with vital statistics.

VAERS mortality update - Dr. John Su (CDC)
Dr. Su gave an update on death reports submitted to VAERS through March 22 (N=2,051). This was a more systematic and comprehensive data summary than previously reported to VaST. 197 (9.5%) reports included death certificates or autopsy findings; the remaining reports are considered under investigation as VAERS awaits death certificate data and autopsy reviews. For total deaths as well as for those with death certificate or autopsy findings, data were presented by vaccine manufacturer, age group and sex. Cause of death was also reported by vaccine manufacturer and by age group. Reports are mostly males aged 65 and older. Time to death is mostly between 0-4 days after COVID-19 vaccination. The most common causes of death are unknown or unclear (this category is not static and data will shift into another category once more information is received), cardiovascular, or COVID-19. There are no patterns to indicate safety concerns at this time.

Questions and discussion

1. There was continued discussion around the value of presenting descriptive data from VAERS.
2. The value of presenting data by time since vaccination was discussed as well as the value of doing temporal scan analyses. Due to bias resulting from events more proximal to vaccination more likely to be reported, most felt temporal scan analyses were not useful.

VA ADERS - Dr. Fran Cunningham (VA)
Dr. Cunningham provided an overview of VA ADERS fatal event reporting and a summary of deaths to date. Among 205 deaths, 72 have been reviewed. Chart reviews started in March and 4 have been completed. These are yet to be validated. Demographic data indicate that death cases are mostly male, age ranging 53-100 years.

DoD VAERS - Dr. Limone Collins (DoD)
Dr. Collins provided a summary report of DoD VAERS data. 499 AE reports were submitted to DoD VAERS through 3/19/21. There were 113 serious reports (16 deaths). Dr. Collins presented reports by manufacturer and age group, gender, race/ethnicity, CONUS versus OCONUS and active duty status. Among 16 deaths, 5 were in persons younger than age 65 years.

VSD mortality study - Dr. Stan Xu (KPSC)
Dr. Xu presented the study plans for assessing mortality after COVID-19 vaccination among members enrolled in collaborating Vaccine Safety Datalink (VSD) sites. This analysis compared recipients of COVID-19 vaccination with those who received flu vaccinations in the last 2 years (at least one dose of influenza vaccine in 2019-2020) but have not received COVID-19 vaccination. The outcome of interest was all deaths except those related to COVID-19. Mortality rates and preliminary results based on a single site were described, which did not show any increased risk after dose 1 or dose 2.

Vaccine safety monitoring among residents of skilled nursing facilities - Dr. Barbara Bardenheier (Brown University)

Dr. Bardenheier presented follow-up analyses from the vaccine safety monitoring among residents of 284 Genesis skilled nursing facilities since December 18, 2020, when COVID-19 vaccination began. This study assessed adverse event rates from dose 1 (n=8,553) and dose 2 (n=8,371) and among residents not vaccinated (n=11,072). There were 76 deaths in the vaccinated group versus 126 in the unvaccinated group; the lower mortality among the vaccinated group is likely due to the healthy vaccinee effect. There were no significant safety signals in the Genesis analyses.

Combined Systems Safety Monitoring Report
DRAFT
March 29, 2021
Confidential

VaST meeting and comments:
The VaST session was focused on deaths reported after Covid-19 vaccination. This session was a follow-up to previous VaST sessions in which reported deaths were presented and discussed. VaST felt they need to more completely review the data in VAERS as well as other data. Today, there were presentations on processes and procedures for evaluating death reports to VAERS, and data from VAERS, VA ADERS, DoD, VSD, and the Genesis study.

VSD:
The preliminary analyses from the VSD Mortality Study and as well as follow-up analyses from the Genesis study answered many questions that VaST has had about mortality. These analyses highlighted the importance of good comparators.

While the VSD study provides population data with denominators, there are limitations to the VSD data. Nevertheless, the VSD data are very reassuring. Analyses in the younger age groups will be important.

One of the limitations of VSD is the delay in obtaining data. VaST members would like to see data across the VSD sites; currently about 35% of the VSD population is included in the analyses.

VAERS and other data:
VaST appreciated the presentation of processes and procedures for evaluating deaths, and the more comprehensive and systematic presentation of the VAERS death data. It was important to see the data from VA ADERS and DoD.

While there are many limitations of VAERS death data, these data are important because VAERS encompasses the entire country and some data are available early.

The value of proportional ratios and temporal scan analyses was raised. Most members felt that proportional ratios would not be helpful due to the nature of the Covid-19 vaccination program. Other comments included that empirical Bayesian (EB) mining should be done before temporal scans, with scans conducted as a refinement activity. Most members felt that temporal scan analyses in spontaneous reporting systems like VAERS would be impacted by serious reporting bias and would not be helpful.

Communications and EB data mining:
There was not enough time on the call for the communications or the EB data mining presentations. VaST looks forward to hearing those presentations on a future call.

Table 1. COVID-19 vaccine monitoring systems reviewed by the VaST – Pfizer BioNTech (recommended for use in persons age ≥ 16 years)

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) (Data through 3/22/2021)	All health events, adverse events of special interest[a]	US population	72,981,111 total doses administered	Descriptive and empirical Bayesian data mining	931 death reports • 148 LTCF death reports • 463 (82%) death reports for those aged 65 or above	Anaphylaxis associated with vaccination, first detected by reports from UK and early reporting in the US; assessed by followup with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021) Deaths less then expected based on background rates (last updated Jan 27)
VA ADERS (Data through 3/23/2021)	All health events	VA employees and Veteran patients	1.7 million doses administered	Descriptive	71 death reports • Median age 78	No concerns raised
DoD VAERS (Data through 3/19/2021)	All health events, adverse events of special interest	Active duty and beneficiaries	976,479 vaccines administered	Descriptive	227 total AE reports • 54 serious AE reports • 7 death reports	No concerns raised
Indian Health Services (IHS)[b]	All health events, adverse events of special interest[a]					
Active Surveillance						
V-safe (Data through 3/13/2021)		Vaccinees who enroll	2,267,127 persons enrolled; 26,091 pregnancies[c]	Descriptive	623 reports overall (all submitted to VAERS) • 57 serious reports • Solicited reactions higher after dose 2 than dose 1	No concerns raised

V-safe Pregnancy Registry (Data through 3/19/2021)		Vaccinees who enroll	1,926 enrolled	Descriptive	Pregnancy and neonatal outcomes of interest within background rates	No concerns raised
Department of Veterans Affairs (VA) Active Surveillance System (Data through 2/27/21)	Pre-specified health outcomes[a]	Veteran Patients	563,937 first doses; 353,565 second doses	Descriptive; historical comparator analysis)	No signals in the analyses for dose 1 or dose 2	No signals as of February 27
Vaccine Safety Datalink (VSD) [b] (Data through 2/27/21)	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	546,507 first doses administered; 248,130 second doses admi nistered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	No signals in analyses for combined mRNA vaccines, combined dose 1 and dose 2	No signals as of February 27
Vaccine Safety Datalink (VSD) Mortality Study (Vaccinated through 2/27 and death data through 3/20/21)	Deaths	VSD sites enrolled in the mortality study; vaccinated before 2/27 and number of deaths before 3/20	219,570 first doses administered; 105,919 second doses administered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	0.8 dose 1 mortality rate per 100 person-years 0.7 dose 2 mortality rate per 100 person-years 1.0 comparator mortality rate per 100 person-years	No signals for death as of March 20
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
Centers for Medicare and Medicaid Services (CMS)[b]	Pre-specified health outcomes[a]					
BEST initiative[b]	Pre-specified health outcomes[a]					
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/r	

					ecs/grade/covid-19-pfizer-biontech-vaccine.html	

[a]See Table 4 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 2. COVID-19 vaccine monitoring systems reviewed by the VaST – Moderna (recommended for use in persons age ≥ 18 years)

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) (Data through 3/22/2021)	All health events, adverse events of special interest[a]	US population	67,249,447 total doses administered	Descriptive and empirical Bayesian data mining	1,071 pregnancy reports • 132 LTCF death reports • 872 (82%) death reports for those aged 65 or above	Anaphylaxis associated with vaccination, first detected by early reporting in the US; assessed by followup with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021) Deaths less then expected based on background rates (last updated Jan 27)
VA ADERS (Data through 3/23/2021)	All health events	VA employees and Veteran patients	2.05 million doses administered	Descriptive	133 death reports • Median age 83	No concerns raised
DoD VAERS (Data through 3/19/2021)	All health events, adverse events of special interest	Active duty and beneficiaries	852,548 vaccines administered	Descriptive	268 total AE reports • 59 serious AE reports • 10 death reports	No concerns raised
Indian Health Services (IHS)[b]	All health events, adverse events of special interest[a]					
Active Surveillance						
V-safe (Data through 3/13/2021)		Vaccinees who enroll	2,627,416 persons enrolled; 23,064 pregnancies[c]	Descriptive	126 reports overall (all submitted to VAERS) • 27 serious reports • Solicited reactions higher after dose 2 than dose 1	No concerns raised

V-safe Pregnancy Registry (Data through 3/19/2021)		Vaccinees who enroll	1,597 enrolled	Descriptive	Pregnancy and neonatal outcomes of interest within background rates	No concerns raised
Department of Veterans Affairs (VA) Active Surveillance System (Data through 2/27/21)	Pre-specified health outcomes[a]	Veteran Patients	759,473 first doses; 286,128 second doses	Descriptive; historical comparator analysis, Vaccinated and unvaccinated concurrent comparison (to be done)	No signals in analysis for dose 1 Signal for anaphylaxis (n = 4) in second dose recipients	Only signal for anaphylaxis, as identified earlier in other post-authorization safety monitoring
Vaccine Safety Datalink (VSD) [b] (Data through 2/27/21)	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	504,558 first doses administered; 207,408 second doses administered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	No signals in analyses for combined mRNA vaccines, combined dose 1 and dose 2	No signals as of February 27
Vaccine Safety Datalink (VSD) Mortality Study (Vaccinated through 2/27 and death data through 3/20/21)	Deaths	VSD sites enrolled in the mortality study; vaccinated before 2/27 and number of deaths before 3/20	220,799 first doses administered; 86,650 second doses administered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	0.6 dose 1 mortality rate per 100 person-years 0.7 dose 2 mortality rate per 100 person-years 1.0 comparator mortality rate per 100 person-years	No signals for death as of March 20
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
Centers for Medicare and Medicaid Services (CMS)[b]	Pre-specified health outcomes[a]					

BEST initiative[b]	Pre-specified health outcomes[a]					
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-pfizer-biontech-vaccine.html	

[a]See Table 4 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]at the time of vaccination

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

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) (Data through 3/22/2021)	All health events, adverse events of special interest[a]	US population	3,090,712 total doses administered	Descriptive and empirical Bayesian data mining	18 death reports • 1 LTCF death report • 13 (72%) death reports for those aged 65 or above	No concerns raised
VA ADERS (Data through 3/23/2021)	All health events	VA employees and Veteran patients	Data not yet available	Descriptive	1 death report	
DoD VAERS (Data through 3/19/2021)	All health events, adverse events of special interest	Active duty and beneficiaries	28,640 vaccines administered	Descriptive	4 total AE reports • 0 serious AE reports • 0 death reports	No concerns raised
Indian Health Services (IHS)[b]	All health events, adverse events of special interest[a]					
Active Surveillance						
V-safe (Data through 3/13/2021)		Vaccinees who enroll	74,609 persons enrolled; 498 pregnancies[c]	Descriptive	No serious reports	No concerns raised
V-safe Pregnancy Registry (Data through 3/19/2021)		Vaccinees who enroll	Data not yet available	Descriptive		
Department of Veterans Affairs (VA) Active Surveillance System	Pre-specified health outcomes[a]	Veteran Patients				

Vaccine Safety Datalink (VSD) [b]	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	Data not yet available	Descriptive; Sequential analysis will be added when available	Data not yet available	
Vaccine Safety Datalink (VSD) Mortality Study (Vaccinated through 2/27 and death data through 3/20/21)	Deaths	VSD sites enrolled in the mortality study; vaccinated before 2/27 and number of deaths before 3/20	Data not yet available	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	Data not yet available	
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
Centers for Medicare and Medicaid Services (CMS)[b]	Pre-specified health outcomes[a]					
BEST initiative[b]	Pre-specified health outcomes[a]					
Vaccine Trials (Manufacturer)					See GRADE tables [HYPERLINK "https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/03-COVID-Gargano.pdf"]	

[a]See Table 4. for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 4. Health systems and pre-specified health outcomes

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

Optic neuritis (ON)	x[1,2]				
Seizures / convulsions (convulsion is now an LLT under PT seizure)	x	x			x
Stroke	x	x		x	x
Thrombocytopenia	x				
Transverse myelitis (TM)	x	x		x	x
Vaccination during pregnancy/adverse pregnancy outcomes	x				x
Venous thromboembolism (VTE)	x	x			-
Pulmonary embolism	-	x		x	x
Deep vein thrombosis	-	-		x	x

[1]Health outcomes are counted, but adverse event reports are not abstracted
[2]Diagnoses are grouped and reported as "Other clinically serious neurologic AEs" in VAERS
[3]Health outcomes are counted, and no sequential analysis is conducted
[4]Only includes narcolepsy
*TBD

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/5/2021 4:08:26 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]; Dooling, Kathleen L (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]; Kulldorf, Martin [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]; Mullen, Jennifer (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]; 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]
Subject: [EXTERNAL] VaST - Agenda for April 5 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL
Attachments: Adverse events english ACIP 4_05_21.pdf; FDA VAERS data mining Baer 4_04_21.pdf; RCA results_20210405_VAST.pdf; VSD RCA Covid-19 vax - VaST methods 4-05-2021.pdf; 2021_04_05 VaST Meeting Agenda.docx

Dear all,

This email includes the VaST agenda for today (below and attached) as well as 4 slide sets. The agenda attached has more information regarding approximate times for talks and discussion.

Agenda:
Announcements, Meeting Expectations and Processes
Israel's Covid-19 vaccine safety data (Emilia Anis, Israel MOH)
FDA methods for data mining (Bethany Baer, FDA)
FDA CMS RCA (Richard Forshee, FDA)
VSD and VA RCA, overview of plans (Tom Shimabukuro, CDC and Fran Cunningham, VA)

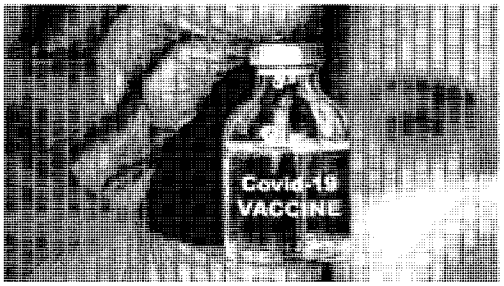
The VaST call link information should be on your calendars.
Reminder - all VaST documents and communications are confidential.

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

Adverse events following vaccination COVID-19

Data updated March 31st 2021



Division of Epidemiology

Public health services

Ministry of Health Israel

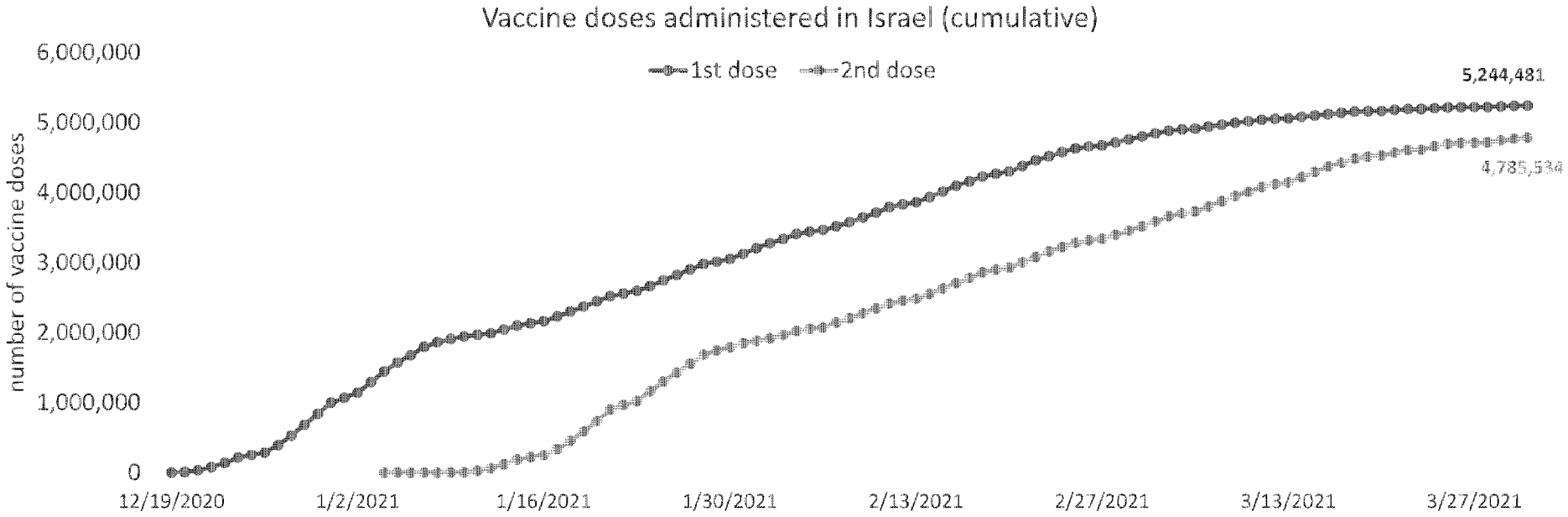
Sources of adverse events reports

Sources of adverse events reports include:

- Hospitals
- HMOs
- Emergency Medical Services - MDA (for individuals who are vaccinated in nursing homes)
- The Medical Department and the Patient Safety Unit at the MoH
- Israeli Defense Forces (IDF)

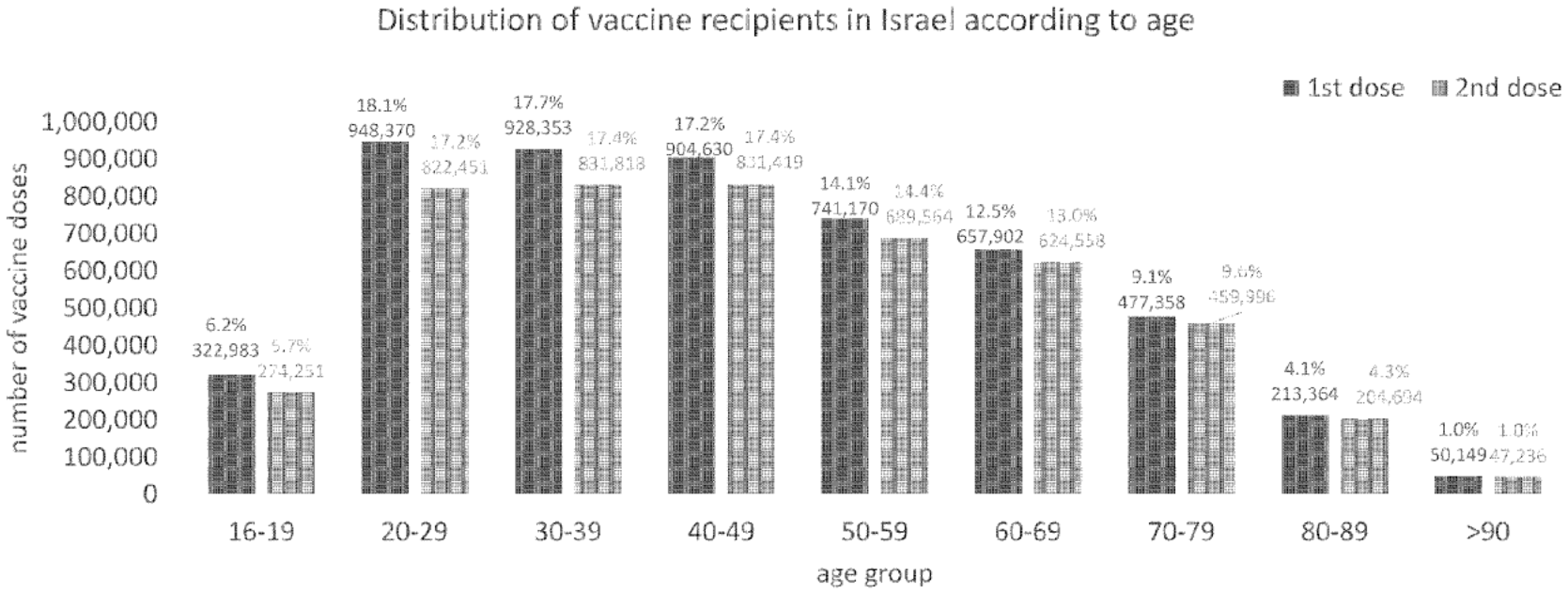
משרד הבריאות

Vaccine doses administered in Israel



Updated 31/03/2021

Distribution of vaccine recipients according to age

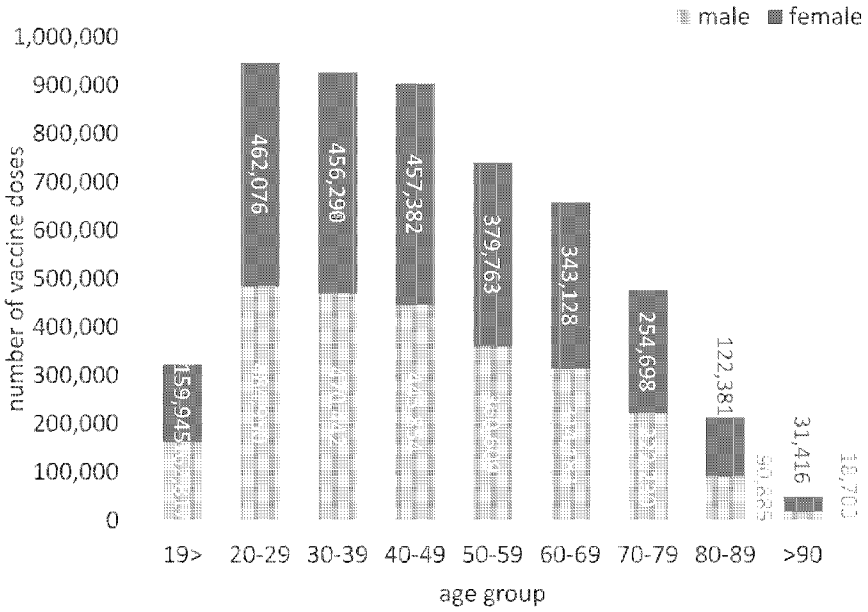


AgeGroup	16-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90<
Vaccine coverage by age group 1st dose	55.3%	72.9%	77.6%	82.3%	87.2%	88.7%	97.3%	94.6%	97.4%
Vaccine coverage by age group 2nd dose	47.0%	63.2%	69.5%	75.7%	81.1%	84.2%	93.7%	90.8%	91.7%

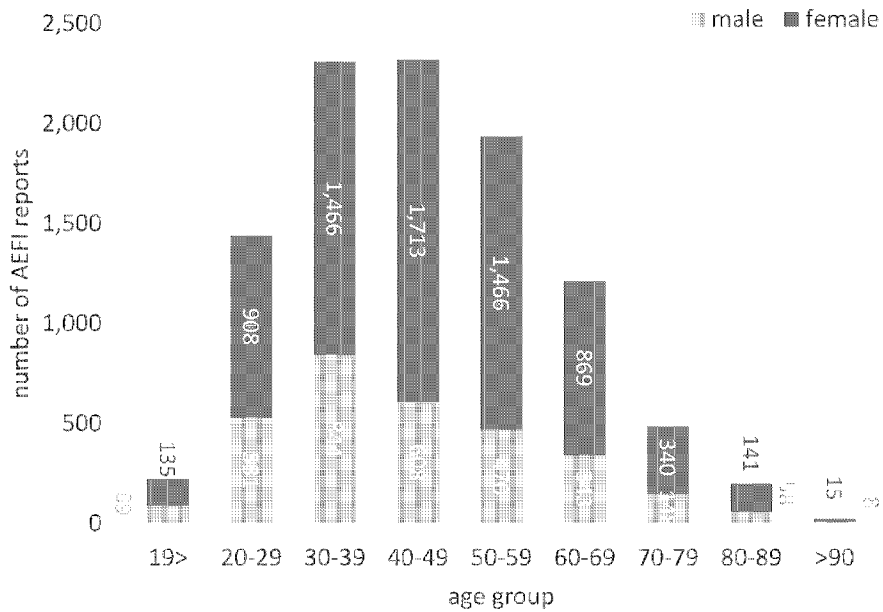
Updated 31/03/2021

Age and sex distribution among vaccine recipients and those who reported adverse events - FIRST DOSE

Distribution according to age group and sex among recipients of first vaccine dose.



Distribution according to age group and sex among individuals reporting adverse events following first dose vaccination.



Women and younger individuals are more likely to report adverse reactions following vaccination relative to their proportion among the vaccine recipient population

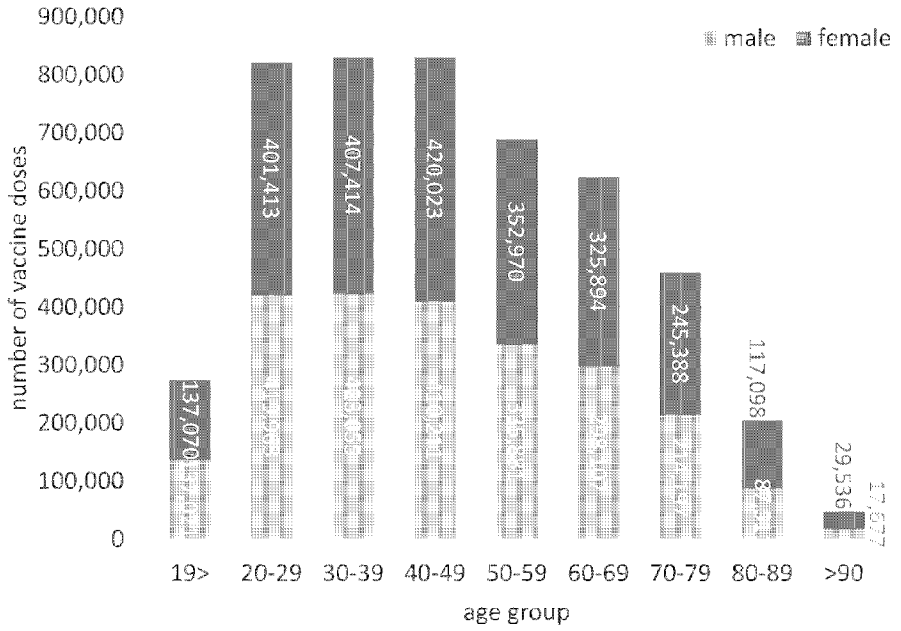
Updated 31/03/2021

PSICOVID_00008720

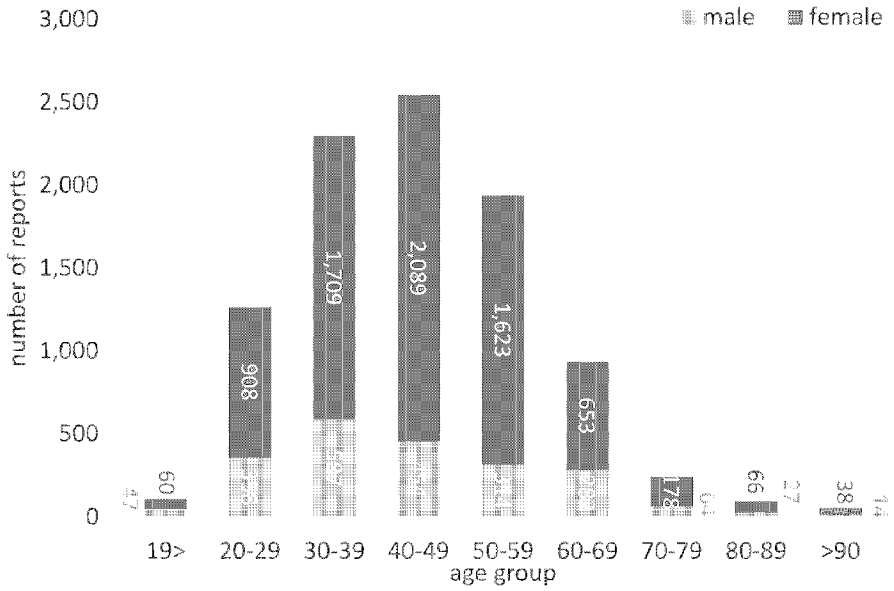
משרד הבריאות

Age and sex distribution among vaccine recipients and those who reported adverse events - SECOND DOSE

Distribution according to age group and sex among recipients of second vaccine dose.



