Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/12/2021 5:12:01 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]; 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]) [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] RE: VaST - Agenda for April 12 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL
Attachments: nejmoa2104882.pdf; nejmoa2104840.pdf; VAERS for VaST 12 Apr 2021_mod2.pdf

Attached is a slightly modified VAERS presentation and two articles of interest.

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From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD)
Sent: Monday, April 12, 2021 10:45 AM
To: Anderson, Steven (FDA/CBER) <[redacted]>; Beresnev, Tatiana (NIH) [C] <[redacted]>; Broder, Karen (CDC/DDID/NCEZID/DHQP) <[redacted]>; Calvert, Geoffrey M. (CDC/NIOSH/WTCHP) <[redacted]>; Clark, Matthew (IHS/ALB) <[redacted]>; Clark, Thomas A. (CDC/DDID/NCIRD/DVD) <[redacted]>; Cohn, Amanda (CDC/DDID/NCIRD/OD) <[redacted]>; Collins, Limone <[redacted]>; Cunningham, Fran <[redacted]>; Daley, Matt <[redacted]>; Destefano, Frank (CDC/DDID/NCEZID/DHQP) <[redacted]>; Dooling, Kathleen L. (CDC/DDID/NCIRD/DVD) <[redacted]>; Edwards, Kathy <[redacted]>; Farizo, Karen (FDA/CBER) <[redacted]>; Forshee, Richard (FDA/CBER) <[redacted]>; Gee, Julianne (CDC/OID/NCPDCID) <[redacted]>; Helfand, Rita (CDC/DDID/NCEZID/OD) <[redacted]>; Hiers, Susan G. (CDC/DDID/NCIRD/OD) <[redacted]>; Hopkins, Bob <[redacted]>; Jackson, Lisa <[redacted]>; Kelman, Jeffrey A. (CMS/CM) <[redacted]>; Kulldorf, Martin <[redacted]>; LaPorte, Kathleen (CDC/DDID/NCIRD/ID) <[redacted]>; Lee, Grace <[redacted]>; MacNeil, Jessica R. (CDC/DDID/NCIRD/OD) <[redacted]>; Markowitz, Lauri (CDC/DDID/NCIRD/DVD) <[redacted]>; Marquez, Paige L. (CDC/DDID/NCEZID/DHQP) <[redacted]>; Mbaeyi, Sarah (CDC/DDID/NCIRD/OD) <[redacted]>; Mullen, Jennifer (CDC/DDID/NCEZID/DHQP) <[redacted]>; Myers,

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Subject: VaST - Agenda for April 12 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL

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

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BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

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SUMMARY

We report findings in five patients who presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against coronavirus disease 2019 (Covid-19). The patients were health care workers who were 32 to 54 years of age. All the patients had high levels of antibodies to platelet factor 4–polyanion complexes; however, they had had no previous exposure to heparin. Because the five cases occurred in a population of more than 130,000 vaccinated persons, we propose that they represent a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia.

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THE EUROPEAN MEDICINES AGENCY HAS APPROVED FIVE VACCINES against coronavirus disease 2019 (Covid-19), and more than 600 million doses have been administered globally.[1] In Norway, older adults living in institutional settings and health care professionals who are in close contact with patients with Covid-19 have been prioritized to receive the BNT162b2 mRNA Covid-19 vaccine (Pfizer–BioNTech). In addition, the ChAdOx1 nCoV-19 vaccine (AstraZeneca) has been administered to health care professionals younger than 65 years of age who do not have close contact with patients with Covid-19. As of March 20, 2021, when administration of the vaccine was paused, a total of 132,686 persons in Norway had received the first dose of the ChAdOx1 nCoV-19 vaccine and none had received the second dose.[2]

Within 10 days after receiving a first immunization with ChAdOx1 nCoV-19, five health care workers 32 to 54 years of age presented with thrombosis in unusual sites and severe thrombocytopenia. Four of the patients had major cerebral hemorrhage. Here we describe this vaccine-induced syndrome of severe thrombosis and thrombocytopenia found among these five patients admitted to Oslo University Hospital.

CASE REPORTS

Patient 1 was a 37-year-old woman with headaches that developed 1 week after vaccination with ChAdOx1 nCoV-19. At presentation to the emergency department the next day, she had fever and persistent headaches. She was found to have severe thrombocytopenia (Table 1). Computed tomography (CT) of the head showed

Table 1. Characteristics of the Patients.*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age — yr	37	42	32	39	54
Sex	Female	Female	Male	Female	Female
Preexisting conditions	Pollen allergy	Pollen allergy	Asthma	None	Hypertension
Medication on admission	Contraceptive pill	Contraceptive vaginal ring	None	None	Hormone-replacement therapy, antihypertensive agents
Time from vaccination to admission — days	8	10	7	10	7
Symptoms	Fever, headaches, visual disturbances	Headaches, drowsiness	Back pain	Headaches, abdominal pain	Headaches, hemiparesis
Location of thrombosis	Cortical veins, left transverse sinus, and sigmoid left sinus	Cortical veins, left transverse sinus, and left sigmoid sinus	Portal vein, left hepatic vein, splenic vein, azygos vein, hemiazygos vein, and several basivertebral veins	Inferior sagittal sinus, vein of Galen, straight sinus, right transverse sinus, and right sigmoid sinus	Cortical veins, superior sagittal sinus, both transverse sinuses, and left sigmoid sinus
Platelet count nadir — per mm^3	22,000	14,000	10,000	70,000	19,000
D-dimer peak — mg/liter	>35	>35	>35	13	>35
INR peak	1.2	1.0	1.1	1.3	1.1
aPTT peak — sec	25	31	25	25	29
Fibrinogen nadir — g/liter†	2.1	0.8	2.3	1.2	1.2
SARS-CoV-2 antibody test results					
Nucleocapsid protein	Negative	Negative	Negative	Negative	Negative
Spike protein	Positive	Positive	Positive	Positive	Positive
Anticoagulation treatment	Initial low dose of LMWH	Reduced dose of LMWH	Reduced dose of LMWH	Reduced dose of LMWH	Heparin (5000 IU)
No. of platelet units transfused	7	19	2	0	2
Other treatment	None	Methylprednisolone (1 mg/kg), IVIG (1 g/kg)	Prednisolone (1 mg/kg), IVIG (1 g/kg)	Prednisolone (1 mg/kg), IVIG (1 g/kg)	Methylprednisolone (1 mg/kg), IVIG (1 g/kg)
Outcome	Fatal	Fatal	Full recovery	Full recovery	Fatal

* The abbreviation aPTT denotes activated partial thromboplastin time, INR international normalized ratio, IVIG intravenous immune globulin, LMWH low-molecular-weight heparin, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† The reference range used for fibrinogen at Oslo University Hospital is 1.9 to 4.0 g per liter.

thrombosis in the left transverse and sigmoid sinuses. Because of the low platelet count, a reduced dose of dalteparin (2500 IU daily) was given. The next day, her clinical condition deteriorated, and a new CT scan showed a massive cerebellar hemorrhage and edema in the posterior fossa. She was treated with platelet transfusions and decompressive craniectomy. During surgery, massive and uncontrollable edema developed. The patient died on day 2 after surgery.

Patient 2 was a 42-year-old woman who had headaches 1 week after vaccination with ChAdOx1 nCoV-19. Her condition worsened rapidly, and she presented with reduced consciousness at presentation to the emergency department 3 days later. Her platelet count was 14,000 per cubic millimeter. ADAMTS13 activity was found to be normal. CT venography revealed venous thrombosis with occlusion of the transverse and sigmoid sinuses and hemorrhagic infarction in the left hemisphere. Hemicraniectomy was performed, and treatment with dalteparin at a dose of 2500 IU daily was initiated. She received multiple platelet transfusions over the following days. On day 8, methylprednisolone (1 mg per kilogram of body weight per day) and intravenous immune globulin (1 g per kilogram per day) were administered. The platelet count increased thereafter (Fig. 1). However, the patient died after 2 weeks in the intensive care unit (ICU) from increased intracranial pressure and severe cerebral hemorrhagic infarction on day 15.

Patient 3, a 32-year-old man, presented to the emergency department with a backache 7 days after vaccination with ChAdOx1 nCoV-19. He had no preexisting conditions apart from asthma. No clinical signs of bleeding and no neurologic deficits were evident. Blood tests showed severe isolated thrombocytopenia (Table 1). A thoracoabdominal CT scan showed thrombosis of several branches of the portal vein with occlusion of the left intrahepatic portal vein and left hepatic vein. In addition, thrombosis was observed in the splenic vein, the azygos vein, and the hemiazygos vein. Contrast-enhanced magnetic resonance imaging (MRI) of the spine showed areas of hypointensity in several thoracic vertebrae and basivertebral veins, indicating compromised venous drainage. He was treated with intravenous immune globulin (1 g per kilogram per day for 2 days) and prednisolone (1 mg per kilogram per day). Dalteparin was administered at a dose of 5000 IU (one dose on the first day and two doses on the second day), after which the platelet count returned to normal and the dose was increased to 200 IU per kilogram per day (Fig. 1). An abdominal CT scan indicated partial resolution of thrombosis. He was discharged from the hospital on day 12 in good health with warfarin and tapering doses of prednisolone.

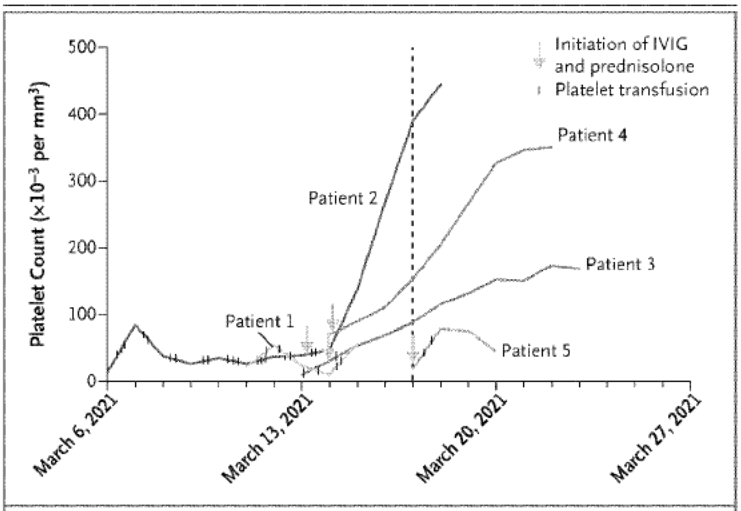

Figure 1. **Platelet Count Responses to Treatment.**
The vertical dashed line indicates the time at which the results of platelet factor 4 (PF4)–polyanion antibody tests were known. IVIG denotes intravenous immune globulin.

Patient 4, a previously healthy 39-year-old woman who was vaccinated with ChAdOx1 nCoV-19, presented to the emergency department with abdominal pain and headaches 8 days after vaccination. A mild thrombocytopenia was revealed. An abdominal ultrasound examination was normal, and she was discharged. The headaches increased in intensity, and she returned to the emergency department 2 days later. Cerebral CT with venography showed massive thrombosis in the deep and superficial cerebral veins and right cerebellar hemorrhagic infarction. The platelet count was 70,000 per cubic millimeter. She was afebrile and had no signs of infection and no neurologic deficits. Treatment with dalteparin (200 IU per kilogram per day), prednisolone (1 mg per kilogram per day), and intravenous immune globulin (1 g per kilogram per day for 2 days) was started. The platelet count was normalized within 2 days (Fig. 1). Follow-up CT venography showed recanalization in the affected cerebral venous sinuses. When she was

discharged after 10 days, the symptoms had resolved. Her anticoagulation treatment was changed from dalteparin to warfarin, and treatment with prednisolone was continued in tapering doses.

Patient 5, a 54-year-old woman with a history of hypertension who was receiving hormone-replacement therapy, presented to the emergency department with stroke symptoms that had been present when she woke up from sleep, including hemiparesis on the left side of her body, 1 week after vaccination with ChAdOx1 nCoV-19. The platelet count was 19,000 per cubic millimeter, and CT of the head showed a right frontal hemorrhage. She received a platelet transfusion before she was transferred to our hospital, where treatment with methylprednisolone (1 mg per kilogram per day) and intravenous immune globulin (1 g per kilogram per day for 2 days) was commenced. A CT scan with venography showed a massive cerebral vein thrombosis with global edema and growth of hematoma (Table 1, and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Venous recanalization was achieved 4 hours after admission by endovascular intervention with thrombectomy after administration of 5000 IU of unfractionated heparin. During the procedure, a fully dilated right pupil was observed, and decompressive hemicraniectomy was performed immediately. Two days later, treatment was withdrawn because of an uncontrollable increase in intracranial pressure.

METHODS

ETHICAL CONSIDERATIONS

Written informed consent for publication was obtained from all patients. In the event that the patient was not able to provide consent, a relative of the patient provided written informed consent. The authors vouch for the accuracy and completeness of the data in this report.

IMMUNOASSAYS AND FUNCTIONAL AND SEROLOGIC TESTING

Antibodies to platelet factor 4 (PF4) in complex with poly(vinyl sulfonate) (heparin analogue) in patient serum were tested with a LIFECODES PF4 IgG enzyme-linked immunosorbent assay (ELISA) (Immucor) in accordance with the manufacturer's instructions (dilution, 1:50), including a confirmatory inhibition test with heparin in high concentration. Serial dilution of serum in an ELISA was also performed.[3] Patient serum was also evaluated in a functional test with the use of heparin-induced multiple-electrode aggregometry on a Multiplate analyzer (Dynabyte Medical).[4,5] Here, the ability of serum to aggregate platelets was measured in the presence of saline buffer and in the presence of unfractionated heparin at high concentration (96 IU per milliliter) and low concentration (0.96 IU per milliliter).

Serum antibodies to the spike and nucleocapsid proteins of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were measured with the Roche Elecsys platform and with an in-house bead-based assay for IgG antibodies to full-length recombinant proteins.[6]

RESULTS

LABORATORY TESTING

Levels of D-dimer were elevated at the time of admission in all patients. The international normalized ratio (INR) and activated partial thromboplastin time were within the normal range. The fibrinogen level was lower than normal in Patient 2 and was slightly lower than normal in Patients 4 and 5 (Table 1). The C-reactive protein level was moderately elevated in Patients 1, 3, and 5. Screening for thrombophilia with proteins C and S and antithrombin was negative. Antiphospholipid antibodies were detected only in Patient 3, who had a slightly elevated anticardiolipin IgG antibody level of 43 IgG phospholipid (GPL) units. Levels of complement proteins (C1q, C4, and C3) and activation products (sC5b-9) were within the normal range in all patients. No patients had signs of hemolysis, and ADAMTS13 activity was normal in the one patient in whom it was assessed.

PLATELET IMMUNOLOGIC TESTING

All five patients had high levels of IgG antibodies to PF4–polyanion complexes, as indicated by strikingly high optical density values — in the range of 2.9 to 3.8 — measured by ELISA. The reactivity was efficiently inhibited by heparin in all samples (Fig. 2). Functional activity of serum from a patient with typical heparin-induced

thrombocytopenia was compared with that of serum from our patients. Platelets from the patient with heparin-induced thrombocytopenia were not activated unless low levels of heparin were added, and platelet aggregation was efficiently reduced by high heparin levels (Fig. 3). Platelets in serum from Patients 1, 3, 4, and 5 were clearly activated in the absence of added heparin. The platelet aggregation curve for Patient 2 was not a sigmoid curve and was considered to be inconclusive. Platelet aggregation was inhibited efficiently by high-dose heparin in Patients 3 and 4 but was inhibited less efficiently in Patients 1 and 5.

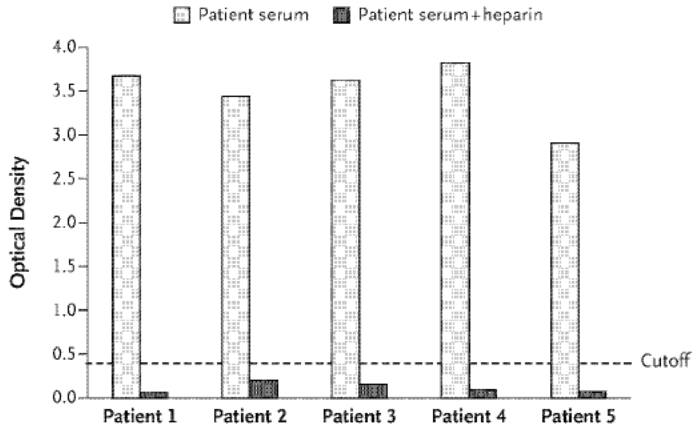

Figure 2. **IgG PF4–Polyanion Detection in Serum.**
IgG PF4–polyanion antibodies in serum from the patients were measured by enzyme-linked immunosorbent assay. Serum from all the patients showed strong reactivity that was efficiently inhibited (>97%) by the addition of a saturating dose of heparin (100 IU per milliliter). Samples were run in duplicate. A mean optical density of 0.4 or higher indicates the presence of antibodies.

COVID-19 SEROLOGIC TESTING

All five patients were negative for antibodies to SARS-CoV-2 nucleocapsid protein. Thus, previous infection with SARS-CoV-2 was highly unlikely. The levels of antibodies to spike protein varied with the assay, but anti-spike binding was detected in at least one assay in all five patients. The variation most likely reflects the fact that the anti-spike vaccine response was in an early phase.

DISCUSSION

We present five cases of severe venous thromboembolism in unusual sites and concomitant thrombocytopenia that occurred 7 to 10 days after vaccination for Covid-19. Four of the patients had severe cerebral venous thrombosis with intracranial hemorrhage, and the outcome was fatal in three. Thrombotic thrombocytopenic purpura and immune thrombocytopenic purpura were not suspected because of the absence of hemolysis and because of the good response to platelet transfusions, respectively. A common denominator in all five patients was a high level of antibodies to PF4–polyanion complexes. We therefore propose that these cases represent a vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia (VITT).

All the patients had strikingly high levels of antibodies to PF4–polyanion complexes. Although the optical density values may not be directly comparable between studies, it is worth noting that 5 to 7% of blood donors have detectable PF4–heparin antibodies; however, typical blood donors rarely have levels yielding an optical density higher than 1.6.[7] Moreover, in patients with typical heparin-induced thrombocytopenia, optical density values higher than 2 are unusual.[8] Nearly all healthy adults have a reservoir of B cells specific for PF4–heparin complexes; production of "heparin-induced thrombocytopenia–like" antibodies by these B cells is kept in check by immune regulatory mechanisms.[9,10]

In contrast to platelet aggregation in patients with typical heparin-induced thrombocytopenia, platelet aggregation in our patients was less dependent on physiological levels of heparin and was less sensitive to inhibition with high-dose heparin. Since Patients 1, 2, 3, and 4 had received low-molecular-weight heparin before blood samples were obtained, we cannot rule out the presence of circulating complexes containing antibodies bound to PF4 and low-molecular-weight heparin. Such complexes are generally disrupted in the presence of a high concentration of unfractionated heparin (96 IU per milliliter), but this was not observed in all cases. Moreover, Patient 5 had not received heparin. Collectively, these results suggest that the serum in these patients contained immune complexes with a mixture of antibody specificities similar

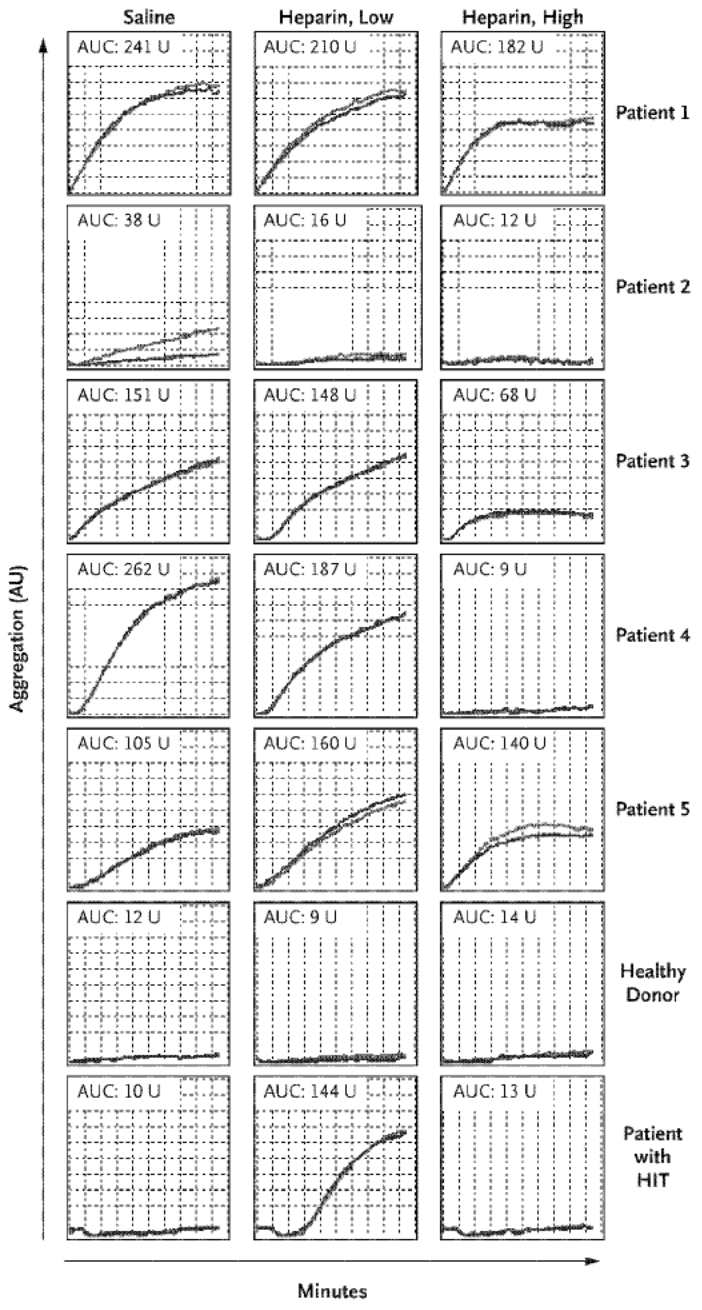

Figure 3. **Platelet-Aggregating Potential of Serum in Functional Testing.**
Aggregation of donor platelets after incubation with serum from the patients was measured by whole-blood impedance aggregometry. The measurements were performed in the presence of low or high heparin concentrations and in the absence of added heparin (saline). Serum from a healthy donor and serum from a patient with typical heparin-induced thrombocytopenia (HIT) are also shown. The red and blue lines represent duplicate measurements. AU denotes arbitrary units, and AUC the area under the curve.

to those described in the serum of patients with autoimmune heparin-induced thrombocytopenia.[8] It has not yet been determined whether the serum in our patients contained antibodies that bound PF4 alone.

Our findings indicate a shared pathophysiological basis of the condition in these five patients and should raise awareness that a syndrome similar to autoimmune heparin-induced thrombocytopenia may occur in some persons after vaccination with ChAdOx1 nCoV-19. By providing a link between thrombosis and the immune system, these results strengthen the view that vaccination may have triggered the syndrome.