Distribution according to age group and sex among individuals reporting adverse events following second dose vaccination

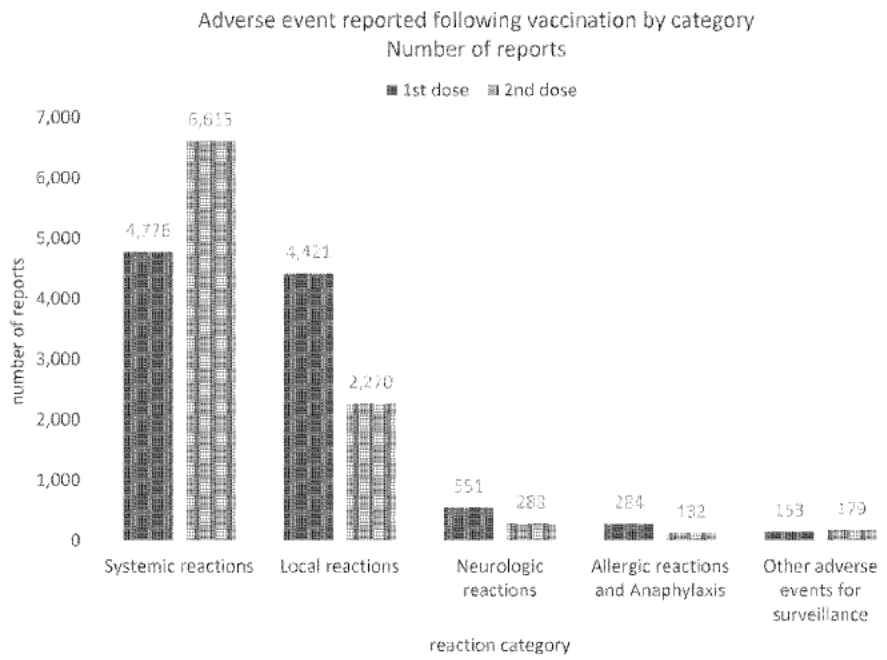


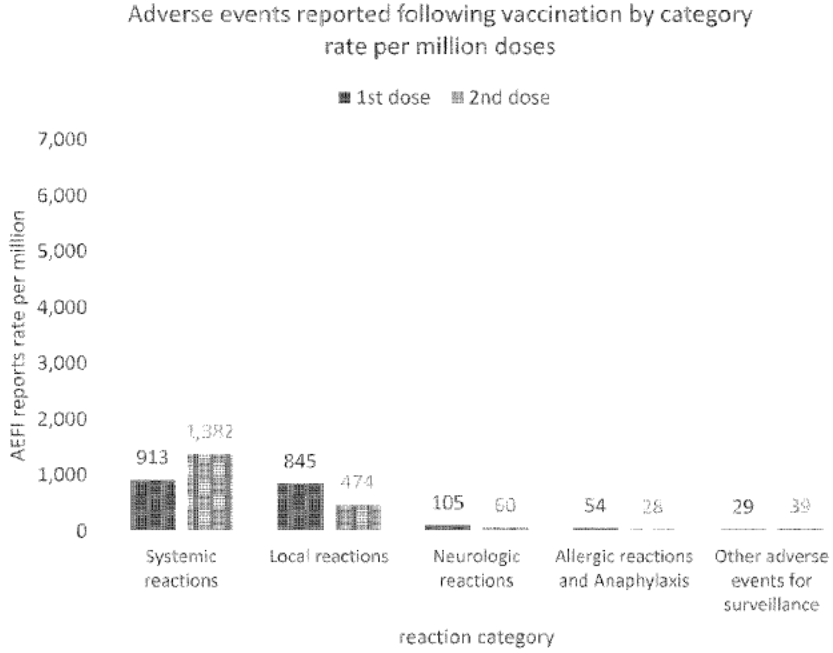
Women and younger individuals are more likely to report adverse reactions following vaccination relative to their proportion among the vaccine recipient population

Updated 31/03/2021

PSICOVID_00008721

Adverse events following vaccination by category





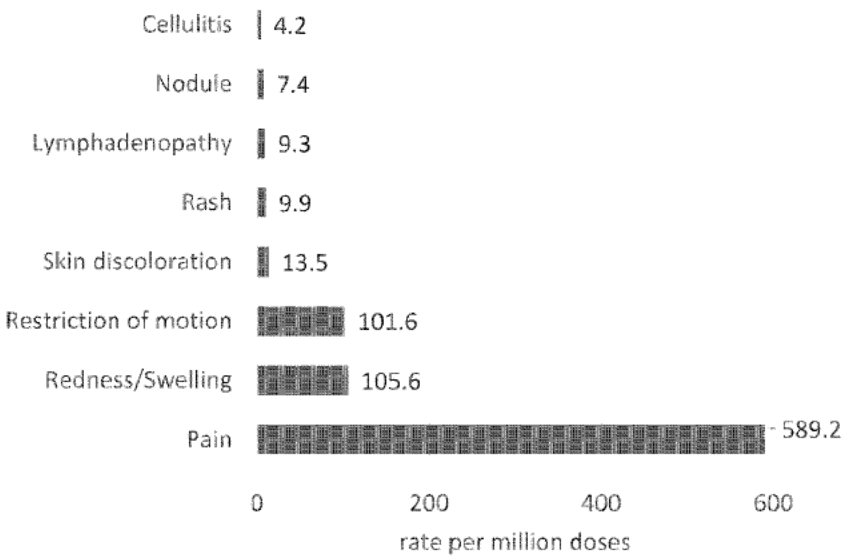
Reports among vaccine recipients
1st dose: 5,244,481 2nd dose: 4,785,534

Updated 31/03/2021

Data is based on adverse events reported to the MoH | Some individuals reported more than one adverse event

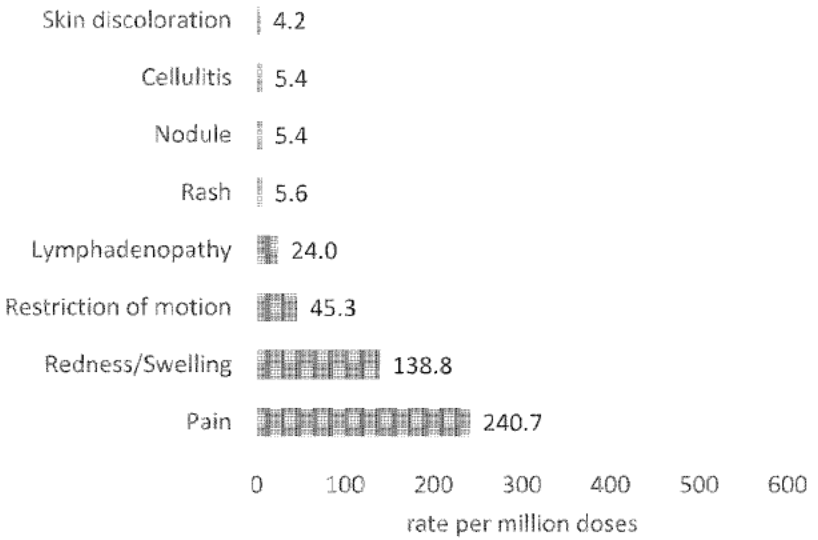
Local reactions

Local reactions (at injection site) reported following vaccination, rate per million doses- first dose



Rate per million vaccine doses out of 5,244,481 vaccine 1st dose recipients

Local reactions (at injection site) reported following vaccination, rate per million doses- second dose



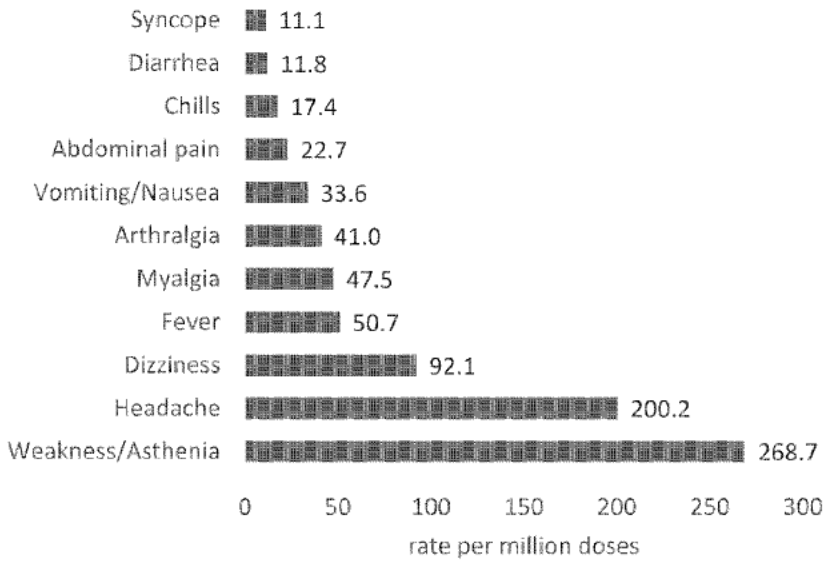
Rate per million vaccine doses out of 4,785,534 vaccine 2nd dose recipients

Updated 31/03/2021

Data is based on adverse events reported to the MoH | Some individuals reported more than one adverse event

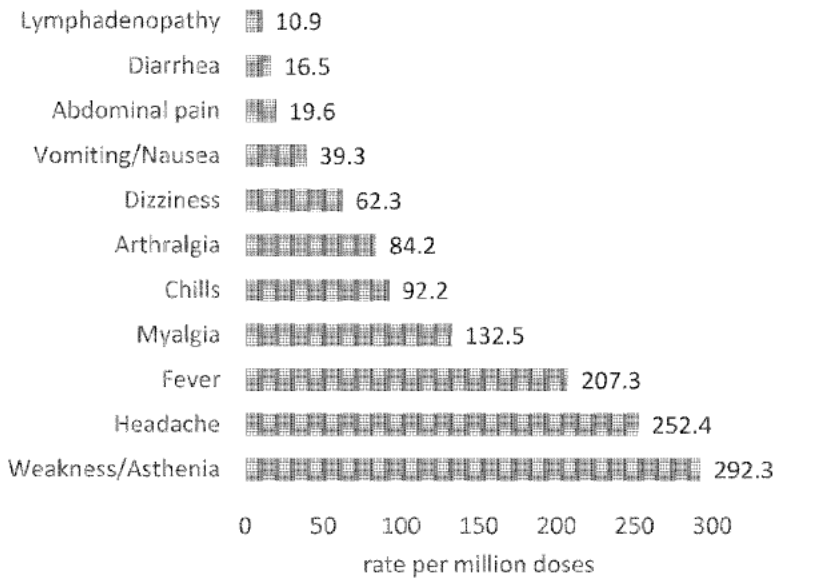
Systemic reactions

General reactions reported following immunization, rate per million doses- first dose



Rate per million vaccine doses out of 5,244,481 vaccine 1st dose recipients

General reactions reported following immunization, rate per million doses- second dose



Rate per million vaccine doses out of 4,785,534 vaccine 2nd dose recipients

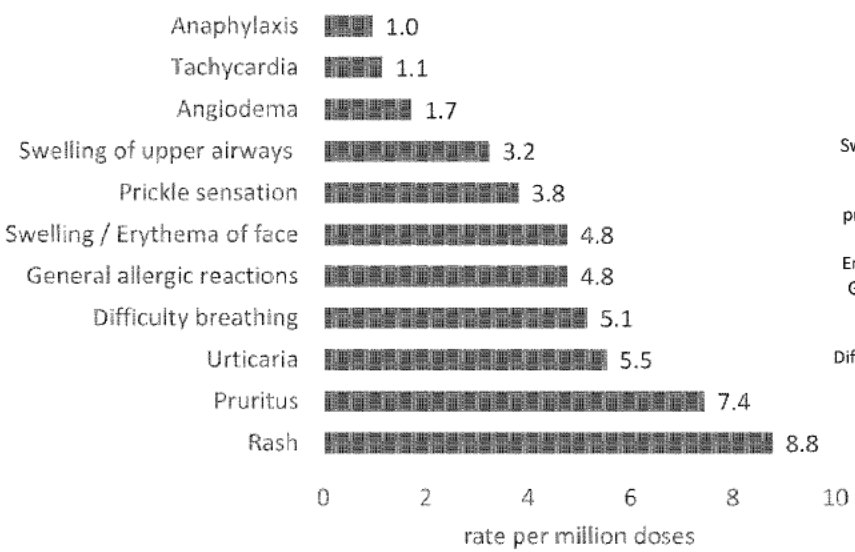
Updated 31/03/2021

Data is based on adverse events reported to the MoH | Some individuals reported more than one adverse event

משרד הבריאות

Allergic reactions

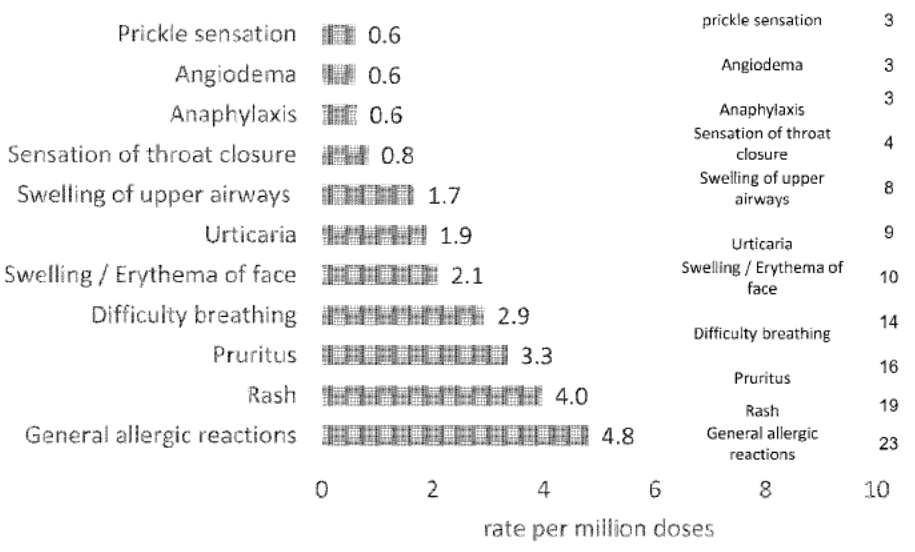
Allergic reactions reported following vaccination, rate per million vaccine doses- first dose



Number of allergic reactions reported 1st dose	
Anaphylaxis	5
Tachycardia	6
Angiodema	9
Swelling of upper airways	17
prickle sensation	20
Swelling / Erythema of face	25
General allergic reactions	25
Difficulty breathing	27
Urticaria	28
Pruritus	39
Rash	46

Rate per million vaccine doses out of 5,244,481 vaccine 1st dose recipients

Allergic reactions reported following vaccination, rate per million vaccine doses- second dose



Number of allergic reactions reported 2nd dose	
prickle sensation	3
Angiodema	3
Anaphylaxis	3
Sensation of throat closure	4
Swelling of upper airways	8
Urticaria	9
Swelling / Erythema of face	10
Difficulty breathing	14
Pruritus	16
Rash	19
General allergic reactions	23

Rate per million vaccine doses out of 4,785,534 vaccine 2nd dose recipients

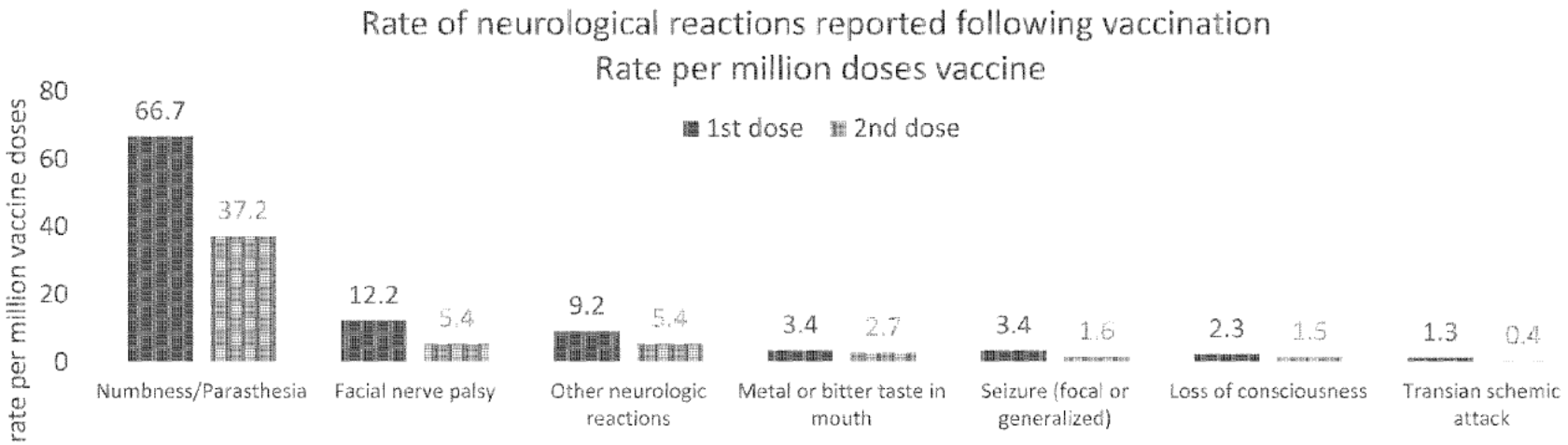
Updated 31/03/2021

Data is based on adverse events reported to the MoH I Some individuals reported more than one adverse event

Neurologic reactions

Number of neurologic reactions reported

	Numbness/ Parasthesia	Facial nerve palsy	Other neurologic reactions	Metal or bitter taste in mouth	Seizure (focal or generalized)	Loss of consciousness	Transian ischemic attack
1st dose	350	64	48	18	18	12	7
2nd dose	178	26	25	13	8	7	2



Updated 31/03/2021

Data is based on adverse events reported to the MoH I Some individuals reported more than one adverse event

משרד הבריאות

Neurologic reactions

		Bell's palsy (1 case pregnant)		Blurred vision		Sudden sensorineural hearing loss		Abducens nerve palsy		Vertigo		Occulomotor nerve palsy		Trigeminal neuralgia		Seizures		Transiant Ischemic Attack		Guillain Barré syndrome (1 case exacerbation)		Multiple sclerosis (1 case exacerbation, 1 new case)		Brachial plexitis	
		1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose
Age group	**<20**	1	1													2	1								
	20-29	3	2		1	1								1		2	1	1		1					
	30-39	7	2	3		1	1									2	1								
	40-49	13	5	2	3		2			1						1	5	1				1			
	50-59	11	10	6	1	2	1				1					2				1					
	60-69	16	4	2		1	1	1	1	1	2	1				1		1		1	1			1	
	70-79	9	2			1			1							4		1	1	1		1			
	80-89	4				1	2		1							4		3							
	>90																		1						
	Total	**64**	**26**	**13**	**5**	**7**	**7**	**1**	**3**	**2**	**3**	**1**		**1**		**18**	**8**	**7**	**2**	**4**	**1**	**2**		**1**	
Follow-up second dose		**38**	Not relevant	**10**	Not relevant	**5**	Not relevant	**1**	Not relevant	**0**	Not relevant	**1**	Not relevant	**1**	Not relevant	**12**	Not relevant	**6**	Not relevant	**1**	Not relevant	**2**	Not relevant	**1**	Not relevant
Expected number of cases in population age 16 and older, for same time period of vaccination project and same population group		168	128	51	39	180	135	41	30	465	341	17	12	41	31	1372	1018	1258	920	139	110	334	260	13	9

The observed numbers are compared to the morbidity data in hospitalized patients from 2017-2019 which includes morbidity data reported among all individuals 16 years and older from the corresponding periods – *i.e* morbidity cases following the first and second dose is compared to morbidity cases in hospitalized patients from December - March and January - March respectively.

NOTE: In addition to the data presented in the table, the MoH monitors other reactions for which expected numbers cannot be presented.

Updated 31/03/2021

Data is based on adverse events reported to the MoH I Some individuals reported more than one adverse event

Other adverse events of interest

Other AEs of interest following vaccination (rate per million vaccine doses) compared to expected rates in the general population according to morbidity data from the corresponding periods of years 2017-2019

Other adverse events of interest	Medical diagnosis	AE rates following first dose (Dec-Mar)	Expected rates (hospitalization data Dec-Mar 2017-2019)	AE rates following second dose (Jan-Mar)	Expected rates (hospitalization data Jan-Mar 2017-2019)
Hematological	Thrombocytopenia	0.6	26.9	0.4	21.0
	Purpura	0.2	21.2	Not reported	15.2
Infections	Sepsis	0.2	71.1	Not reported	53.5
	Herpes zoster	3.4	44.2	3.6	33.4
	Herpes simplex	1.3	15.2	1.3	10.5
	Necrotizing Fasciitis	0.2	6.5	Not reported	4.8
Neurological	Transiant Ischemic Attack	1.3	201.8	0.4	147.6
	Encephalitis	0.2	1.4	Not reported	1.1
	Diplopia (double vision)	0.4	9.3	0.6	6.8
	Acute hearing loss	1.3	28.9	1.5	21.6
	Shoulder weakness and severe pain	0.2	2.1	Not reported	1.5
	Facial weakness and severe pain	0.2	6.6	Not reported	5.0
	Blurred vision	2.5	8.2	1.0	6.3
	Vertigo	0.4	59.7	0.6	43.3
	Guillian barre syndrome	0.8	22.3	0.2	17.7

Note: Despite normalization to the number of vaccinees, observed and expected rates cannot be directly compared, because the observed cases are counted differently than the expected ones. The observed cases count morbidity within a time window of a defined event (vaccine administration). The expected cases are calculated by the cumulative incidence over several calendar months. However, the expected cases do give a general order of magnitude for comparison of morbidity following vaccine administration.

The observed rates are compared to the morbidity data in hospitalized patients from 2017-2019 which includes morbidity data reported among all individuals 16 years and older from the corresponding periods – *i.e* morbidity rates following the first and second dose is compared to morbidity rates in hospitalized patients from December - March and January - March respectively.
NOTE: In addition to the data presented in the table, the MoH monitors other reactions for which expected rates cannot be presented.

Data is based on adverse events reported to the MoH

Updated 31/03/2021

Other adverse events of interest

Other AEs of interest following vaccination (rate per million vaccine doses) compared to expected rates in the general population according to morbidity data from the corresponding periods of years 2017-2019

Other adverse events of interest	Medical diagnosis	AE rates following first dose (Dec-Mar)	Expected rates (hospitalization data Dec-Mar 2017-2019)	AE rates following second dose (Jan-Mar)	Expected rates (hospitalization data Jan-Mar 2017-2019)
Cardiovascular	Myocardial infarction	0.6	746.1	0.2	554.1
	Heart failure	0.4	859.2	Not reported	648.6
	Subarachnoid hemorrhage	0.2	19.9	Not reported	14.2
	Vasculitis	Not reported	7.3	0.2	4.5
	Pericarditis	1.0	48.7	2.1	36.6
	Myocarditis (including Perimyocarditis)	1.1	21.3	11.7	15.6
	Cardiac tamponade	0.2	3.8	Not reported	2.5
	Venous thrombosis (DVT)	Not reported	65.2	0.6	48.1
	Superficial venous thrombosis	Not reported	3.6	0.2	2.7
	Atrial Fibrillation	0.4	560.4	0.6	414.3
	Stroke	1.0	649.1	0.2	475.6
	Pulmonary embolism	0.2	78.0	0.2	56.4
	Pericardial effusion	0.4	33.9	0.2	26.8
Ophthalmological	Retinopathy	0.2	0.8	Not reported	0.5
Rheumatology	Arthritis	Not reported	252.7	0.2	191.6

Note: Despite normalization to the number of vaccinees, observed and expected rates cannot be directly compared, because the observed cases are counted differently than the expected ones. The observed cases count morbidity within a time window of a defined event (vaccine administration). The expected cases are calculated by the cumulative incidence over several calendar months. However, the expected cases do give a general order of magnitude for comparison of morbidity following vaccine administration.

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NOTE: In addition to the data presented in the table, the MoH monitors other reactions for which expected rates cannot be presented.

Data is based on adverse events reported to the MoH

Updated 31/03/2021
PSICOVID_00008729

Other adverse events of interest

Other AEs of interest following vaccination (rate per million vaccine doses) compared to expected rates in the general population according to morbidity data from the corresponding periods of years 2017-2019

Other adverse events of interest	Medical diagnosis	AE rates following first dose (Dec-Mar)	Expected rates (hospitalization data Dec-Mar 2017-2019)	AE rates following second dose (Jan-Mar)	Expected rates (hospitalization data Jan-Mar 2017-2019)
Pregnant (rate calculated out of women ages 16-49 whom received the vaccine)	Missed abortion	1.3	1909.4	Not reported	1473.1
	IUFD	1.3	71.6	Not reported	53.8
	CMV	Not reported	3.8	0.7	3.2
Respiratory	Pleuritis	0.2	2.4	Not reported	1.7
	Pulmonary edema	Not reported	259.8	0.2	196.0
	Severe acute respiratory syndrome	Not reported	177.5	0.2	132.9
Organ damage	Acute liver damage	0.2	3.9	Not reported	2.8
	Acute kidney damage	0.2	227.4	Not reported	168.7
Other	Erythema Multiforme	0.2	3.4	Not reported	2.6
	Loss of smell (anosmia)/loss of taste (ageusia)	1.3	1.8	1.0	1.2
	Appendicitis	Not reported	315.9	0.2	235.3
	Acute thyroiditis	Not reported	2.4	0.2	1.9
	Multiple sclerosis (1 relapse and 1 new diagnosis)	0.4	53.6	Not reported	41.8
	Hemorrhagic cystitis	0.2	4.9	Not reported	3.9
	rhabdomyolysis	Not reported	20.6	0.2	16.0

Note: Despite normalization to the number of vaccinees, observed and expected rates cannot be directly compared, because the observed cases are counted differently than the expected ones. The observed cases count morbidity within a time window of a defined event (vaccine administration). The expected cases are calculated by the cumulative incidence over several calendar months. However, the expected cases do give a general order of magnitude for comparison of morbidity following vaccine administration.

The observed rates are compared to the morbidity data in hospitalized patients from 2017-2019 which includes morbidity data reported among all individuals 16 years and older from the corresponding periods – *i.e* morbidity rates following the first and second dose is compared to morbidity rates in hospitalized patients from December - March and January - March respectively.
NOTE: In addition to the data presented in the table, the MoH monitors other reactions for which expected rates cannot be presented.

Data is based on adverse events reported to the MoH

Updated 31/03/2021
PSICOVID_00008730

Myocarditis following vaccination

To date, 62 cases of myocarditis following vaccination have been reported

Myocarditis after first dose (N=6)

- 4 males, 2 females
- 1 case myocarditis, 5 cases of Perimyocarditis
- 4 events occurred within 10 days of receiving the vaccine,1 event occurred within 2 weeks and 1 event occurred within 3 weeks following vaccination.
- 3 cases with comorbidities (HTN, dyslipidemia)
- All cases were discharged from the hospital and are under observation in the community
- 2 cases received a second dose with no adverse reactions reported

Myocarditis after second dose (N=56)

- 50 males and 6 females
- 37 cases of Myocarditis, 19 cases of Perimyocarditis
- 23 events occurred within 10 days of receiving the vaccine, 2 events occurred within 2 weeks, 1 events occurred within 3 weeks, 2 events occurred within 4 weeks following vaccination.
- 28 cases with comorbidities (HTN, smoking, asthma, dyslipidemia, DM, hypercholesterolemia)
- 53 cases were discharged from the hospital and are under observation at community level. 1 case is under investigation, 2 cases died (1 case fulminant myocarditis, 1 case is still under investigation)
- None of the cases reported adverse reactions after receipt of the first dose

Data is based on adverse events reported to the MoH

Updated 31/03/2021

Pericarditis following vaccination

To date, 15 cases of Pericarditis following vaccination have been reported

Pericarditis after first dose (N=5)

- 3 males, 2 females
- All events occurred within 4 days of receiving the vaccine.
- 2 cases with comorbidities (history of Pericarditis, heart valve)
- All cases were discharged from the hospital and are under observation in the community
- 3 cases received a second dose with no adverse reactions reported

Pericarditis after second dose (N=10)

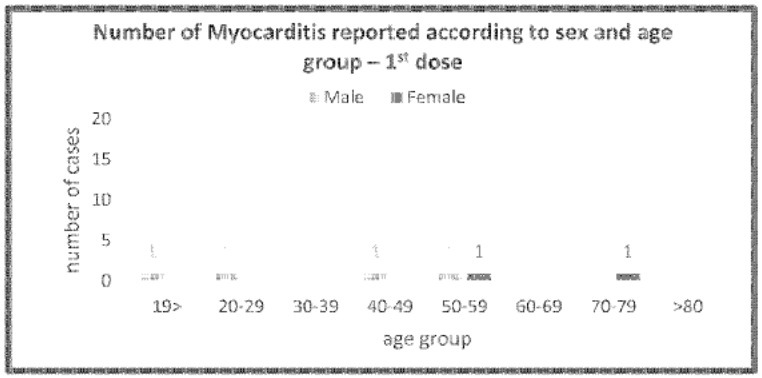
- 6 males and 4 females
- 8 events occurred within 7 days of receiving the vaccine, 1 events occurred within 3 weeks, 1 events occurred within 5 weeks following vaccination.
- 8 cases with comorbidities (HTN, obesity, hypercholesterolemia, dyslipidemia, renal disease)
- 9 cases were discharged from the hospital and are under observation at community level. 1 is under investigation.
- None of the cases reported adverse reactions after receipt of the first dose

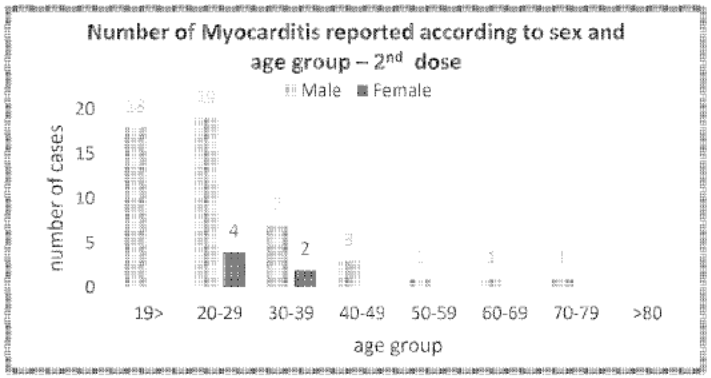
Data is based on adverse events reported to the MoH

Updated 31/03/2021

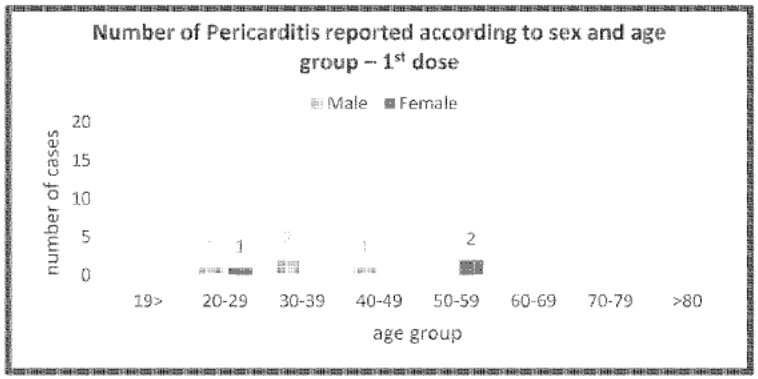
Myocarditis / Pericarditis following vaccination

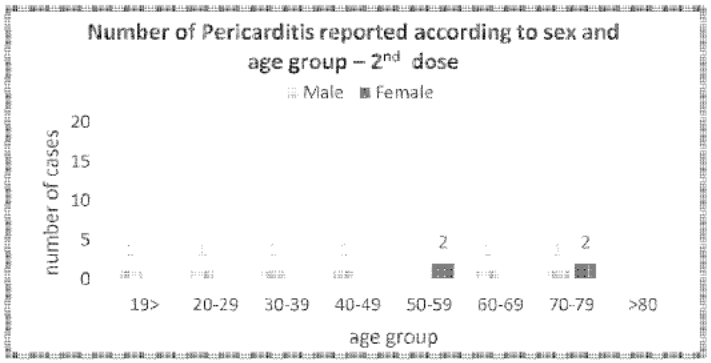
Myocarditis / Perimyocarditis





Pericarditis



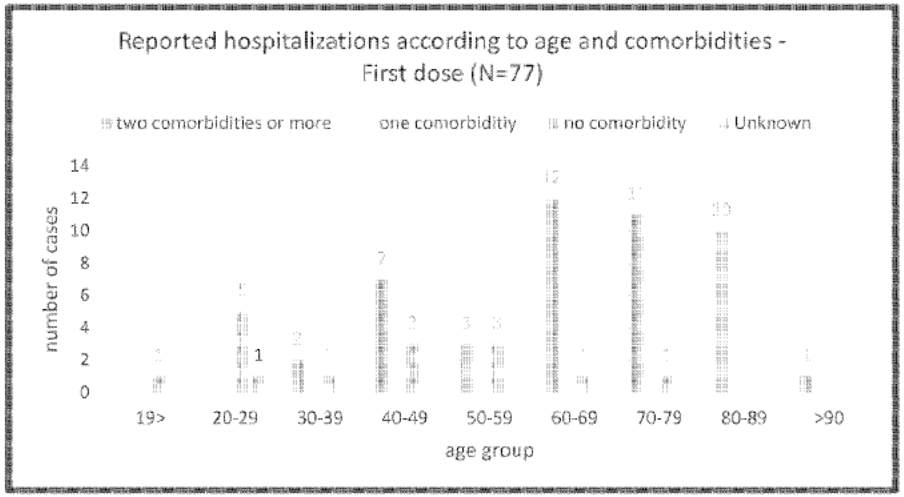


Data is based on adverse events reported to the MoH

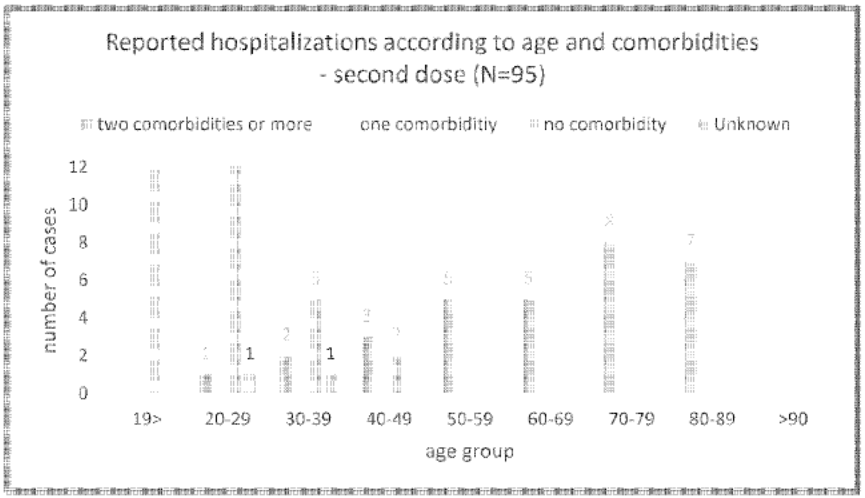
Updated 31/03/2021

PSICOVID_00008733

Hospitalizations reported following vaccination



Among 77 hospitalizations following receiving the first dose , 34 cases were related to neurological diseases out of which 30 cases had comorbidities, 25 hospitalization were related to underlying cardiovascular diseases out of which 18 had comorbidities, 6 hospitalizations were related to allergic reactions, 2 infectious and 7 hospitalizations were related to other underlying diseases. 3 hospitalizations were related to pregnancy complications.



Among 95 hospitalization following receiving the second dose , 75 cases were related to cardiovascular diseases and of those 38 were with significant underlying diseases. 10 hospitalizations were related to underlying neurological diseases and of those 8 were with significant underlying diseases and 4 hospitalizations were related to underlying respiratory diseases, and 8 hospitalizations were related to other underlying diseases.

Reports among vaccine recipients
1st dose: 5,244,481 2nd dose: 4,785,534

Data is based on adverse events reported to the MoH

Updated 31/03/2021

PSICOVID_00008734

משרד הבריאות

Deaths reported following vaccination

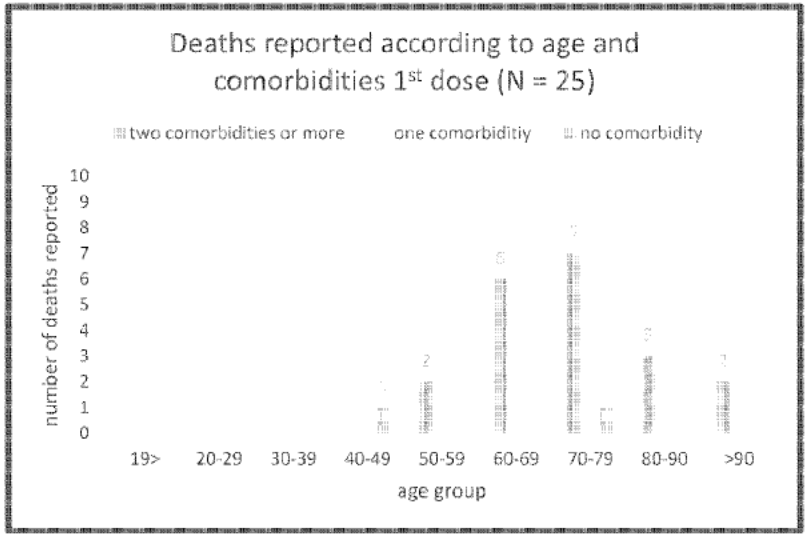
- **48 persons were reported to die in proximity to vaccination (up to 30 days following vaccination).**
- **42 deaths occurred within 10 days following vaccination**
- **Out of 48 reported cases, 14 are <60 y old:**
  - **2 were diagnosed in ER with myocarditis (1 case fulminant myocarditis, 1 case still under investigation)**
  - **2 PM in cases of sudden death excluded myocarditis in one and showed blocked LAD.**
  - **10 cases are under investigation: relatively young persons with sudden death.**

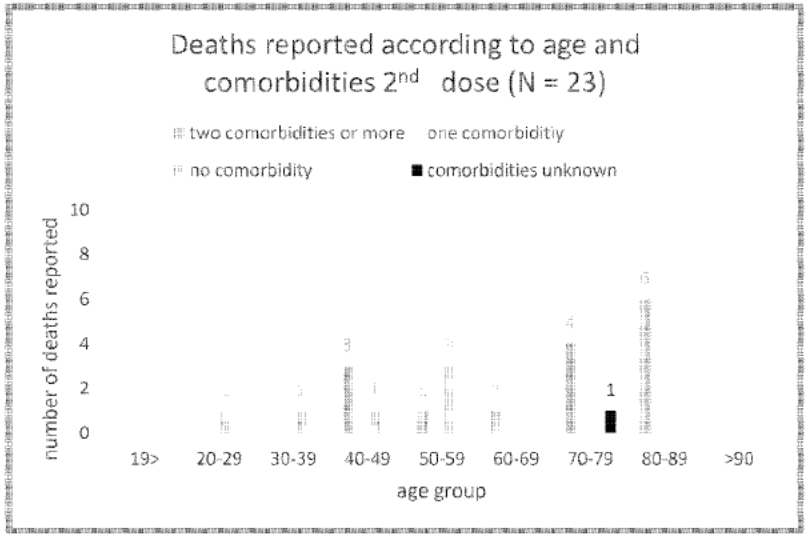
Reports among vaccine recipients
1st dose: 5,244,481 2nd dose: 4,785,534

Data is based on adverse events reported to the MoH

Updated 31/03/2021

Deaths reported following vaccination





Reports among vaccine recipients
1st dose: 5,244,481 2nd dose: 4,785,534

Data is based on adverse events reported to the MoH

Updated 31/03/2021

Deaths reported following vaccination observed and expected

Age group	Mortality cases reported following 1st dose	Mortality cases expected all causes (Dec-Mar)	Sudden death reported following 1st dose	Sudden death expected (Dec-Mar)	Mortality cases reported following 2nd dose	Mortality cases expected all causes (Jan-Mar)	Sudden death reported following 2nd dose	Sudden death expected (Jan-Mar)	Total cases reported
Male									
20-29	0	74	0	0	0	48	0	0	0
30-39	0	108	0	0	1	72	1	0	1
40-49	0	235	0	1	4	165	4	1	4
50-59	2	564	2	5	3	392	2	4	5
60-69	4	1220	1	5	2	865	0	3	6
70-79	6	2353	0	6	1	1727	0	3	7
80<	3	4349	0	9	3	3153	0	6	6
Female									
20-29	0	30	0	0	1	20	0	0	1
30-39	0	59	0	0	0	41	0	0	0
40-49	1	139	1	0	0	95	0	0	1
50-59	1	336	1	1	1	235	1	1	2
60-69	3	773	0	1	0	561	0	1	3
70-79	2	1714	1	4	4	1252	0	3	6
80<	3	5398	0	13	3	3889	0	10	6
Total	**25**	17,352	**6**	45	**23**	12,515	**8**	**32**	**48**

Note: Despite normalization to the number of vaccinees, observed and expected rates cannot be directly compared, because the observed cases are counted differently than the expected ones. The observed cases count deaths within a time window of a defined event (vaccine administration). The expected cases are calculated by the cumulative incidence over several calendar months. However, the expected cases do give a general order of magnitude for comparison of deaths following vaccine administration.

No specific signal associated with all causes of death and specifically sudden death

The overall mean of expected total deaths in the population of Israel 2015-2018, for December-March for the first dose, and January-March for the second dose, normalized for the number of vaccinated persons.

Data is based on adverse events reported to the MoH

Updated 31/03/2021

PSICOVID_00008737

משרד הבריאות

COVID-19 vaccination Israel
"BACK TO LIFE"

FDA VAERS Data Mining

Bethany Baer, MD
Medical Officer, Division of Epidemiology
Center for Biologics Evaluation and Research, FDA

ACIP Vaccine Safety Team Meeting
April 5, 2021

Disclaimer

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

FDA VAERS Data Mining

- Goal of data mining: identify any adverse events that are disproportionally reported for one vaccine compared to other vaccines
- Vaccine + adverse event (AE) = vaccine-AE pair
- Compare the number of reports of an adverse event after a vaccine with number of reports for that adverse event after all vaccines in VAERS

Empiric Bayes Geometric Mean (EBGM)

- Statistical model fit to the entire VAERS database uses Multi-item Gamma Poisson Shrinker (MGPS) algorithm to account for instability with small numbers*
- The model produces the Empiric Bayes Geometric Mean (EBGM)
- EBGM is calculated using observed to expected vaccine-AE pair ratios

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

Adjustments

- EBGM statistic is adjusted for potential confounders:
  - Age – Six age groupings + unknown age
    - Infant (0-23.9 mos), child (2-8.9 yrs), teen (9-18.9 yrs), adult1 (19-44.9 yrs), adult2 (45-64.9 yrs), adult3 (≥65 yrs)
  - Gender
  - Year Received
- Data mining conducted using Empirica Signal software by Oracle

EB05 Threshold

- Technically, any EBGM value above one indicates disproportional reporting
- 90% Confidence Interval around the EBGM with EB05 signifying the lower 5% bound and EB95 signifying the upper 5% bound.
- Standard Threshold: EB05 ≥ 2

Different Assessments

- FDA analyses include an overall score for all reports
- Additional assessments include EB05 scores for the following subgroups:
  - US reports
  - US Age groups
  - US Gender
  - US Serious and fatal reports
- Data mining results reviewed at different intervals based on length of time vaccine has been licensed and number of VAERS reports received for the product
- Currently reviewing data mining runs weekly for COVID-19 vaccines

Limitations

- Hypothesis generating tool only
  - An elevated EB05 score is not necessarily a safety signal
- Absence of disproportionality does not confirm the absence of a safety signal
- Passive reporting of VAERS database
  - Impacted by stimulated reporting
  - Underreporting
  - Incomplete or variable reporting
  - Unverified reports

Limitations (cont.)

- Potential statistical interaction with concomitant vaccines
- Confounding by indication
- MedDRA constraints – Based on coding hierarchy
  - Preferred Terms may not best capture a pathophysiologic process

Evaluation of a Data Mining Finding

- Case series review - look for patterns, consider possible explanations
- Characterize the finding:
  - unexpected?
  - clinically significant?
  - serious?
- Other Epidemiologic methods
  - Active surveillance
  - Potential for formal pharmacoepidemiologic study in a different database – e.g., CMS, VSD, Sentinel

Questions?

FDA U.S. FOOD & DRUG ADMINISTRATION

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

Office of Biostatistics & Epidemiology, CBER

Last Updated: April 2, 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 incidence rate (IR) of 15 AESIs among COVID-19 vaccinees versus the "Expected" incidence rate
- "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 and PE

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

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 1.37 to 1.21 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 1.56 to 1.39 and remained statistically significant.

***data through observation week 14, 3/13/2021**

Quality Assurance and Potential Associations

Quality Assurance

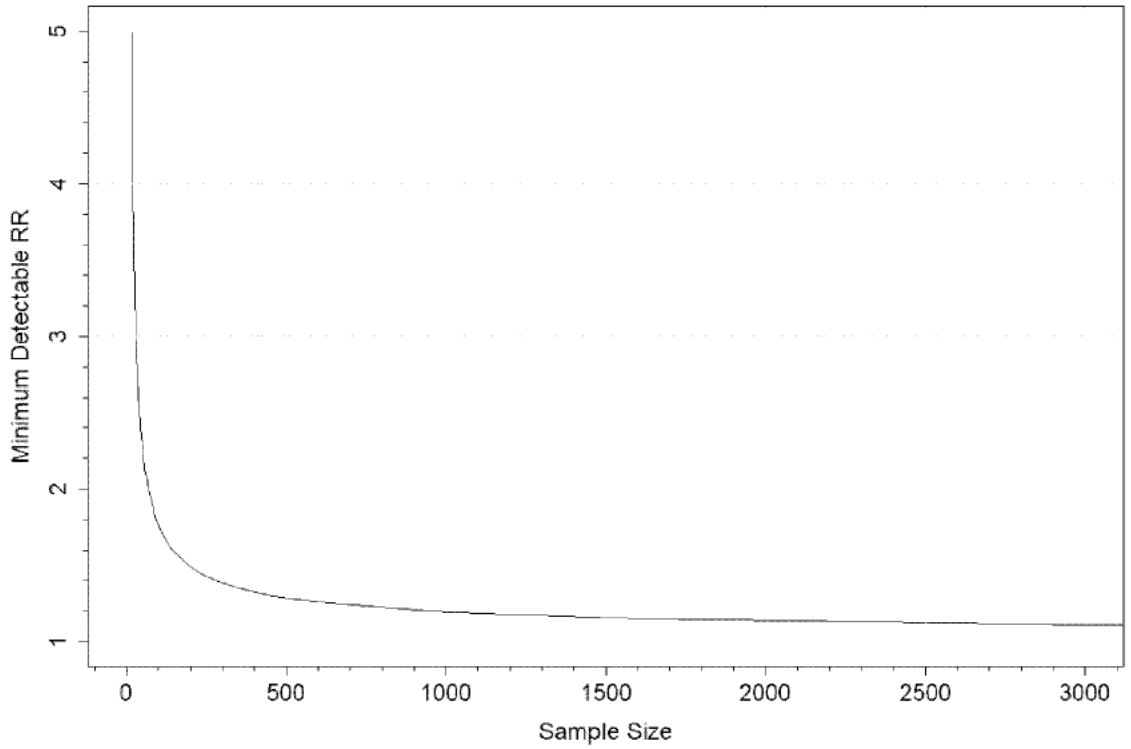
- Several analyses were performed to evaluate data quality, including:
  - Seasonality through stratification
    - PMaxSPRT sensitivity analysis using Jan-Mar background rates resulted in no association for AMI and delayed observed association for PE post-Pfizer.
  - Potential duplication of vaccines,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

Further Characterization for Two Potential Associations

- 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')
- Additional analyses are in progress
  - Residual confounding
  - Temporal scan statistics to assess whether any of the AESIs are temporally clustered
  - Patient claim profiles
  - Requesting a sample of charts

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

- Crude rates are elevated but RR is below 1.5 for both AMI and PE
- Further analysis is ongoing
- Inferential analyses are planned
- System is working to detect possible elevated rates for further investigation

Questions to VaST members

- How do we communicate these RCA results to the public ?
- How to address the trade-off of the uncertainty of self-controlled studies using pre-vaccination intervals versus 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?

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:

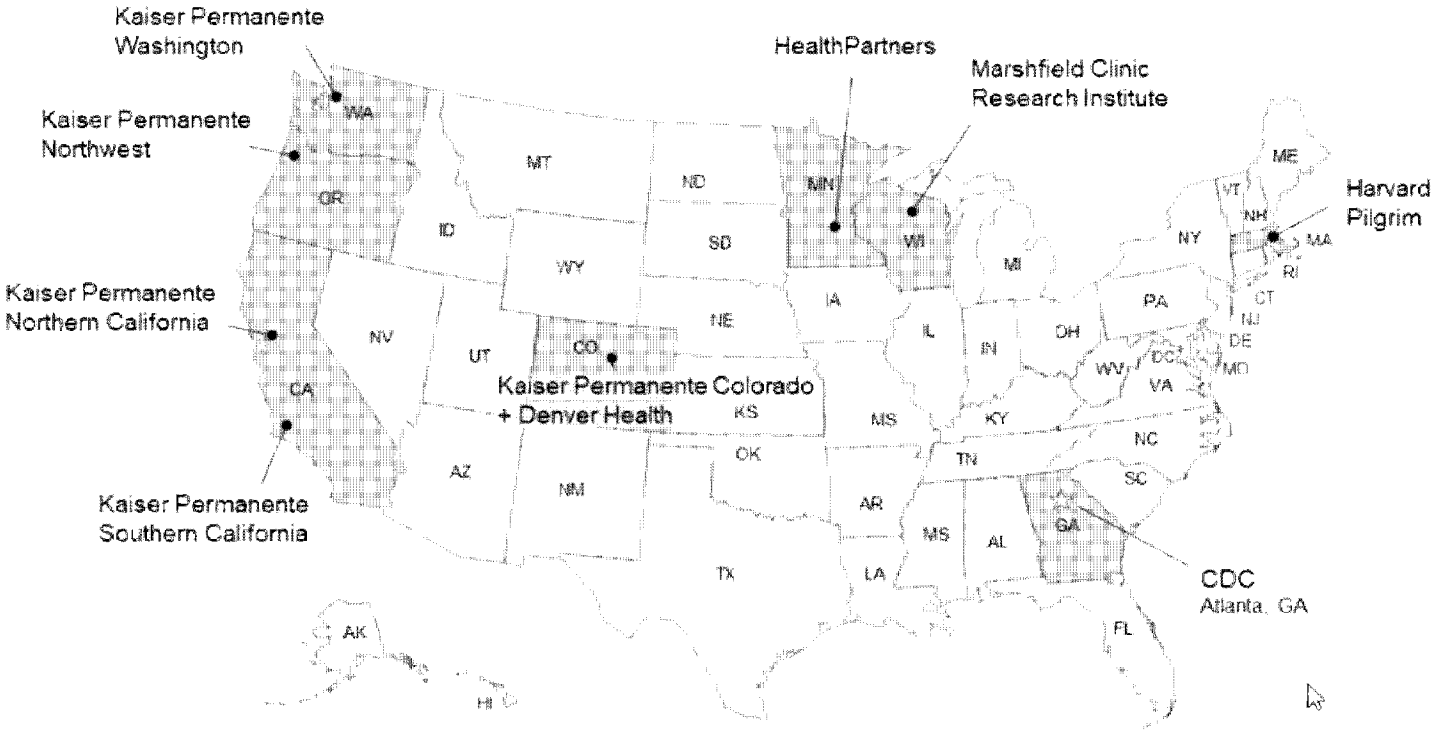
- To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

- 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

VSD Analytic Overview

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

Vaccinated concurrent comparators in a comparison interval after COVID-19 vaccination.

- Analyses are stratified in risk sets anchored to the calendar dates of outcome events.
- Analyses are stratified by age group, sex, race/ethnicity, and VSD site, as well as by calendar date.

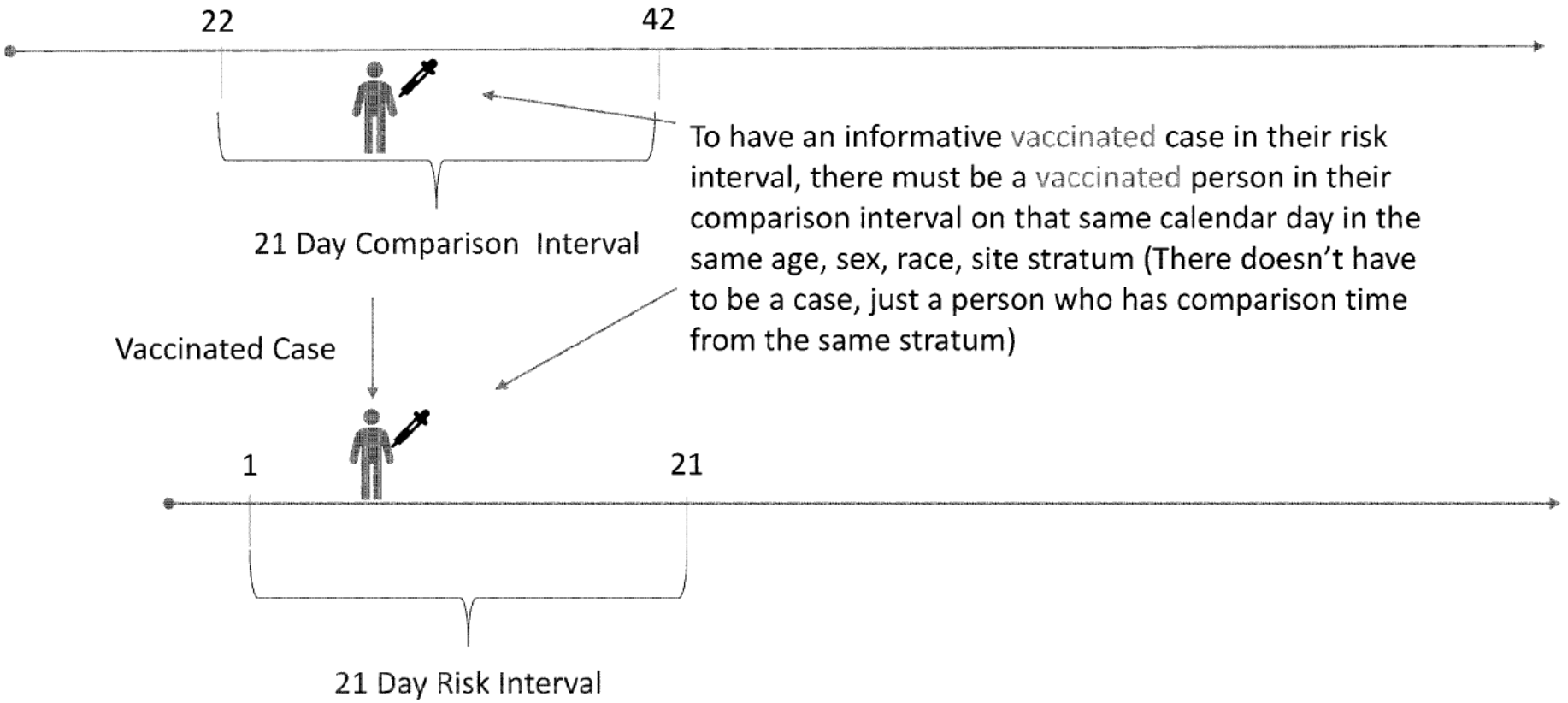
Unvaccinated concurrent comparators in a comparison interval in those not vaccinated.

- Analyses are stratified in risk sets anchored to the calendar dates of outcome events.
- Analyses are stratified by age group, sex, race/ethnicity, and VSD site, as well as by calendar date.

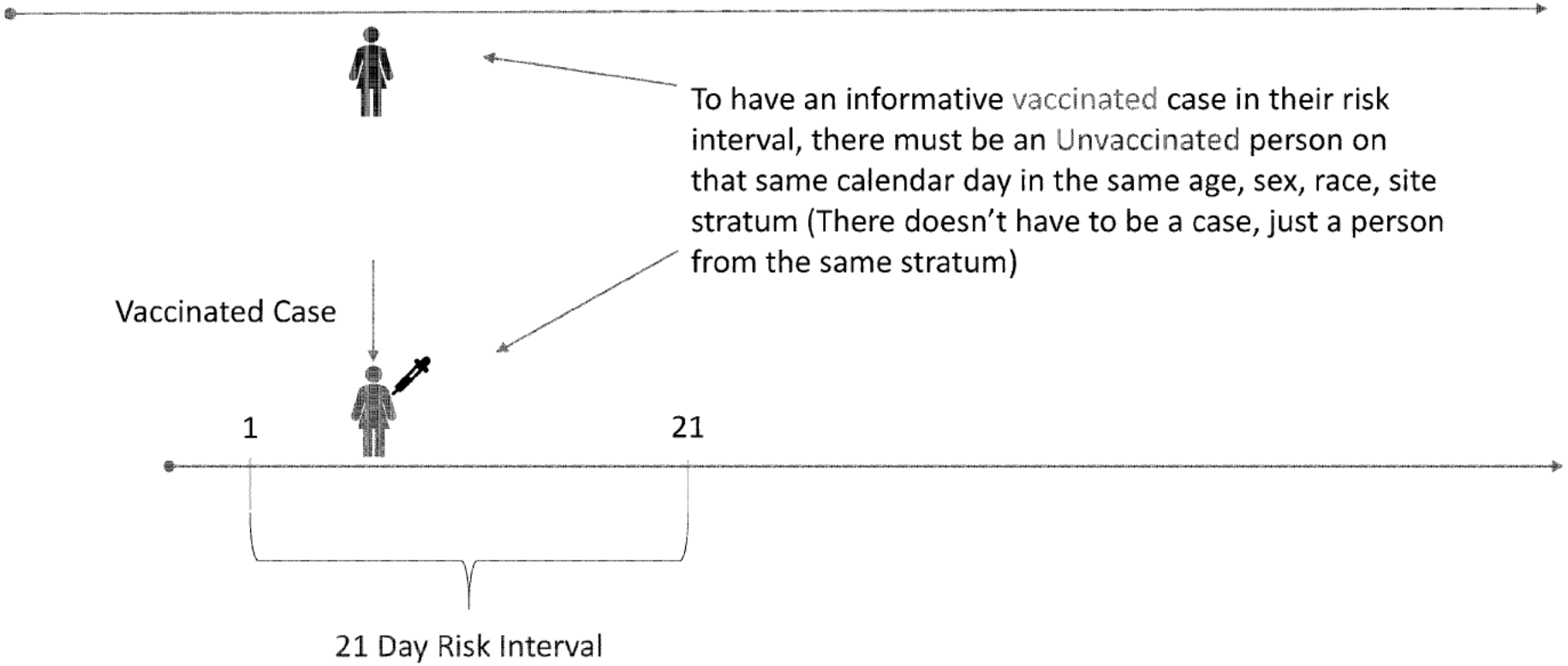
Supplemental Analysis

- Self-controls in a comparison interval after COVID-19 vaccination.

Vaccinated Comparison



Unvaccinated Comparison



VSD Analytic Advantages and Limitations

Design	Advantages	Limitations
Primary Sequential Analysis		
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
Weekly Analysis		
Unvaccinated concurrent	- Well-adjusted for calendar time - Able to conduct the analysis earlier in time when there is limited vaccinated comparison person time	- Bias from comorbidities, demographics, and propensities that may be associated with both the outcome and vaccination status
Supplemental Analysis		
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

VSD – Additional Data Analysis Planned

- The VSD plans to conduct a stratified concurrent vaccinated analysis for those 65 years and older for:
  - Acute myocardial infarction, VTE and Pulmonary Embolism

- The VSD will conduct an analysis for the 1-21 risk interval for a:
  - Product specific both dose combined analysis
  - Total combined (both doses and product) mRNA vaccine analysis

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
- Marshfield Clinic Research Institute:
  - 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

VSD Analytic Overview

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 in those not vaccinated
  - 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.

VaST Agenda – April 5, 2021

Open session
1:30 - 3:00

1:30-1:35 - Announcements, Meeting Expectations and Processes

1:35-1:55 - Israel's Covid-19 vaccine safety data (Emilia Anis, Israel MOH)

1:55-2:05 - Discussion

2:05-2:15 - FDA methods for data mining (Bethany Baer, FDA)

2:15-2:20 - Discussion

2:20-2:40 - FDA CMS RCA (Richard Forshee, FDA)

2:40-2:45 - VSD and VA RCA, overview of plans (Tom Shimabukuro and Fran Cunningham)

2:45-3:00 - Discussion

Message

From: Forshee, Richard [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC6A16C85D124B81893BEB85A6929867-FORSHEE]
Sent: 4/6/2021 4:39:08 PM
To: Markowitz, Lauri (CDC) [redacted]
CC: Shimabukuro, Tom (CDC) [redacted]; Gee, Julianne M (CDC) [redacted]; Anderson, Steven [redacted]
Subject: RE: [EXTERNAL] VaST planning

Hi Lauri,

Steve and I had been thinking about giving an update on April 19. I can give a brief update on April 12 if you think that would be helpful.