In these cases, the characteristic antibodies were first identified after the initiation of anticoagulation treatment with low-molecular-weight heparin for life-threatening thrombosis and thrombocytopenia (Fig. 1). With the antibody results in hand, the clinicians faced the dilemma of deciding which anticoagulant to administer during this syndrome, which is usually associated with heparin. However, platelet counts were increasing after concomitant treatment with intravenous immune globulin and prednisolone had been initiated, and no clinical evidence suggested that thrombosis was increasing. Moreover, there were significant concerns that administration of anticoagulation alternatives to heparin or low-molecular-weight heparin might lead to aggravation of the ongoing intracerebral hemorrhage. Fondaparinux has a longer half-life than low-molecular-weight heparin, and a well-documented reversal strategy for factor Xa inhibitors is not available. It is worth noting that platelet counts continued to increase in all the patients despite continuation of treatment with low-molecular-weight heparin (Fig. 1). This finding may reflect the efficacy of early treatment with intravenous immune globulin, which has proved to be highly effective against spontaneous heparin-induced thrombocytopenia.[11]

Treating severely ill patients such as those described in this report is always challenging. The most important implication of our findings is that physicians should have a low threshold for requesting ELISA testing for PF4–polyanion antibodies, including confirmatory functional

testing, in patients who have unexpected symptoms after vaccination.

Although rare, VITT is a new phenomenon with devastating effects for otherwise healthy young adults and requires a thorough risk–benefit analysis. The findings of our study indicate that VITT may be more frequent than has been found in previous studies in which the safety of the ChAdOx1 nCoV-19 vaccine has been investigated.[12]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.

ABSTRACT

BACKGROUND

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

METHODS

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.

RESULTS

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Additional studies with PF4 or PF4–heparin affinity purified antibodies in 2 patients confirmed PF4-dependent platelet activation.

CONCLUSIONS

Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)

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Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are the most important countermeasure to fight the coronavirus 2019 (Covid-19) pandemic. From December 2020 through March 2021, the European Medicines Agency approved four vaccines on the basis of randomized, blinded, controlled trials: two messenger RNA–based vaccines — BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) — that encode the spike protein antigen of SARS-CoV-2, encapsulated in lipid nanoparticles; ChAdOx1 nCov-19 (AstraZeneca), a recombinant chimpanzee adenoviral vector encoding the spike glycoprotein of SARS-CoV-2; and Ad26.COV2.S (Johnson & Johnson/Janssen), a recombinant adenovirus type 26 vector encoding SARS-CoV-2 spike glycoprotein.

As of April 7, 2021, more than 82 million vaccine doses had been administered in the European Union; in Germany, approximately one quarter of vaccine recipients had received the ChAdOx1 nCov-19 vaccine.[1] Beginning in late February 2021, several cases of unusual thrombotic events in combination with thrombocytopenia were observed in patients after vaccination with ChAdOx1 nCov-19.

INDEX CASE

A previously healthy 49-year-old health care worker received her first dose of ChAdOx1 nCov-19 in mid-February 2021 (day 0). Over the next few days, she reported having minor symptoms (fatigue, myalgia, and headache). Beginning on day 5, she reported having chills, fever, nausea, and epigastric discomfort; she was admitted to a local hospital on day 10.

Laboratory results are shown in Table 1. The platelet count was 18,000 per cubic millimeter, and the D-dimer level was 35 mg per liter (reference value, <0.5). The results of other blood tests were normal except for γ-glutamyltransferase and C-reactive protein levels, which were elevated. SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction assay of a nasopharyngeal swab was negative.

Computed tomography (CT) showed portal-vein thrombosis and peripheral pulmonary emboli. The patient received a platelet concentrate and was transferred to a tertiary hospital. On arrival, she had epigastric discomfort and nausea but was otherwise in good condition (blood pressure, 125/88 mm Hg; heart rate, 65 beats per minute; temperature, 36.5°C). The physical examination was unremarkable except for moderate epigastric pain on palpation. She received intravenous antibiotics, analgesia, and one 4000-unit dose of low-molecular-weight heparin (enoxaparin), given subcutaneously.

The following day, the platelet count and fibrinogen level remained low, and the D-dimer and aminotransferase levels increased. The abdominal pain worsened, and repeat CT imaging showed progression of portal-vein thrombosis to include the splenic and upper mesenteric veins; in addition, small thrombi were visualized in the infrarenal aorta and both iliac arteries. Low-dose intravenous unfractionated heparin (500 IU per hour) was initiated but was stopped shortly thereafter because of a sudden onset of tachycardia and concern for gastrointestinal bleeding. The lactate level was 3.7 mmol per liter, and the patient was transferred to the intensive care unit. Repeat CT imaging revealed diffuse gastrointestinal bleeding with reduced perfusion of the intestinal wall and pancreas by splanchnic-vein thrombosis, along with ascites. She received red-cell and platelet transfusions, prothrombin complex concentrates, and recombinant factor VIIa but died on day 11. In addition to the diagnosed medical findings, autopsy revealed cerebral venous thrombosis.

CASE SERIES

By March 15, 2021, an additional 10 patients for whom clinical data were available were found to have one or more thrombotic complications beginning 5 to 16 days after vaccination with ChAdOx1 nCov-19. Characteristics of all 11 patients (including the index case) are presented in Table 2. Thrombotic events included cerebral venous thrombosis (in 9 patients), splanchnic-vein thrombosis (in 3 patients), pulmonary embolism (in 3 patients), and other types of thrombi (in 4 patients); 5 of 10 patients had more than one thrombotic event. Included in this analysis is one patient (Patient 11) who presented with fatal cerebral hemorrhage. The results of brain neuropathological analysis were pending at the time of this report, and cerebral venous thrombosis had not been ruled out; postmortem serum was available for testing for platelet-activating antibodies.

Table 1. **Laboratory Characteristics of the Index Patient.***

Laboratory Analysis	Reference Value	Day 10		Day 11	
		8:00 a.m.	8:00 p.m.	8:00 a.m.	8:00 p.m.
Hemoglobin (g/dl)	12.0–16.0	12.3	11.3	10.9	9.1
Platelet count (per mm^3)	150,000–350,000	18,000	37,000	25,000	13,000
Leukocytes (per mm^3)	4000–10,000	6,600	7,100	10,900	15,500
Activated partial thromboplastin time (sec)	<35	34	41.6	37.9	32.3
International normalized ratio	0.9–1.1	1.4	1.3	1.2	1.3
Thrombin time (sec)	<21	NA	25.7	NA	23.7
Fibrinogen (mg/dl)	200–400	NA	101	126	78
D-dimer (mg/liter)	<0.5	35	142	NA	NA
Aspartate aminotransferase (U/liter)	<35	33	88	160	98
Alanine aminotransferase (U/liter)	<35	46	94	167	155
γ-Glutamyltransferase (U/liter)	<40	141	110	103	78
Lactate dehydrogenase (U/liter)	<250	NA	337	NA	344
C-reactive protein (mg/dl)	<0.5	8.8	7.6	8.7	6.8
Lactate (mmol/liter)	<1.6	0.9	NA	1.7	3.6

* NA denotes not assessed.

Among these patients, the median age was 36 years (range, 22 to 49); 9 of 11 were women. All the patients presented with concomitant thrombocytopenia (median nadir of platelet count, approximately 20,000 per cubic millimeter; range, 9000 to 107,000). One patient had preexisting von Willebrand disease, anticardiolipin antibodies, and factor V Leiden. None of the patients had received heparin before the onset of symptoms or the diagnosis of thrombosis. Given the striking clinical resemblance of this disorder to autoimmune heparin-induced thrombocytopenia (a prothrombotic thrombocytopenic disorder that can be triggered by heparin and certain other anions and that features heparin-independent platelet-activating properties), serum obtained from 4 of the 11 patients was referred for immediate investigation of platelet-activating antibodies directed against platelet factor 4 (PF4)–heparin. After characterizing the antibodies in serum obtained from Patients 1 through 4, we subsequently obtained serum from 5 of the 7 remaining patients. In addition, our reference laboratory received further serum samples from patients who were suspected of having prothrombotic thrombocytopenia related to ChAdOx1 nCov-19 vaccination. (No detailed clinical information regarding these patients was available at the time of this report.)

METHODS

We purified platelets from whole blood (obtained from healthy volunteers) that had undergone anticoagulation with adenine citrate dextrose solution A. None of the volunteers had been taking antiplatelet drugs or had been vaccinated in the previous 10 days. We prepared platelets using methods that have been described previously.[2,3] In a subgroup of experiments, platelets were preincubated in buffer with ChAdOx1 nCov-19 (1:2000 dilution) and washed before use. Washed platelets (75 microliters) were incubated with either buffer, a low-molecular-weight heparin (reviparin [Abbott]), or PF4 (Chromatec) in either the presence or absence of the FcγIIa receptor–blocking antibody IV.3. In some experiments, unfractionated heparin (100 IU per

Table 2. Clinical and Laboratory Summary of 11 Patients with Available Clinical Information.*

Variable	Patient Number										
	1	2	3	4	5	6	7	8	9	10	11
Platelet nadir (per mm^3)	13,000	107,000	60,000	9,000	23,000	75,000	29,000	16,000	13,000	8,000	NA because of death
CVT	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Pending†
Splanchnic-vein thrombosis‡	Yes	No	No	No	Yes	No	No	No	No	Yes	No
Pulmonary embolism	Yes	Yes	No	No	Yes	No	No	No	No	No	No
Other thrombosis	Aortoiliac	No	No	No	Right intraventricular, iliofemoral vein, IVC	No	No	Widespread microvascular (brain, lungs, kidneys)§	Multiple organ thrombi§	No	Cerebral hemorrhage†
Symptom onset (no. of days after vaccination)	5	6	9	7	13	7	8	8	16	11	12¶
INR peak	1.40	1.12	NA	1.66	1.25	1.05	1.34	NA	1.70	NA	NA
PTT peak (sec)	41.6	29.0	NA	46.6	64.8	23.0	45.0	NA	46.1	NA	NA
D-dimer peak (mg/liter)	142.0	1.8	13.0	NA	NA	2.6	>33.0	NA	21.0	>35.0	NA
Fibrinogen nadir (mg/dl)	78	568	NA	NA	173	NA	210	NA	40	80	NA
PF4–heparin ELISA (optical density)	3.16	3.08	3.50	3.40	1.20	NA	NA	2.02	3.51	2.35	2.16
PF4-dependent platelet-activation assay	Pos	Pos‖	Pos	Pos	Pos	NA	NA	Pos	Pos	Pos	Pos
Heparin treatment	Yes	LMWH**	Unknown	Yes	Yes	Unknown	Yes	No	No	No	No
Other medical condition	No	No	No	CND	VWD-I; FVL ACL-Abs	No	No	No	No	No	Unknown
Outcome	Fatal	Recovering	Unknown	Fatal	Recovering	Recovering	Recovering	Fatal	Fatal	Fatal	Fatal

* Data are listed for the first four patients (including the index patient) who were assessed and who had detailed laboratory results and for another seven patients who had thrombocytopenia, thrombosis, or fatal bleeding and for whom clinical information was available. One of the 11 patients was taking an oral contraceptive; two other patients had a hormonal intrauterine device. ACL-Abs denotes anticardiolipin antibodies, CND chronic neurologic disorder, CVT cerebral venous (sinus) thrombosis (indicating the presence of cerebral-vein thrombosis, sinus thrombosis, or both), ELISA enzyme-linked immunosorbent assay, FVL factor V Leiden, INR international normalized ratio, IUD intrauterine device, IVC inferior vena cava, LMWH low-molecular-weight heparin, NA not available, PF4 platelet factor 4, Pos positive, PTT partial thromboplastin time, and VWD-I type 1 von Willebrand disease.

† Brain neuropathological results were pending at time of this report; CVT had not been ruled out.

‡ Splanchnic-vein thrombosis indicates thrombosis of the portal, mesenteric, splenic, or hepatic veins.

§ These were postmortem findings.

¶ This is the day that the body of the deceased was found.

‖ The sample that had an initial negative result on the PF4-enhanced platelet-activation assay was subsequently shown to test positive when tested against other platelet donors.

** Treatment with low-molecular-weight heparin was associated with clinical improvement and rising platelet counts (107,000 to 132,000 over a period of 3 days). The patient was then switched to a direct oral anticoagulant when the ELISA showed positive results for antibodies against PF4–heparin, with further clinical and platelet-count recovery.

milliliter) was added to inhibit PF4-dependent reactions, or ChAdOx1 nCov-19 (1:50 dilution) was added per well. Serum was coincubated with PF4 and platelets in the presence of immune globulin (Privigen IVIG [CSL Behring]) at a concentration of 10 mg per milliliter. After establishing assay conditions using serum from the initial four patients, we investigated another 24 serum samples that tested positive on immunoassay to validate our findings. We refer to this modified platelet-activation test as the PF4-enhanced platelet-activation test.

To measure direct antibody binding, we used two immunoassays, a PF4–heparin enzyme-linked immunosorbent assay (ELISA) and a PF4 ELISA, with antibody binding measured by a secondary antihuman IgG, as described previously.[4] In addition, antibodies from two serum samples were affinity purified by immobilized PF4–heparin and immobilized PF4, and the purified antibodies were tested in the assays. (Details about this method are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

We defined reactivity on ELISA according to the optical-density units as strong (≥2.00), intermediate (1.00 to 1.99), or weak (0.50 to 0.99). On the PF4-enhanced platelet-activation test, reactivity was graded according to the time that had elapsed until platelet aggregation,[5] with shorter reaction times indicating stronger platelet activation (strong activation, 1 to 5 minutes; intermediate activation, >5 to 15 minutes; and weak activation, >15 to 30 minutes).

RESULTS

All 11 patients in the initial analysis had moderate-to-severe thrombocytopenia and unusual thrombosis, particularly cerebral venous thrombosis and splanchnic-vein thrombosis (Table 2). We also found evidence of disseminated intravascular coagulation in 5 of the patients on the basis of the combination of greatly elevated D-dimer levels (>10.0 mg per liter) and one or more abnormalities in the international normalized ratio, partial thromboplastin time, or fibrinogen level. (Of the 6 patients with available fibrinogen levels, 4 had hypofibrinogenemia.)

Although evaluating the outcomes of different management strategies was not the goal of our study, we noted with interest the clinical course of Patient 2, who presented with pulmonary embolism and mild thrombocytopenia (platelet count, 107,000 per cubic millimeter), without disseminated intravascular coagulation. This patient received therapeutic-dose low-molecular-weight heparin for 3 days, with clinical improvement and an increase in the platelet count to 132,000; at that time, a positive result on PF4–heparin ELISA was obtained, and the patient was switched to oral apixaban, with continued clinical and laboratory recovery.

Table 2 also shows results of the PF4–heparin ELISA, including for the first 4 patients in whom detailed laboratory studies were performed. Serum obtained from these patients showed strong reactivity on PF4–heparin ELISA, with optical densities of more than 3.00 units (reference value, <0.50); all reactivity reactions were inhibited to less than 0.50 units by the addition of heparin (100 IU per milliliter). Figure 1 shows the serologic profile of the 4 initial patients, as assessed by means of the platelet-activation assay. Three of the four serum samples showed weak-to-moderate reactivity at buffer control, which was inhibited by low-molecular-weight heparin. In three of the samples, PF4 (10 μg per milliliter) greatly enhanced reactivity; serum from Patient 2 subsequently showed strong platelet activation in the presence of PF4 when retested along with platelets from other volunteers. All reactions were blocked by monoclonal antibody IV.3 and immune globulin at a dose of 10 mg per milliliter, which indicated that platelet activation had occurred through platelet Fcγ receptors (Fig. 1A). None of the controls showed platelet activation (data not shown).

Platelet activation was enhanced when platelets were pelleted from platelet-rich plasma, resuspended in washing buffer, preincubated (1:2000) with ChAdOx1 nCov-19, centrifuged, and resuspended in the final suspension buffer or when they were coincubated in the suspension buffer with ChAdOx1 nCov-19 (1:50). The monoclonal antibody IV.3 blocked PF4-dependent platelet activation in all 7 samples that were tested.

Figure 1B shows the results of platelet activation in serum samples obtained from 24 patients with clinically suspected vaccine-induced immune thrombotic thrombocytopenia who tested positive on the screening PF4–heparin ELISA. Whereas approximately half the serum samples (13 of

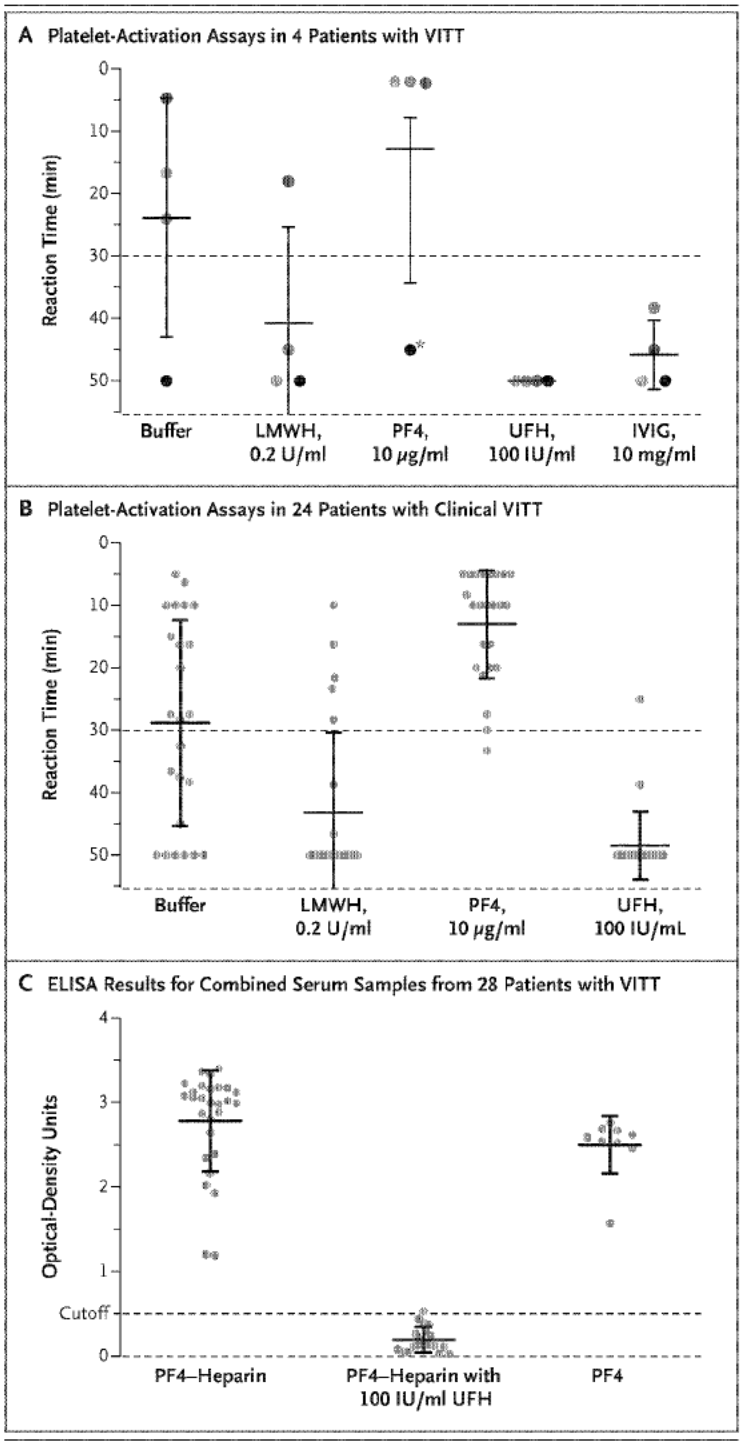


Figure 1. Reactivity of Patient Serum on Platelet-Activation Assays and Immunoassays.

Panel A shows the results of platelet-activation assays in serum samples obtained from the first 4 patients with vaccine-induced immune thrombotic thrombocytopenia (VITT) who were assessed in the study. The four colors in each experiment indicate the results obtained in the four samples; values are expressed as means, with I bars indicating standard errors. The platelet-activation assay is performed by adding 20 μl of patient serum to 75 μl of washed platelets per well of a microtiter plate that contains the other reagents as indicated. Reactivity is expressed semiquantitatively as reaction time, with a shorter reaction time indicating stronger platelet-activating levels. A reaction time of more than 30 minutes indicates background or clinically insignificant reactivity. The asterisk indicates the reactivity of the outlier serum, which was strongly positive on subsequent retesting along with platelets of other volunteers in the presence of platelet factor 4 (PF4). Panel B shows the results of platelet-activation assays in serum samples obtained from an additional 24 patients with clinical VITT. The reactivity pattern resembles that observed in the 4 patients who were initially investigated. The serum caused variable platelet activation in the presence of buffer, which for most samples was inhibited in the presence of low-molecular-weight heparin but was strongly enhanced in the presence of PF4; in contrast, high levels of unfractionated heparin inhibited the reaction in all but one serum sample. Panel C shows the results of PF4–heparin and PF4 immunoassays of serum obtained from patients with VITT (including all 28 samples represented in Panels A and B) that showed PF4-dependent platelet activation. The results, which were obtained with the use of a microplate reader with a 450-nm filter, include all 28 PF4–heparin enzyme-linked immunosorbent assay (ELISA) experiments (with the addition of 100 IU per milliliter of heparin in 19 experiments) and the results of 10 PF4 ELISA experiments. The cutoff for a negative result is 0.50 optical-density units. LMWH denotes low-molecular-weight heparin, UFH unfractionated heparin, and IVIG intravenous immune globulin.

24) showed platelet activation at buffer control, most samples (19 of 24) were inhibited by low-molecular-weight heparin; almost all samples (22 of 24) showed platelet activation by the addition of PF4. All but one serum sample was inhibited by a high dose of heparin.

Figure 1C shows strong reactivity of the serum samples obtained from all 28 patients (including Patients 1, 2, 3, 4, 5, 8, 9, 10, and 11) in results on both PF4–heparin and PF4 ELISA, with inhibition by high heparin doses. Antibodies that were affinity purified with the use of either immobilized PF4 or immobilized PF4–heparin showed the same reactivity pattern as the original serum — in other words, they strongly activated platelets in the presence of 10 μg per milliliter of PF4, an effect that was completely inhibited by a high concentration of heparin.