Thanks,
--Rich

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <[redacted]>
Sent: Tuesday, April 6, 2021 11:52 AM
To: Forshee, Richard <[redacted]>
Cc: Shimabukuro, Tom (CDC) <[redacted]>; Gee, Julianne M (CDC) <[redacted]>
Subject: [EXTERNAL] VaST planning

Rich,

We had a VaST planning call today with the co-chairs and there was a suggestion that you be on the agenda to present FDA CMS data for the next two weeks (April 12 and 19) -- for any short updates (or longer ones) you might have. Let me know if you have any questions.

Thank you,
Lauri

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

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Monday, April 5, 2021 4:16 PM
To: Baer, Bethany (FDA/CBER) <[redacted]>; Forshee, Richard (FDA/CBER) <[redacted]>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; Wharton, Melinda (CDC/DDID/NCIRD/ISD) <[redacted]>
Subject: VaST - thank you

Thanks to both of you for the clear and informative presentations to VaST today. We will be in touch as we plan the agenda for the coming weeks. Rich, let us know when you might have further data to present from CMS.

Lauri and Melinda

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/6/2021 4:44:53 PM
To: Forshee, Richard [redacted]
CC: Shimabukuro, Tom (CDC) [redacted]; Gee, Julianne M (CDC) [redacted]; Anderson, Steven [redacted]
Subject: RE: [EXTERNAL] VaST planning

Hi Rich,
I think a brief (even verbal) update next week would be good and then a longer one on April 19.
Thank you,
Lauri

From: Forshee, Richard <[redacted]>
Sent: Tuesday, April 6, 2021 12:39 PM
To: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <[redacted]>
Cc: Shimabukuro, Tom (CDC/DDID/NCEZID/DHQP) <[redacted]>; Gee, Julianne (CDC/DDID/NCEZID/DHQP) <[redacted]>; Anderson, Steven (FDA/CBER) <[redacted]>
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VaST Co-Lead

Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

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Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/9/2021 6:53:52 PM
To: Anderson, Steven [redacted]; Bell, Beth [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]; Dooling, Kathleen L (CDC) [redacted]; Edwards, Kathy [redacted]; Farizo, Karen [redacted]; Forshee, Richard [redacted]; Gee, Julianne M (CDC) [redacted]; Hamburger, Tanya (CDC) [redacted]; Helfand, Rita (CDC) [redacted]; Hiers, Susan G (CDC) [redacted]; Hopkins, Bob [redacted]; Jackson, Lisa [redacted]; Kelman, Jeffrey A (CMS) [redacted]; Kulldorf, Martin [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]; 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]
Subject: [EXTERNAL] VaST - Draft minutes and report from April 5 (CONFIDENTIAL)
Attachments: 2021-04-05 - VaST Report Data Table DRAFT.docx; 2021-04-05 VaST Meeting Minutes Draft.docx

Dear VaST members and attendees,

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

The next VaST call is April 12, 1:30 – 3:00 pm EDT. The agenda will include presentations from DoD and updates/analyses from various safety monitoring systems conducted to explore the findings presented to VaST this week.

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

Combined Systems Safety Monitoring Report
DRAFT
April 5, 2021
Confidential

VaST meeting and comments:

The VaST session included a presentation from the Israeli Ministry of Health on post authorization safety monitoring of their Pfizer-BioNTech vaccination program, FDA VAERS data mining, and FDA analysis of active surveillance through CMS.

Israeli Ministry of Health. VaST appreciated the excellent presentation of data from Israel's spontaneous reporting system. The signal for myocarditis that colleagues from Israel described should be further examined in U.S. safety monitoring systems.

FDA VAERS data mining. The data mining presentation was helpful to hear and reassured VaST about the thorough analytic approach to examining the VAERS data.

FDA analyses of active surveillance through CMS. The signal reported in the CMS claims data for pulmonary embolus (PE) for Pfizer-BioNTech needs to be further evaluated and plans are in place to do this. Next week VaST would like to hear plans for further investigation in VSD and VA. VaST agreed with FDA that further signal assessment is needed before this signal is communicated to the public. There have been no signals in VSD to date for any vaccine or prespecified outcome.

Future analyses requested

Data should be examined in other systems not only for PE but also for acute myocardial infarction and for myocarditis (based on data from Israel). In addition, VaST would like to see data on Bell's palsy, venous thromboembolism and cavernous sinus thrombosis. These outcomes should be examined for all three available vaccines and results should be examined for consistency across safety surveillance systems and methods.

Table 1. COVID-19 vaccine monitoring systems reviewed by the VaST – Pfizer BioNTech (recommended for use in persons age ≥ 16 years)

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) (Data through 3/22/2021)	All health events, adverse events of special interest[a]	US population	72,981,111 total doses administered	Descriptive and empirical Bayesian data mining	931 death reports • 148 LTCF death reports • 463 (82%) death reports for those aged 65 or above	Anaphylaxis associated with vaccination, first detected by reports from UK and early reporting in the US; assessed by followup with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021) Deaths less then expected based on background rates (last updated Jan 27)
VA ADERS (Data through 3/23/2021)	All health events	VA employees and Veteran patients	1.7 million doses administered	Descriptive	71 death reports • Median age 78	No concerns raised
DoD VAERS (Data through 3/19/2021)	All health events, adverse events of special interest	Active duty and beneficiaries	976,479 vaccines administered	Descriptive	227 total AE reports • 54 serious AE reports • 7 death reports	No concerns raised
Indian Health Services (IHS)[b]	All health events, adverse events of special interest[a]					
Active Surveillance						
V-safe (Data through 3/13/2021)		Vaccinees who enroll	2,267,127 persons enrolled; 26,091 pregnancies[c]	Descriptive	623 reports overall (all submitted to VAERS) • 57 serious reports • Solicited reactions higher after dose 2 than dose 1	No concerns raised

V-safe Pregnancy Registry (Data through 3/19/2021)		Vaccinees who enroll	1,926 enrolled	Descriptive	Pregnancy and neonatal outcomes of interest within background rates	No concerns raised
Department of Veterans Affairs (VA) Active Surveillance System (Data through 2/27/21)	Pre-specified health outcomes[a]	Veteran Patients	563,937 first doses; 353,565 second doses	Descriptive; historical comparator analysis)	No signals in the analyses for dose 1 or dose 2	No signals as of February 27
Vaccine Safety Datalink (VSD) [b] (Data through 2/27/21)	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	546,507 first doses administered; 248,130 second doses admi nistered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	No signals in analyses for combined mRNA vaccines, combined dose 1 and dose 2	No signals as of February 27
Vaccine Safety Datalink (VSD) Mortality Study (Vaccinated through 2/27 and death data through 3/20/21)	Deaths	VSD sites enrolled in the mortality study; vaccinated before 2/27 and number of deaths before 3/20	219,570 first doses administered; 105,919 second doses administered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	0.8 dose 1 mortality rate per 100 person-years 0.7 dose 2 mortality rate per 100 person-years 1.0 comparator mortality rate per 100 person-years	No signals for death as of March 20
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and Medicaid Services (CMS)[b] (Data through 3/13/2021)	Pre-specified health outcomes[a]	CMS population 65 and above		Historical comparator analysis	Relative risk of 1.21 for AMI, after seasonality adjustment. The RR was not statistically significant. Relative risk of 1.39 for PE, after seasonality adjustment. The RR was statistically significant.	Further investigation from other databases is needed in order to properly assess the signals.

BEST initiative[b]	Pre-specified health outcomes[a]					
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-pfizer-biontech-vaccine.html	

[a]See Table 4 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 2. COVID-19 vaccine monitoring systems reviewed by the VaST – Moderna (recommended for use in persons age ≥ 18 years)

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) (Data through 3/22/2021)	All health events, adverse events of special interest[a]	US population	67,249,447 total doses administered	Descriptive and empirical Bayesian data mining	1,071 pregnancy reports • 132 LTCF death reports • 872 (82%) death reports for those aged 65 or above	Anaphylaxis associated with vaccination, first detected by early reporting in the US; assessed by followup with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021) Deaths less then expected based on background rates (last updated Jan 27)
VA ADERS (Data through 3/23/2021)	All health events	VA employees and Veteran patients	2.05 million doses administered	Descriptive	133 death reports • Median age 83	No concerns raised
DoD VAERS (Data through 3/19/2021)	All health events, adverse events of special interest	Active duty and beneficiaries	852,548 vaccines administered	Descriptive	268 total AE reports • 59 serious AE reports • 10 death reports	No concerns raised
Indian Health Services (IHS)[b]	All health events, adverse events of special interest[a]					
Active Surveillance						
V-safe (Data through 3/13/2021)		Vaccinees who enroll	2,627,416 persons enrolled; 23,064 pregnancies[c]	Descriptive	126 reports overall (all submitted to VAERS) • 27 serious reports • Solicited reactions higher after dose 2 than dose 1	No concerns raised

V-safe Pregnancy Registry (Data through 3/19/2021)		Vaccinees who enroll	1,597 enrolled	Descriptive	Pregnancy and neonatal outcomes of interest within background rates	No concerns raised
Department of Veterans Affairs (VA) Active Surveillance System (Data through 2/27/21)	Pre-specified health outcomes[a]	Veteran Patients	759,473 first doses; 286,128 second doses	Descriptive; historical comparator analysis, Vaccinated and unvaccinated concurrent comparison (to be done)	No signals in analysis for dose 1 Signal for anaphylaxis (n = 4) in second dose recipients	Only signal for anaphylaxis, as identified earlier in other post-authorization safety monitoring
Vaccine Safety Datalink (VSD) [b] (Data through 2/27/21)	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	504,558 first doses administered; 207,408 second doses administered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	No signals in analyses for combined mRNA vaccines, combined dose 1 and dose 2	No signals as of February 27
Vaccine Safety Datalink (VSD) Mortality Study (Vaccinated through 2/27 and death data through 3/20/21)	Deaths	VSD sites enrolled in the mortality study; vaccinated before 2/27 and number of deaths before 3/20	220,799 first doses administered; 86,650 second doses administered	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	0.6 dose 1 mortality rate per 100 person-years 0.7 dose 2 mortality rate per 100 person-years 1.0 comparator mortality rate per 100 person-years	No signals for death as of March 20
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and	Pre-specified health outcomes[a]	CMS population 65 and above		Historical comparator analysis	No signals in the analysis	No signals as of April 2

Medicaid Services (CMS)[b] (Data through 3/13/2021)						
BEST initiative[b]	Pre-specified health outcomes[a]					
Vaccine Trials (Manufacturer)					See GRADE tables https://www.cdc.gov/vaccines/acip/recs/grade/covid-19-pfizer-biontech-vaccine.html	

[a]See Table 4 for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]at the time of vaccination

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

Vaccine Safety Program	Outcomes Monitored	Population Monitored	Population captured	Analyses	Selected Results	Assessment/action
Passive Surveillance						
Vaccine Adverse Event Reporting System (VAERS) (Data through 3/22/2021)	All health events, adverse events of special interest[a]	US population	3,090,712 total doses administered	Descriptive and empirical Bayesian data mining	18 death reports • 1 LTCF death report • 13 (72%) death reports for those aged 65 or above	No concerns raised
VA ADERS (Data through 3/23/2021)	All health events	VA employees and Veteran patients	Data not yet available	Descriptive	1 death report	
DoD VAERS (Data through 3/19/2021)	All health events, adverse events of special interest	Active duty and beneficiaries	28,640 vaccines administered	Descriptive	4 total AE reports • 0 serious AE reports • 0 death reports	No concerns raised
Indian Health Services (IHS)[b]	All health events, adverse events of special interest[a]					
Active Surveillance						
V-safe (Data through 3/13/2021)		Vaccinees who enroll	74,609 persons enrolled; 498 pregnancies[c]	Descriptive	No serious reports	No concerns raised
V-safe Pregnancy Registry (Data through 3/19/2021)		Vaccinees who enroll	Data not yet available	Descriptive		
Department of Veterans Affairs (VA) Active Surveillance System	Pre-specified health outcomes[a]	Veteran Patients				

Vaccine Safety Datalink (VSD) [b]	Pre-specified health outcomes[a]	Patients enrolled in participating health care organization	Data not yet available	Descriptive; Sequential analysis will be added when available	Data not yet available	
Vaccine Safety Datalink (VSD) Mortality Study (Vaccinated through 2/27 and death data through 3/20/21)	Deaths	VSD sites enrolled in the mortality study; vaccinated before 2/27 and number of deaths before 3/20	Data not yet available	Descriptive; Vaccinated and unvaccinated concurrent comparison, sequential analyses	Data not yet available	
Defense Medical Surveillance System (DMSS)[b]	Pre-specified health outcomes[a]					
FDA - Centers for Medicare and Medicaid Services (CMS)[b]	Pre-specified health outcomes[a]	CMS population 65 and above		Historical comparator analysis	Data not yet available	Data not yet available
BEST initiative[b]	Pre-specified health outcomes[a]					
Vaccine Trials (Manufacturer)					See GRADE tables [HYPERLINK "https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/03-COVID-Gargano.pdf"]	

[a]See Table 4. for the complete list of health outcomes
[b]Data are currently being processed and will be reported when received
[c]At the time of vaccination

Table 4. Health systems and pre-specified health outcomes

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

Optic neuritis (ON)	x[1,2]				
Seizures / convulsions (convulsion is now an LLT under PT seizure)	x	x			x
Stroke	x	x		x	x
Thrombocytopenia	x				
Transverse myelitis (TM)	x	x		x	x
Vaccination during pregnancy/adverse pregnancy outcomes	x				x
Venous thromboembolism (VTE)	x	x			-
Pulmonary embolism	-	x		x	x
Deep vein thrombosis	-	-		x	x

[1]Health outcomes are counted, but adverse event reports are not abstracted
[2]Diagnoses are grouped and reported as "Other clinically serious neurologic AEs" in VAERS
[3]Health outcomes are counted, and no sequential analysis is conducted
[4]Only includes narcolepsy
*TBD

VaST meeting notes - DRAFT
April 5, 2021
Confidential

Presentation slides were distributed; presentations are only briefly summarized in meeting notes. Chat notes not answered verbally on the call are available but have not been incorporated into the minutes.

Participants

Expert consultant members: Beth Bell, Kathy Edwards, Mat Daley, Bob Hopkins (Co-Chair), Lisa Jackson, Grace Lee (Co-Chair), Veronica McNally, Rob Schechter, Keipp Talbot, Patricia Whitley-Williams

Ex officio and liaison members: Tatiana Beresnev, Matthew Clark, Limone Collins, Karen Farizo, Jeff Kelman, Martin Kulldorf, Mary Rubin, Judith Steinberg, Hui Lee Wong

CDC: Karen Broder, Tom Clark, Rita Helfand, Susan Hiers, Kathleen LaPorte, Lauri Markowitz (CDC Co-lead), Michael McNeil, Tanya Myers, Sara Oliver, Eddie Shanley, David Shay, Tom Shimabukuro, Mark Sotir, John Su, Eric Weintraub, Melinda Wharton (CDC Co-lead), Jared Woo

Technical SMEs: Steve Anderson, Bethany Baer, Fran Cunningham, James Donahue, Bruce Fireman, Richard Forshee, Kristin Goddard, Kayla Hanson, Ned Lewis, Narayan Nair, Ousseny Zerbo

Israel Ministry of Health: Deniz Ainbinder, Emilia Anis, Dana Arad, Noa Cedar, Michal Hirsch, Lital Keinan, Sharon Olsha, Hadas Rotem

Agenda

- Administrative issues and announcements
- Israel's Covid-19 vaccine safety monitoring
- FDA methods for data mining
- FDA CMS Rapid Cycle Analysis (RCA)
- VSD and VA RCA and overview of plans

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

- Reminders about COI and confidentiality
- VaST meetings expectations and procedures overview
- Doses distributed: 207,891,295; Doses administered: 165,053,746 (last updated: April 4)
    - Doses distributed: Pfizer-BioNTech: 105,077,895; Moderna: 94,119,599; J&J/Janssen: 8,693,900
    - Doses administered: Pfizer- BioNTech: 84,810,406; Moderna: 76,038,9333; J&J/Janssen: 4,054,089; Unknown: 150,318
    - First doses: 106,214,924; Fully vaccinated: 61,416,536
    - These data are posted on the CDC website and are updated regularly ([HYPERLINK "https://covid.cdc.gov/covid-data-tracker/" \l "vaccinations).%E2%80%AF" \t "_blank"]

Data from Israel's spontaneous reporting system – Dr. Emilia Anis, Israeli Ministry of Health

Dr. Anis presented on adverse events, hospitalizations, and deaths following vaccination. The Israel Ministry of Health analysis included data from hospital, HMO, emergency medical services (nursing home), medical department, and the military. Vaccine coverage for age groups 50-59, 60-69- 70-79, 80-89, and 90+ is above 80% for first and second doses while 20-29, 30-39, and 40-49 age categories have above 60% coverage.

Women and younger individuals were more likely to report adverse reactions following vaccination relative to their proportion among the vaccine recipient population. Systemic reactions were more common after the second dose; local reactions were more common after the first dose.

There were 62 reports (first dose: 6; second dose: 56) of myocarditis and 15 reports (first dose: 5; second dose: 10) of pericarditis. There were 77 hospitalizations reported after the first dose and 95 after the second dose. There were 48 deaths reported within 30 days of vaccination, of which 42 reports were within 10 days. There is no specific signal associated with all causes of death and specifically sudden death.

Questions and discussion

1. For Bell's Palsy, why are there more expected after dose 1 compared to dose 2?
    - The expected number for the first dose is calculated for a period of 3 months while for the second dose for a period of 2 months. The higher number reported after the first dose compared with the second dose could be due to underreporting after the second.
2. Do you have information on expected background rates of myocarditis in young adults?
    - Background data should be available within 3 weeks
3. Were most of the myocarditis cases reported from the military? Or were they reported in all the surveillance groups?
    - They were reported from all sources (i.e. hospitals, military, etc.)
    - In all groups, most frequently in young men aged 16 to 30 years.
4. What data sources will you have available to determine background rates of myocarditis, particularly in males aged 19-29 years?
    - Background data from hospitals and from the army
7. Did the myocarditis patients have elevated troponins and also EKG changes?
    - Yes. ECG changes, elevated troponin, and positive MRI. Also, three had a heart biopsy.
5. Were there individuals who recently had COVID-19 infection?
    - They were in the minority. They used antibody tests to see if they were exposed and most did not have vaccine after COVID. The 2nd dose was associated with higher antibody titers.
8. Are the death reports spontaneous reports?
    - Yes, they are reports are made by the medical staff.

FDA VAERS data mining – Dr. Bethany Baer, FDA

Dr. Baer presented on FDA VAERS data mining, which attempts to identify any adverse events that are disproportionally reported for one vaccine compared to other vaccines. This is done by comparing the number of reports of an adverse event after a vaccine with number of reports for that adverse event after all vaccines in VAERS.

Multi-item Gamma Poisson Shrinker is used to analyze VAERS and the Empiric Bayes Geometric Mean (EBGM) is calculated. The model is adjusted by age (6 categories), gender, and year received. The standard threshold for significance is EB05 is greater than 2. The main limitations include that it is a hypothesis generating tool, absence of disproportionality does not confirm the absence of a signal, passive reporting of data in VAERS.

Questions and discussion

1. Adjusting the numbers to the pandemic? Is underreporting stable over calendar time? Is there a way to qualitatively or quantitatively adjust?
    - Currently the standard adjustment is by year of receipt. Moving forward, they will explore different adjustments and different backgrounds
2. What are the current findings for death, myocarditis, and Bell's palsy?
    - Currently, all have an EB05 < 2.
    - The following information was provided by Dr. Baer after the call: The preferred terms of "death," "myocarditis," and "facial paresis" were used and all had an EB05 ≤ 1.0 for the 3 COVID vaccines on the US weekly vaccine data mining run (adjusted for age, gender, and year of report receipt; data lock point 4/1/2021). These results are subject to many limitations, as discussed during the VaST meeting on 4/5.

FDA analyses of active surveillance through CMS – Dr. Richard Forshee, FDA

Dr. Forshee presented historical comparator analysis of pulmonary embolism (PE) and acute myocardial infarction (AMI) using CMS data for adults aged 65 years and older. Background rates are standardized for nursing home (Y/N), age, sex, and race.

For Pfizer-BioNTech, AMI and PE had an association that met the threshold for further QC and sensitivity analysis. After seasonality adjustment (RR decreased from 1.56 to 1.39), PE remained statistically significant. Further analyses are being considered to determine the validity of the signal.

Questions and discussion

1. Does seasonality adjustment mean that the prior background rate based on annual data was switched to a background rate based on data for the relevant season?
    - Yes, the January-March time period is used for the seasonality analysis.
2. Did any of the AESI besides PE achieve a significant level?
    - No, only PE for Pfizer-BioNTech.
3. Did you exclude patients with recent COVID-19 infection?
    - Claims diagnosis codes are used, but a big limitation is that asymptomatic cases cannot be excluded.
4. Will you assess other windows besides 28 days?
    - Only 28-day windows for now. The FDA is planning on a temporal scan analysis for clustering.
    - It was suggested that variable length follow-up be investigated when doing the temporal scan analysis
5. Does 365-day clean window include high risk predisposing/associated factors? e.g. prior VTE or anticoagulation for PE
    - Only for AMI and PE.

6. It might be interesting to know if the increased rate of PE in 2021 was present among unvaccinated people with and without history of COVID-19.
7. Are the PEs in all settings? And all are based on ICD-10 diagnoses (not based on imaging)?
    - They include inpatient, outpatient, and provider claims. These are based on ICD-10 codes.
    - Seems like PE in outpatient settings might be less likely to be a true incident case; it may reflect that a patient is being evaluated for PE but not necessarily confirmed, whereas a hospital code is likely more specific.
8. Were nursing home patients included?
    - Yes, there was an adjustment for nursing status because of higher AMI and PE risk.
9. What is the timeline for when the signal can be confidently assessed?
    - Currently looking into medical records
    - Looking into more claims data

VSD and VA RCA and overview of plans – Drs. Tom Shimabukuro, CDC, and Fran Cunningham, VA

Drs. Tom Shimabukuro and Fran Cunningham provided brief overview of plans for exploration of this CMS signal in VSD and the VA RCA. These will be presented at the call next week.

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/12/2021 2:45:13 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]; Dooling, Kathleen L (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]; Kulldorf, Martin [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]; Mullen, Jennifer (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]; 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]
Subject: [EXTERNAL] VaST - Agenda for April 12 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL
Attachments: 2021 Apr 12 Myocarditis COVID-19 Vaccines Engler-Finalv5 10slides.pdf; MPC Following mRNA SARS-CoV-2 Vaccines VaST 20210411.pdf; VAERS for VaST 12 Apr 2021_mod1.pdf; VSD RCA Covid-19 vax - update VaST - 04-12-2021-final.pdf; Department of Veterans Affairs COVID-19 RCA 04-12-21_Final.pdf; 2021_04_12 VaST Meeting Agendav2.docx

Dear all,

This email includes the VaST agenda for today (below and attached) as well as slide sets. The agenda attached has more information regarding approximate times for talks and discussion.
There has been a change in the agenda and although the slide presentations from the VA and VSD RCAs are included here, those are for information only and will be presented/discussed on a future call.

Agenda:
Emerging Issues (Dr. Shimabukuro, CDC)
DoD myocarditis cases (Drs. Jay Montgomery and Renata Engler, DoD)
VAERS update (Dr. John Su, CDC)
Discussion

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

Further Considerations Related to Cluster of Cases Consistent with Hypersensitivity Myocarditis in Temporal Association with COVID-19 Vaccines in the Context of Lessons Learned

Renata J. M. Engler, MD, FACAAI, FAAAAI, FACP
COL (retired), Medical Corps, USA)
Consultant, DHA Immunization Healthcare Division
Red Cross Volunteer, Allergy-Immunology-Immunization, Walter Reed Bethesda
Professor, Medicine and Pediatrics (Secondary)
Uniformed Services University of the Health Sciences
Presentation Date: 2021 April 12
Questions: [redacted]
and [redacted]
[redacted] *(Cell and text)*

Disclaimer/Non-Disclosure Agreement

The views presented are those of the speaker/author and do not necessarily represent the views of the Department of Defense or its components.

This presentation contains confidential pre-publication case information intended for internal use by CISA. No material in this presentation may be used or distributed without permission of the authors.

Representative Case #1
Additional Considerations for Causality Assessment

- **Overview of Case Presented by Dr. Montgomery: Added Data Review for Dx Exclusions, FU**
- **Initial Laboratory Data: 24-25 Jan 2021 (Vaccine Date: 21 Jan 2021)**
  - Troponin T Gen5 (ng/L) nl range 0-19: sequential: 493.5 → 662 → 602.3 → 29.9 (28 Jan)
  - C-Reactive Protein: 1.520 mg/dL (0.000-0.500) → normalized to 0.07 mg/dL by 28 Jan
  - CBC: Hct/Hgb 41.1%/13.9 g/dL; Platelets **148→150X10^3** (166-407); differential % normal except for **eosinophil count** (6.4%) with **absolute eos counts: 400→600/mcL (0-400**). Note: absolute counts/mcL: neutrophil ct 3100 lymphocyte ct 3100, monocyte ct 1300, with basophil ct 100.
  - Lipid panel mg/dL: Chol 137, Trigl 125, HDL 41; Chol/HDL 3.3; LDL 79; Chol Non-HDL 96
  - **Normal or Negative**: Drug screening panel; TSH; broad infectious disease screening (see table); metabolic panel; magnesium; creatinine; nuclear antibody (IFA); Antimyocardial Ab (sarcolemma, intermyofibrillar)
- **Chest X-Ray:** Normal with no mediastinal adenopathy, infiltrates or cardiomegaly
- **Transesophageal Echocardiogram**: normal ejection fraction with no structural abnormalities
- **Coronary angiography (2021 Jan 24)**: normal coronary arteries with EF 60-65%
- **Cardiac MRI**: Diagnostic for Myocarditis as detailed earlier
  - Sarcoidosis considered “but unlikely in absence of mediastinal or hilar adenopathy” and normal CXR

Infectious Disease Screening 2021

Date 2021	Testing	Assay	Result			
Jan 25-6	EBV Virus Ig	Capsid IgG U/mL Capsid IgM Nuclear IgG	**40.3 (H)** <36.0 **84.1 (H)**	HSV 1+2 Glycoprotein	HSV1 IgG Index HSV2 IgG	**27.60 (H)** <0.91
	HIV-1+2 Ag/Ab		Negative	Coxsackie B1-6	B1 B2	Negative Negative
	HHV 6	DNA + IgM titer;G index	NEG;<1:20;<0.90		B3	Negative
	CMV	IgG AU/mL IgM	**8 (H)** <30		B4 B5	Negative Negative
	HSV 1+2	IgM ratio	<0.91		B6	Negative
	Parvovirus B19	IgG Index IgM	**2.6 (H)** 0.1	RPR	Reagin Ab	Non-Reactive
	Respiratory Panel	**Nasopharynx swabs**		Hepatitis C	Antibody	Negative
	Coronavirus RNA	HKU1,229E,	NOT detected	Coronavirus	NL63, OC43	NOT detected
	Metapneumovirus	PCR	NOT detected	Adenovirus	DNA	NOT detected
	Influenza A	RNA	NOT detected	Influenza B	PCR	NOT detected
	Parainfluenza	RNA: 1, 2, 3, 4	NOT detected	Rhinovirus	Enterovirus RNA	NOT detected
	Bordetella pertussis	+parapertussis DNA	NOT detected	Chlamydophilia	Pneumoniae DNA	NOT detected
	Mycoplasma	Pneumoniae DNA	NOT detected	Respiratory	Syncytial RNA	NOT detected
	SARS CoV2	RNA	NOT detected			

Applying Case Definition Used for Smallpox Vaccine Myocarditis/Pericarditis

- **Probable Myocarditis with no Other Etiology Identified but no Histology (2003 Criteria)**
  - **Given positive cardiac MRI**: Discussion that this should be a **Confirmed case of Myocarditis in temporal association with COVID-19 Vaccine**
  - NO evidence of other etiologies associated with myocarditis
  - **Temporal association with vaccine doses: Day 22 after 1st dose, 8-10 hours after 2nd dose**
- **Cardiology Feb 5 (Day 15): recurrence of symptoms → started high dose aspirin again**
  - Meds: continue colchicine 0.6 mg 2X/day, aspirin 975 mg 3X/day (restart) and pantoprazole 20 mg
  - EKG: HR 80; NSR; PR 126; QRS 82; QTc 410; new TWI in leads II, III, aVF and V6
  - HS Troponin T Gen5: 7.8 ng/L (down from 29 at discharge)
- **Allergy-Immunology-Immunization Healthcare – March 5 (Day 43)**
  - Ongoing mild exercise associated chest pain symptoms persist
    - *3 flights of stairs slowly limit; Walking briskly for 10 min or more*
  - History of possible allergic rhinitis in certain geographic locations (no skin testing to date)
  - 15Mar21 Labs: CBC normal HCT/Hgb (44.6/14/6); WBC 11.0 (Abs$X10^3$: PMN 6.2; Lymp 3.5; mono 0.9)
- **Review of Systems: Comprehensive** 5Mar21 unremarkable except for musculoskeletal and documented symptoms related to dyspnea and chest pains primarily with mild exercise

Historical Perspectives on Myocarditis After Smallpox (SPV) Vaccine

Data Source	N=	# Cases	Percent %	1 in
Historical Data[1]				
New York - 1947	~6,000,000	1	0.00002%	~50,000
Finland 1877-1879	60,000	10	0.02%	~5,000
CDC-Dryvax ®-2004 (Epi)	40,449	21	0.05%	~2,000
DoD-Dryvax 2004 ®- (Epi)[2]	**~1,200,000**	**140**	**0.01%**	**~10,000**
Prospective Studies[1]				
Helle (Finland) 1974	234	8	3.4%	~30
Ahlborg (Sweden) 1963	286	3	1.0%	~100
Acambis FDA Data[2003-4]	*All Studies*		*15 punctures*	
Acambis-Dryvax®-All[1]	868	3	0.35%	~289
Acambis-ACAM2000®-All[1]	2983	7	0.23%	~426

DoD-MHS Experience:

Retrospective Epidemiologic Studies using case clusters well characterized by a network of clinical experts in AEFI evaluation and care support

- **Relative Risk** compared to pre-vaccine population incidence: 7.46-fold (6.89, 8.48) Am J Epidemiol. 2004; 160:642-51.