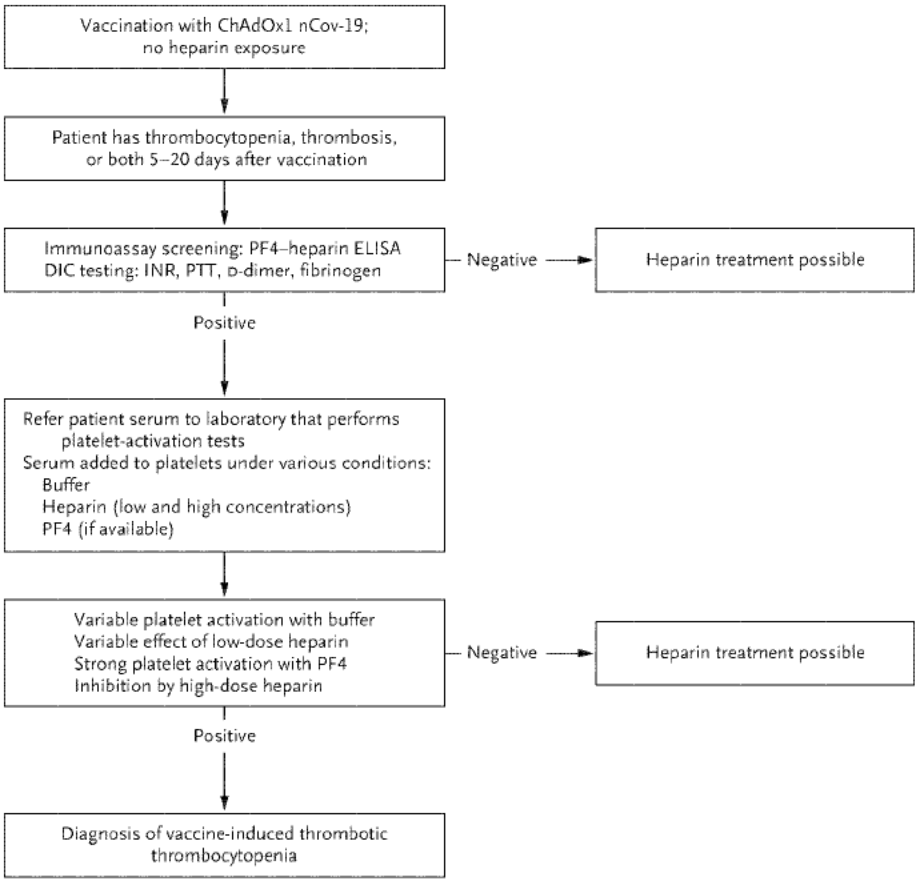
DISCUSSION

The clinical picture of moderate-to-severe thrombocytopenia and thrombotic complications at unusual sites beginning approximately 1 to 2 weeks after vaccination against SARS-CoV-2 with ChAdOx1 nCov-19 suggests a disorder that clinically resembles severe heparin-induced thrombocytopenia, a well-known prothrombotic disorder caused by platelet-activating antibodies that recognize multimolecular complexes between cationic PF4 and anionic heparin.[6] However, unlike the usual situation in heparin-induced thrombocytopenia, these vaccinated patients did not receive any heparin to explain the subsequent occurrence of thrombosis and thrombocytopenia.

In recent years, it has been recognized that triggers other than heparin can cause a prothrombotic disorder that strongly resembles heparin-induced thrombocytopenia on both clinical and serologic grounds, including certain polyanionic drugs (e.g., pentosan polysulfate,[7] antiangiogenic agent PI-88,[8] and hypersulfated chondroitin sulfate[8]). Such a prothrombotic syndrome has also been observed in the absence of preceding exposure to any polyanionic medication, such as after both viral and bacterial infections[9,10] and knee-replacement surgery.[11,12] These various clinical scenarios with apparent nonpharmacologic triggers have been classified under the term autoimmune heparin-induced thrombocytopenia.[13] Unlike patients with classic heparin-induced thrombocytopenia, patients with autoimmune heparin-induced thrombocytopenia have unusually severe thrombocytopenia, an increased frequency of disseminated intravascular coagulation, and atypical thrombotic events. Serum from these patients strongly activate platelets in the presence of heparin (0.1 to 1.0 IU per milliliter) but also in the absence of heparin (heparin-independent platelet activation). When these unusual antibodies are observed in patients who have thrombocytopenia without preceding heparin exposure, the term "spontaneous" heparin-induced thrombocytopenia syndrome[13,14] has been used. Sometimes, patients in whom heparin-induced thrombocytopenia develops after exposure to heparin present with atypical clinical features, such as an onset of thrombocytopenia beginning several days after stopping heparin (delayed-onset heparin-induced thrombocytopenia[15,16]) or thrombocytopenia that persists for several weeks despite the discontinuation of heparin (persisting or refractory heparin-induced thrombocytopenia[17,18]). Serum from these patients also shows the phenomenon of heparin-independent platelet-activating properties.

These clinical features that resemble those of autoimmune heparin-induced thrombocytopenia were observed in the patients with vaccine-induced immune thrombotic thrombocytopenia. The serum usually showed strong reactivity on the PF4–heparin ELISA. Moreover, serum showed variable degrees of platelet activation in the presence of buffer that was in most cases greatly enhanced in the presence of PF4 (Fig. 1A and 1B). More strikingly, most serum showed inhibition, rather than increased activation, in the presence of low-dose low-molecular-weight heparin (0.2 U per milliliter of anti–factor Xa). In addition, antibodies from two patients, which were affinity purified on either immobilized PF4 or immobilized PF4–heparin, strongly activated platelets but only in the presence of PF4. Enhancement of platelet activation by PF4 is also a feature of heparin-induced thrombocytopenia[19,20] and has been used to enhance detection of platelet-activating antibodies in diagnostic testing for this adverse drug reaction.[21] Whether these antibodies are autoantibodies against PF4 induced by the strong inflammatory stimulus of vaccination or antibodies induced by the vaccine that cross-react with PF4 and platelets requires further study.

Although we found enhanced reactivity of patient serum with platelets in the presence of ChAdOx1 nCov-19, this is likely to be an in vitro artifact. It is well known that adenovirus binds to platelets[22] and causes platelet activation.[22,23] Furthermore, the amount of adenovirus in a 500-microliter vaccine injection administered 1 or 2 weeks earlier would seem unlikely to contribute to subsequent platelet activation observed in these patients. However, interactions between the vaccine and platelets or between the vaccine and PF4 could play a role in pathogenesis. One possible trigger of these PF4-reactive antibodies could be free DNA in the vaccine. We have previously shown that DNA and RNA form multimolecular complexes with PF4, which bind antibodies from patients with heparin-induced thrombocytopenia and also induce antibodies



Treatment Options	Comment
High-dose intravenous immune globulin (1 g per kg for 2 days)	Raises platelet count and decreases hypercoagulability (by analogy with autoimmune HIT); inhibits platelet activation by platelet-activating anti-PF4 antibodies (platelet Fcγ receptors)
Anticoagulants often used to treat heparin-induced thrombocytopenia	Direct oral Xa inhibitors (apixaban, rivaroxaban) Direct thrombin inhibitors (argatroban, bivalirudin) Indirect (antithrombin-dependent) Xa inhibitors: danaparoid (not available in U.S.), fondaparinux
Platelet transfusions	Avoid unless presence of bleeding (theoretical prothrombotic risk)
Vitamin K antagonist	Contraindicated during acute thrombocytopenia and disseminated intravascular coagulation (microthrombosis associated with protein C depletion)

Figure 2. **Potential Diagnostic and Therapeutic Strategies for Management of Suspected Vaccine-Induced Immune Thrombotic Thrombocytopenia.**

Shown is a decision tree for the evaluation and treatment of patients who have symptoms of thrombocytopenia or thrombosis within 20 days after receiving the ChAdOx1 nCov-19 vaccine and who have had no heparin exposure. The diagnostic and therapeutic strategies in such patients differ from those in patients with autoimmune heparin-induced thrombocytopenia (HIT).[13] DIC denotes disseminated intravascular coagulation, INR international normalized ratio, PF4 platelet factor 4, and PTT partial thromboplastin time.

against PF4–heparin in a murine model.[24] Unfortunately, other Covid-19 vaccines were not available to us for testing.

Our findings have several important clinical implications. First, clinicians should be aware that in some patients, venous or arterial throm-

bosis can develop at unusual sites such as the brain or abdomen, which becomes clinically apparent approximately 5 to 20 days after vaccination. If such a reaction is accompanied by thrombocytopenia, it can represent an adverse effect of the preceding Covid-19 vaccination. To date, this reaction has been reported only with the ChAdOx1 nCov-19 vaccine, which has been used in approximately 25% of vaccine recipients in Germany and in 30% of those in Austria.

Second, ELISA to detect PF4–heparin antibodies in patients with heparin-induced thrombocytopenia is widely available and can be used to investigate patients for potential postvaccination thrombocytopenia or thrombosis associated with antibodies against PF4.[25] A strongly positive ELISA result that is obtained in a patient who has not been recently exposed to heparin would be a striking abnormality.

Third, we have shown that these antibodies recognize PF4 and that the addition of PF4 greatly enhances their detectability in a platelet-activation assay. Since vaccination of millions of persons will be complicated by a background of thrombotic events unrelated to vaccination, a PF4-dependent ELISA or a PF4-enhanced platelet-activation assay may be used to confirm the diagnosis of vaccine-induced immune thrombotic thrombocytopenia through this novel mechanism of postvaccination formation of platelet-activating antibodies against PF4. Although treatment decisions such as administering intravenous immune globulin and starting anticoagulation do not need to await laboratory diagnosis, detection of these unusual platelet-activating antibodies will be highly relevant for case identification and future risk–benefit assessment of this and other vaccines.

Figure 2 shows a potential diagnostic and therapeutic strategy for managing this novel prothrombotic thrombocytopenic disorder. One consideration is to administer high-dose intravenous immune globulin to inhibit Fcγ receptor–mediated platelet activation. This recommendation parallels emerging experience in the treatment of severe autoimmune heparin-induced thrombocytopenia in which high-dose intravenous immune globulin has resulted in rapid increases in platelet count and de-escalation of hypercoagulability.[12,26] We found that the addition of immune globulin in doses that are readily achieved clinically was effective in inhibiting platelet activation by patients' antibodies. Clinician reluctance to start anticoagulation may be tempered by administering high-dose intravenous immune globulin to raise the platelet count, especially when a patient presents with severe thrombocytopenia and thrombosis, such as cerebral venous thrombosis.

Given the parallels with autoimmune heparin-induced thrombocytopenia, anticoagulant options should include nonheparin anticoagulants used for the management of heparin-induced thrombocytopenia,[27] unless a functional test has excluded heparin-dependent enhancement of platelet activation. Finally, we suggest naming this novel entity vaccine-induced immune thrombotic thrombocytopenia (VITT) to avoid confusion with heparin-induced thrombocytopenia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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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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* * 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

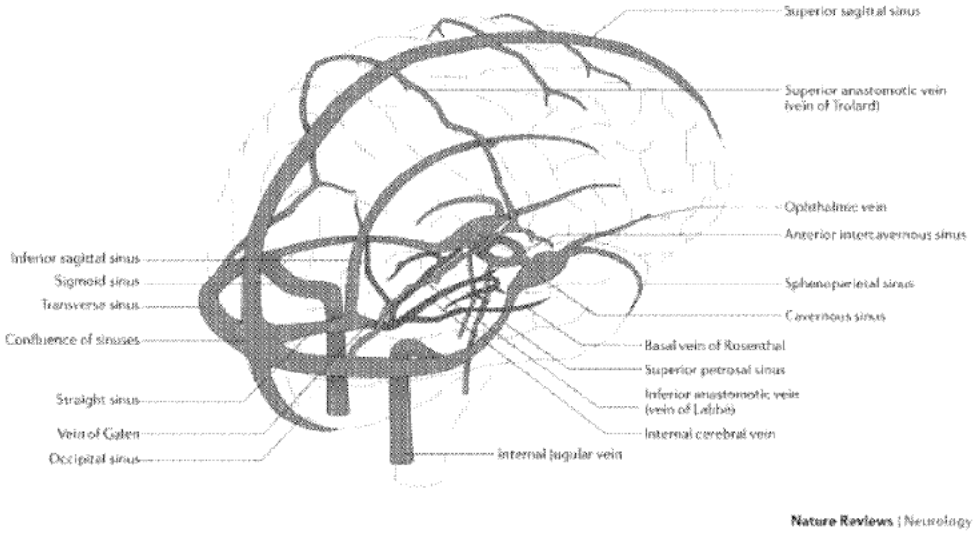
- Estimated annual incidence of myopericarditis ~ 1 to 2 per 100,000 population*
- Assumed risk period of 15.3% (Pfizer) and 14.4% (Moderna) of a calendar year
- Assume doses administered = vaccinated population, adjusted for proportion by dose number
    - As of Apr 11, 63% of Pfizer was Dose 1; 64% 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 11,
  - 96,586,783 doses of Pfizer's vaccine administered – no reports of CVST
  - 83,847,244 doses of Moderna's vaccine administered – 3 reports of CVST
  - 6,453,740 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; 3/6 obese; 3-4 (+) thrombocytopenia
- 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

[redacted]

TTY: [redacted] www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/15/2021 10:43:45 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]gov]; 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]) [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 12 (CONFIDENTIAL)
Attachments: 2021_04_12_VaST minutes_draft.docx; 2021-04-12 - VaST Report Data Table DRAFT.docx

Dear VaST members and attendees,

It has been a busy week and our Monday VaST call seems more than just a few days ago!
Attached are the draft minutes and summary report from the call. Please let us know if there are any corrections or comments.

The next VaST call is April 19, 1:30 – 3:00 pm EDT.
The agenda will include further evaluation of CVST and follow-up of the CMS RCA signal for PE.

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
April 12, 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, Martin Kulldorf, Grace Lee (Co-Chair), Veronica McNally, Laura Riley, Rob Schechter, Keipp Talbot, Patricia Whitley-Williams

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

CDC: Karen Broder, Denise Cardo, Tom Clark, Frank Destefano, Julianne Gee, Rita Helfand, Susan Hiers, Megan Lindley, Lauri Markowitz (CDC Co-lead), Jessica MacNeil, Paige Marquez, Sarah Mbaeyi, Michael McNeil, Jennifer Mullen, 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, Fran Cunningham, Richard Forshee, Kwan Hur, Narayan Nair

DHA: Renata Engler, Bruce McClenathan, Jay Montgomery, Margaret Ryan

Agenda

- Announcements
- Emerging issues
- Defense Health Agency (DHA)
- VAERS

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

- Reminders about COI and confidentiality
- VaST meetings expectations and procedures overview
- Doses distributed: 237,796,105; Doses administered: 187,047,131 (last updated: April 11)
    - Doses distributed: Pfizer-BioNTech: 118,670,955; Moderna: 102,932,700; J&J/Janssen: 16,192,450
    - Doses administered: Pfizer- BioNTech: 96,586,783; Moderna: 83,847,244; J&J/Janssen: 6,453,740; Unknown: 159,364
    - First doses: 119,242,902; Fully vaccinated: 72,630,892
    - 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"]

Emerging issues – Dr. Tom Shimabukuro, CDC

Dr. Shimabukuro provided updates on planned publications of safety of mRNA vaccines during pregnancy and the VSD RCA data. The pregnancy manuscript is expected to be published next week and will report that there are no safety concerns thus far. The VSD RCA publication will include RCA to date in mRNA vaccines using vaccine concurrent comparator and unvaccinated concurrent comparator.

Myocarditis Following mRNA SARS-CoV-2 Vaccines and Further Considerations – Drs. Jay Montgomery and Renata Engler, DHA

Dr. Montgomery gave an overview of 14 cases of myocarditis in male service members following mRNA vaccines and reviewed one case in detail as an example. The cases were hospitalized with acute chest pain within 30 days of vaccination and all met the CDC case definition for probable myocarditis. In the majority of patients, all clinical symptoms resolved within days to a few weeks. DHA feels there is a high likelihood that cardiac symptoms following COVID-19 vaccination represent a hypersensitivity eosinophilic myocarditis.

Dr. Engler presented additional clinical details on myocarditis cases and historical perspectives of myocarditis/pericarditis following smallpox vaccination.

Questions and discussion

1. Was the impression that these were hypersensitivity eosinophils myocarditis based on cardiac biopsy? Was other testing performed to make this diagnosis?
    - With improvements in cMRI, many feel that diagnosis of myocarditis can be made without biopsy. Their experience with Smallpox vaccine associated myocarditis including three biopsies, supports hypersensitivity myocarditis of the eosinophilic type. None of the cases had any suggestion of hypereosinophilic syndrome.
2. What about Echovirus? Enterovirus?
    - Viral studies included Parvo, Coxsackie/enterovirus, CMV, HHV-6, HSV-1
3. Were these individuals exercising vigorously in relationship to the administration of their COVID vaccines?
    - The relationship between exercise and myocarditis is not causal, but rather exercise has been associated with increase morbidity or mortality (Bethesda study); exercise can elevate troponin levels but not to the degree seen in the post vaccine myocarditis patients (10-400 times upper limits of normal). However, at this time there is not sufficient information from the cohort upon which to advance a hypothesis (9 unknowns, 4 yes, 1 no).
4. Was there a temporal pattern of symptoms after onset? Did chest pain increase over 12 hours after onset, for example.
    - In most cases there was an increase after symptom onset, with mild-moderate chest pain initially. In a few patients, pain was sudden and more severe, but no pattern was seen.
5. Can you provide an estimate of a denominator of vaccinated individuals? And can you remind us denominators by age group?
    - About 640k received 2nd dose as of end of March. Stratifications by age group are not readily available.

VAERS – Dr. John Su, CDC

Dr. Su reviewed the case definitions of myocarditis, pericarditis, and cerebral venous sinus thrombosis (CVST) and presented the associated VAERS data. The number of reported cases for myopericarditis (N=97: Pfizer-BioNTech 43; Moderna 54; J&J 0) does not exceed the anticipated number of cases. The estimated annual incidence of myopericarditis is 1-2 per 100,000.

Questions and discussion – Myopericarditis

1. Regarding the risk periods used in the slides, how were the 15.3% and 14.4% calculated?
    - These correspond to 56 and 53 days; the midpoint of the time during which these vaccines have been in use was selected as the risk period (so 112 days/2 = 56 days).
2. How do the VAERS myopericarditis numbers compare with reports after other vaccines in the same age group, such as e.g. influenza. Was there a similar time distribution?
    - The COVID-19 vaccine myopericarditis numbers have not been compared to the influenza vaccine numbers yet.

Questions and discussion – CVST

1. Do you have the ability to chart reports to VAERS in relation to when the first stories appeared in the news about blood clots? Whether causal or not causal, it seems that news reports could promote reporting to VAERS.
    - Yes, can look at this.
2. Did any of the cases have a workup for HIT?
    - Yes, and CISA is looking into these cases.
3. How did the cases present?
    - They presented with thrombocytopenia as well as headache, and CVST
    - NEJM describing these cases post AZ vaccine are in an article, see below.
    - EMA noted in their press conference that there was a numeric imbalance in the J&J RCT, so thromboembolism was something they were keeping an eye out for.
    - In Europe, to date, no specific risk factors have been identified. They are currently still evaluating the situation.
4. Have hematologists been consulted?
    - CDC is aware of publications from Germany. Currently, hematologists from Vanderbilt and Johns Hopkins are begin consulted
    - Treatment guidance is usually provided from professional groups, not CDC. That being said, treatment guidance is avoidance of heparin and prompt therapy with IVIG and non-heparin anticoagulants.
5. This appears to be a problem mainly for young women, but there is uncertainty.
    - The cases in Europe for the AZ vaccine was ~2:1 females to males compared to what we have seen with J&J vaccine.
    - There have not been any pregnant patients as this time correct?
        - None of the 6 reported patients were pregnant
    - In the J&J COVID-19 vaccine RCT, there was one case of CVST with thrombocytopenia in a 25-year-old vaccinated male.
6. There was discussion about reaching out the manufacturer to obtain more information, including about cases after J&J Ebola vaccine or other pre-licensure trials of adenovirus vector vaccines. It was noted that J&J has been asked to provide information to EMA. VaST will work with the ACIP COVID-19 vaccine work group and contact the manufacturer.
7. What is the age distribution of the CVST cases in Europe?

- The age ranges from 22-54 for the AZ vaccine (NEJM reports)
- The age ranges from 18-48 (median 33) for the J&J vaccine cases in VAERS

8. What is the proposed mechanism since CVST has not been observed after the mRNA vaccines?
    - Unclear; possibly due to differences between DNA and RNA vaccines?
9. The most striking and concerning finding to date is the disproportionate number of reports after J&J vaccine compared with no cases of CVST with thrombocytopenia after the mRNA vaccines.

Questions and discussion – CVST communication

1. What are the next steps? How will the communication process proceed?
    - FDA interested to hear discussions on VaST today.
    - There are multiple discussions planned between CDC and FDA on what actions to take and how to proceed with dissemination of the information. A joint statement FDA-CDC will be released.
2. VaST members were particularly concerned about appropriate treatment, which is not heparin, and getting information out to providers.
    - CDC has several avenues to get information to the public health community and the health care providers.
3. The risk-benefit balance needs to be discussed with the ACIP COVID-19 Vaccine workgroup
    - U of Cambridge's approach to benefit risk in a publication, see below.
4. There was discussion about the timing of further communications of fainting and vasovagal episodes that led to closure of several vaccination sites last week and concern about confusion and mixed messages. When further communications are made about those, it can be stressed that they are not related to CVST. The presyncopal events can also be discussed in the context similar events after other vaccinations.

Articles of interest

- Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination – [HYPERLINK "https://www.nejm.org/doi/full/10.1056/NEJMoa2104840?query=featured_home"]
- Guidance produced from the Expert Haematology Panel (EHP) focused on Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT) - [HYPERLINK "https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf"]
- Communicating the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine – [HYPERLINK "https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/976877/CovidStats_07-04-21-final.pdf"]

Combined Systems Safety Monitoring Report
DRAFT
April 12, 2021
Confidential

COVID-19 Vaccine Safety Technical (VaST) Subgroup report from April 12, 2021 meeting

The VaST session included presentations on a series of myocarditis cases following COVID-19 vaccination from the Defense Health Agency and a summary from the Vaccine Adverse Event Reporting System (VAERS) on myopericarditis and cerebral sinus venous thrombosis (CSVT) cases. Other scheduled presentations were postponed until next week to allow more time to discuss the emerging information on CVST.

CDC provided a summary of cases of CSVT reported to VAERS through April 10, 2021. Three cases have been reported following the Moderna mRNA vaccine (82.6M doses administered) and there have been no cases reported following the Pfizer-BioNTech mRNA vaccine (94.7M doses administered); none of the three cases following the Moderna vaccine were associated with thrombocytopenia. To date, six cases have been reported among recipients of the Johnson & Johnson vaccine (5.9M doses administered) and available clinical information suggests that most of the cases among recipients of the Johnson & Johnson vaccine were associated thrombocytopenia and all occurred in persons younger than age 50 years. These cases among recipients of the Johnson & Johnson vaccine are clinically similar to recently reported cases from Europe following the AstraZeneca COVID-19 vaccine, a different adenoviral vector COVID-19 vaccine that is not authorized for use in the United States (Schultz et al. DOI: 10.1056/NEJMoa2104882 and Greinacher et al. DOI: 10.1056/NEJMoa2104840).

- Given the availability of other vaccines for prevention of COVID-19 in the United States, consideration of the risks and benefits for use of the Johnson & Johnson vaccine in specific subgroups needs to be urgently addressed.

- Information about this potential life-threatening adverse event should be promptly provided to clinicians to enhance early recognition and appropriate treatment of persons who develop thrombosis with thrombocytopenia following vaccination.

- VaST recommends timely and transparent communication to the public about these findings, also highlighting that global safety monitoring efforts and VAERS have enabled the CDC and FDA to rapidly detect these adverse events.