Prospective Study of 1081 vaccinees (2004-2012)

- **Incidence** of Clinical Post-Vaccine MPC: **4.63 per 1000** (95% CI 1.50-10.79) compared to 2.2 per 100,000 (1.3 million) with **RR 214** (95% CI: 65, 558) [**NOTE**: similar to ACAM2000® data]
- **Incidence of new onset cardiac symptoms** in the window of risk compared to cohort to FLU vaccine recipients: **10.6% versus 2.6%** (p<0.001)
- **Incidence of impacting cardiac symptoms** (VAS>3/10 severity) lasting more than 2 days: **8.8% versus 1.6%** (p<0.001)

PLoS One. 2015 Mar 20;10(3):e0118283.

- *Unpublished data: blinded Half-dose Flu study is consistent with these frequencies*

[1] Data Source: FDA-VRBPAC Meeting 2007 May 17

[2] Military Health System/DoD Experience and Legacy IHB (Vaccine Healthcare Centers Network)

Vaccine Side Effects: Case Definition for New Onset Cardiac Symptoms
Majority of Vaccine Safety Studies do NOT Itemize as Separate Side Effect

How frequent are new onset post-vaccine cardiac symptoms (chest pain, dyspnea at rest or with exertion, palpitations) on day 4-30 following SPV versus TIV (influenza)?

Epidemiologic case definitions for post-SPV MPC (confirmed, probable, suspect) includes any cardiac symptoms. (MMWR 2003;52:492-6)

Randomized Blinded Full versus Half-Dose TIV Study Incident rate of new onset chest pain (day 1-3 post) with severity >6/10 on the VAS (Visual Analogue Scale) with at least 2 days of pain (*unpublished data*)

- ✓ **Full Dose TIV** (N=638): 1.1%
- ✓ **Half Dose TIV** (N=631): 0.16% (P<0.05)

[Any new onset chest pain >4/10 VAS: 2.1% vs 0.95%]

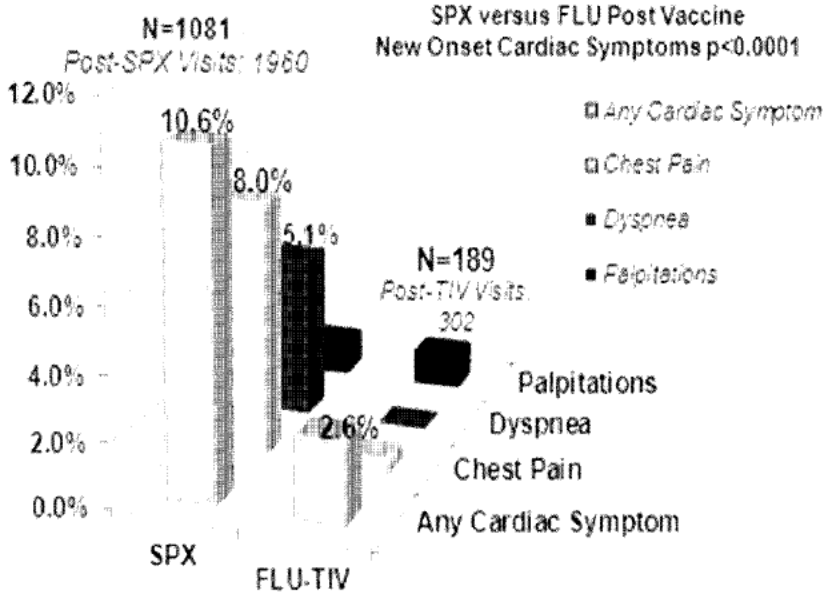
Arch Intern Med 2008;168(22):2405-14)

VAERS COVID-19 vaccines (all): Military, Dec 20-Mar 31 with CHEST PAIN (18-59 years, Onset 0-30 days): 24/695 (4.9%) Male 20/314 (6.4%): Female 14/378 (3.7%) [using CDC Wonder]

Disclaimer: NOT incidence data

Prospective Observational Study

Incidence of New Onset Cardiac Symptoms
Pre-Post Smallpox (SPX) versus FLU-TIV Vaccine

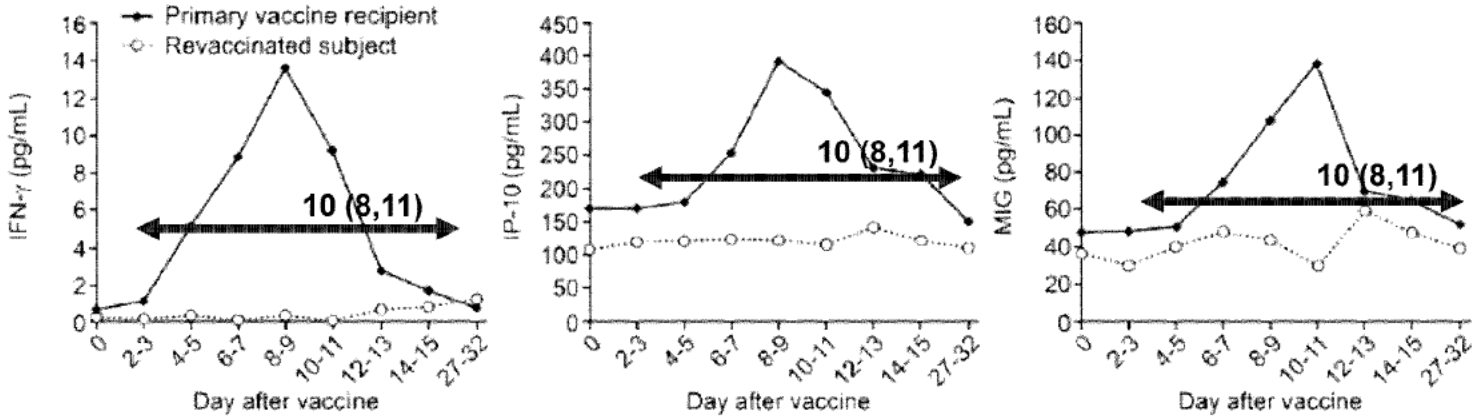


PLoS One. 2015 Mar 20;10(3):e0118283. https://pubmed.ncbi.nlm.nih.gov/2579370

Serial Cytokine Measurements in Smallpox (SPV) Vaccinees (N=42)
Significant Correlations Between Symptoms & Patterns of Serum Cytokines

J Infect Dis 2010;201 (15 April): 1183-1191.

DoD IHD/DHA MPC Registry
Vaccine Date: 2002-2016
>2.4 million doses
348 cases MPC adjudicated
Probable or Confirmed: 296
Days to Cardiac Symptoms
Median: 10 IQR: 8, 11
Range: 1-35



Peak Levels in Primary Naïve Vaccinees (days)

1. **IFN-g**: interferon-g (8-9);
2. **IP-10:** IFN-inducible protein–10 (8-9);
3. **MIG** (CXCL9)**:** monokine induced by interferon-g (10-11);
4. **IL-6:** interleukin-6 (8-9);
5. **G-CSF:** granulocyte colony-stimulating factor (6-7);
6. **GM-CSF**: granulocyte-macrophage colony-stimulating factor (12-13);
7. **sICAM-1:** soluble intercellular adhesion molecule–1.

NO Inquiry about chest pain/dyspnea: N=42
N=27 Naïve 1st Dose: Majority with symptoms

Symptom	**Headache 70%** Cytokine (*P* value)	
Fatigue	IFN-γ ($P < 0.002$), IL-6 ($P < 0.001$), and IP-10 ($P < 0.001$), MIG ($P < 0.001$) and G-CSF ($P = 0.006$)	**96%**
Lymphadenopathy	IFN-γ ($P < 0.001$) and IP-10 ($P = 0.009$)	**89%**
Myalgia	IFN-γ ($P = 0.008$), MIG ($P < 0.001$), and G-CSF ($P < 0.002$)	**63%**
Pruritis	sICAM-1 ($P = 0.004$)	
Chills	G-CSF ($P < 0.001$) and GM-CSF ($P < 0.001$)	

V-safe After Vaccination Health Checker

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html

- **New Individualized App to Monitor Symptoms and Health Status**
  - NO mention of cardiac symptoms in list of side effects: chest pain, shortness of breath, palpitations
  - Missed opportunity to collect possible cases of cardiac adverse events as many individuals lump chest pain into myalgias (muscle aches)
- **VRBPAC Meeting 10 Dec 2020:** PFIZER-BIONTECH COVID-19 VACCINE (BNT162, PF-07302048)
  - Adverse Events Reported in >1%: Fatigue (5.5% vs 1.4%), **Myalgia (4.8% vs 0.7%),** Arthralgia (1.1% vs 0.4%)
  - Subjects reporting at least **1 serious adverse event** from Dose 1 to 1 month after dose 2
    - *Chest pain: 1 case out of 18,801 with comparable report in placebo*
    - *Non-cardiac chest pain: 1 in vaccine cohort non in placebo*
  - QUESTION: are cases of new onset chest pain, shortness of breath hidden in the side effect group and just considered part of the background systemic myalgias, fatigue bucket?
- **Historical Perspective**: No cardiac symptoms itemized/described in most of the early smallpox vaccine publications that included side effects descriptions → Believed to be very rare and not a problem with US strain only with the European Lister strain.
  - **If you do not ask, you will not see it, but does that mean it does not exist?**

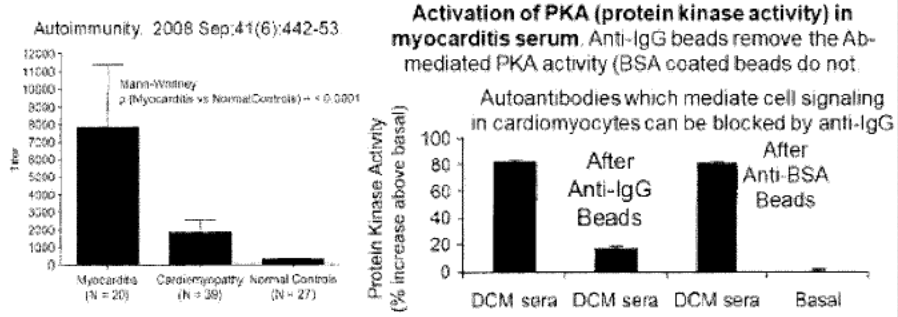
Critical Questions for Evolving Vaccine Safety Surveillance And Possible Case Evaluation Needs - 1

- **Possible Subclinical Myocarditis is NOT Rare** (*PLoS One. 2015 Mar 20;10(3):e0118283.)*
  - Prospective study of 1081 health young subjects receiving the SPV for the 1st time
    - *31/1081: Pre-to-post vaccine increases in cardiac specific troponin (not high sensitivity)*
      - Case definition created with Dr. Leslie Cooper and Allen S. Jaffe at Mayo Clinic
        - cTnT elevations ≥0.02 ng/mL with the pre-vaccine level <0.01 ng/mL OR pre-to post change (run in the same assay) of 0.02 ng/mL increase from baseline.
        - There were no cases in the TIV prospective study cohort.
    - Incidence per 1000 vaccinees*: 28.68 (95% CI 19.5-40.7) compared to TIV 0 (95% CI 0-19.5): P=0.016*
- **Prevalence & Findings of Subclinical Influenza Infection-associated Cardiac Abnormalities**
  - Japanese patients: 102 with influenza were enrolled for ECG, ECHO, cardiac enzymes
    - *21.6% (22) had cardiac findings: ST-T abnormalities, pericardial effusion, diastolic dysfunction, and cardiac enzyme elevation.*
    - *5 had mild elevation of CKMB but none had troponin elevation (assay details not provided)*
    - *18/22 were retested 14 days later: 11/18 resolved all findings*
- **Literature on Autopsy Data of Young People Post Trauma – shows patchy scarring in the myocardium consistent with past myocarditis, resolution and only mild injury** *(undiagnosed)*
  - Communication from Dr. Leslie Cooper

Critical Questions for Evolving Vaccine Safety Surveillance And Possible Case Evaluation Needs - 2

- **Hypersensitivity Myocarditis and Infection Associated Myocarditis Severity**
  - Evolving data that auto-antibodies against myosin and beta-adrenergic receptors are pathogenic in these settings. *Autoimmunity. 2008 Sep;41(6):442-53.*
    - *Under study in the setting of SARS-CoV-2 infection associated myocarditis*
    - *Myocarditis serum → Activation of PKA (protein kinase) in cardiac myocytes (in-vitro) induces cell death; Anti-IgG beads remove the antibody mediated PKA activity while BSA coated beads do not.*
  - Could testing for these autoantibodies enable identification of cases benefiting from corticosteroid therapy to preserve and/or reverse decreased cardiac function (ejection fraction) without need for a biopsy?
    - *Goal: provide reassurance that if this occurs, successful treatment is available*

Biologic Activity of Cardiac Autoantibodies



Myocarditis (any cause) as well as progressive disease & dilated cardiomyopathy (DCM):

- Specificity of IgG Abs mediating PK activation demonstrated through in-vitro stimulation and inhibition assays
- Ab quantitative levels significantly higher in MPC than DCM
- Mouse model of autoimmune myocarditis using cardiac myosin as antigen

Autoantibodies may also play a role in POTS disease (dysautonomia)

Challenges Going Forward with COVID-19 Vaccines and Cardiac Symptoms as well as Myocarditis/Pericarditis (MPC) Association

- **Incidence of cardiac symptoms post COVID-19 vaccines: unknown → add to V-Safe app**
  - New onset chest pain, exercise &/or positional associated pain and/or shortness of breath, palpitations
- **Type of Vaccine:** Does this occur more frequently with one vaccine than another?
- **Risk factors for development of MPC**
  - Suggested in MPC and smallpox vaccine experience: atopy, 1-2 cardiovascular disease risk factors (excluding tobacco use), other drug hypersensitivities
- **Response to steroids with focus on normalizing severe reductions in ejection fraction**
  - Dramatic responses seen with severe post-SPV experience → is biopsy always required for use?
  - Mayo Clinic case report: Lancet. 2003 Oct 25;362(9393):1378-80
- **Autoimmunity:** Are the **biomarkers anti-myosin and anti-beta adrenergic receptor autoantibodies** increased in patients with post-vaccine MPC? Is it factor for other MPC cases?
  - Is it present before the vaccine is administered?
- **Outcomes: Specifics of Recovery and Risks of Delayed Complications**
  - Ventricular tachycardia, cardiomyopathy, death, delayed arrhythmias
- **Communication of Relative Benefit-Risk → Disease Cardiac Risk → HIGHER than vaccine**
  - **Danger**: literature with other drug eosinophilic hypersensitivity myocarditis can be scary ("life-threatening") and is NOT the experience with most vaccine associated case reports in the literature – **treatable!**

Update on Myopericarditis and Cerebral Venous Sinus Thrombosis after COVID-19 Vaccines Reported to the Vaccine Adverse Event Reporting System (VAERS), Dec 14, 2020 – Apr 5, 2021

John R. Su, MD, PhD, MPH

Apr 12, 2021

Myopericarditis

Case Definition*

Myocarditis

≥1 of the following is present:
- Elevated cardiac enzymes
- Imaging showing decreased left ventricular function

AND ≥1 of the following is present:
- Dyspnea
- Palpitations
- Non-pleuritic chest pain

AND ≥1 of the following is present:
- ST- or T-wave abnormalities
- Atrial or ventricular arrhythmia
- Conduction delays or blocks
- Frequent atrial or ventricular ectopy

Pericarditis

1 of the following is present:
- Pericardial rub
- EKG with diffuse ST elevation, or PR depression without reciprocal ST depression
- Echocardiogram showing an abnormal collection of pericardial fluid (effusion)

AND
- Pleuritic chest pain without another attributable cause (e.g., pneumonia)

* Histopathology evidence (e.g., biopsy, autopsy) of myocardial or pericardial inflammation = "confirmed" case (from *MMWR* (May 30, 2003)

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AND

- Pleuritic chest pain without another attributable cause (e.g., pneumonia)

* Histopathology evidence (e.g., biopsy, autopsy) of myocardial or pericardial inflammation = "confirmed" case (from *MMWR* (May 30, 2003)

* * meeting either case definition = "case" of myopericarditis for VAERS

Reported myopericarditis (N=97) — demographics*

	Pfizer-BioNTech (n = 43)	Moderna (n = 54)	Total (N = 97)
Median age, years (range)	40 (21 to 84)	33 (18 to 84)	36 (18 to 84)
Median time to symptom onset, days (range)	3 (day of vaccination to 34)	3 (day of vaccination to 33)	3 (day of vaccination to 34)
Male	21 (49%)	34 (63%)	55 (57%)
Female	21 (49%)	19 (35%)	40 (41%)
Not reported	1 (2%)	1 (2%)	2 (2%)
After Dose 1; Dose 2**	14; 21	25; 25	39; 46

*processed as of Apr 5, 2021; 0 reports after Janssen's vaccine

** of reports with dose number data available

Reported myopericarditis (N=97) – by abstraction status*

Complete	Case** (n = 21)	Not a case (n=18)	Total (n = 39)
Pfizer-BioNTech	10 (50%)	10 (50%)	20 (100%)
Moderna	11 (58%)	8 (42%)	19 (100%)

Incomplete[1]	Case** (n = 22)	Not a case (n=36)	Total (n = 58)
Pfizer-BioNTech	8 (35%)	15 (65%)	23 (100%)
Moderna	14 (40%)	21 (60%)	35 (100%)

*processed as of Apr 5, 2021; no reports after Janssen's vaccine ** "case" = met case definition

[1] pending review of medical records to confirm reported signs, symptoms, and diagnostic test findings

Observed vs expected reporting rates

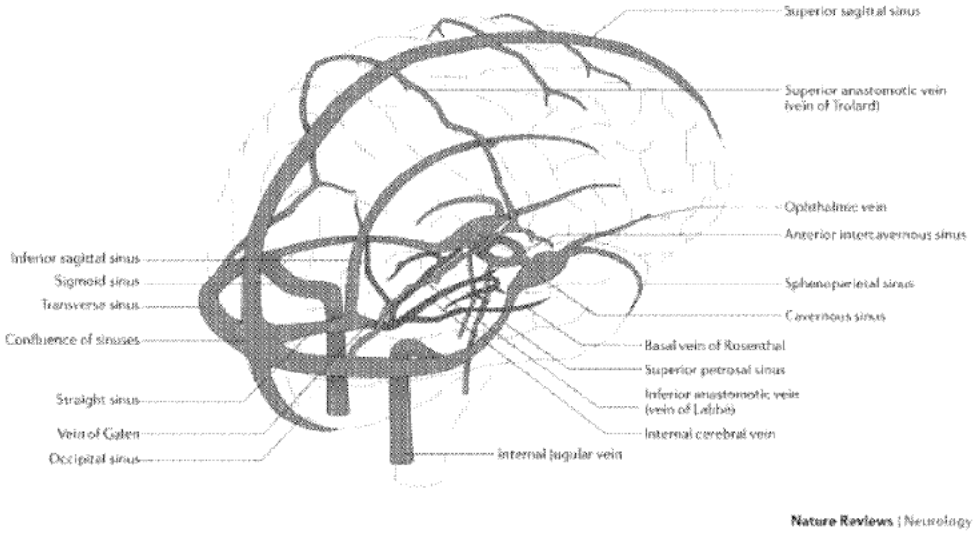
- Estimated annual incidence of myopericarditis ~ 1 to 2 per 100,000 population*
- Assumed risk period of 15.3% (Pfizer) and 14.4% (Moderna) of a calendar year
- Assume doses administered = vaccinated population, adjusted for proportion by dose number
    - As of Apr 11, 63% of Pfizer was Dose 1; 64% of Moderna was Dose 1
- Expected background myopericarditis after Pfizer
    - After Dose 1 = **86 cases** (**14** cases reported)
    - After Dose 2 = **50 cases** (**21** cases reported)
- Expected background myopericarditis after Moderna
    - After Dose 1 = **71 cases** (**25** cases reported)
    - After Dose 2 = **40 cases** (**25** cases reported)
- **Reported cases of myopericarditis after COVID-19 vaccines do not exceed anticipated background cases**

* Systematic review; manuscript submitted; separate estimates for myocarditis and pericarditis not available

Cerebral venous sinus thrombosis (CVST)

CVST – a brief background

- Thrombosis within large vessels draining blood from the brain
- Est ~ 5,000 cases annually*
- Mostly among people 20–50 years of age; female
- Risks: pregnancy, usual coagulation risks (e.g., OCPs)
- Symptoms typically include headache, nausea, vomiting, other neurologic symptoms
  - Presentation acute → weeks, months



* http://www.med.umich.edu%2F1libr%2FStroke%2FSinusVeinThrombosis.pdf&usg=AOvVaw3qjvm4UOFcHN-eR4O3Kyf8

CVST after COVID-19 vaccines

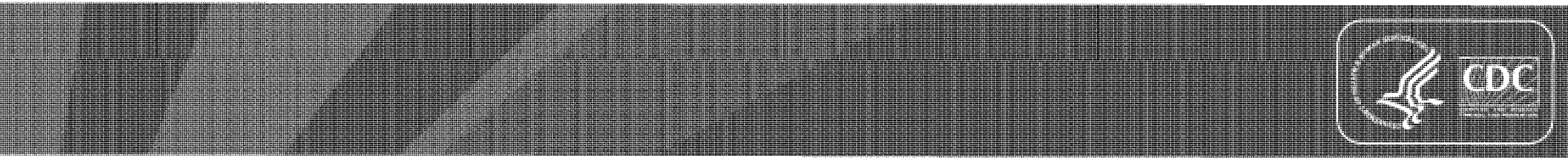
- As of Apr 10,
  - 94,715,143 doses of Pfizer's vaccine administered – no reports of CVST
  - 82,622178 doses of Moderna's vaccine administered – 3 reports of CVST
  - 5,972,101 doses after Janssen's vaccine – 6 reports of CVST
    - Median age = 33 years (range: 18 to 48)
    - Median time to onset = 9 days (range: 2 to 16)
    - All 6 reports among females
    - 1/6 (+) OCP use; no other risk factors identified
- Obtaining medical records; continuing surveillance

Thanks!

Acknowledgements

VAERS Team and deployed abstractors; GDIT (VAERS contractor); Clinical Immunization Safety Assessment (CISA) Project; VTF Safety Team leadership; state, local partners

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov



Extra Slides

Preferred Terms (PTs) used to identify reported myopericarditis

Atypical mycobacterium pericarditis
Autoimmune myocarditis
Autoimmune pericarditis
Bacterial pericarditis
Coxsackie myocarditis
Coxsackie pericarditis
Cytomegalovirus myocarditis
Cytomegalovirus pericarditis
Enterovirus myocarditis
Eosinophilic myocarditis
Hypersensitivity myocarditis
Immune-mediated myocarditis
Myocarditis
Myocarditis bacterial
Myocarditis helminthic
Myocarditis infectious
Myocarditis meningococcal
Myocarditis mycotic
Myocarditis post infection
Myocarditis septic
Pericarditis
Pericarditis adhesive
Pericarditis constrictive
Pericarditis helminthic
Pericarditis infective
Pericarditis mycoplasmal
Pleuropericarditis
Purulent pericarditis
Viral myocarditis
Viral pericarditis

Observed vs expected reporting rates

- Estimated annual incidence of myopericarditis ~ 1 to 2 per 100,000 population*
- Assumptions estimating risk period:
  - Use of Pfizer-BioNTech vaccine = Dec 14 to Apr 5 = 112 days
  - Use of Moderna vaccine = Dec 21 to Apr 5 = 105 days
  - Each vaccinated person contributes 52.5 to 56 person-days (mid-point of risk period), or ~14.4% to 15.3% of a calendar year
  - Doses administered = vaccinated population, adjusted for proportion by dose number
    - As of Apr 11, 63% of Pfizer was Dose 1; 64% of Moderna was Dose 1
- Expected background myopericarditis after Pfizer = [(88,795,447 doses administered*0.63)/(1 per 100K population)]*15.3% = **86 cases after Dose 1**
- Expected background myopericarditis after Moderna = [(77,458,292 doses administered*.64)/(1 per 100K population)]*14.4% = **71 cases after Dose 1**

* Systematic review; manuscript submitted

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:

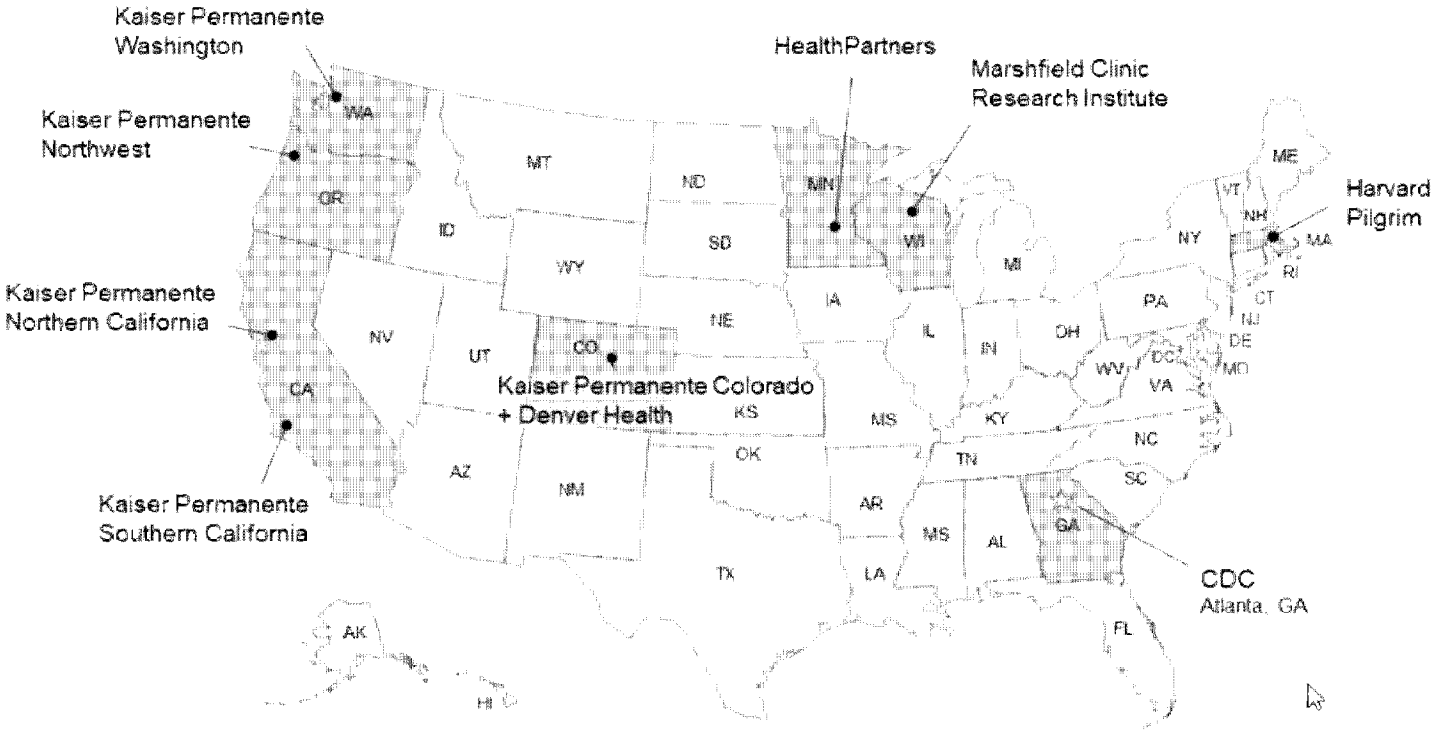
- To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

- 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

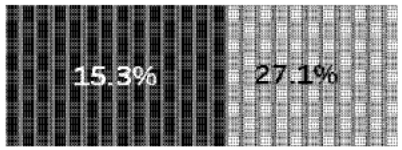


- Established in 1990
- Collaborative project between CDC and Nine Integrated Health Care Organizations

Vaccine Uptake (Data Through 4/03/21)

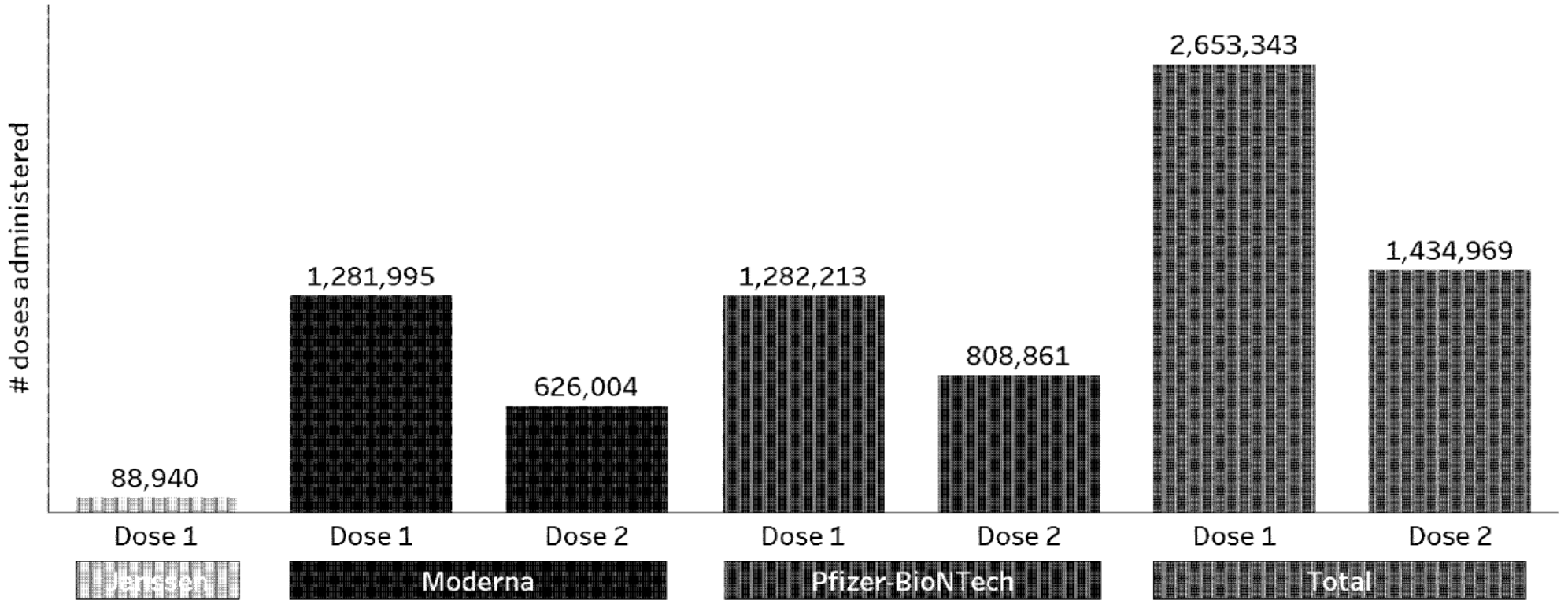
VSD COVID-19 Vaccine Totals

Total Doses Administered	Total Doses Admin per 100K	# People Initiating Vaccination	Completed Series
4,088,312	42,334	2,653,343	1,523,909
+530,270 since last week	+5,471 since last week	+310,955 since last week	+239,310 since last week