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) (Myopericarditis data through 4/5/2021 and CVST data through 4/11/2021)	All health events, adverse events of special interest[a]	US population	96,586,783 total doses administered	Descriptive and empirical Bayesian data mining	43 myopericarditis reports • 10 confirmed cases • Median age: 40 years 0 reports of cerebral venous sinus thrombosis	Anaphylaxis associated with vaccination, first detected by reports from UK and early reporting in the US; assessed by follow-up with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021) Myopericarditis not above background rates
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 Myocarditis case series presented	No concerns raised Myopericarditis to be further investigated with more robust systems
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) (Myopericarditis data through 4/5/2021 and CVST data through 4/11/2021)	All health events, adverse events of special interest[a]	US population	83,847,244 total doses administered	Descriptive and empirical Bayesian data mining	54 myopericarditis reports • 11 confirmed cases • Median age: 33 years 3 reports of cerebral venous sinus thrombosis (without thrombocytopenia)	Anaphylaxis associated with vaccination, first detected by early reporting in the US; assessed by follow-up with providers, chart review, CISA consultations; clinical guidance changed (initially in December 2020 and last updated March 5, 2021) Myopericarditis not above background rates
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 Myocarditis case series presented	Myopericarditis to be further investigated with more robust systems
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) (Myopericarditis data through 4/5/2021 and CVST data through 4/11/2021)	All health events, adverse events of special interest[a]	US population	3,090,712 total doses administered	Descriptive and empirical Bayesian data mining	0 reports of myopericarditis 6 reports of cerebral venous sinus thrombosis with thrombocytopenia • Median age: 33 years • All in females	Combined with data from Europe, data are concerning; ACIP COVID-19 vaccine WG and secretariat alerted
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

Message

From: Markowitz, Lauri (CDC/DDID/NCIRD/DVD) [redacted]
Sent: 4/19/2021 3:40:34 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]) [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]
CC: Kwan.Hu[redacted]; Rao, Agam K (CDC) [redacted]; laurie.a.aukes[redacted]; belongia.edward[redacted]; donahue.james[redacted]; bruce.fireman[redacted]; kristin.x.goddard[redacted]; hanson.kayla[redacted] kieke.burney[redacted]; Nicola.Klein[redacted]; Ned.Lewis[redacted]; mcclure.david[redacted]; ousseny.x.zerbo[redacted]
Subject: [EXTERNAL] VaST - Agenda for April 19 (1:30 - 3 pm ET) and presentations - CONFIDENTIAL
Attachments: 2021_04_19 VaST Meeting Agenda .docx; 1_TTS for VaST 19 Apr 2021.pdf; 2_AZ update 041921.pdf; 3_VSD RCA Covid-19 vax - update VaST - 04-19-2021-final.pdf; 4_Department of Veterans Affairs COVID-19 RCA 04-19-21_Final Update.pdf; 5_FDA VaST RCA results_20210419.pdf

Dear all,

This email includes the VaST agenda for today (below and attached) as well as 5 slide sets.

Three issues will be covered on the call: 1) update and refinement of cerebral venous sinus thrombosis (CVST)/thrombosis with thrombocytopenia syndrome (TTS) signal, 2) refinement of pulmonary embolism signal from CMS data, 3) myocarditis. The agenda attached has more information regarding approximate times for talks and discussion.

Also, the link to the new Brighton definition case definition for TTS is here:
https://brightoncollaboration.us/thrombosis-with-thrombocytopenia-syndrome-case-finding-definition/

VaST agenda overview:
Admin and announcements
CVST/TTS
- VAERS (John Su, CDC)
- CISA brief update (Karen Broder, CDC)
- GACVS update (Rita Helfand, CDC)

Rapid cycle analyses (RCA) - include data for TTS and CMS signal

VSD RCA (Eric Weintraub, KPNC)
VA RCA (Fran Cunningham, VA)
FDA CMS RCA (Richard Forshee, FDA)

Myocarditis

Follow-up and plans (Tom Shimabukuro, CDC)

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

Lauri Markowitz and Melinda Wharton

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

VaST Agenda – April 19, 2021

Open session
1:30 - 3:00

Three general topics for agenda today:

- Thrombosis with thrombocytopenia syndrome (TTS) signal
- PE signal from CMS data
- Myocarditis

1:30-1:35 - Announcements

1:35-1:50 - VAERS – TTS (John Su, CDC)

1:50-1:55 - Discussion

1:55-2:00 - CISA brief update (Karen Broder, CDC)

2:00-2:10 - GACVS (Rita Helfand, CDC)

2:10-2:15 - Discussion

2:15-2:45 - Rapid Cycle Analyses (RCA)

VSD RCA (Eric Weintraub, KPNC)

VA RCA (Fran Cunningham, VA)

FDA CMS RCA (Richard Forshee, FDA)

2:45-2:55 - Discussion

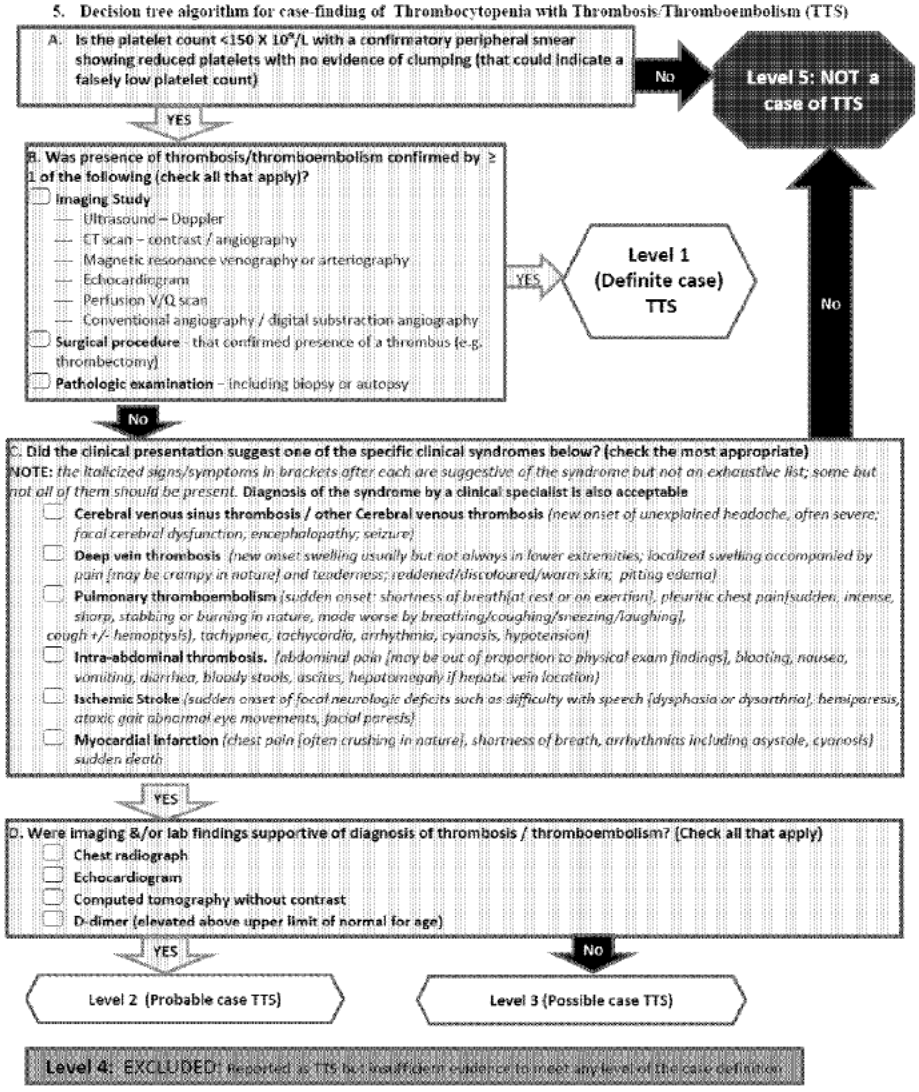
2:55-3:00 - Myocarditis, general plans (Tom Shimabukuro, CDC)

Reports of Thrombosis with Thrombocytopenia Syndrome (TTS) after Janssen COVID-19 vaccine, Mar 2 – Apr 16, 2021

April 19, 2021

John Su, MD, PhD, MPH

Case definition and case reports



Thrombocytopenia (<150,000 per mm^3)

AND either

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

OR

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

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

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

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

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

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

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

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

Initial and late signs and symptoms among CVST patients*, n=7 (patients listed in no particular order)

	Initial features	Late features
Patient 1	Headaches, lethargy	Severe headache, left-sided weakness, vomiting
Patient 2	Headaches	Severe headache, aphasia
Patient 3	Headaches, vomiting, fever	Left arm weakness, right gaze deviation, left neglect
Patient 4	Headaches, chills, myalgias	Severe abdominal pain and fever
Patient 5	Headache, chills, dyspnea, fever	Bruising, unilateral leg swelling, loss of consciousness
Patient 6	Back pain, bruising	Headache, abdominal pain
Patient 7	Headaches, vomiting	Neck pain, photophobia

*All were hospitalized and admitted to the intensive care unit

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

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

*All were hospitalized and admitted to the intensive care unit

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

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

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

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

Hematology test results among TTS patients, N=9

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

*Platelet factor 4 heparin induced thrombocytopenia

Treatment and outcomes among TTS patients, N=9

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

* 7 of these patients received argatroban; 1 received bivalirudin

Summary

PSICOVID_0000896

Summary

- The most recent draft Brighton Collaboration case definition for Thrombosis with Thrombocytopenia Syndrome (TTS) includes CVST *and other thrombi*; **thrombocytopenia is the hallmark of this syndrome**
- Based upon this definition, **9** reports of TTS to VAERS as April 16, 2021
  - Median age = 37 years (range: 18–59 years)
  - Median time to symptom onset 9 days (range 6–15 days)
  - No obvious patterns of risk factors detected
- Clinical features of Janssen cases are similar to those observed following the AstraZeneca COVID-19 vaccine in Europe
- Both Janssen and AstraZeneca vaccines contain replication-incompetent adenoviral vectors (human [Ad26.COV2.S] for Janssen and chimpanzee [ChAdOx1] for AstraZeneca)

Next steps

- Continue enhanced monitoring in VAERS and other vaccine safety systems (e.g., Vaccine Safety Datalink [VSD])
  - VSD: ~113K Janssen doses administered, 0 cases in risk interval(s)
- Investigate potential cases through detailed clinical reviews/chart reviews
- Examine potential approaches to better quantify risk
  - Can crudely estimate for CVST
  - Other thrombi?...
  - In combination with thrombocytopenia?

Acknowledgments

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

Centers for Disease Control and Prevention

COVID-19 Vaccine Task Force

COVID-19 Vaccine Task Force, Vaccine Safety Team

Immunization Safety Office

Division of Healthcare Quality Promotion

Clinical Immunization Safety Assessment Project

Vaccine Adverse Event Safety Network

Extra Slides

Platelets and thrombocytopenia (low platelets)*

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

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

Cerebral venous sinus anatomy

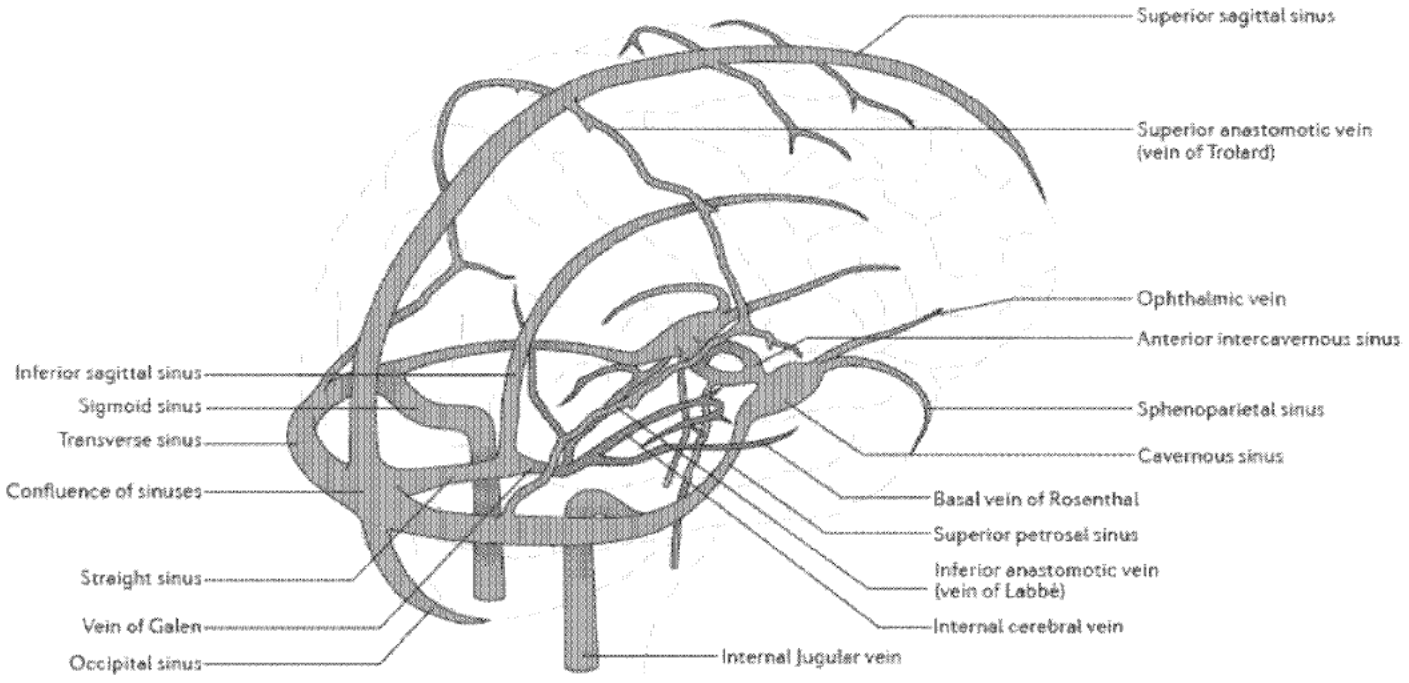


Figure 1 | **Anatomy of the cerebral venous system.** Diagram showing the main components of the cerebral venous system. Blue vessels represent the deep venous system.

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

CVST signs and symptoms

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

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

Cerebral venous sinus thrombosis (CVST)

Background epidemiology[1-3]

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

Risk factors[4]

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

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

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

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

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

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

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

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

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

Summary (cont.)

- **For clinicians**
  - Maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the Jansen COVID-19 vaccine, including severe headache, backache, new neurologic symptoms, severe abdominal pain, shortness of breath, leg swelling, petechiae (tiny red spots on the skin), or new or easy bruising. Obtain platelet counts and screen for evidence of immune thrombotic thrombocytopenia.
  - In patients with a thrombotic event and thrombocytopenia after the Jansen COVID-19 vaccine, evaluate initially with a screening PF4 enzyme-linked immunosorbent (ELISA) assay as would be performed for autoimmune HIT. Consultation with a hematologist is strongly recommended.
  - Do not treat patients with thrombotic events and thrombocytopenia following receipt of Janssen COVID-19 vaccine with heparin, unless HIT testing is negative.
  - If HIT testing is positive or unable to be performed in patient with thrombotic events and thrombocytopenia following receipt of Jansen COVID-19 vaccine, non-heparin anticoagulants and high-dose intravenous immune globulin should be strongly considered.
  - Report adverse events to VAERS, including serious and life-threatening adverse events and deaths in patients following receipt of COVID-19 vaccines as required under the Emergency Use Authorizations for COVID-19 vaccines.

Summary (cont.)

- **For public health**
  - Encourage healthcare providers and the public to report all serious and life-threatening adverse events and deaths following receipt of COVID-19 vaccines to VAERS as required under the EUAs for COVID-19 vaccines.
  - Disseminate information to healthcare providers in your jurisdictions.
- **For the public**
  - If you have received the Janssen COVID-19 vaccine and develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination, contact your healthcare provider, or seek medical care.
  - Report adverse events following receipt of any COVID-19 vaccine to VAERS.
  - If you are scheduled to receive the Janssen vaccine, please contact your healthcare provider, vaccination location, or clinic to learn about additional vaccine availability.

Astrazeneca and Thromboembolism with Thrombocytopenia

Drs Rita Helfand and Shanthi Pal

On behalf of

Global Advisory Committee on Vaccine Safety (GACVS) and WHO Pharmacovigilance Regulation and Safety Team

19 April 2021

Signals (being) reviewed by WHO and GACVS C19 subcommittee (since 22 Dec'20)	Pfizer-BioNTech BNT162b2 vaccine	Moderna mRNA-1273 vaccine	Oxford University – Astra Zeneca AZD1222 vaccine & Covishield (AZ-SII)	Others
Anaphylaxis	x	x		
Deaths	X	X		
Flu-like reactions			x	
Thromboembolic events			x	
Myocarditis				
Lymphadenopathy				
Hypertension				
Etc				

WHO GACVS's Deep-dive: Reports of Thromboembolic Events - March, 2021

World Health Organization

Summary : Several regulatory agencies paused use of AstraZeneca (AZ) vaccine after reports of small numbers of people with blood clots, some with low platelets, occurring after vaccination

GACVS sub-committee reviewed data from EMA, UK, India, and the global database

EMA: 18 cases of cerebral venous sinus thrombosis (CVST) of 20 million vaccines

UK's MHRA: 5 cases of CVST after 11 million vaccines

Conclusion:

- The vaccine continues to have a **positive benefit-risk profile**

- Available data: **no overall increase in clotting conditions** such as deep venous thrombosis or pulmonary embolism following administration of COVID-19 vaccines.

- **Very rare and unique thromboembolic events in combination with thrombocytopenia**, such as CVST, have been reported following vaccination with AZ COVID-19 vaccine in Europe; **it is not certain they were caused by vaccination**.

Investigation: Update April (Still evolving) - 1:

EMA: As of 3/22 (mostly EU and UK):

62 cases of CVST, most with thrombocytopenia and 24 cases of Splanchnic venous thrombosis; 18 fatal.
Around 25M doses administered

As of 4/4:

169 cases of CVST and 53 of splanchnic venous thrombosis. 34M doses administered in EU and UK

Rate estimate 1/100,000 doses, slightly less in UK (about 1/250k)

EMA conclusions:

Causal association is **plausible**

Based on clinical, mechanistic, epi findings. **Unable to identify definitive cause to date** but possibly similar to atypical **heparin-induced thrombocytopenia** (HIT) (two NEJM articles 4/9)

no specific risk factors to date: most < 60 years old and female, but given different ways vaccine used, unable to conclude age and gender risk factors to date

Investigation: Update April (Still evolving) - 2:

World Health Organization

EMA cont:

Benefit/risk ratio still **favorable** to use of vaccine

Added unusual blood clots with low platelets to the label as a **very rare side effect of Vaxzevria**

Healthcare provides should remain aware of the possibility of rare cases of blood clots with low platelets **within 2 weeks of vaccination**

Patients should seek medical assistance immediately if they have the following symptoms:

shortness of breath, chest pain, swelling of legs, persistent abdominal pain, neurologic symptoms, including severe and persistent headaches or blurred vision; tiny blood spots under the skin beyond the injection site.

Requested studies to provide more information

e.g., mechanisms, risk factors, etc.

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

Share

News 07/04/2021

EMA confirms overall benefit-risk remains positive

EMA's safety committee (PRAC) has concluded today that unusual blood clots with low blood platelets should be listed as very rare side effects of Vaxzevria (formerly COVID-19 Vaccine AstraZeneca).

In reaching its conclusion, the committee took into consideration all currently available evidence, including the advice from an ad hoc expert group.

EMA is reminding healthcare professionals and people receiving the vaccine to remain aware of the possibility of very rare cases of blood clots combined with low levels of blood platelets occurring within 2 weeks of vaccination. So far, most of the cases reported have occurred in women under 60 years of age within 2 weeks of vaccination. Based on the currently available evidence, specific risk factors have not been confirmed.

People who have received the vaccine should seek medical assistance immediately if they develop symptoms of this combination of blood clots and low blood platelets (see below).

UK- MHRA 7 April 2021

Through March 31: **79 reports of clots with low platelets**:

44 CVST with thrombocytopenia; 35 in other major veins. 19 deaths (11 < 50 yrs)

51 women, 28 men, aged 18-79 yrs. More women have received AZ Vaccine

Benefits continue to outweigh risks

but **careful consideration** be given to people who are at **higher risk of specific types of blood clots** because of medical conditions

Imposed **no age restrictions** (but their NITAG recommended those 18-29 yrs at low risk of infections get other vaccines). Noted slightly higher incidence in younger adults

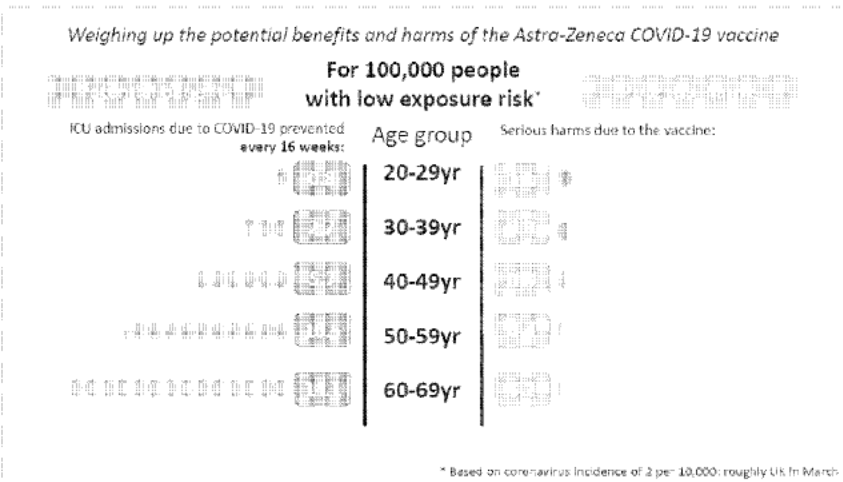
Continue to give second doses

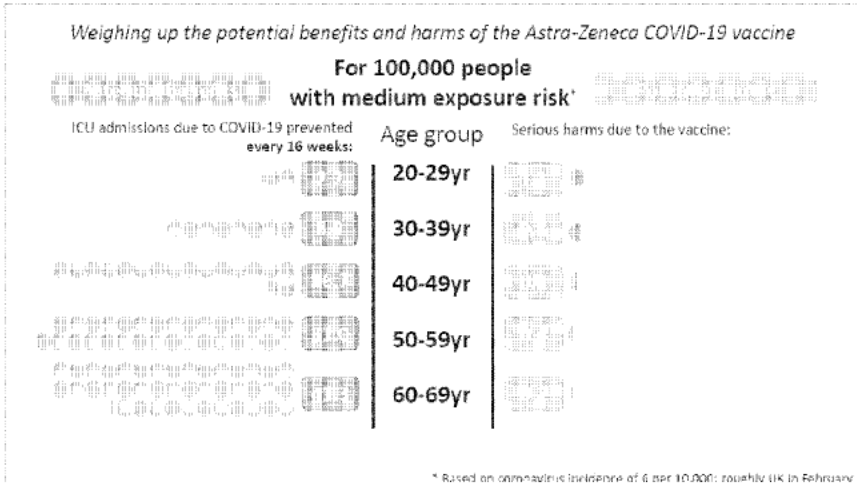
Link to vaccine of extremely rare blood clots with lower platelets stronger but more work needed – about **4/million**

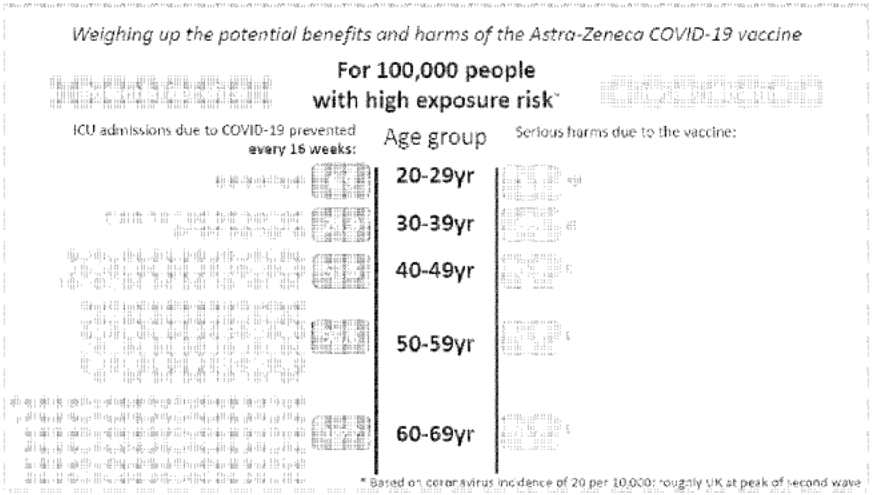
not seeing evidence of thromboembolism without low platelets

Potential benefits of the Astra-Zeneca COVID-19 vaccine continue to outweigh risks

https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots







Updated WHO Statement 07 April

World Health Organization

Causal relationship is plausible but not confirmed

Will continue to gather and review further data

Whilst concerning, these are rare events

balance against risk of deaths due to COVID-19

If severe symptoms (such as those listed in EMA statement), seek urgent medical care

Educate healthcare providers and persons being vaccinated

Need for harmonized case definitions

Need for active surveillance and further data

Full GACVS committee meeting 13 April

GACVS Meeting 13 April 2021 - 1

World Health Organization

Rare new adverse event called Thrombosis with Thrombocytopenia Syndrome (TTS) with Vaxzevria and Covishield. Brighton collaboration working on case definition

Not seen after mRNA vaccines to date

Biological mechanism being investigated

'platform specific' mechanism related to adenvovirus-vectored vaccines cannot be excluded.

Risk is low: Estimates to date 1/250,000 in UK and 1/100,000 in EU

Countries need to perform benefit-risk analysis, accounting for local epidemiology (including incidence and mortality from COVID-19 disease), age groups targeted for vaccination, and availability of alternative vaccines

GACVS supports further research into understanding mechanisms, epidemiology, and clinical syndromes, including risk factors, including age-related and gender-related risk

World Health Organization

GACVS Meeting 13 April 2021 - 2

Thrombosis in specific sites (such as brain and abdomen) appear to be a key feature of TTS

Clinicians should be alert to new, severe, persistent headache or other symptoms, such as severe abdominal pain and shortness of breath, with onset between 4-20 days after adenovirus-vectored COVID-190 vaccination

measure platelet levels, radiological imaging for thrombosis

alternate therapy (e.g., not heparin)

Communications regarding need to evaluate and report all potential cases

Continue safety monitoring of all vaccines

Need for open, transparent and evidence-based communications

Some Observations

World Health Organization

Learn from EU/UK

Unique clinical entity

thrombosis, not bleeding

Age/Gender still not resolved

Similarities with HIT but not identical – (e.g., very low platelets, higher PF4)

Implications for the world

Relevant links

WHO: https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield)

EU EMA: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

UK MHRA: https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots

UK JCVI: https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement/jcvi-statement-on-use-of-the-astrazeneca-covid-19-vaccine-7-april-2021

UK benefit/risk: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/976877/CovidStats_07-04-21-final.pdf

UK Haematology Experts: https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf

EMA Press Briefing: EMA press conference 7th April - YouTube

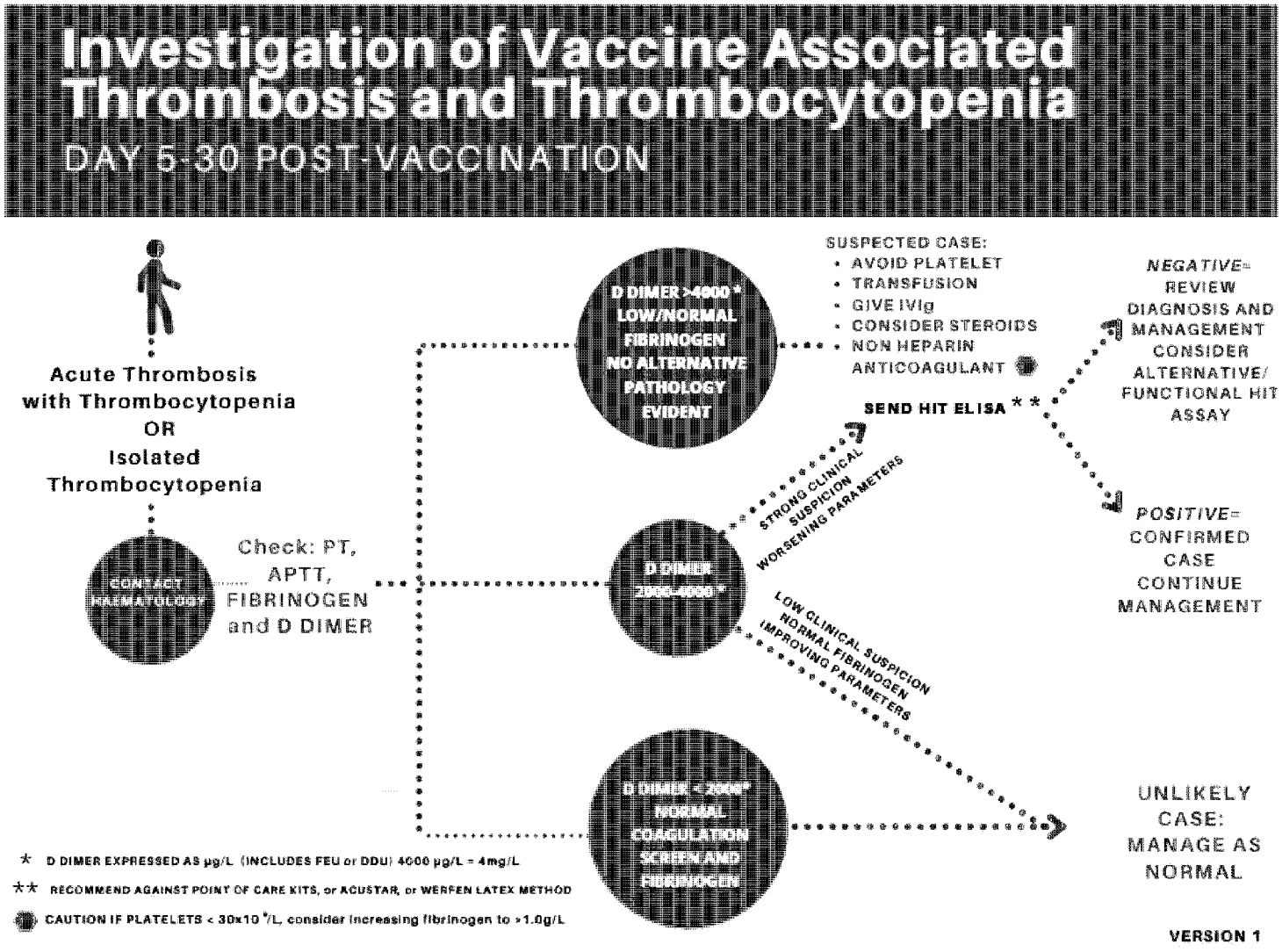
World Health Organization

Thank you. Questions?

Rita Helfand and Shanthi Pal

UK Expert Haemotology Panel 7 April 2021

World Health Organization



WHO GACVS Deep-dive: Reports of Thromboembolic Events March 2021- 2

World Health Organization

Recommendations:

- **Adequate education** should be provided to health-care professionals and persons being vaccinated to recognize the signs and symptoms of all serious adverse events after vaccinations with all COVID-19 vaccines, so that people may seek and receive prompt and relevant medical care and treatment.

- The GACVS subcommittee recommends that countries **continue to monitor the safety of all COVID-19 vaccines** and promote reporting of suspected adverse events.

- The GACVS subcommittee also agrees with the European Medicines Agency's plans to **further investigate and monitor for these events**.

The statement was prepared by PVG and GACVS, posted on WHO website on March 19th 2021.

- https://www.who.int/news/item/19-03-2021-statement-of-the-who-global-advisory-committee-on-vaccine-safety-(gacvs)-covid-19-subcommittee-on-safety-signals-relate

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:

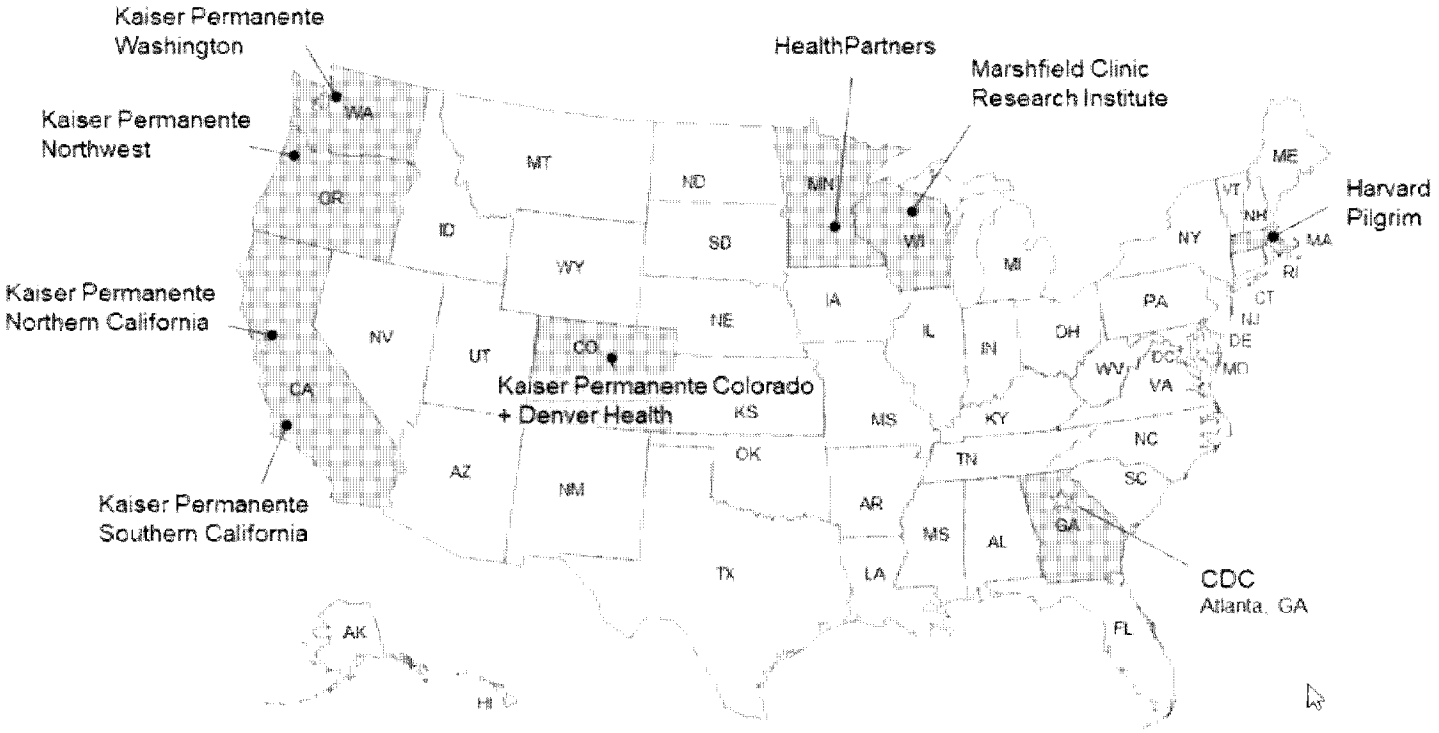
- To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

- 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)

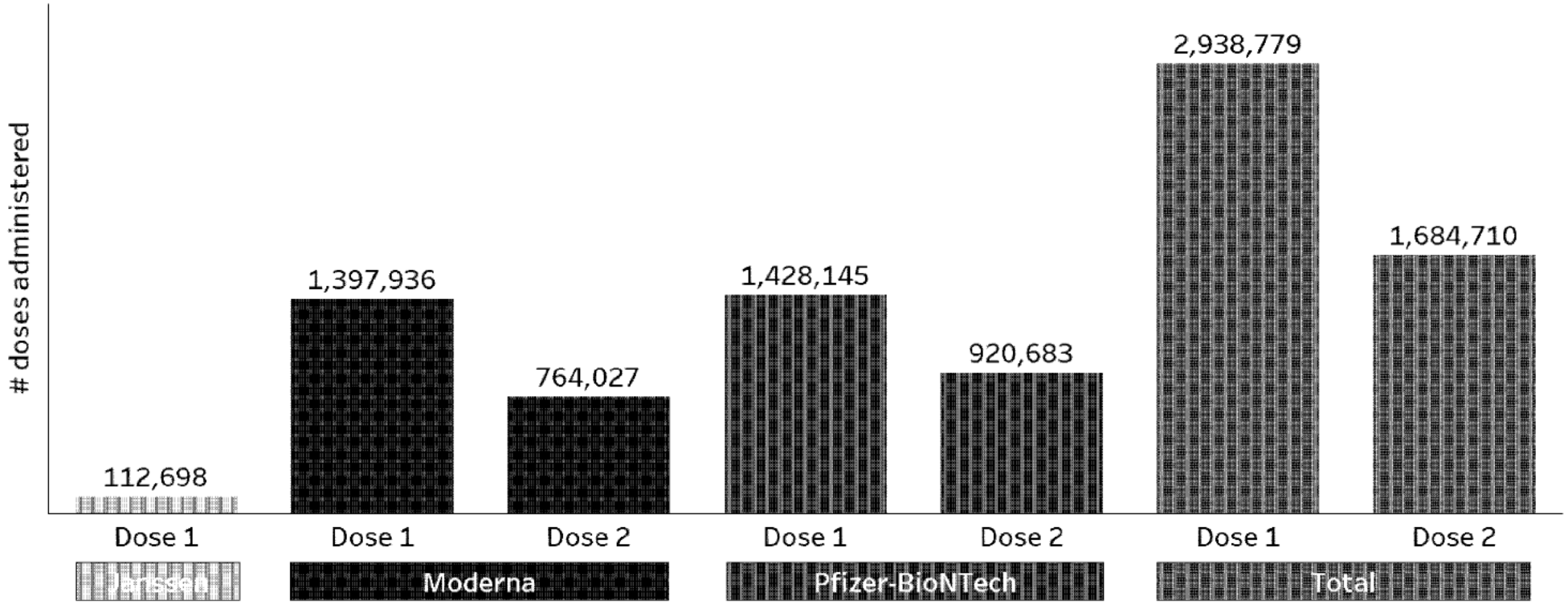
Participating VSD Healthcare Organizations



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

Vaccine Uptake (Data Through 4/10/21)

VSD COVID-19 Vaccine Totals



Analysis
(Data Through 4/10/21)

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 (settings = E, I)	PE	N

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

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21	Venous thromboembolism (settings = E, I, O)	VTE	N
22	Pulmonary embolism (settings = E, I)	PE	N

I67.6	Nonpyogenic thrombosis of intracranial venous system (Per SME, Cavernous Sinus Syndrome is NOT CVST & should be excluded)
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

Primary Analyses: Vaccinated Concurrent Comparison "Sequential Analysis"

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

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

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute disseminated encephalomyelitis	1	.	0.03 - ne	0.677	0.677	no
Acute myocardial infarction	313	0.88	0.70 - 1.11	0.265	0.880	no
Appendicitis	208	0.88	0.68 - 1.14	0.322	0.855	no
Bell's palsy	208	1.06	0.79 - 1.42	0.724	0.390	no
CVST	6	1.16	0.23 - 8.70	0.908	0.612	no
Disseminated intravascular coagulation	12	0.75	0.21 - 3.50	0.656	0.792	no
Encephalitis / myelitis / encephalomyelitis	3	0.31	0.04 - 2.93	0.275	0.959	no
Guillain-Barré syndrome (Automated)	5	1.92	0.23 - 49.19	0.625	0.486	no
Stroke, hemorrhagic	134	0.94	0.66 - 1.37	0.731	0.670	no
Stroke, ischemic	538	1.14	0.94 - 1.38	0.181	0.099	no
Immune thrombocytopenia	19	0.85	0.33 - 2.42	0.722	0.730	no
Myocarditis / pericarditis	18	0.64	0.27 - 1.60	0.325	0.892	no
Seizures	102	1.03	0.68 - 1.60	0.894	0.490	no
Thrombotic thrombocytopenic purpura	1	.	0.01 - ne	0.787	0.787	no
Venous thromboembolism	332	1.23	0.97 - 1.58	0.088	0.050	no
Pulmonary embolism	276	0.99	0.77 - 1.27	0.918	0.566	no

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

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CVST	6	1.16	0.23 - 8.70	0.908	0.612	no
Disseminated intravascular coagulation	12	0.75	0.21 - 3.50	0.656	0.792	no
Encephalitis / myelitis / encephalomyelitis	3	0.31	0.04 - 2.93	0.275	0.959	no
Guillain-Barré syndrome (Automated)	5	1.92	0.23 - 49.19	0.625	0.486	no
Stroke, hemorrhagic	134	0.94	0.66 - 1.37	0.731	0.670	no
Stroke, ischemic	538	1.14	0.94 - 1.38	0.181	0.099	no
Immune thrombocytopenia	19	0.85	0.33 - 2.42	0.722	0.730	no
Myocarditis / pericarditis	18	0.64	0.27 - 1.60	0.325	0.892	no
Seizures	102	1.03	0.68 - 1.60	0.894	0.490	no
Thrombotic thrombocytopenic purpura	1	.	0.01 - ne	0.787	0.787	no
Venous thromboembolism	332	1.23	0.97 - 1.58	0.088	0.050	no
Pulmonary embolism	**276**	**0.99**	**0.77 - 1.27**	**0.918**	**0.566**	**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 Janssen 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]		Sequential Test[2]	
			95% Confidence Interval	2-sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute myocardial infarction	5	.	0.10 - ne	0.564	0.564	no
Appendicitis	2	.	0.05 - ne	0.645	0.645	no
Bell's palsy	5	.	0.74 - ne	0.087	0.087	no
Stroke, ischemic	4	4.33	0.21 - 288.27	0.443	0.417	no
Seizures	0	0.00	0.00 - 7.92	0.294	0.294	no
Venous thromboembolism	4	0.30	0.03 - 3.19	0.297	0.957	no
Pulmonary embolism	2	0.42	0.02 - 15.86	0.582	0.914	no

[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
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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	5	.	0.10 - ne	0.564	0.564	no
Appendicitis	2	.	0.05 - ne	0.645	0.645	no
Bell's palsy	5	.	0.74 - ne	0.087	0.087	no
Stroke, ischemic	4	4.33	0.21 - 288.27	0.443	0.417	no
Seizures	0	0.00	0.00 - 7.92	0.294	0.294	no
Venous thromboembolism	**4**	**0.30**	**0.03 - 3.19**	**0.297**	**0.957**	**no**
Pulmonary embolism	**2**	**0.42**	**0.02 - 15.86**	**0.582**	**0.914**	**no**

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

CVST

CVST events in 21-days risk interval after Janssen Vaccine

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

			Weekly Analysis[1]		
Outcome Event	Events in Risk Interval	Events in Unvaccinated	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value
CVST	0	6	0.0	0.00 – 404.49	0.985

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

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

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

Outcome Event	Events in Risk Interval	Events in Comparison Interval[3]	Adjusted Rate Ratio[4]	Weekly Analysis[1] 95% Confidence Interval	Weekly Analysis[1] 2-Sided P-value	Sequential Test[2] 1-sided P-value (Fisher)	Sequential Test[2] 'Signal' 1-sided p < 0.0048
CVST	6	2	1.16	0.23 - 8.70	0.908	0.612	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]**Comparison interval** is 22–42 days after either dose.
[4]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable

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

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

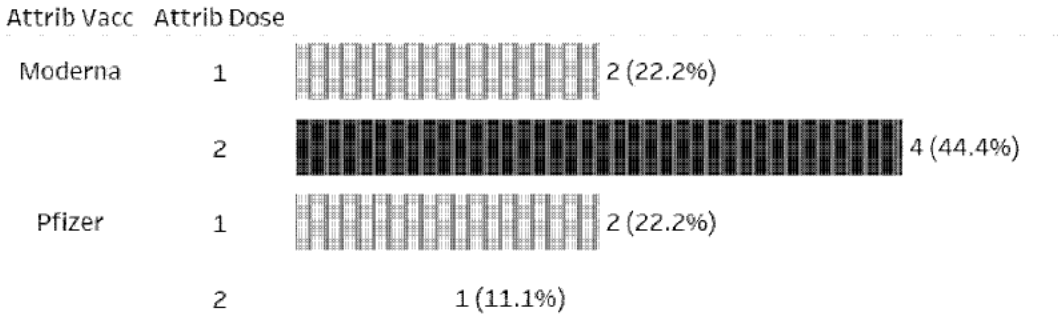
Outcome Event	Events in Risk Interval	Events in Comparison Interval	Adjusted Rate Ratio	Weekly Analysis		Sequential Test	
				95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
CVST (Comparison Interval 22-42)	6	2	1.16	0.23 - 8.70	0.908	0.612	no

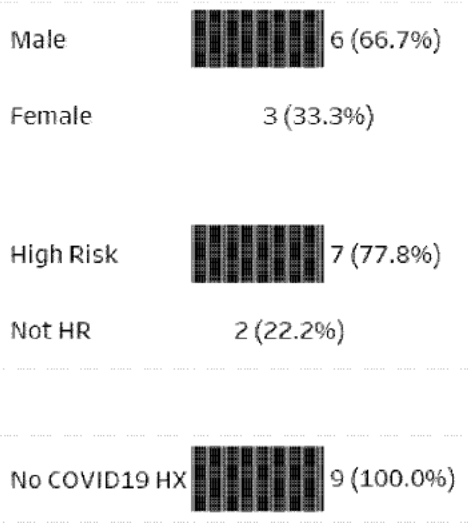
Unvaccinated Comparison

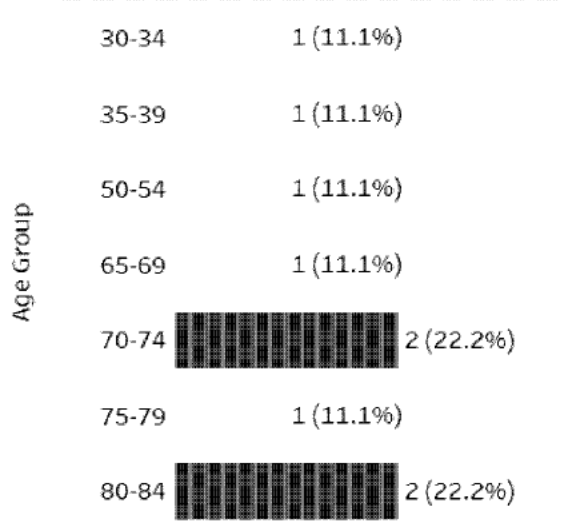
Outcome Event	Events in Risk Interval	Events in Unvaccinated	Adjusted Rate Ratio	Weekly Analysis	
				95% Confidence Interval	2-Sided P-value
CVST	6	48	1.27	0.42 – 3.37	.636

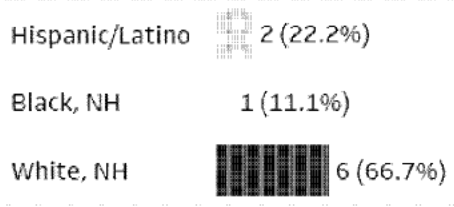
Cerebral Venous Sinus Thrombosis (CVST): mRNA vaccines
Automated Summary