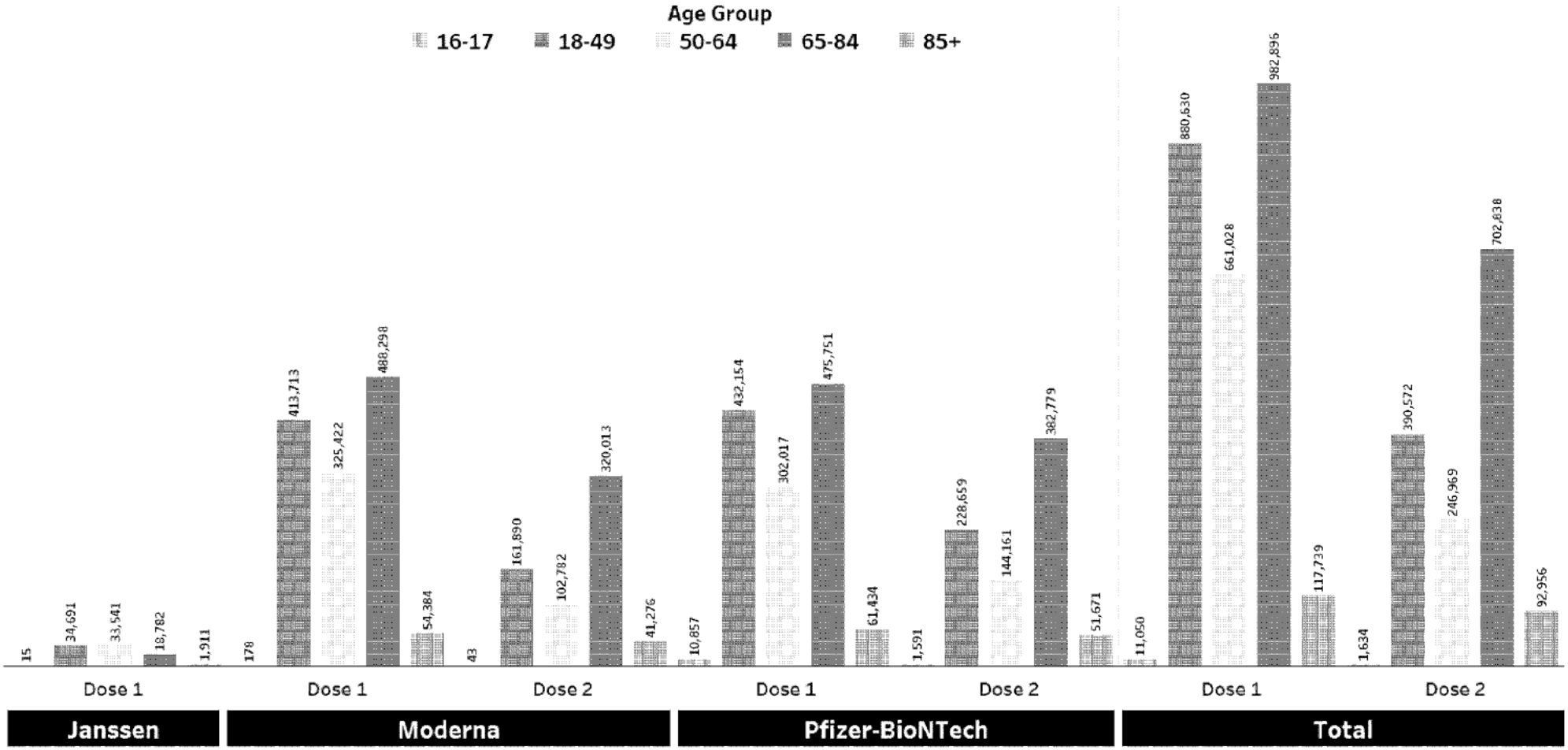


To date, 27.1% of VSD population initiated vaccination and 15.3% is fully vaccinated

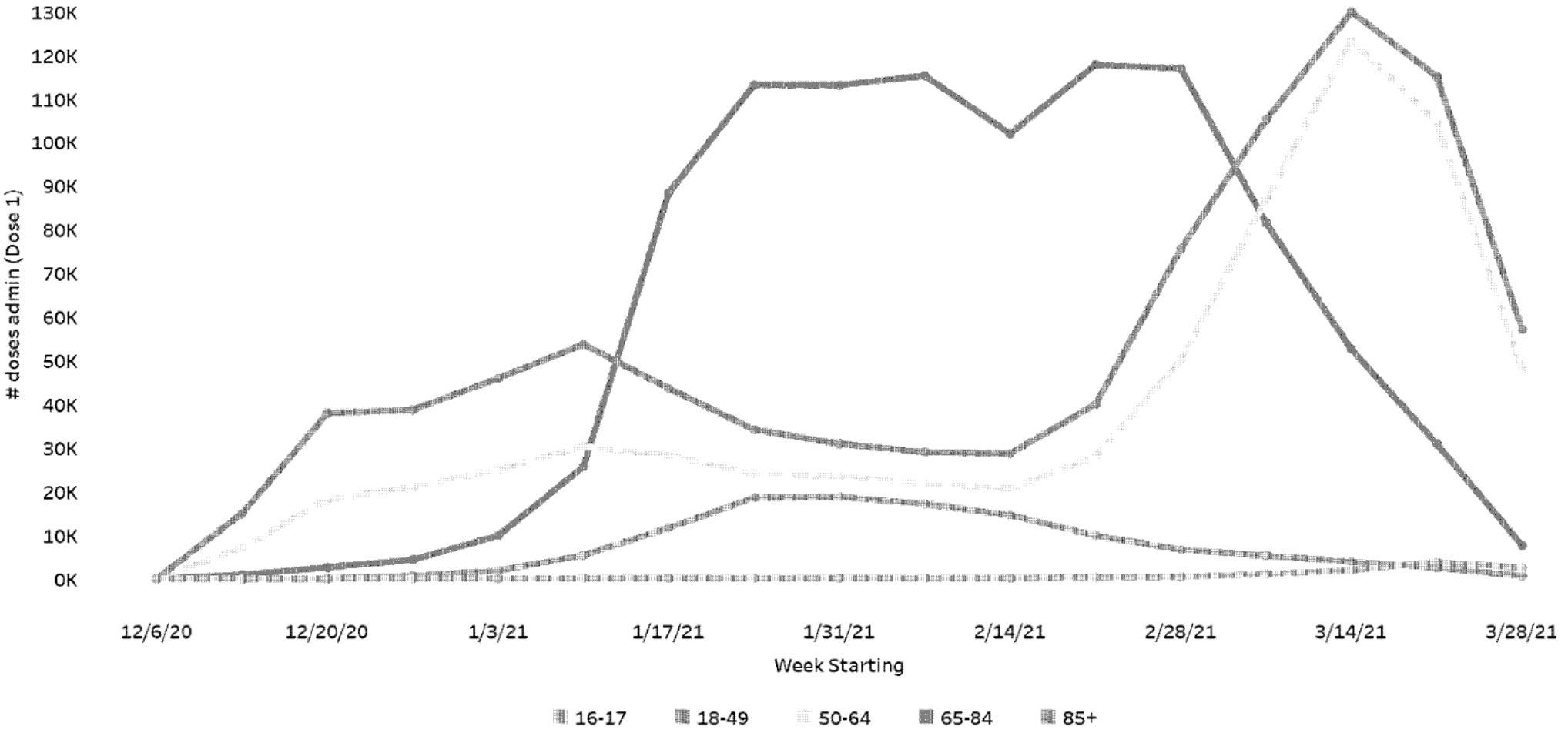
VSD COVID-19 Vaccine Totals



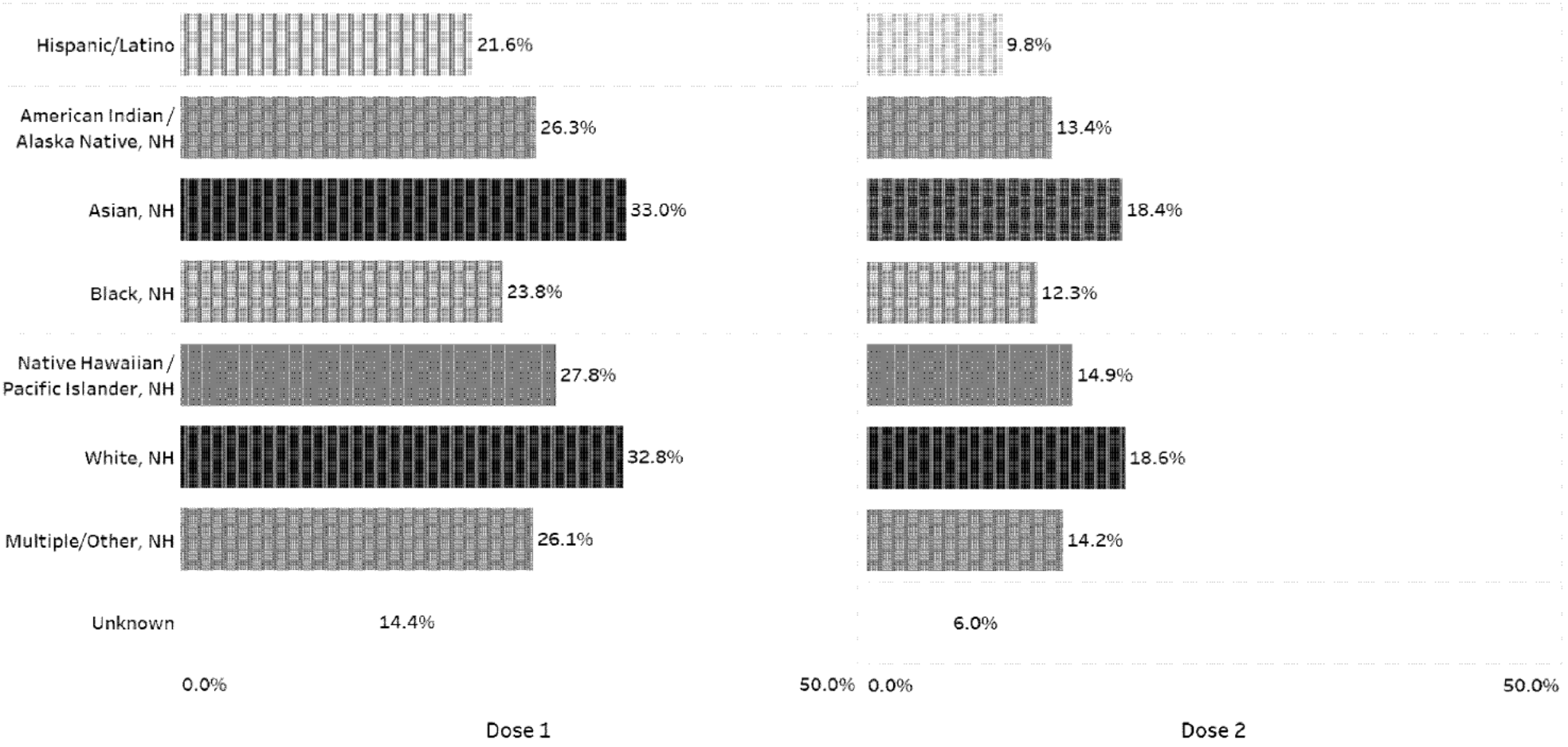
COVID-19 Vaccine Totals by Age Group



Vaccine Totals by Age Group and Week



COVID-19 Vaccine Coverage by Race

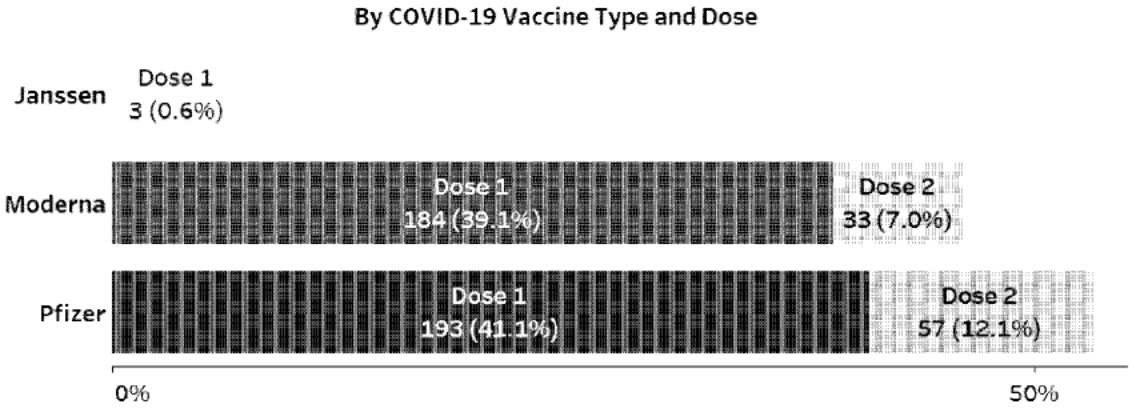


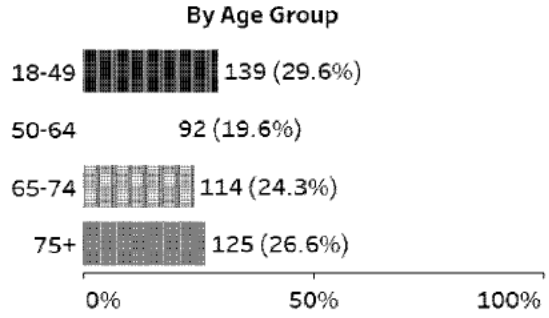
PSICOVID_00008834

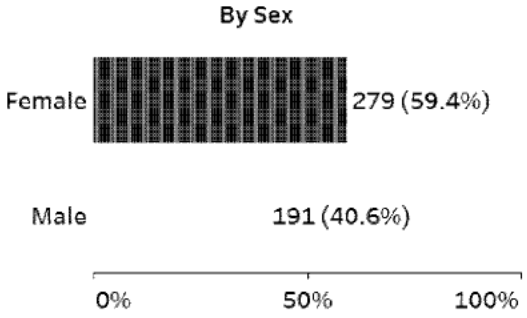
Simultaneous Vaccine Administration with COVID-19 Vaccine

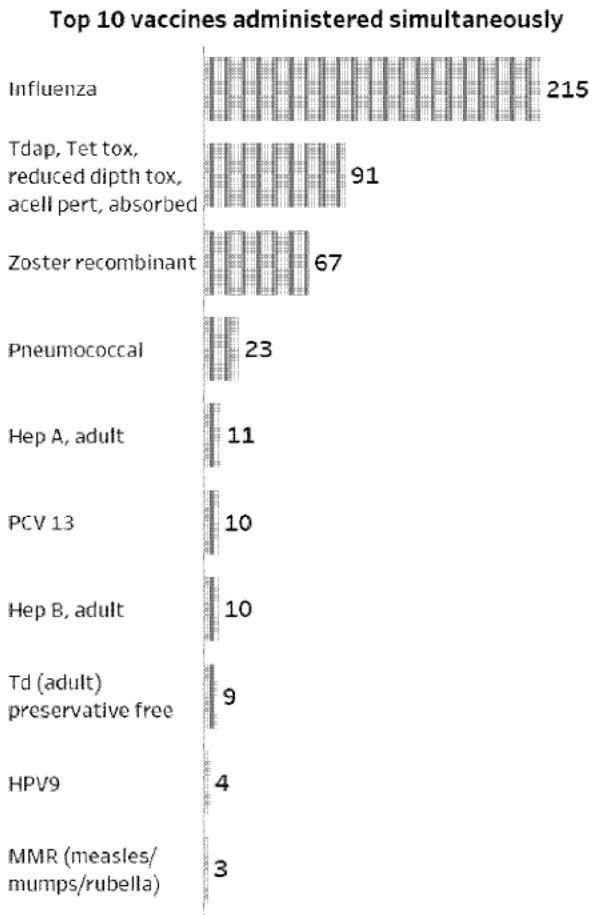
Number of COVID-19 doses admin to date: 4,088,312

Number of people who received simult vaccs: 470









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

COVID-19 Vaccine Totals by Sex, High Risk Status & History of COVID-19 Disease

		Moderna		Pfizer		Janssen	Totals			Denominator & Coverage %		
Category	Variable	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 1	Dose 2	Total Doses	Denominator	Dose 1 Coverage	Series Completion
Sex	Female	731,509	362,635	729,250	471,709	44,293	1,505,052	834,344	2,339,396	5,081,475	29.62	17.29
	Male	539,721	236,648	527,399	317,622	40,961	1,108,081	554,270	1,662,351	4,573,783	24.23	13.01
High Risk	No	615,551	257,065	628,615	355,765	47,241	1,291,407	612,830	1,904,237	6,666,549	19.37	9.90
	Yes	655,679	342,218	628,034	433,566	38,013	1,321,726	775,784	2,097,510	2,988,709	44.22	27.23
History of COVID-19 Disease	**No**	**1,189,826**	**572,275**	**1,182,317**	**746,932**	**78,733**	**2,450,876**	**1,319,207**	**3,770,083**	**8,905,571**	**27.52**	**15.70**
	Yes	**81,404**	**27,008**	**74,332**	**42,399**	**6,521**	**162,257**	**69,407**	**231,664**	**749,687**	**21.64**	**10.13**

Analysis
(Data Through 4/03/21)

Any signal about vaccine safety? 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 (subset of VTE) (settings = E, I)	PE	N

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

Any signal about vaccine safety? 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)		
7	Cerebral Venous Sinus Thrombosis (settings = E, I)		
8	Convulsions / seizures (settings = E, I)		
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
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21	Venous thromboembolism (settings = E, I, O)	VTE	N
22	Pulmonary embolism (subset of VTE) (settings = E, I)	PE	N

I67.6	Nonpyogenic thrombosis of intracranial venous system
G08	Intracranial and intraspinal phlebitis and thrombophlebitis
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic (Per SME, keep I63.6 in CVST and in Ischemic Stroke)

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

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

Primary Analyses: Vaccinated Concurrent Comparison "Sequential Analysis"

Signal Summary of all vaccinated concurrent comparators sequential analyses, by outcome, vaccine & dose

Risk Period Days	Outcome Event	Moderna			Pfizer			Both mRNA Vaccines			Janssen
		Dose 1	Dose 2	Both Doses	Dose 1	Dose 2	Both Doses	Dose 1	Dose 2	Both Doses	Dose 1
1-21	Acute myocardial infarction	No	No	No	No	No	No	No	No	No	No
	Appendicitis	No	No	No	No	No	No	No	No	No	No
	Bell's palsy	No	No	No	No	No	No	No	No	No	No
	Cerebral venous sinus thrombosis	No	No	No	No	No	No	No	No	No	-
	Disseminated intravascular coagulation	No	-	No	No	No	No	No	No	No	-
	Encephalitis / myelitis / encephalomyelitis	-	No	No	No	-	No	No	No	No	-
	Guillain-Barré syndrome	No	No	No	No	No	No	No	No	No	-
	Stroke, hemorrhagic	No	No	No	No	No	No	No	No	No	-
	Stroke, ischemic	No	No	No	No	No	No	No	No	No	-
	Immune thrombocytopenia	No	No	No	No	No	No	No	No	No	-
	Myocarditis / pericarditis	No	No	No	No	No	No	No	No	No	-
	Seizures	No	No	No	No	No	No	No	No	No	-
	Thrombotic thrombocytopenic purpura	-	-	-	No	-	No	No	-	No	-
	Venous thromboembolism	No	No	No	No	No	No	No	No	No	No
	Pulmonary embolism (subset of VTE)	No	No	No	No	No	No	No	No	No	-
1-42	Acute myocardial infarction	No	No	No	No	No	No	No	No	No	-
	Appendicitis	No	No	No	No	No	No	No	No	No	-
	Bell's palsy	No	No	No	No	No	No	No	No	No	-
	Cerebral venous sinus thrombosis	No	No	No	No	No	No	No	No	No	-
	Disseminated intravascular coagulation	No	-	No	No	No	No	No	No	No	-
	Encephalitis / myelitis / encephalomyelitis	-	-	No	No	-	No	No	No	No	-
	Guillain-Barré syndrome	-	-	-	No	No	No	No	No	No	-
	Stroke, hemorrhagic	No	No	No	No	No	No	No	No	No	-
	Stroke, ischemic	No	No	No	No	No	No	No	No	No	-
	Immune thrombocytopenia	No	No	No	No	No	No	No	No	No	-
	Myocarditis / pericarditis	No	No	No	No	No	No	No	No	No	-
	Seizures	No	No	No	No	No	No	No	No	No	-
	Thrombotic thrombocytopenic purpura	-	-	-	No	No	No	No	No	No	-
	Venous thromboembolism	No	No	No	No	No	No	No	No	No	-
	Pulmonary embolism (subset of VTE)	No	No	No	No	No	No	No	No	No	-

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	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
Acute myocardial infarction	280	0.88	0.69 - 1.14	0.335	0.849	no
Appendicitis	173	0.81	0.61 - 1.09	0.159	0.932	no
Bell's palsy	178	1.09	0.79 - 1.53	0.611	0.335	no
Cerebral venous sinus thrombosis	5	0.86	0.16 - 6.68	0.831	0.747	no
Disseminated intravascular coagulation	13	1.29	0.31 - 8.77	0.799	0.540	no
Encephalitis / myelitis / encephalomyelitis	2	0.71	0.05 - 21.35	0.773	0.830	no
Guillain-Barré syndrome (Automated)	4	.	0.29 - ne	0.289	0.289	no
Stroke, hemorrhagic	118	1.02	0.68 - 1.56	0.946	0.515	no
Stroke, ischemic	461	1.04	0.85 - 1.29	0.699	0.369	no
Immune thrombocytopenia	19	1.03	0.38 - 3.23	0.980	0.593	no
Myocarditis / pericarditis	15	0.66	0.24 - 2.03	0.441	0.858	no
Seizures	83	1.02	0.63 - 1.70	0.961	0.530	no
Thrombotic thrombocytopenic purpura	1	.	0.01 - ne	0.785	0.785	no
Venous thromboembolism	298	1.29	0.99 - 1.70	0.060	0.034	no
Pulmonary embolism (subset of VTE)	246	1.07	0.81 - 1.42	0.657	0.354	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

		Weekly Analysis[1]			Sequential Test[2]	
Outcome Event	Events in Risk Interval	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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Guillain-Barré syndrome (Automated)	4	.	0.29 - ne	0.289	0.289	no
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Thrombotic thrombocytopenic purpura	1	.	0.01 - ne	0.785	0.785	no
Venous thromboembolism	298	1.29	0.99 - 1.70	0.060	0.034	no
Pulmonary embolism (subset of VTE)	246	1.07	0.81 - 1.42	0.657	0.354	no

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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

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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Appendicitis	173	0.81	0.61 - 1.09	0.159	0.932	no
Bell's palsy	178	1.09	0.79 - 1.53	0.611	0.335	no
Cerebral venous sinus thrombosis	5	0.86	0.16 - 6.68	0.831	0.747	no
Disseminated intravascular coagulation	13	1.29	0.31 - 8.77	0.799	0.540	no
Encephalitis / myelitis / encephalomyelitis	2	0.71	0.05 - 21.35	0.773	0.830	no
Guillain-Barré syndrome (Automated)	4	.	0.29 - ne	0.289	0.289	no
Stroke, hemorrhagic	118	1.02	0.68 - 1.56	0.946	0.515	no
Stroke, ischemic	461	1.04	0.85 - 1.29	0.699	0.369	no
Immune thrombocytopenia	19	1.03	0.38 - 3.23	0.980	0.593	no
Myocarditis / pericarditis	**15**	**0.66**	**0.24 - 2.03**	**0.441**	**0.858**	**no**
Seizures	83	1.02	0.63 - 1.70	0.961	0.530	no
Thrombotic thrombocytopenic purpura	1	.	0.01 - ne	0.785	0.785	no
Venous thromboembolism	298	1.29	0.99 - 1.70	0.060	0.034	no
Pulmonary embolism (subset of VTE)	246	1.07	0.81 - 1.42	0.657	0.354	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

			Weekly Analysis[1]		Sequential Test[2]	
Outcome Event	Events in Risk Interval	Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Myocarditis / pericarditis	15	0.66	0.24 - 2.03	0.441	0.858	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

			Weekly Analysis[1]		Sequential Test[2]	
Outcome Event	Events in Risk Interval	Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Myocarditis / pericarditis	15	0.66	0.24 - 2.03	0.441	0.858	no

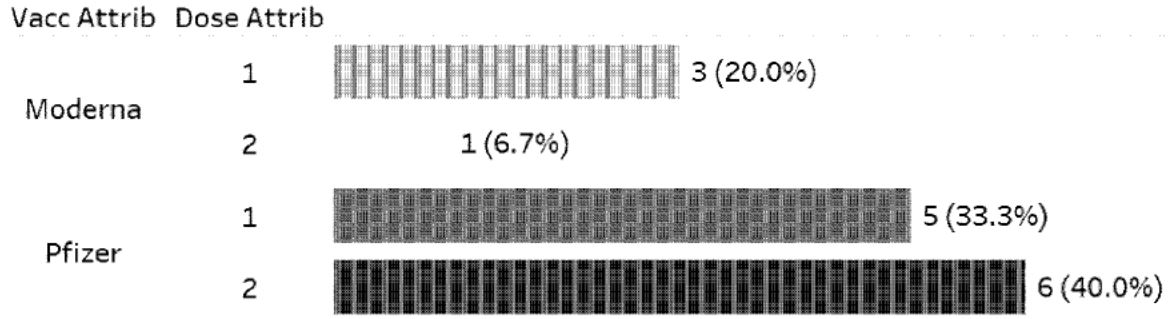
Unvaccinated Comparison

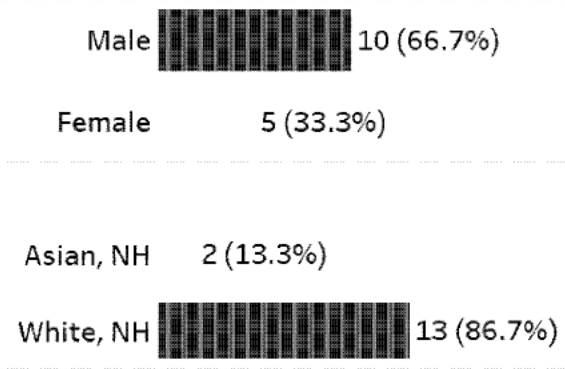
Unvaccinated - 21-day risk interval	Events in Risk Interval	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value
Myocarditis / pericarditis	15	1.04	0.55 - 1.84	0.885

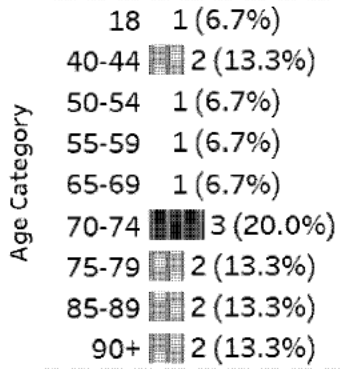
[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to 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.

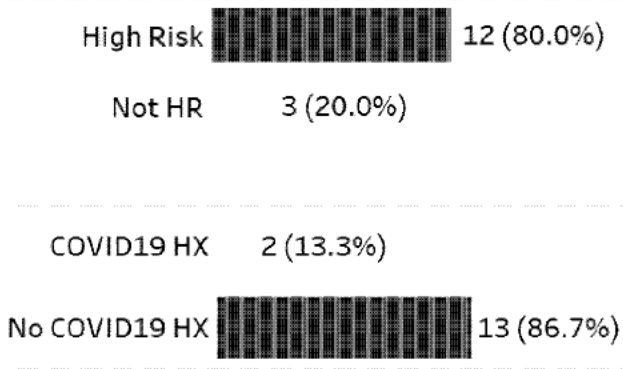
Myocarditis / Pericarditis Case Summary

15 **cases identified in the 1-21 day risk interval**









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

			Weekly Analysis[1]		Sequential Test[2]	
Outcome Event	Events in Risk Interval	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	280	0.88	0.69 - 1.14	0.335	0.849	no
Venous thromboembolism	298	1.29	0.99 - 1.70	0.060	0.034	no
Pulmonary embolism (subset of VTE)	246	1.07	0.81 - 1.42	0.657	0.354	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
[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 (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.