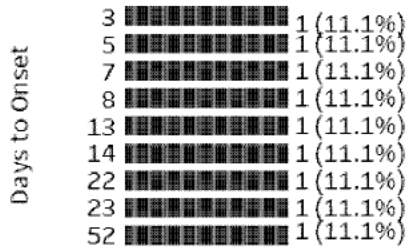
automated cases identified in the 1-84 day risk interval





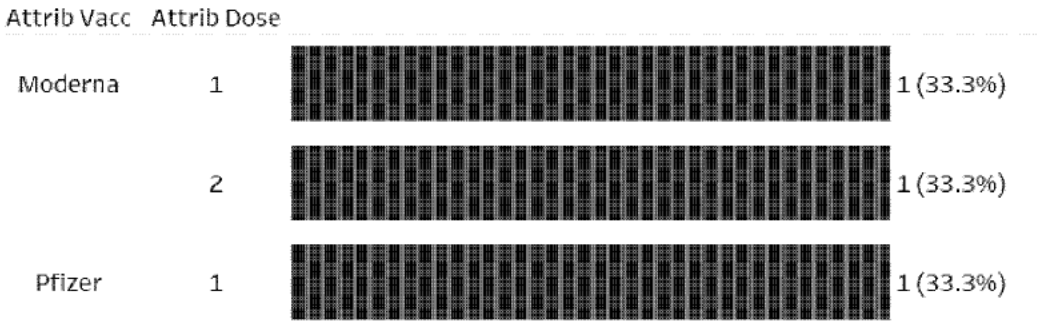


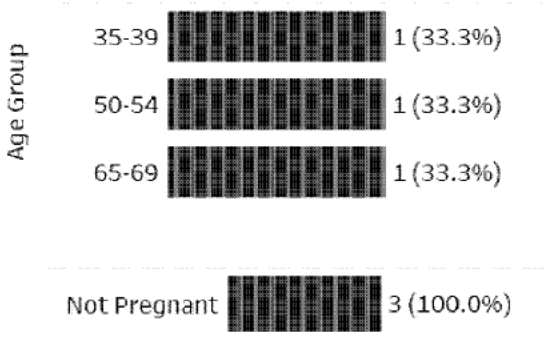


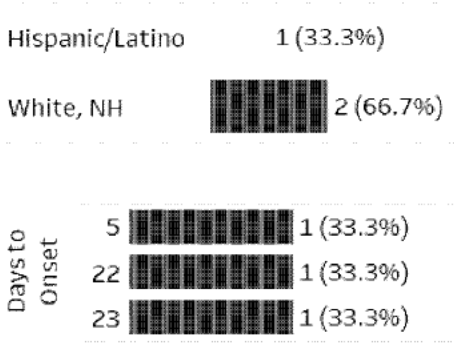


Cerebral Venous Sinus Thrombosis (CVST): mRNA vaccines Automated Summary among Women

automated cases identified in the 1-84 day risk interval among women (N=9 among both sexes)







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

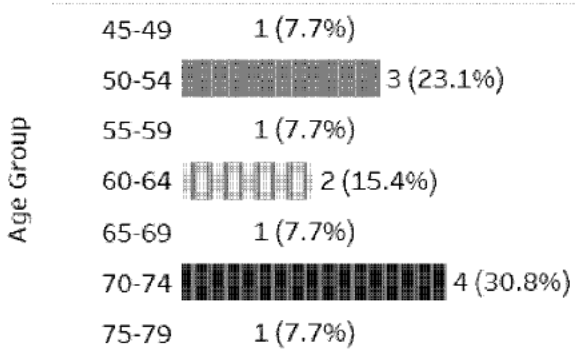
- All 9 (risk and comparison) cases have had a "informal, quick chart review"
- 5 of the 9 cases have been ruled-out
  - 2 cases were history of CVST
  - 2 cases had a head injury
  - 1 case had Chronic Cavernous Sinus Syndrome
- 4 of the 9 cases are potentially CVST cases, all ***without thrombocytopenia***

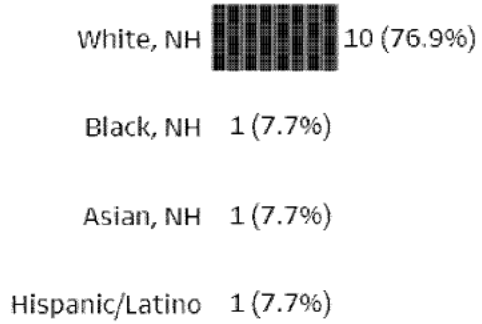
Sex	Age group	Product	Dose	Days post vaccination to dx date	History of COVID
F	35-39	Moderna	2	22 days post Dose 2	No
F	65-69	Pfizer	1 (received Dose 2)	5 days post Dose 1	No
M	80-84	Moderna	2	7 days post Dose 2	No
M	80-84	Pfizer	2	14 days post Dose 2	No

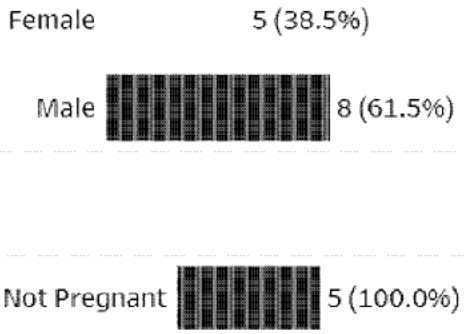
Janssen: investigating other thrombotic events

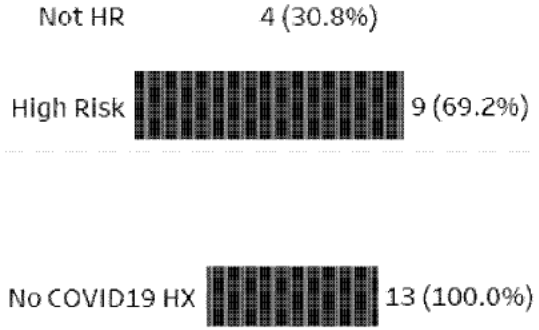
Venous thromboembolism automated summary: Cases after Janssen vaccine during the 42 days after vaccination

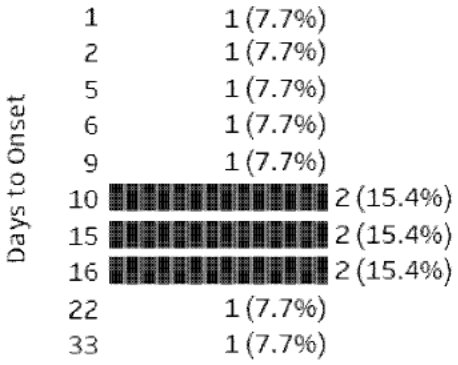
automated cases identified in the 1-42 day risk interval after Janssen vaccine





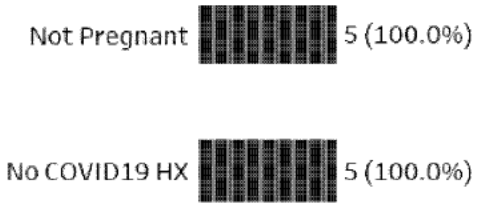


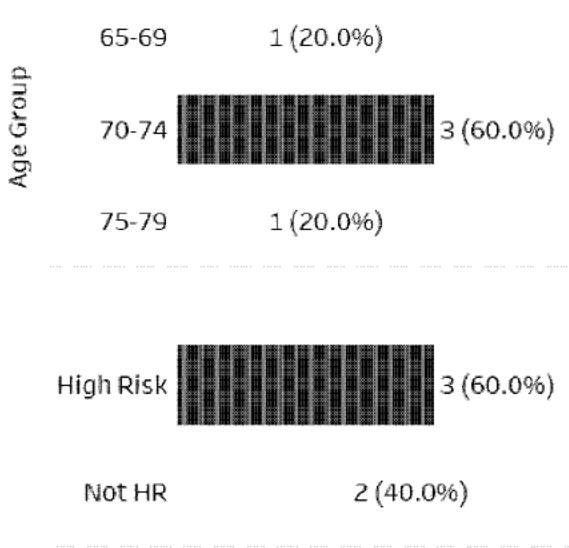


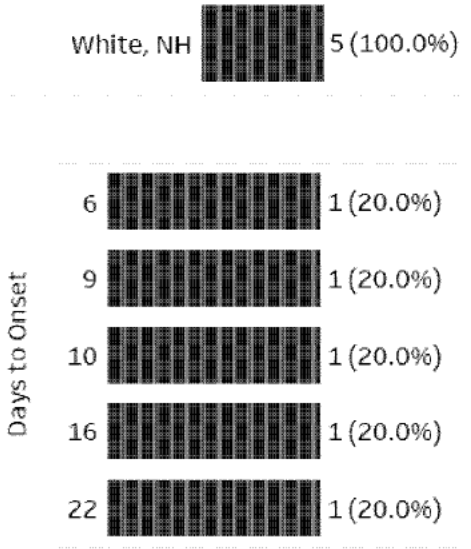


Venous thromboembolism automated summary: Cases after Janssen vaccine during the 42 days after vaccination among women

automated cases identified in the 1-42 day risk interval after Janssen vaccine among women (n=13 among both sexes)

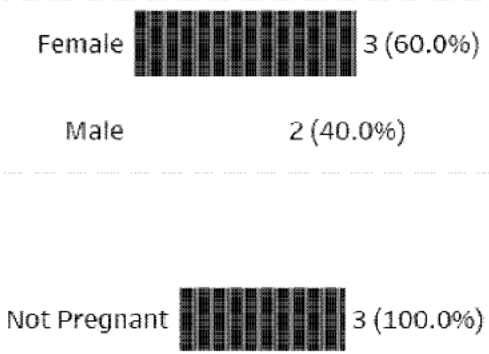


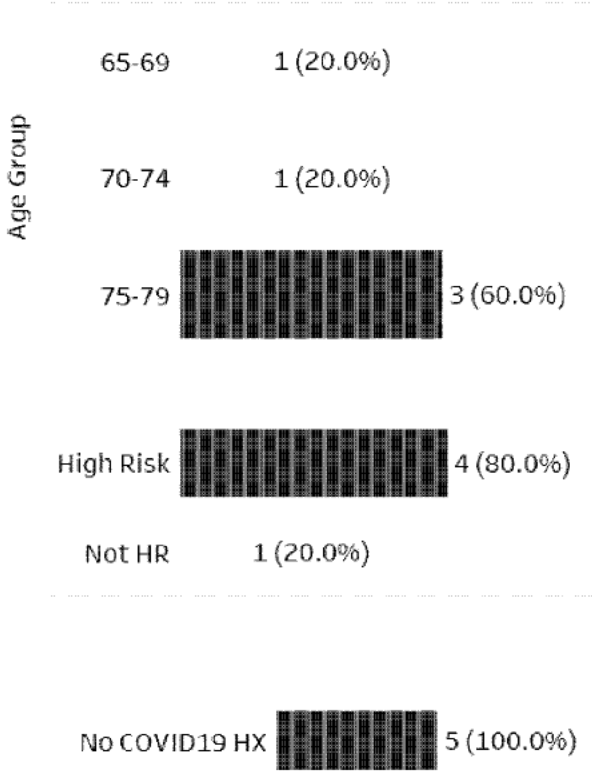


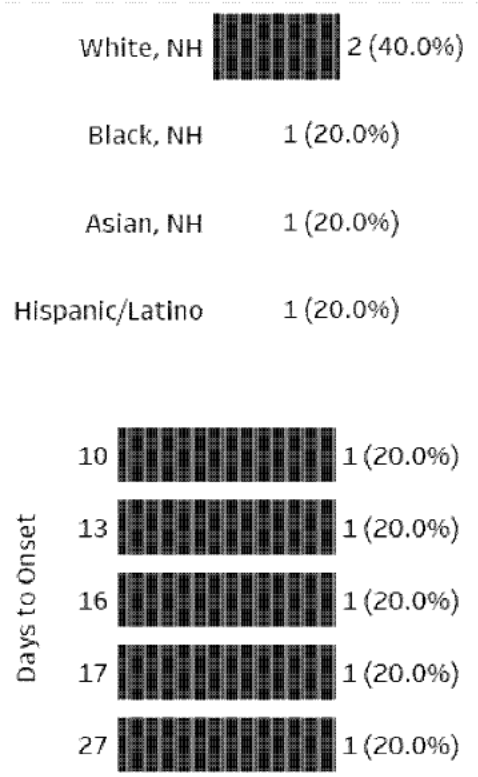


Pulmonary embolism (PE) automated Summary: Cases after Janssen vaccine during the 42 days after vaccination

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

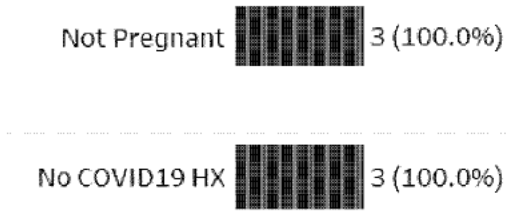


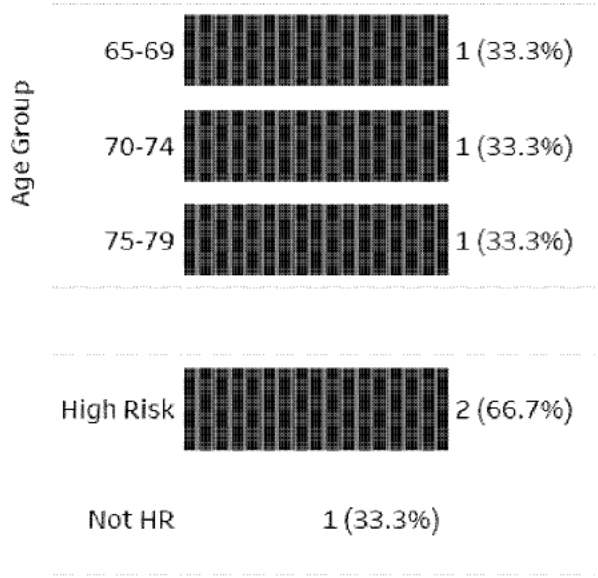


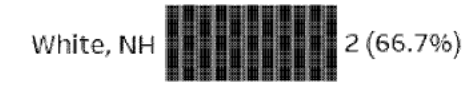


Pulmonary Embolism (PE) Automated Summary: Cases after Janssen vaccine during the 42 days after vaccination among women

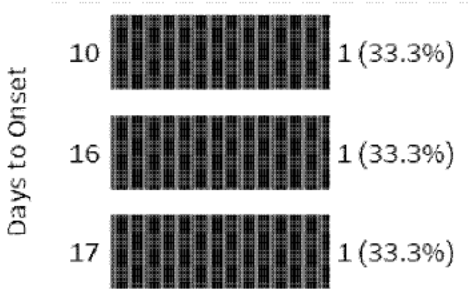
automated cases identified in the 1-42 day risk interval after Janssen vaccine among women (n=5 among both sexes)







Black, NH 1 (33.3%)



Venous Thromboembolism Events After Janssen Quick Chart Review Summary

- 16 VTE/PE cases (including 2 cases diagnosed with both VTE and PE) in 1-42 days following Janssen vaccine
- 5/16 have been quick reviewed so far, 2/16 are in progress, 9/16 to be reviewed
- Of those reviewed, 3/5 (60%) are potential VTE/PE cases with incidence following vaccination
  - 1 female, 2 males
  - None with history of COVID-19 infection or thrombocytopenia noted at time of VTE/PE

Potential incident case of VTE following vaccination	Diagnosis	Sex	Age group	Product	Days post vaccination to electronic diagnosis date	Days post vaccination to symptom onset (chart review)	Thrombocytopenia at time of VTE/PE	History of COVID-19	High risk status	Current status
Yes	PE	F	70-74	Janssen	16 days	16 days	No, elevated platelets	No	Yes	Discharged
No	PE	F	75-79	Janssen	NA	NA	NA	No	NA	NA
Yes	PE	M	75-79	Janssen	27 days	24 days	No	No	Yes	Discharged
Yes	VTE	M	50-54	Janssen	2 days	0 days (confirmed post vaccination)	No	No	Yes	Discharged
No	VTE	M	60-64	Janssen	NA	NA	NA	No	NA	NA

Summary

- No signals observed for all outcomes and all vaccines during the 21 days after vaccination.
- No CVST cases have been observed after the Janssen vaccine.
- There are 4 potential CVST cases after mRNA vaccines, none had thrombocytopenia.

Next Steps

- Complete chart review of all potential vaccinated CVST cases
- We are exploring ways to identify thromboembolic events (e.g., VTE, stroke) with thrombocytopenia (e.g., using platelets counts)
- We will continue to explore and evaluate thrombotic related events for both mRNA and Janssen vaccines
- 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

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

Extra Slides

Thrombotic 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
CVST	6	1.16	0.23 - 8.70	0.908	0.612	no
Disseminated intravascular coagulation	12	0.75	0.21 - 3.50	0.656	0.792	no
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[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

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	18	0.64	0.27 - 1.60	0.325	0.892	no

Unvaccinated Comparison

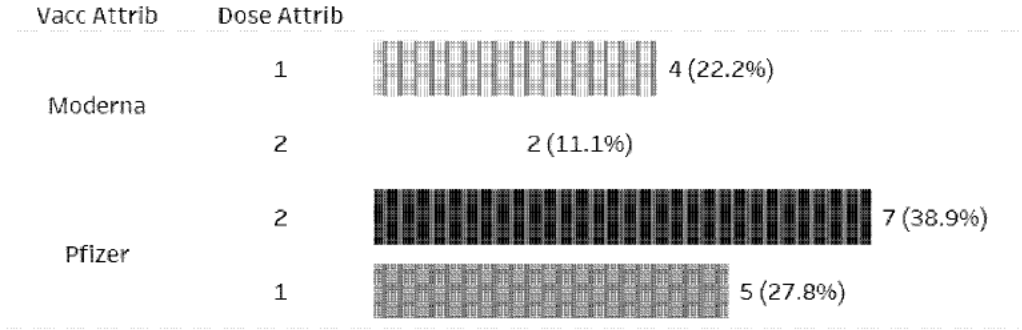
Unvaccinated - 21-day risk interval	Events in Risk Interval	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value
Myocarditis / pericarditis	**18**	**1.04**	**0.59 - 1.78**	**0.866**

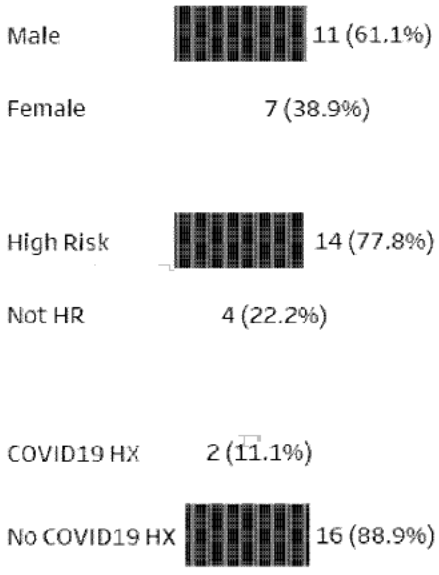
[1]**Weekly analyses** include all data to date, but confidence intervals and p-values do not account for the multiple chances for a false positive signal during surveillance.
[2]**Sequential test** requires 1-sided p < 0.0048 for a signal. This keeps the probability of a false positive signal (due to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

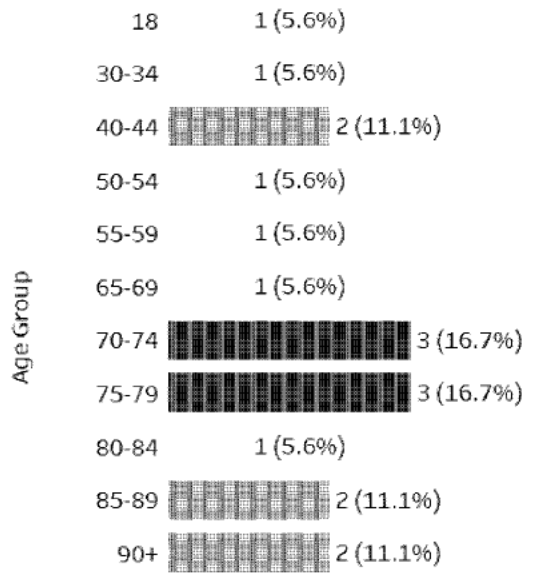
Myocarditis / Pericarditis Automated Summary

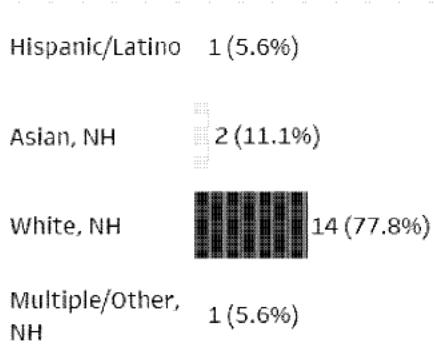
18

cases identified in the 1-21 day risk interval

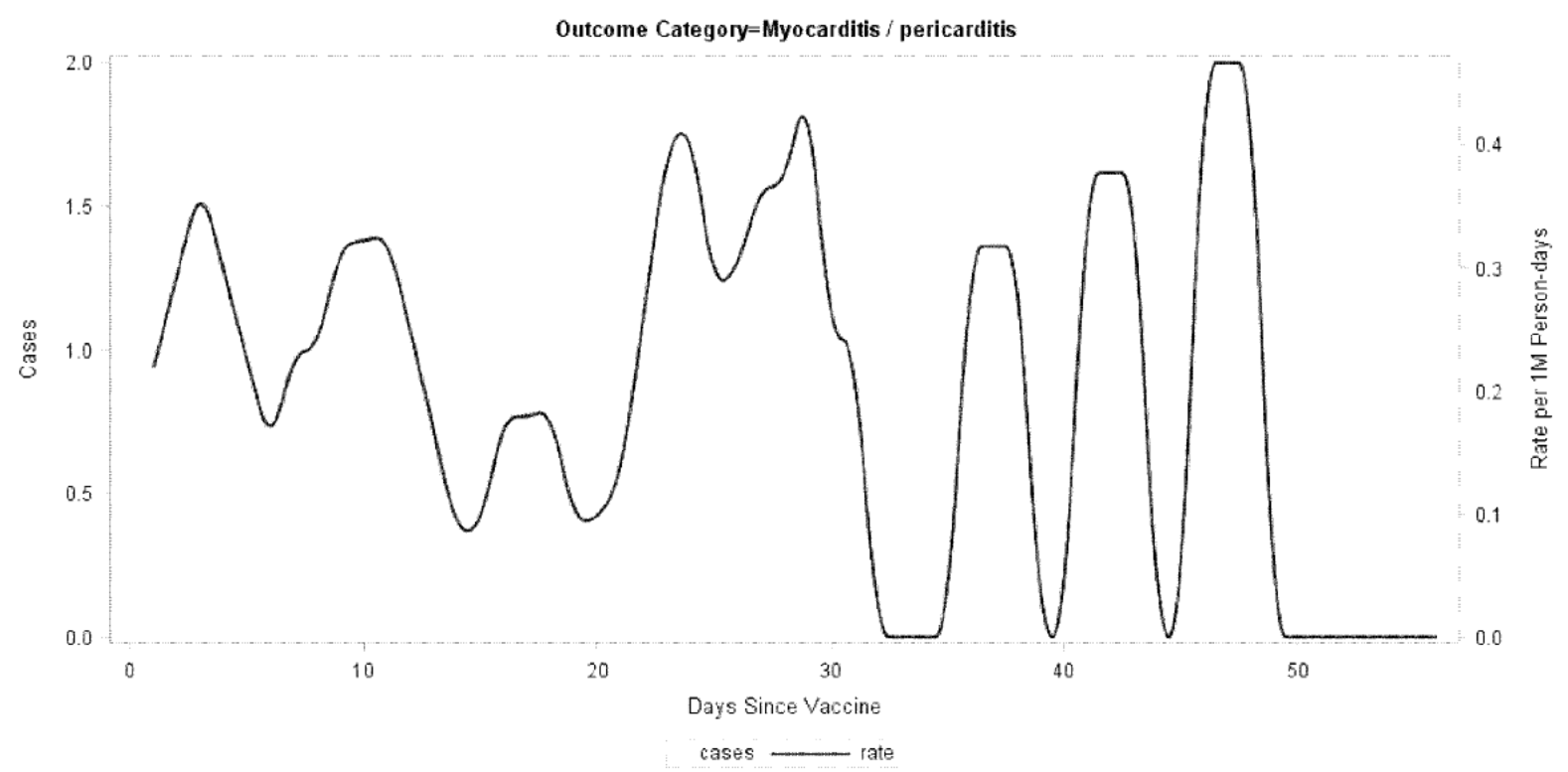








Myocarditis/Pericarditis -- Days since vaccination and Rate per Million Person-Days