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

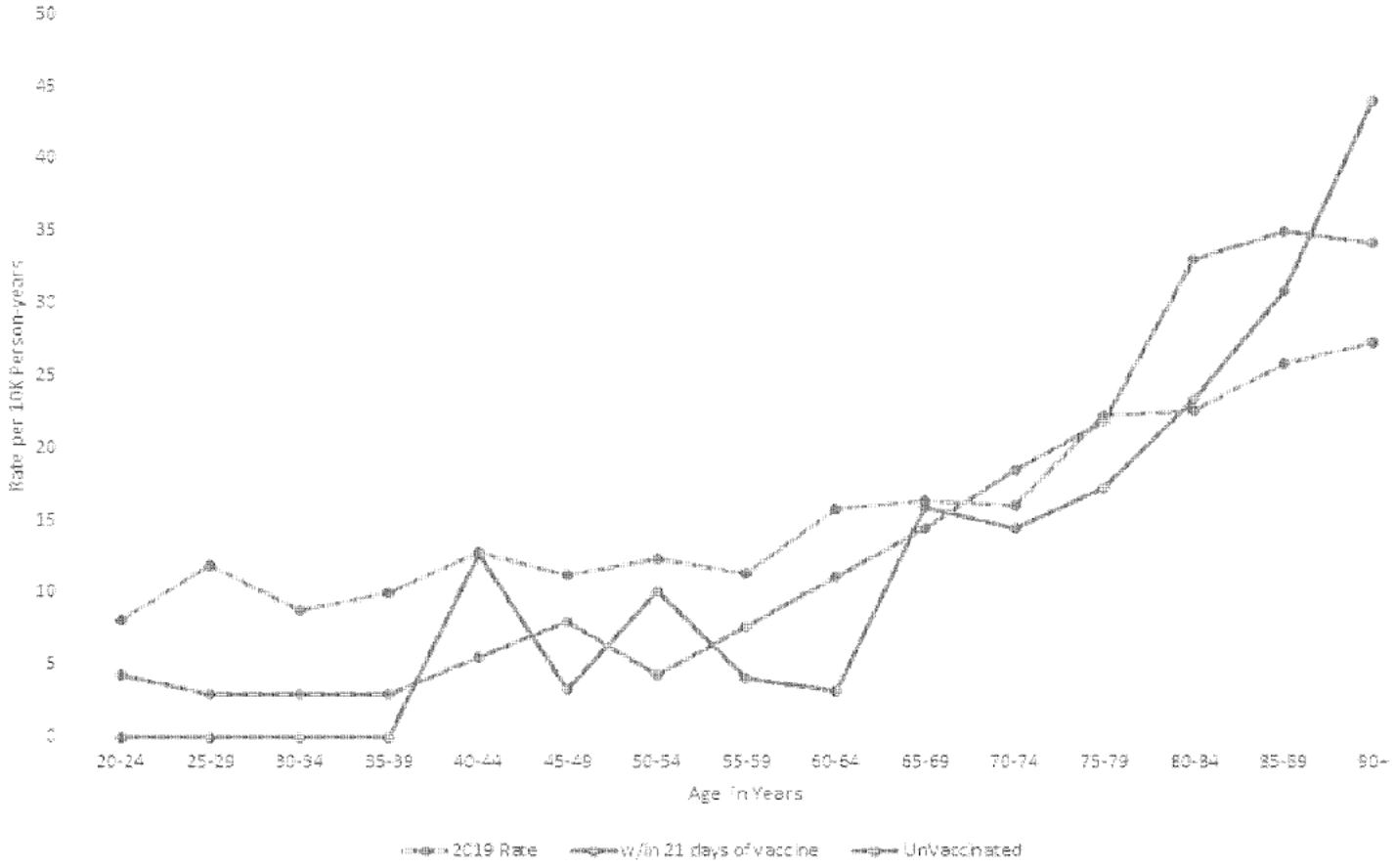
Compared with outcome events in vaccinated comparators on the same calendar days

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
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
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



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

Unvaccinated Comparison

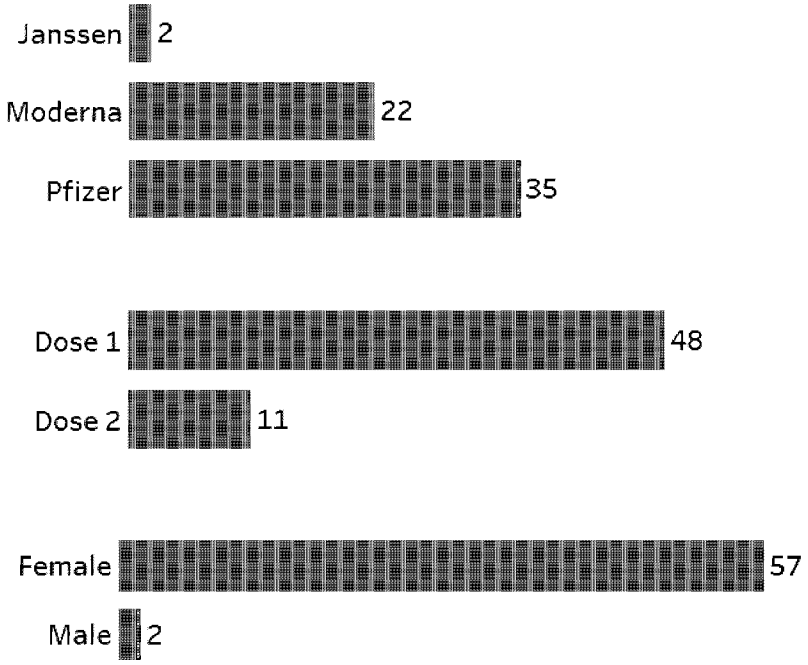
Outcome	Vaccine	Dose	Events in Risk Interval	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value
Pulmonary embolism (subset of VTE)	Both mRNA	Both Doses	167	1.03	0.84 - 1.25	0.780
	Pfizer	Both Doses	89	1.08	0.84 - 1.38	0.524
	Moderna	Both Doses	78	1.00	0.78 - 1.29	0.965

[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.

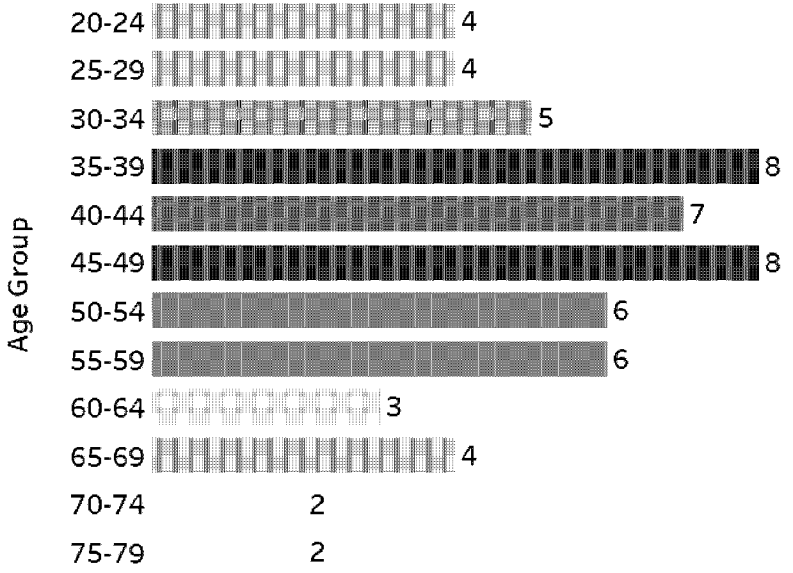
Anaphylaxis Automated Summary

59

Automated cases identified on days 0-1



Age in years ranged from 20-79, with 38 of the cases between ages 25-54



Anaphylaxis Chart Review Summary

- Chart review completed for 36/59 cases*
- 20/36 (56%) cases confirmed as post-vaccination anaphylaxis

	Pfizer (n=12)	Moderna (n=8)
Age in years, median (range)	43 (30-65)	39 (30-67)
Female sex	12 (100%)	8 (100%)
Minutes to symptom onset, median (range)	9 (0-300)	13 (5-30)
Prior history of allergies	9 (75%)	4 (50%)
Prior history of anaphylaxis	6 (50%)	1 (13%)
Dose		
1	12 (100%)	7 (87%)
2	0	1 (13%)
Brighton Collaboration case definition level		
1	4 (33%)	3 (38%)
2	8 (67%)	5 (62%)
No. confirmed cases (95% CI) per million doses	5.7 (3.0-10.0)	4.2 (1.8-8.3)
No. confirmed cases (95% CI) per million first doses	9.4 (4.8-16.4)	5.5 (2.2-11.3)
No. confirmed cases (95% CI) per million female first doses	16.5 (8.5-28.7)	9.6 (3.8-19.7)

*Full review not completed until 30 days after the event

GBS Summary

Outcome	No. Automated Cases	No. Completed Chart Review	No. Chart Confirmed Cases
GBS	7	3	0

- Chart review completed for 3 cases, none were confirmed
  - 1 was miscoded, no mention of GBS in the chart
  - 1 was initially suspected for GBS but ruled out after full work-up
  - 1 history of GBS
- Chart review in progress for 4 cases
  - 2 with quick review completed that suggest incident cases of GBS following vaccination Full review and adjudication are in progress.
  - 2 with pending quick initial review

ADEM & TM Summary

Outcome	No. Automated Cases	No. Chart Confirmed Cases
ADEM	0	0
TM	1	0

- 1 automated case of TM was identified but not confirmed as incident by chart review (symptom onset documented prior to COVID-19 vaccination)

Summary & Next Steps

- No signals identified to date
- Continue to monitor vaccine uptake within the VSD
  - —Monitor by race, sex and high-risk conditions
- Historical Comparators
  - —General age comparable background rates
  - —Rates following well care visits among those that received influenza vaccine in the past 18 months
  - —Planning first analysis next week

Acknowledgements

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  - 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

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

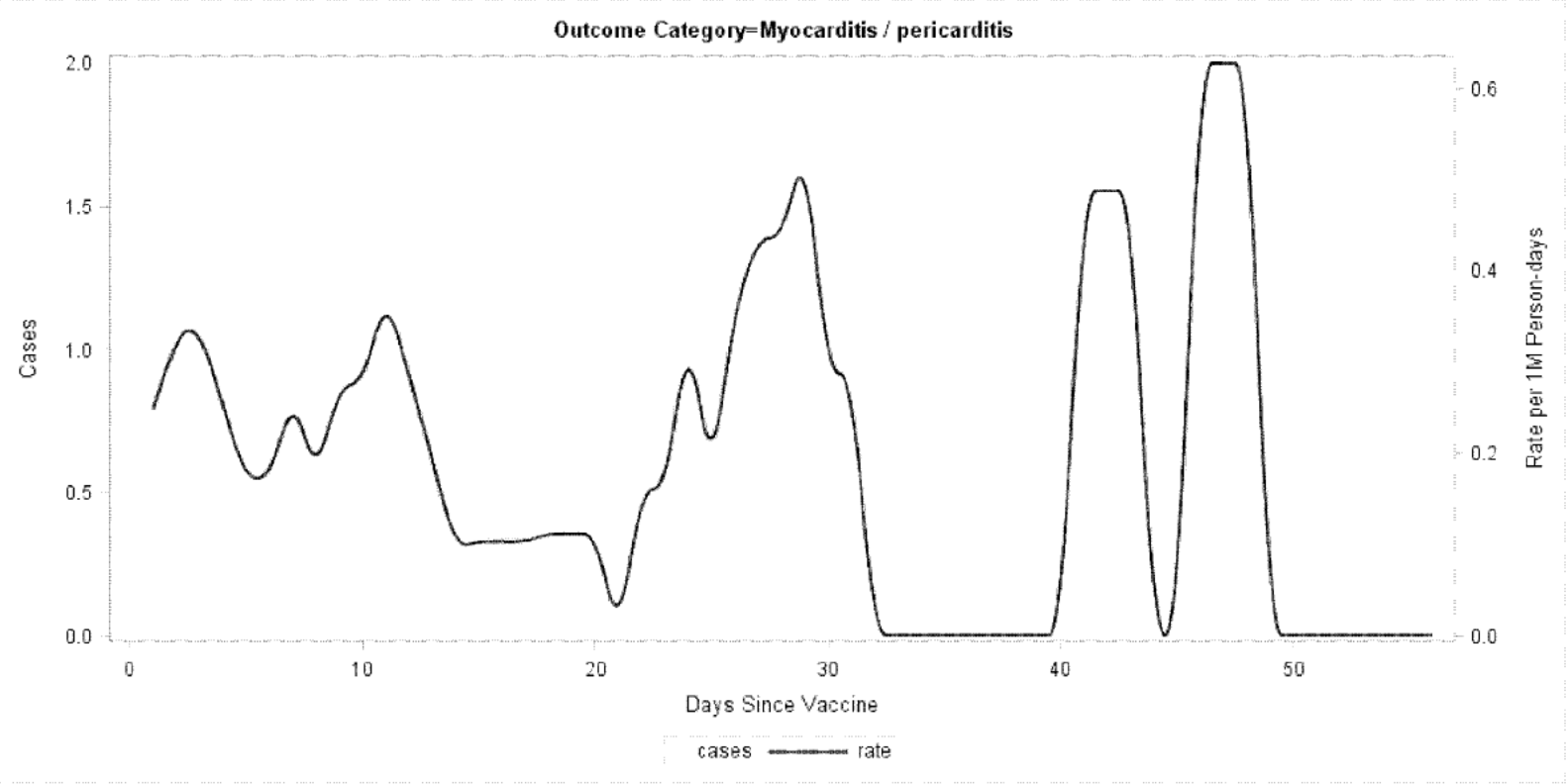
Compared with outcome events in vaccinated comparators on the same calendar days

Week of Analysis	Outcome Event	Events in Risk Interval	Adjusted Rate Ratio	1-Sided P-value (Fisher)
2/7/2021	AMI	11	0.33	0.961
2/14/2021	AMI	21	0.68	0.834
2/21/2021	AMI	31	0.5	0.953
2/28/2021	AMI	61	0.58	0.97
3/7/2021	AMI	113	0.79	0.872
3/14/2021	AMI	153	0.8	0.891
3/21/2021	AMI	199	0.93	0.697
3/28/2021	AMI	242	0.87	0.859
4/4/2021	AMI	280	0.88	0.849

Week of Analysis	Outcome Event	Events in Risk Interval	Adjusted Rate Ratio	1-Sided P-value (Fisher)
1/17/2021	VTE	2	.	0.947
1/24/2021	VTE	5	.	0.835
1/31/2021	VTE	10	.	0.547
2/7/2021	VTE	16	1.11	0.701
2/14/2021	VTE	23	1.86	0.468
2/21/2021	VTE	47	2.53	0.061
2/28/2021	VTE	86	2.07	0.033
3/7/2021	VTE	128	1.67	0.04
3/14/2021	VTE	173	1.41	0.061
3/21/2021	VTE	212	1.42	0.031
3/28/2021	VTE	251	1.25	0.088
4/4/2021	VTE	298	1.29	0.034

Week of Analysis	Outcome Event	Events in Risk Interval	Adjusted Rate Ratio	1-Sided P-value (Fisher)
2/7/2021	PE	12	.	0.419
2/14/2021	PE	19	.	0.225
2/21/2021	PE	31	1.09	0.595
2/28/2021	PE	63	1.28	0.354
3/7/2021	PE	90	1.33	0.257
3/14/2021	PE	127	1.19	0.289
3/21/2021	PE	162	1.04	0.464
3/28/2021	PE	202	1.01	0.514
4/4/2021	PE	246	1.07	0.354

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



Vaccine Safety Datalink (VSD) Weekly COVID-19 Vaccine Summary: April 06, 2021 *

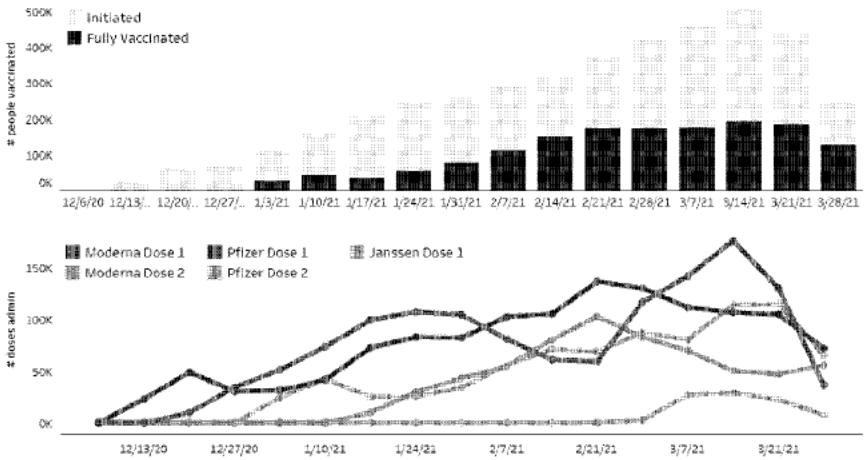
* Visualization published on April 06, 2021; data current as of previous Saturday. VSD population includes individuals 16 years of age and older.

Total # Doses Administered	Total # Doses Admin per 100K	# People Initiating Vaccination	# Fully Vaccinated
4,088,312	42,334	2,653,343	1,523,909
+530,270 since last week	+5,471 since last week	+310,955 since last week	-239,310 since last week

To date, 27.1% of VSD population initiated vaccination and 15.8% is fully vaccinated

No signals have been observed to date.

Number of people vaccinated & doses administered over time, by reporting week start date



Number of events by outcome *

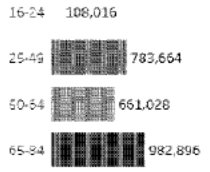
	Janssen	Moderna		Pfizer		Total
	Dose 1	Dose 1	Dose 2	Dose 1	Dose 2	
AMI	5	79	42	100	63	289
ANAPH	2	16	6	30	5	59
ANAPH2		11		11	3	25
APPND	3	59	29	62	38	191
ARDS		1	2	1		4
BP	4	66	32	54	33	189
CVST			2	2	1	5
DIC		4		7	2	13
ENCEPH			2	1		3
GBS		2	1	2	1	6
HSTK	1	29	13	44	33	120
ISTK	2	146	88	146	89	470
ITP		3	6	6	4	19
MISC				3	1	4
MYOC		3	1	5	6	15
NARC		3	2		3	8
PE	2	76	42	71	57	248
SZ		25	9	37	18	89
TM		1				1
TTP				1		1
VTE	8	98	57	87	59	309
Total	27	622	334	670	415	2,068

* 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.

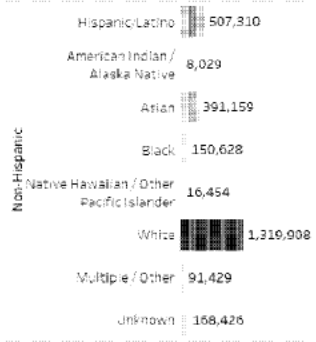
Demographic breakdown of people who initiated vaccination

By Sex

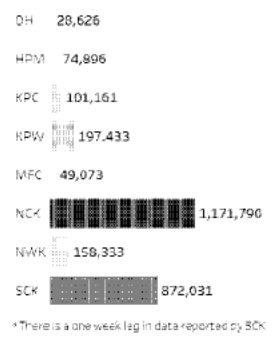
By Age Group



By Race/Ethnicity



By Site *

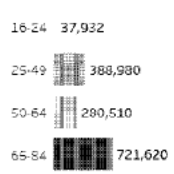


* There is a one week lag in data reported by SCK

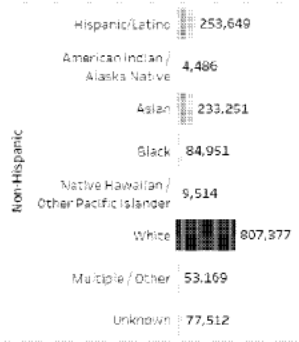
Demographic breakdown of people who are fully vaccinated

By Sex

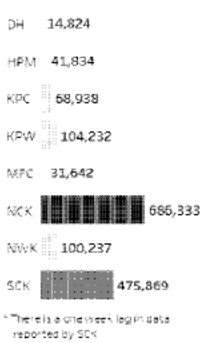
By Age Group



By Race/Ethnicity



By Site *

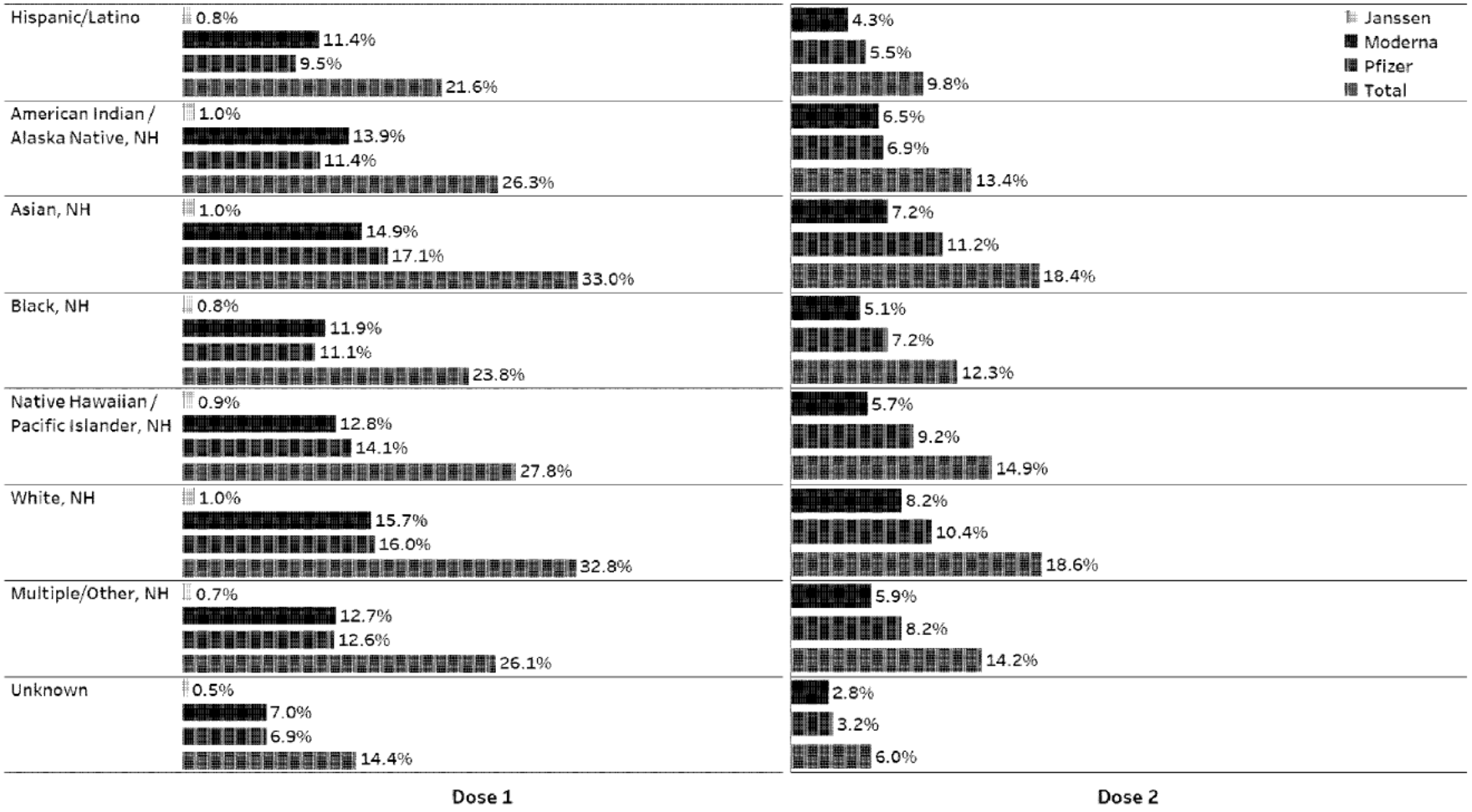


* There is a one week lag in data reported by SCK

COVID-19 Vaccine Totals by Age

	Moderna		Pfizer		Janssen	Totals			Denominator	Coverage %	
Variable	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 1	Dose 2	Total Doses	Denominator	Dose 1 Coverage	Series Completion
16	31	9	3,724	451	3	3,758	460	4,218	140,387	2.68	0.33
17	124	26	5,685	896	12	5,821	922	6,743	142,466	4.09	0.66
18	4,046	522	4,040	1,113	527	8,613	1,635	10,248	140,090	6.15	1.54
19	4,809	811	4,440	1,533	493	9,742	2,344	12,086	138,347	7.04	2.05
20-24	36,586	10,518	34,743	14,968	3,104	74,433	25,486	99,919	742,652	10.02	3.85
25-29	53,354	20,105	54,604	28,182	4,004	111,962	48,287	160,249	806,430	13.88	6.48
30-34	69,772	27,484	73,358	38,968	5,313	148,443	66,452	214,895	890,237	16.67	8.06
35-39	77,685	31,585	82,280	45,080	6,121	166,086	76,665	242,751	870,251	19.08	9.51
40-44	79,293	31,597	82,539	45,866	6,428	168,260	77,463	245,723	804,256	20.92	10.43
45-49	81,487	31,329	83,158	45,754	7,067	171,712	77,083	248,795	759,864	22.60	11.07
50-54	93,675	32,375	90,327	46,586	8,630	192,632	78,961	271,593	787,240	24.47	11.13
55-59	103,970	32,077	95,070	45,531	10,749	209,789	77,608	287,397	792,243	26.48	11.15
60-64	122,101	33,270	105,008	45,436	12,472	239,581	78,706	318,287	767,936	31.20	11.87
65-69	162,391	82,490	154,898	114,419	8,248	325,537	196,909	522,446	624,792	52.10	32.84
70-74	147,182	87,897	143,127	111,774	5,641	295,950	199,671	495,621	518,979	57.03	39.56
75-79	111,602	84,930	108,468	92,362	2,788	222,858	177,292	400,150	329,824	67.57	54.60
80-84	67,419	51,016	68,418	58,534	1,796	137,633	109,550	247,183	205,250	67.06	54.25
85-89	36,485	27,179	39,556	33,339	1,132	77,173	60,518	137,691	120,174	64.22	51.30
90+	19,218	14,063	23,206	18,539	726	43,150	32,602	75,752	73,840	58.44	45.14

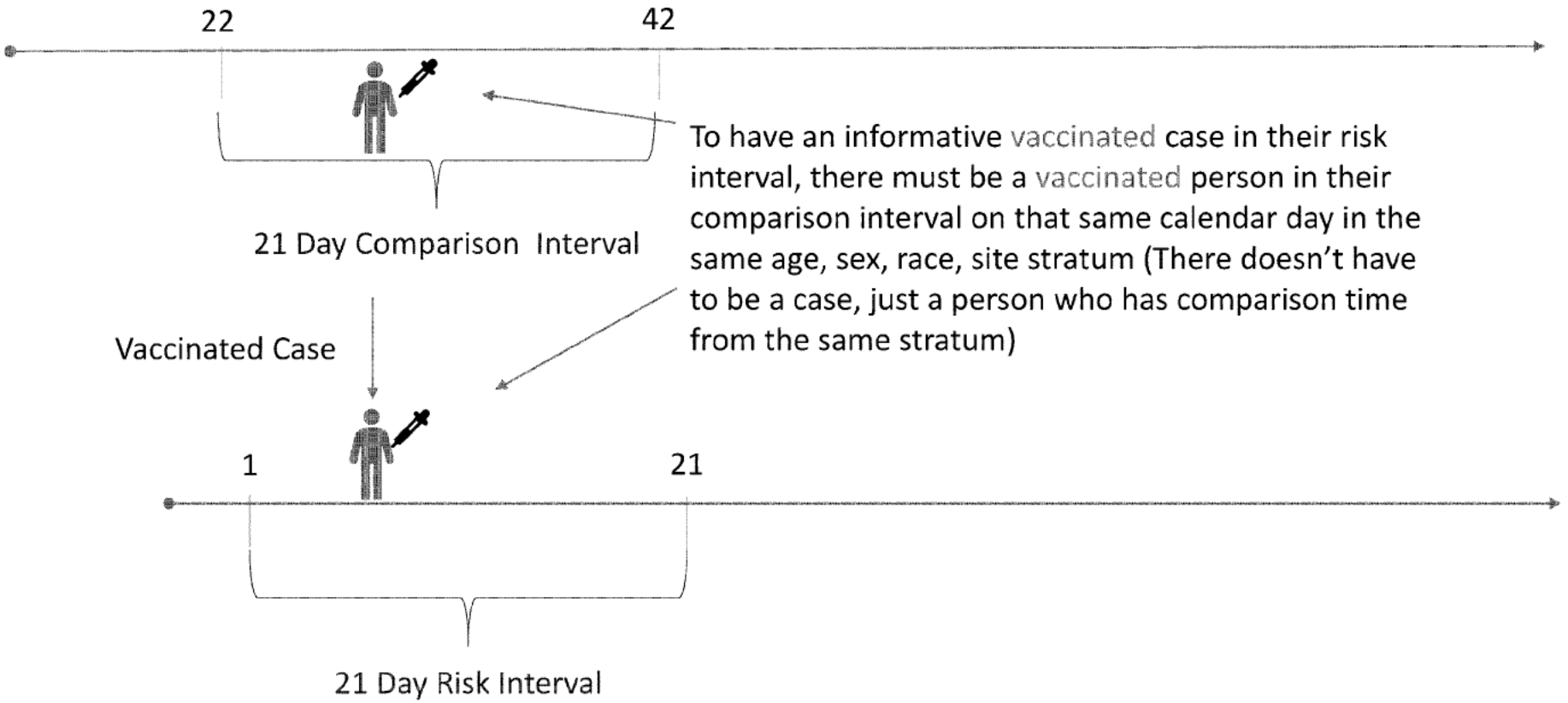
COVID-19 Vaccine Coverage by Race



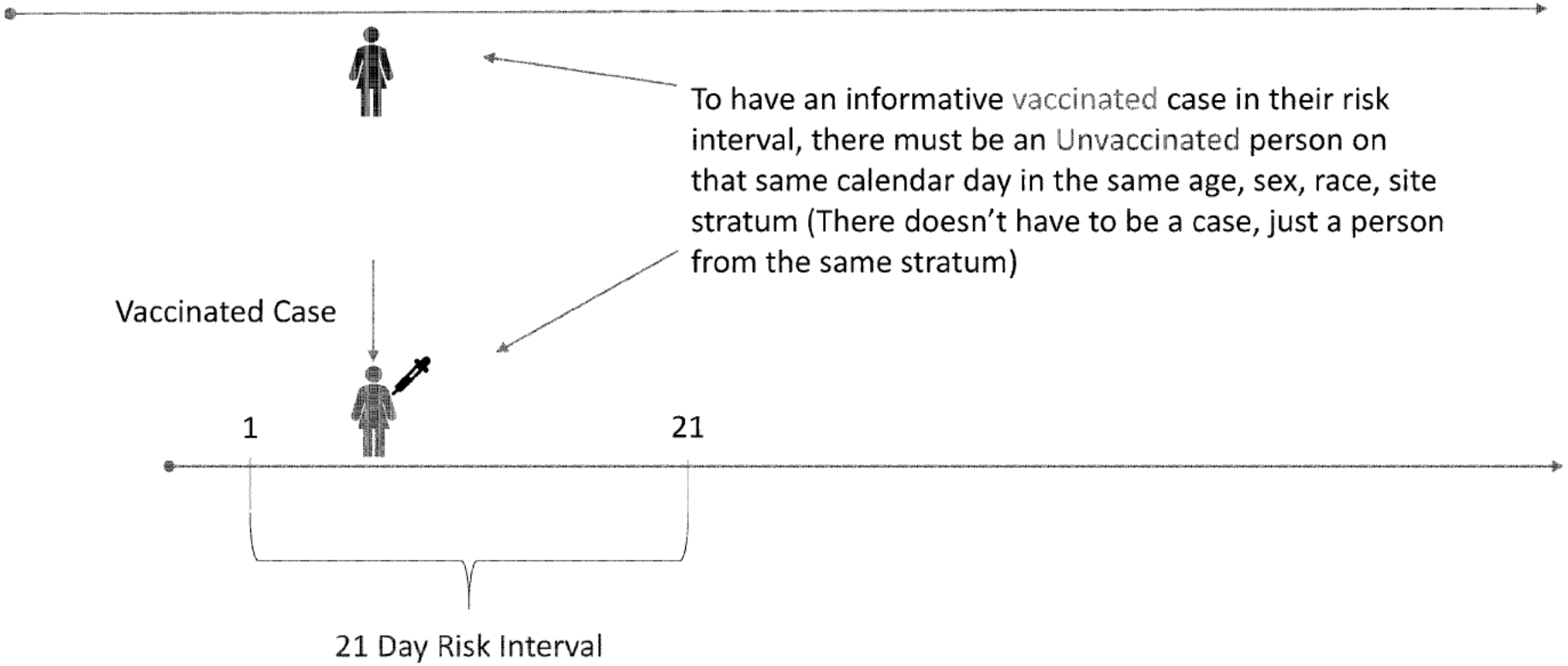
Next Steps

- 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
  - Planning to start in latter half of March

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)	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)	ANAPH	0-1	Yes	Yes	
5	Appendicitis (settings = E, I)	APPND	1-21, 1-42			
6	Bell's palsy (settings = E, I, O)	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)	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)	VTE	1-21, 1-42			30 days
21	Pulmonary embolism (subset of VTE) (settings = E, I)	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.

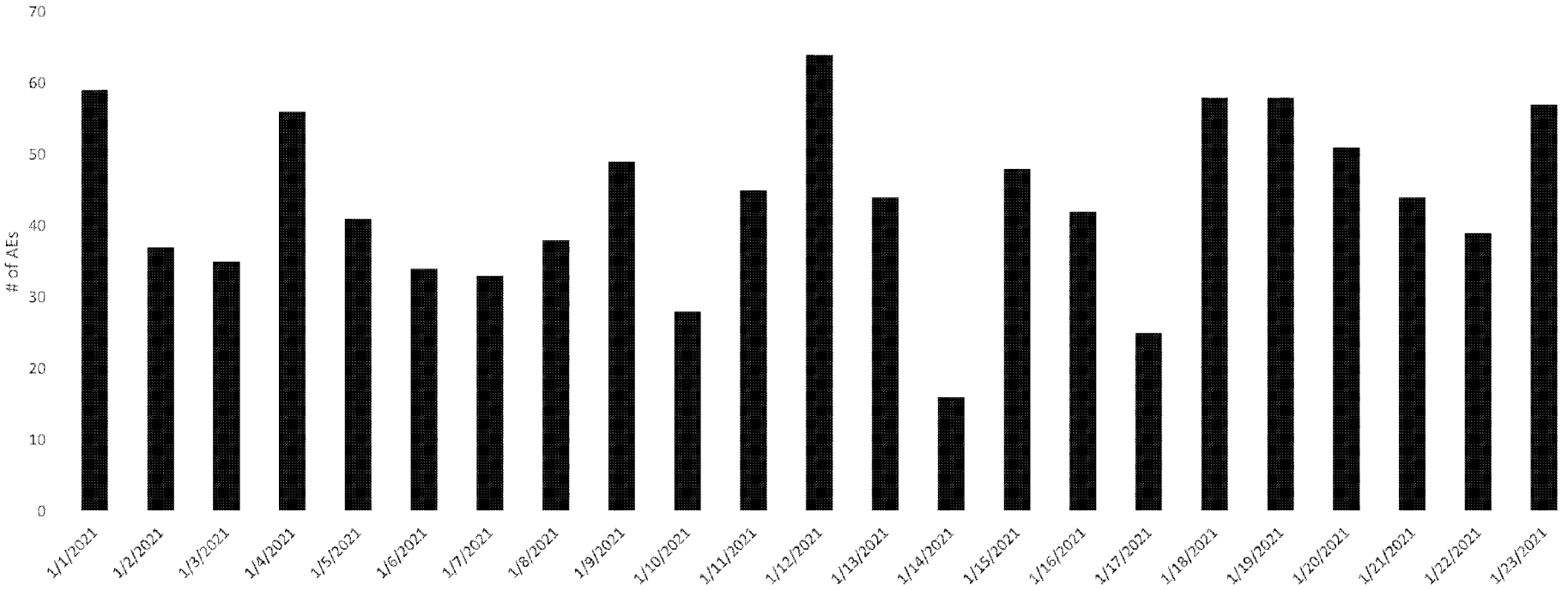
- self-controls in a comparison interval after COVID-19 vaccination.
  - Among the vaccinees who had an outcome event in either the risk interval or the comparison interval, we compare outcome incidence in the risk interval with outcome incidence in the comparison interval.

Analytic Strategies: Aim 1

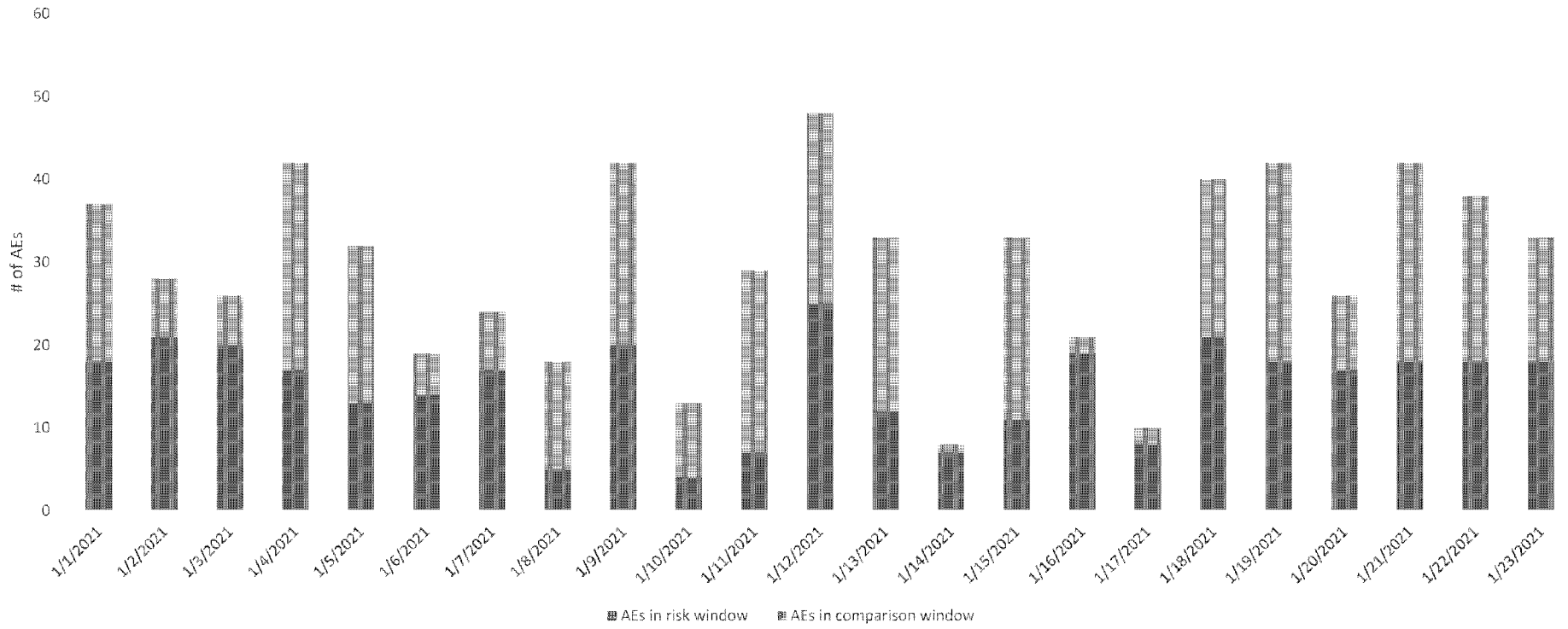
Design	Advantages	Limitations
Primary		
Concurrent Vaccinated	- Not confounded by time-stable co-morbidities, propensities to use health services, or demographics - Follow-up in the comparison interval is on the same calendar dates as follow-up time in the risk interval - Avoids bias that can arise from 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

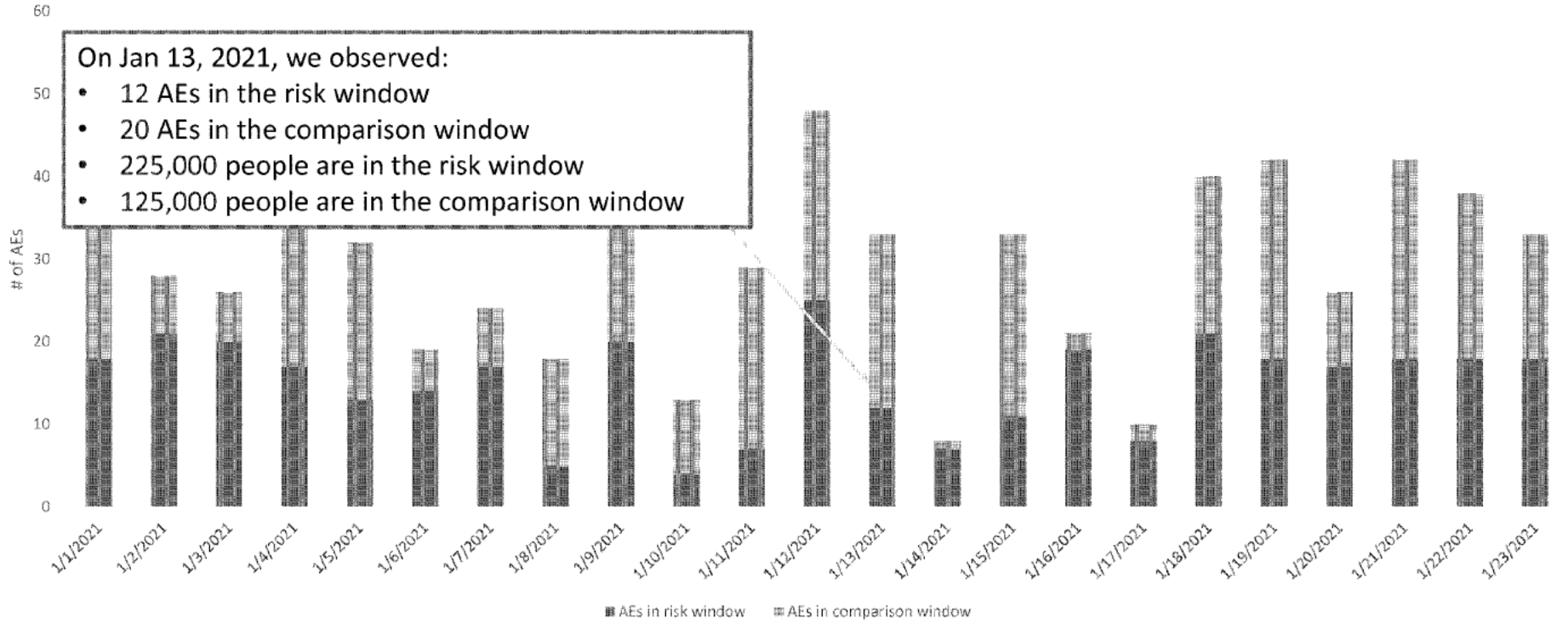
Total # of Events on Each Day



Did the event occur in a risk or comparison interval?



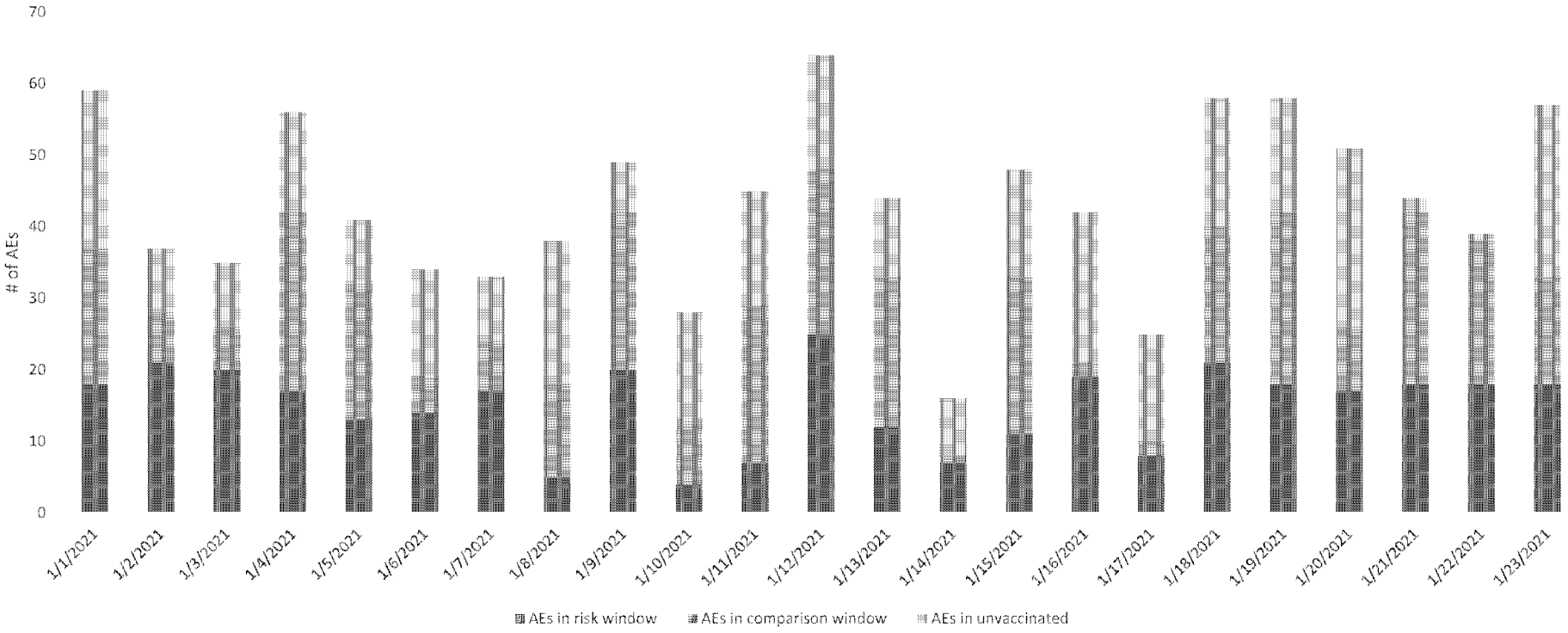
Vaccinated Concurrent Comparator Analyses



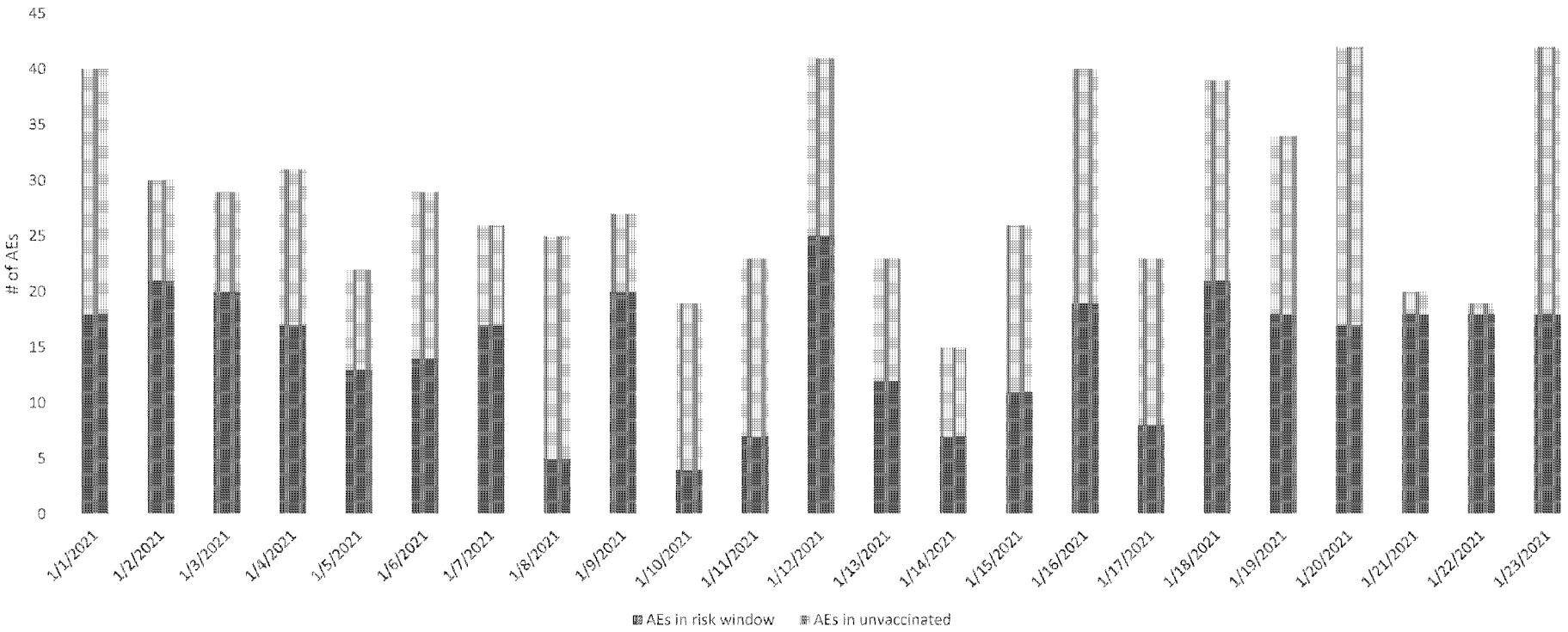
Looking at the data each day in this way, we inherently adjust for variations that occur on different days (e.g., a holiday, every Monday, or a weekend).

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?



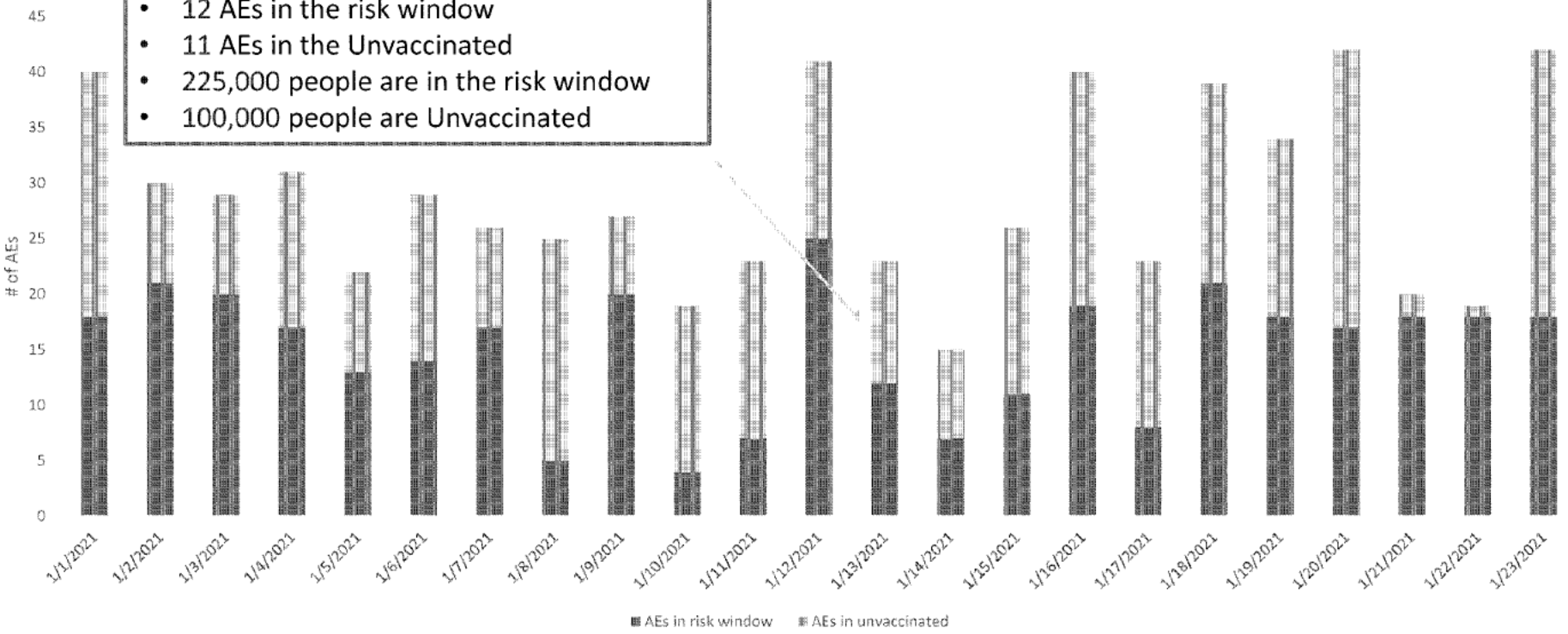
Did the event occur in a risk interval or in the Unvaccinated?



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

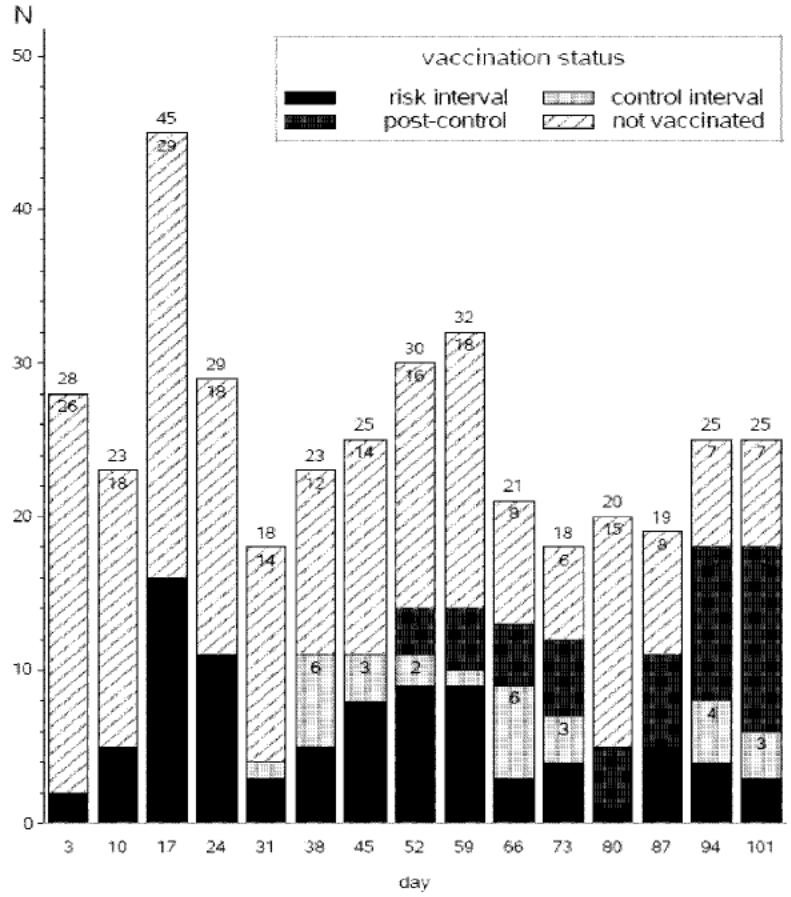


At each analysis, we compute a summary rate ratio (risk vs Unvaccinated) with all the data available to date. This rate ratio is adjusted for calendar time by day

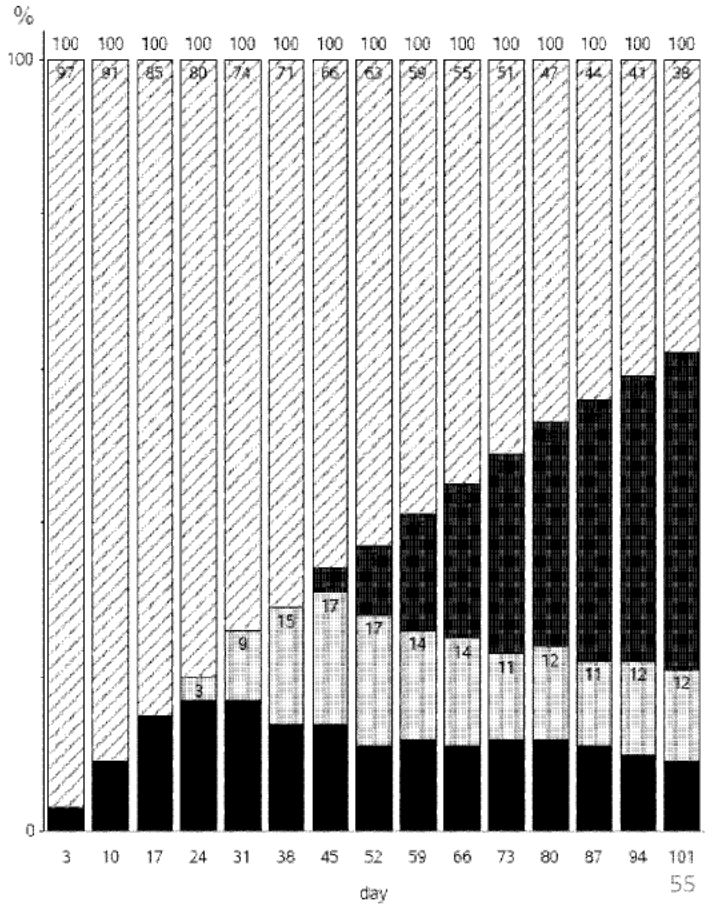
Looking at the data each day in this way, we inherently adjust for variations that occur on different days (e.g., a holiday, every Monday, or a weekend).

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



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.

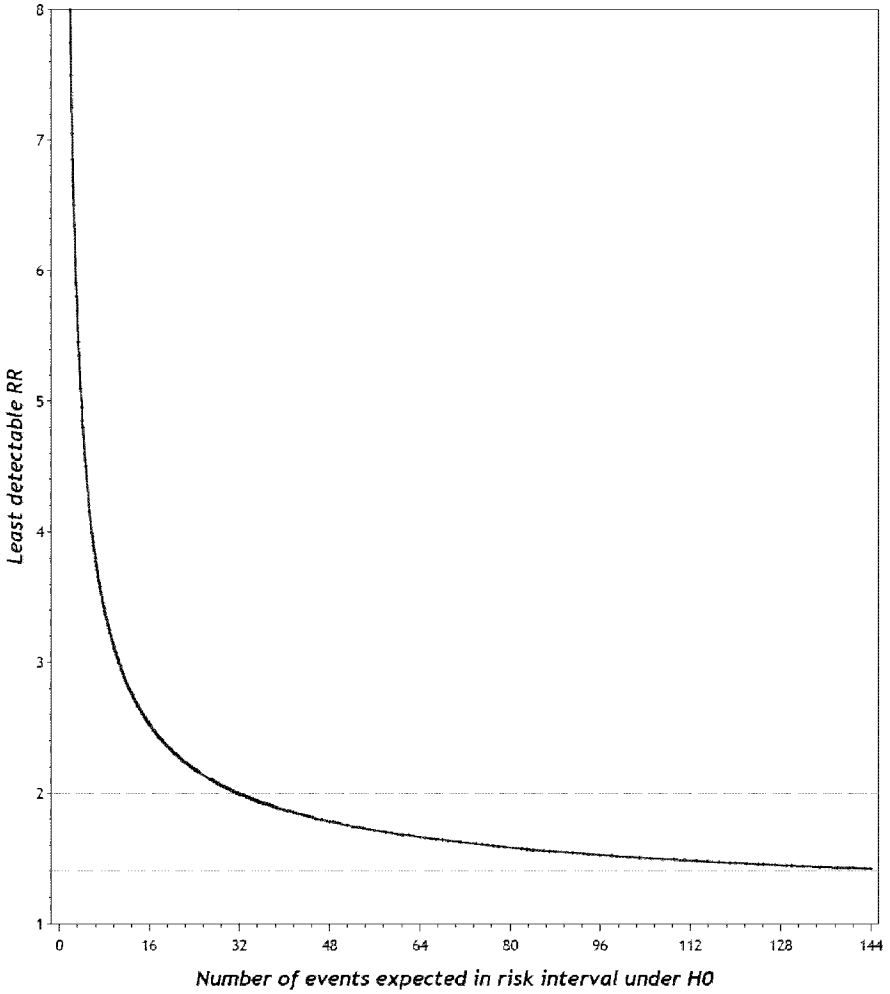
Power (Aim 1)

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

VaST Agenda – April 12, 2021

Open session
1:30 - 3:00

1:30-1:35 - Announcements

1:35-1:40 - Emerging issues (Tom Shimabukuro, CDC)

1:40-2:00 - DoD (Drs. Jay Montgomery and Renata Engler, DoD)

2:00-2:10 - Discussion

2:10-2:15 - VAERS (Dr. John Su)

2:15-3:00 - Discussion