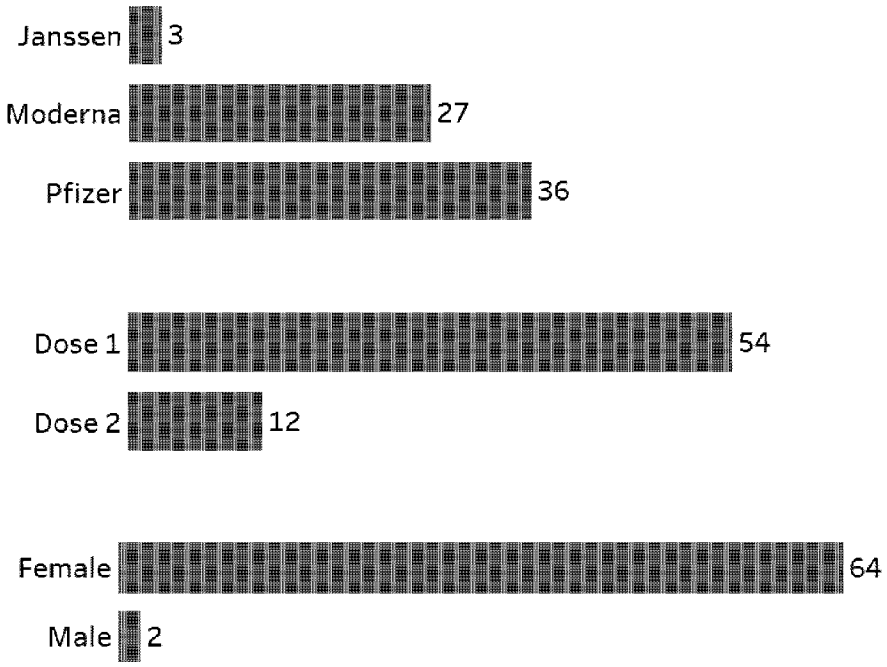


Anaphylaxis and Additional Chart Review Outcomes

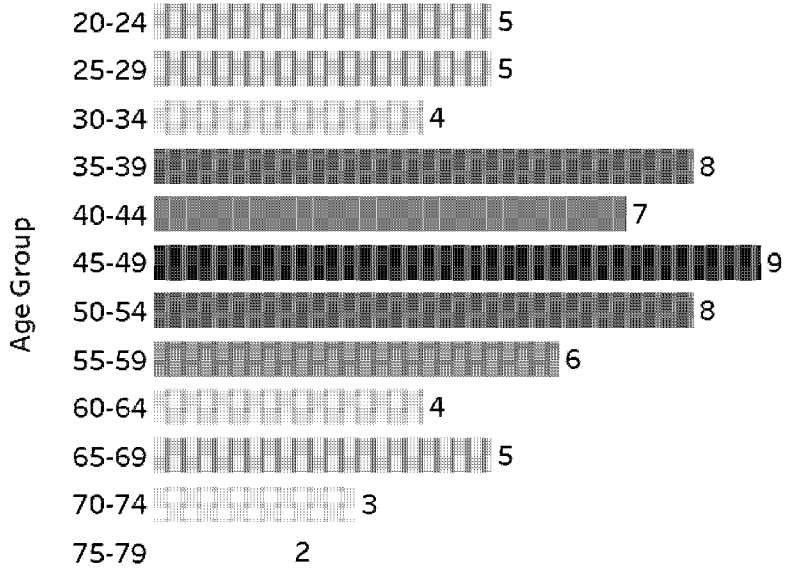
Anaphylaxis Automated Summary

66

Automated cases identified on days 0-1



Age in years ranged from 20-79, with 41 of the cases between ages 25-54



Anaphylaxis Chart Review Summary

- Chart review completed for 40/66 cases*
- 21/40 (52%) cases confirmed as post-vaccination anaphylaxis

	Pfizer (n=13)	Moderna (n=8)
Age in years, median (range)	43 (24-65)	39 (30-67)
Female sex	13 (100%)	8 (100%)
Minutes to symptom onset, median (range)	10 (0-300)	13 (5-30)
Symptom onset within 15 minutes	7 (54%)	5 (62%)
Symptom onset within 30 minutes	10 (77%)	7 (87%)
Prior history of allergies	10 (77%)	4 (50%)
Prior history of anaphylaxis	7 (54%)	1 (13%)
Dose 1	13 (100%)	7 (87%)
Brighton Collaboration case definition level		
1	4 (31%)	3 (38%)
2	9 (69%)	5 (62%)
No. confirmed cases (95% CI) per million doses	5.5 (2.9-9.5)	3.7 (1.6-7.3)
No. confirmed cases (95% CI) per million first doses	9.1 (4.8-15.6)	5.0 (2.0-10.3)
No. confirmed cases (95% CI) per million female first doses	15.9 (8.5-27.2)	8.8 (3.5-18.1)

*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	9	4	1

- Chart review completed for 4 cases, only 1 was confirmed
  - 3 cases not confirmed (1 history of GBS, 1 rule out, 1 miscode)
  - Confirmed case classified as Brighton Level 2, 88 year-old male with onset of symptoms 1 day after Moderna dose 1; noted as recovered with neurologic sequelae as of last follow-up visit and also received Moderna dose 2
- Chart review in progress for 5 cases
  - Quick reviews completed that suggest incident cases of GBS following vaccination; full review and adjudication are in progress

ADEM & TM Summary

Outcome	No. Automated Cases	No. Completed Chart Review	No. Chart Confirmed Cases
ADEM	1	0	0
TM	1	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)
- 1 automated case of ADEM identified, chart review in progress
  - Quick review completed that suggest incident case of ADEM following vaccination; full review and adjudication are in progress

Acute myocardial infarction, Venous thromboembolism, Pulmonary Embolism Additional Analyses

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

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

Outcome Event	Events in Risk Interval	Weekly Analysis[1]			Sequential Test[2]	
		Adjusted Rate Ratio[3,4]	95% Confidence Interval	2-Sided P-value	1-sided P-value (Fisher)	'Signal' 1-sided p < 0.0048
Acute myocardial infarction	313	0.88	0.70 - 1.11	0.265	0.880	no
Venous thromboembolism	332	1.23	0.97 - 1.58	0.088	0.050	no
Pulmonary embolism (subset of VTE)	276	0.99	0.77 - 1.27	0.918	0.566	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

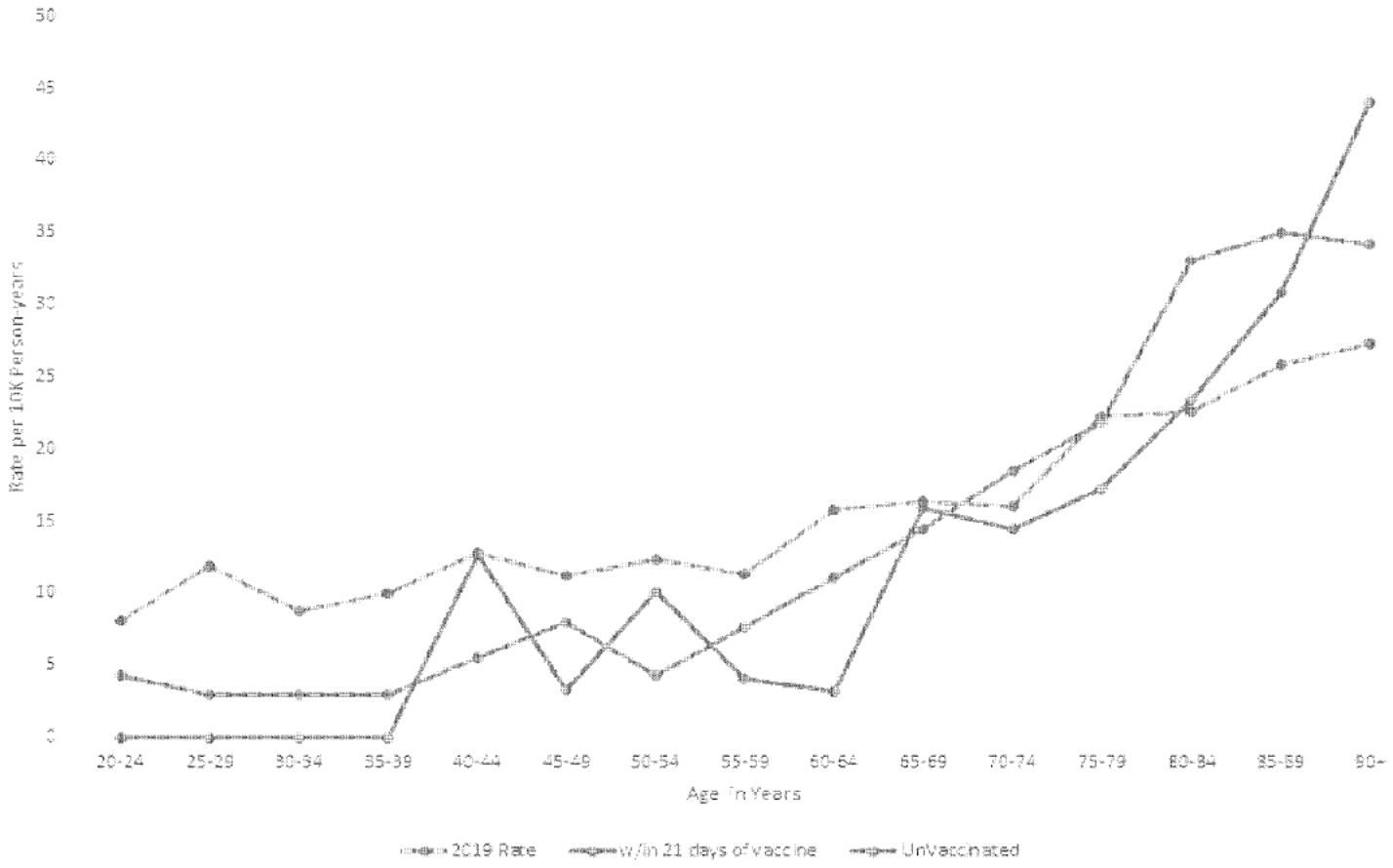
Compared with outcome events in vaccinated comparators on the same calendar days

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.

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)
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	Moderna	Both Doses	78	1.08	0.67 - 1.79	0.779	0.437

Unvaccinated Comparison

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

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

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

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

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

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

Vaccine Safety Datalink (VSD) Weekly COVID-19 Vaccine Summary: April 13, 2021 *

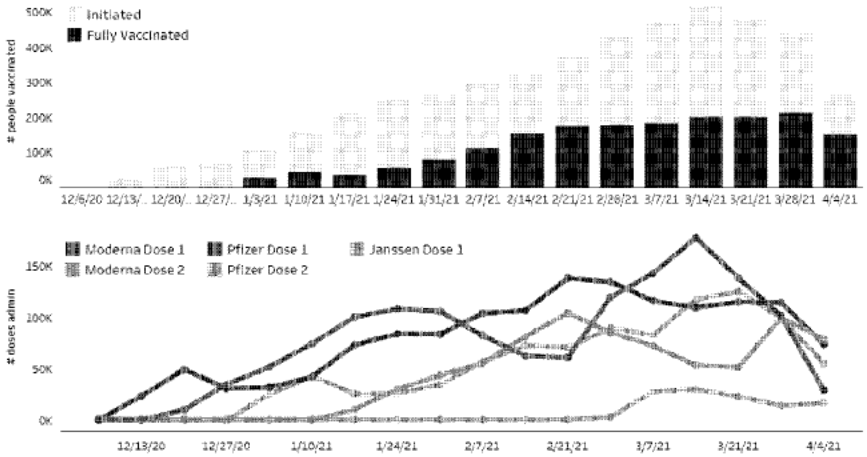
* Visualization published on April 13, 2021; data current as of previous Saturday. VSD population includes individuals 16 years of age and older.

Total # Doses Administered	Total # Doses Admin per 100K	# People Initiating Vaccination	# Fully Vaccinated
4,623,489	47,864	2,938,779	1,797,408
+535,177 since last week	+5,530 since last week	+285,436 since last week	+273,499 since last week

To date, 30.0% of VSD population initiated vaccination and 18.0% 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	
ADEM				1		1
AMI	9	81	58	103	75	326
ANAPH	3	20	7	31	5	66
ANAPH2		15		12	3	30
APPND	4	67	36	71	49	227
ARDS		2	2	1		5
BP	8	76	36	58	44	222
CVST			3	2	1	6
DIC		3		7	2	12
ENCEPH			2	2		4
GBS		2	2	2	1	7
HSTK	1	35	18	44	37	136
ISTK	6	163	112	160	110	551
ITP		3	6	6	4	19
MISC				3	1	4
MYOC		4	2	5	7	18
NARC		1	2		3	6
PE	4	84	49	77	67	281
SZ		32	13	42	16	103
TM		1				1
TTP				1		1
VTE	11	107	62	95	70	345
Total	**46**	**697**	**410**	**723**	**495**	**2,371**

* 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

Female	1,672,595
Male	1,266,184

By Age Group

16-24	134,313
25-49	892,288
50-64	778,365
65-84	1,013,532
85+	120,281

By Race/Ethnicity

Hispanic/Latino	575,430
Non-Hispanic: American Indian / Alaska Native	8,945
Non-Hispanic: Asian	433,642
Non-Hispanic: Black	166,834
Non-Hispanic: Native Hawaiian / Other Pacific Islander	18,348
Non-Hispanic: White	1,448,058
Non-Hispanic: Multiple / Other	96,304
Unknown	191,218

By Site *

DH	33,015
HPM	80,328
KPC	116,834
KPW	209,177
MFC	53,327
NCK	1,277,788
NWK	189,313
SCK	978,997

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

Demographic breakdown of people who are fully vaccinated

By Sex

Female	1,057,551
Male	739,857

By Age Group

16-24	51,344
25-49	472,933
50-64	366,245
65-84	806,067
85+	100,819

By Race/Ethnicity

Hispanic/Latino	308,800
Non-Hispanic: American Indian / Alaska Native	5,394
Non-Hispanic: Asian	274,541
Non-Hispanic: Black	100,727
Non-Hispanic: Native Hawaiian / Other Pacific Islander	11,286
Non-Hispanic: White	943,077
Non-Hispanic: Multiple / Other	59,644
Unknown	93,939

By Site *

DH	17,742
HPM	46,966
KPC	74,542
KPW	114,973
MFC	37,265
NCK	835,713
NWK	126,370
SCK	543,837

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

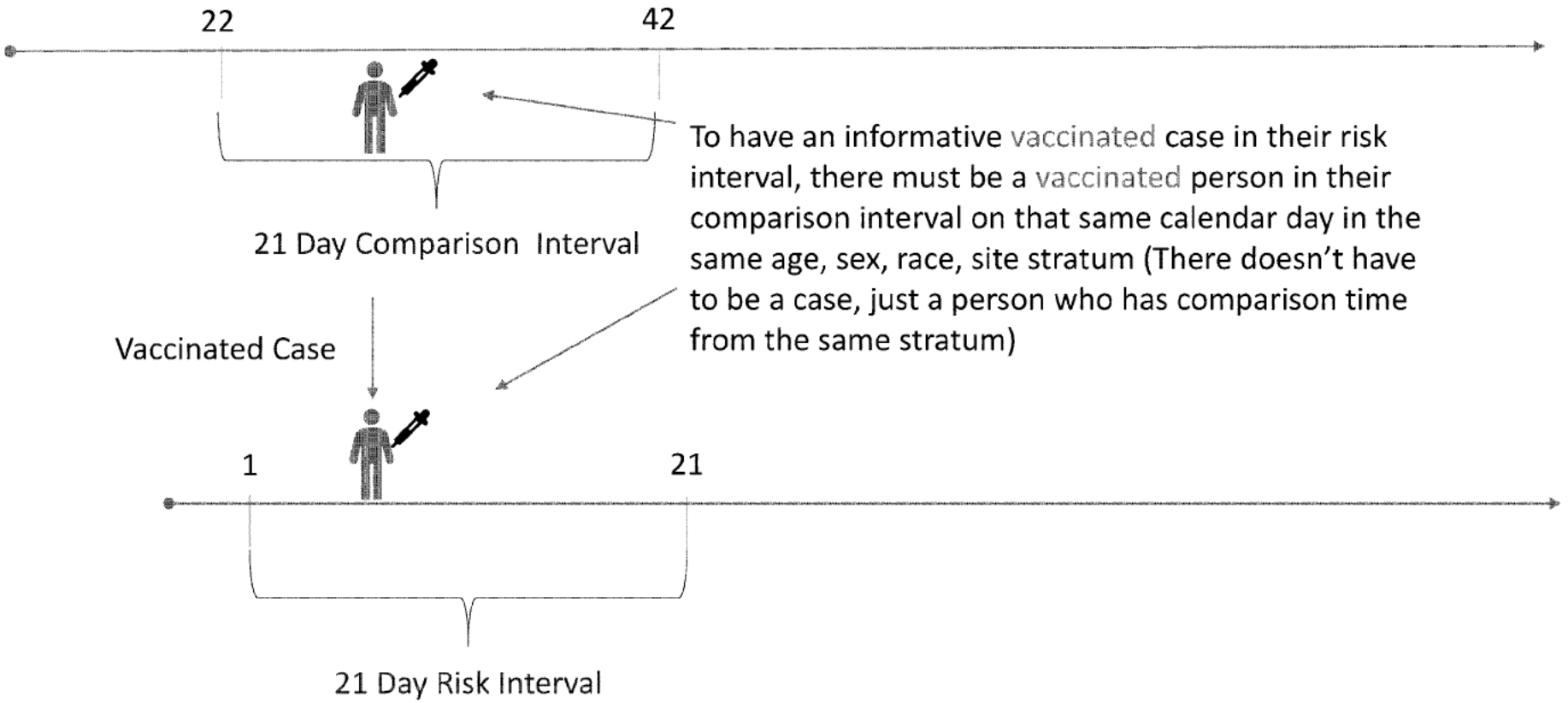
COVID-19 Vaccine Totals by Age

	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	36	14	6,623	762	4	6,663	776	7,439	140,454	4.74	0.56
17	135	50	9,245	1,507	16	9,396	1,557	10,953	142,442	6.60	1.10
18	5,019	917	5,499	1,674	676	11,194	2,591	13,785	140,174	7.99	2.33
19	5,899	1,366	5,641	2,098	672	12,212	3,464	15,676	138,156	8.84	2.99
20-24	42,603	14,228	41,944	18,899	3,924	88,471	33,127	121,598	742,385	11.92	4.99
25-29	60,521	25,286	63,300	33,875	5,037	128,858	59,161	188,019	806,231	15.98	7.96
30-34	78,749	33,739	84,994	46,313	6,582	170,325	80,052	250,377	890,302	19.13	9.73
35-39	86,836	38,434	94,765	53,296	7,568	189,169	91,730	280,899	870,291	21.74	11.41
40-44	88,569	38,646	94,679	54,151	7,873	191,121	92,797	283,918	804,606	23.75	12.51
45-49	91,129	38,457	95,822	53,950	8,607	195,558	92,407	287,965	759,644	25.74	13.30
50-54	108,686	40,511	107,843	56,146	11,183	227,712	96,657	324,369	787,344	28.92	13.70
55-59	120,569	41,130	115,071	56,918	13,601	249,241	98,048	347,289	792,136	31.46	14.09
60-64	140,107	44,824	125,182	59,513	15,649	280,938	104,337	385,275	768,293	36.57	15.62
65-69	168,622	111,090	160,908	128,057	9,142	338,672	239,147	577,819	624,904	54.20	39.73
70-74	152,336	107,475	147,837	122,533	6,308	306,481	230,008	536,489	519,680	58.97	45.47
75-79	113,910	91,987	110,670	97,654	3,158	227,738	189,641	417,379	330,257	68.96	58.38
80-84	68,788	55,389	69,896	61,577	2,061	140,745	116,966	257,711	205,585	68.46	57.90
85-89	37,281	29,590	40,445	34,948	1,310	79,036	64,538	143,574	120,439	65.62	54.67
90+	19,671	15,315	23,693	19,466	910	44,274	34,781	79,055	74,145	59.71	48.14

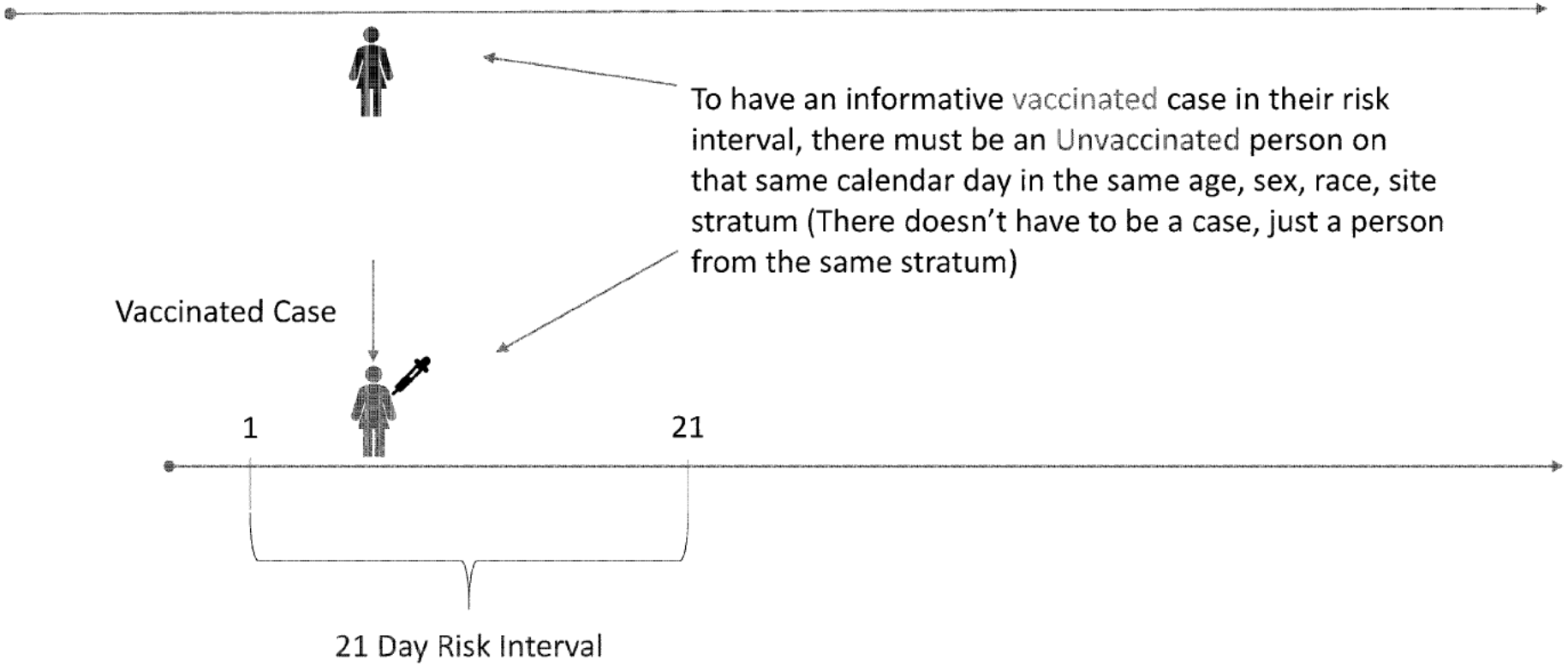
Next Steps

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

Analytic Strategies: Aim 1

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

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

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

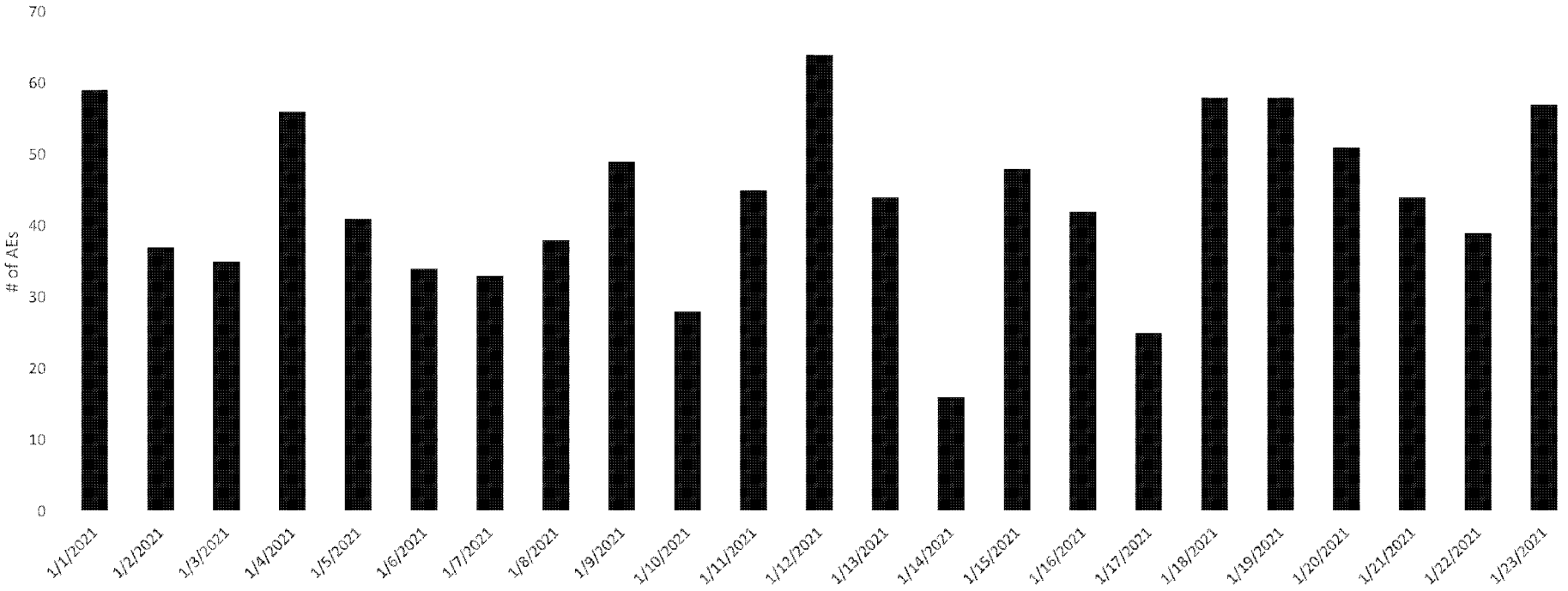
- self-controls in a comparison interval after COVID-19 vaccination.
  - Among the vaccinees who had an outcome event in either the risk interval or the comparison interval, we compare outcome incidence in the risk interval with outcome incidence in the comparison interval.

Analytic Strategies: Aim 1

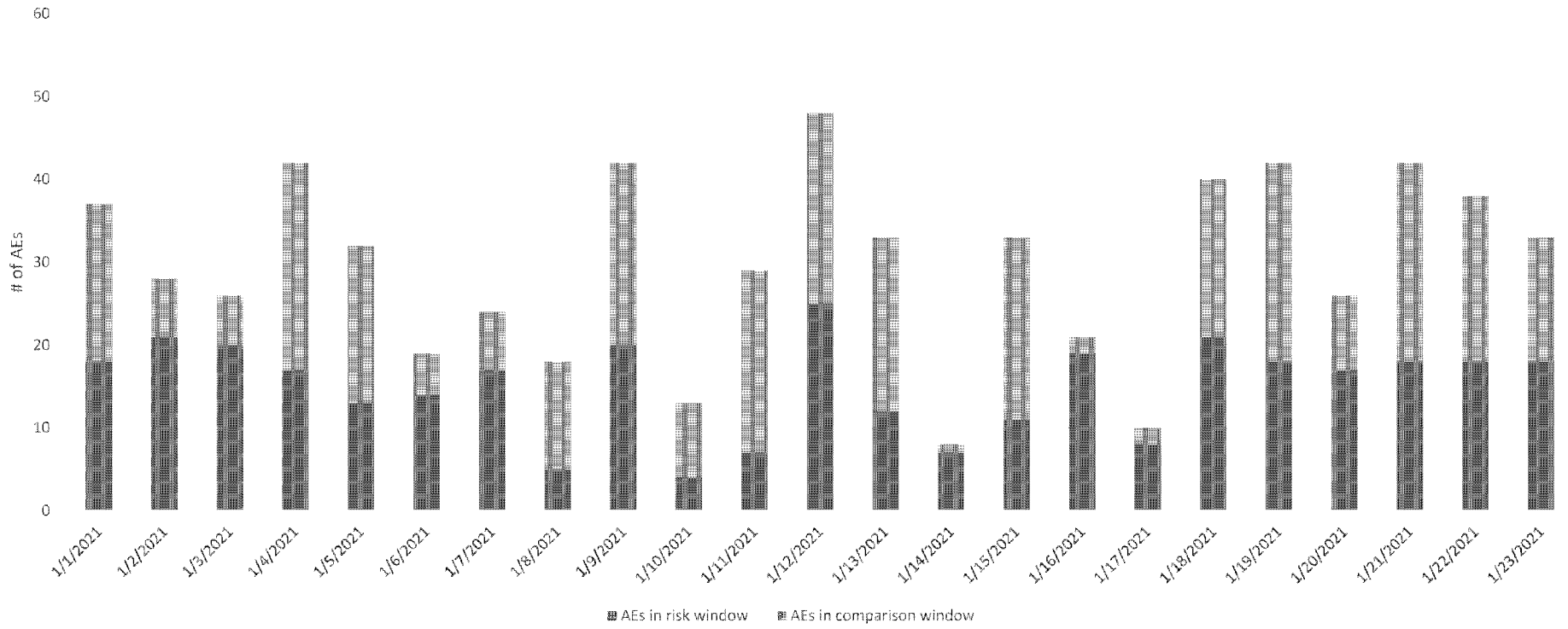
Design	Advantages	Limitations
Primary		
Concurrent Vaccinated	- Not confounded by time-stable co-morbidities, propensities to use health services, or demographics - Follow-up in the comparison interval is on the same calendar dates as follow-up time in the risk interval - Avoids bias that can arise from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

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

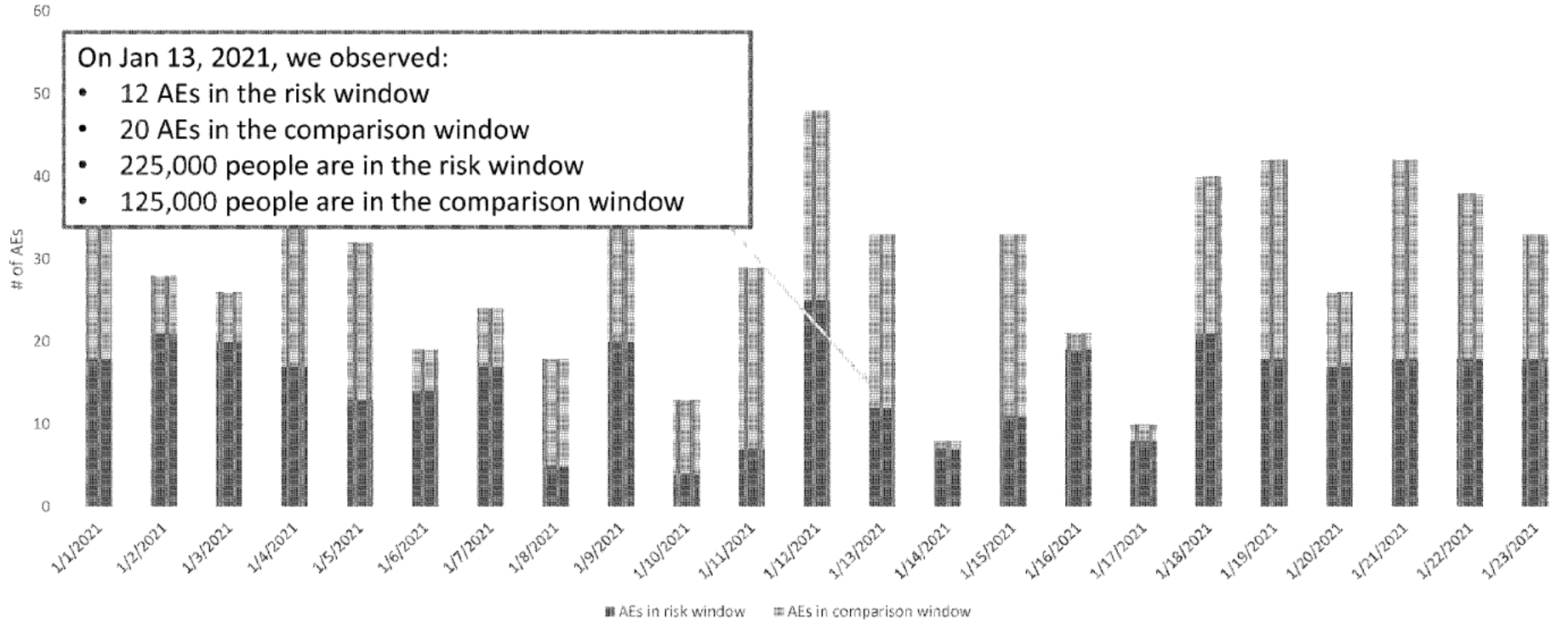
Total # of Events on Each Day



Did the event occur in a risk or comparison interval?



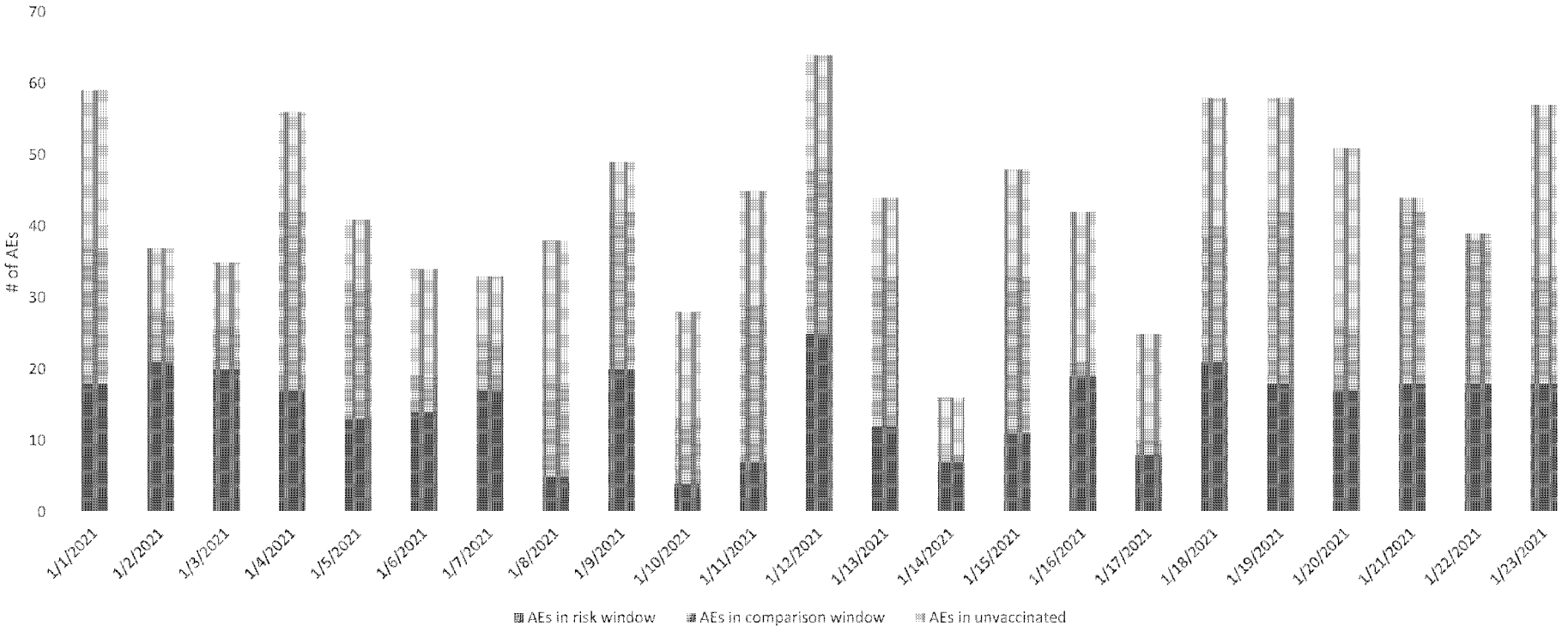
Vaccinated Concurrent Comparator Analyses



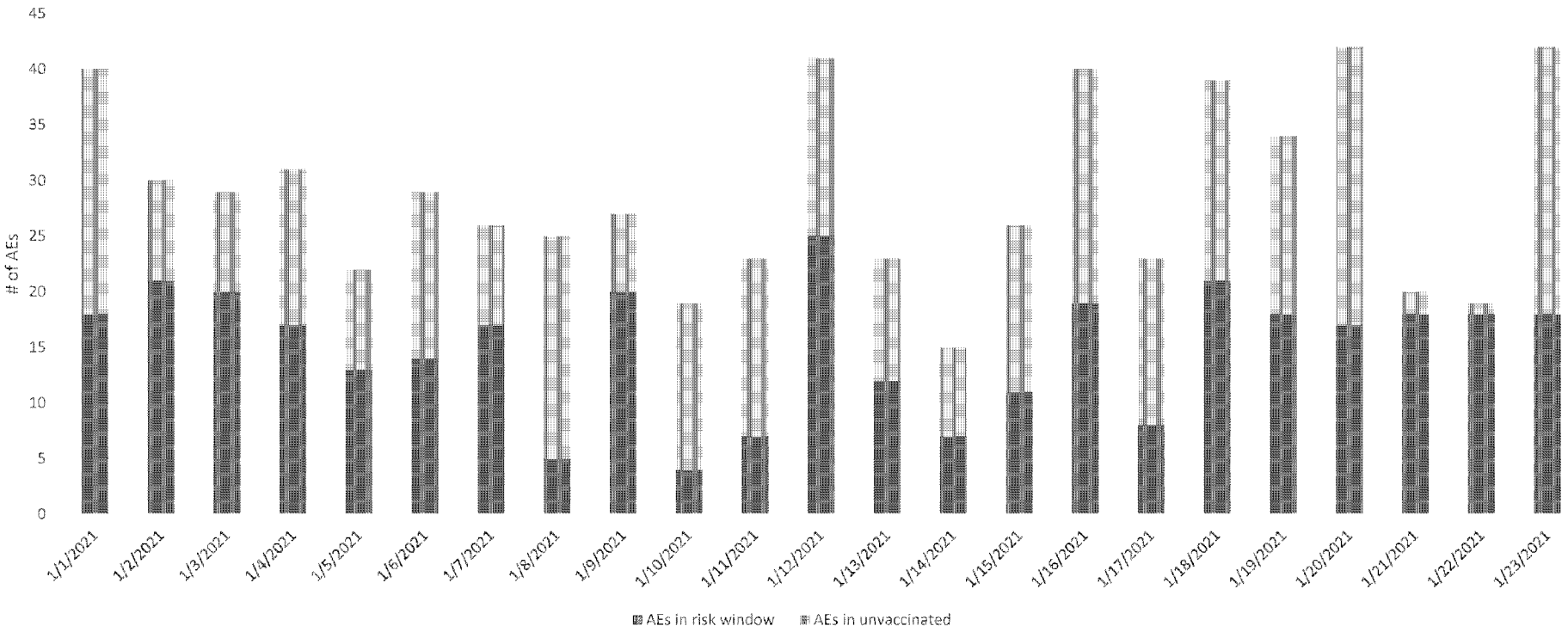
Looking at the data each day in this way, we inherently adjust for variations that occur on different days (e.g., a holiday, every Monday, or a weekend).

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

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



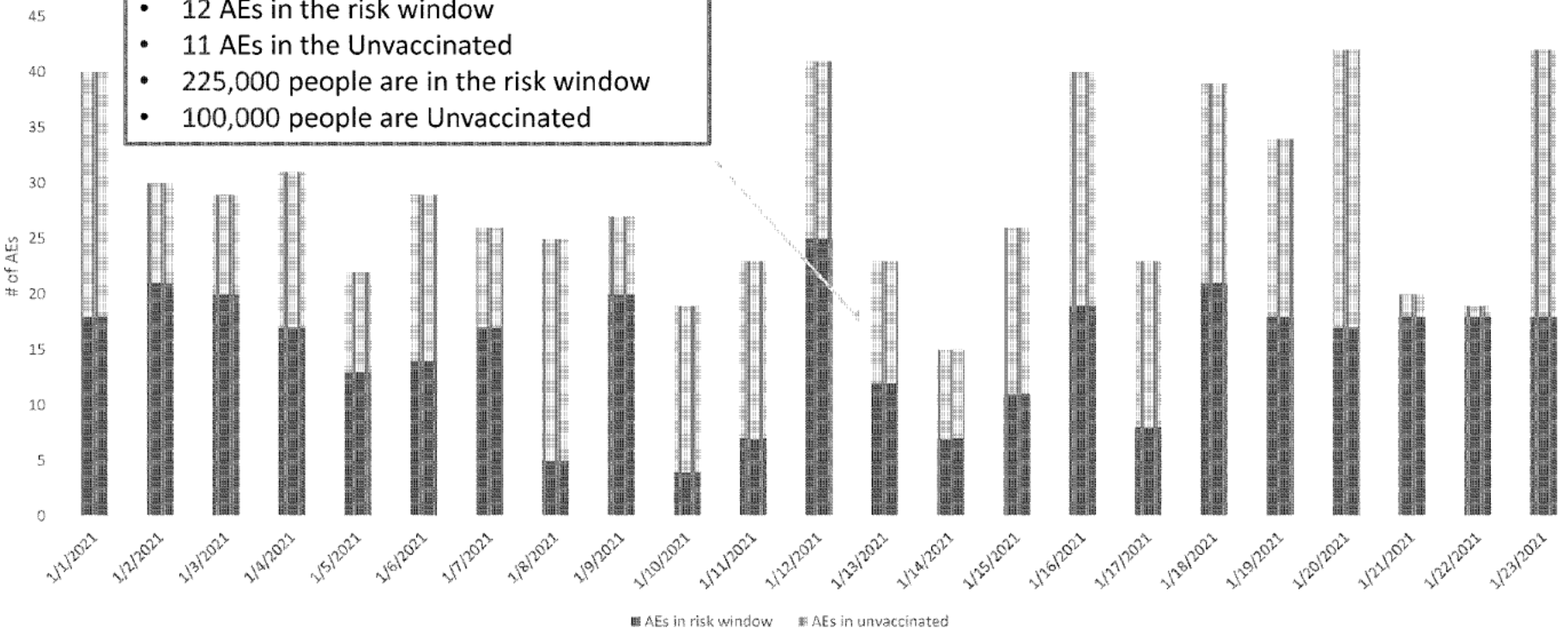
Did the event occur in a risk interval or in the Unvaccinated?



Unvaccinated Concurrent Comparator Analyses

On Jan 13, 2021, we observed:

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

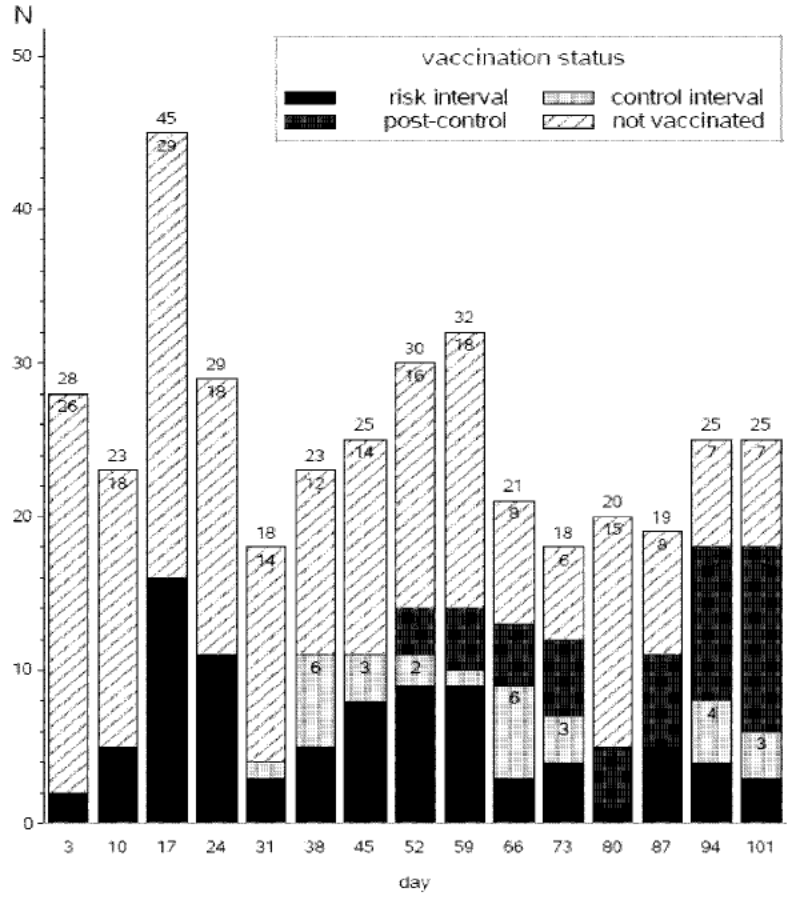


At each analysis, we compute a summary rate ratio (risk vs Unvaccinated) with all the data available to date. This rate ratio is adjusted for calendar time by day

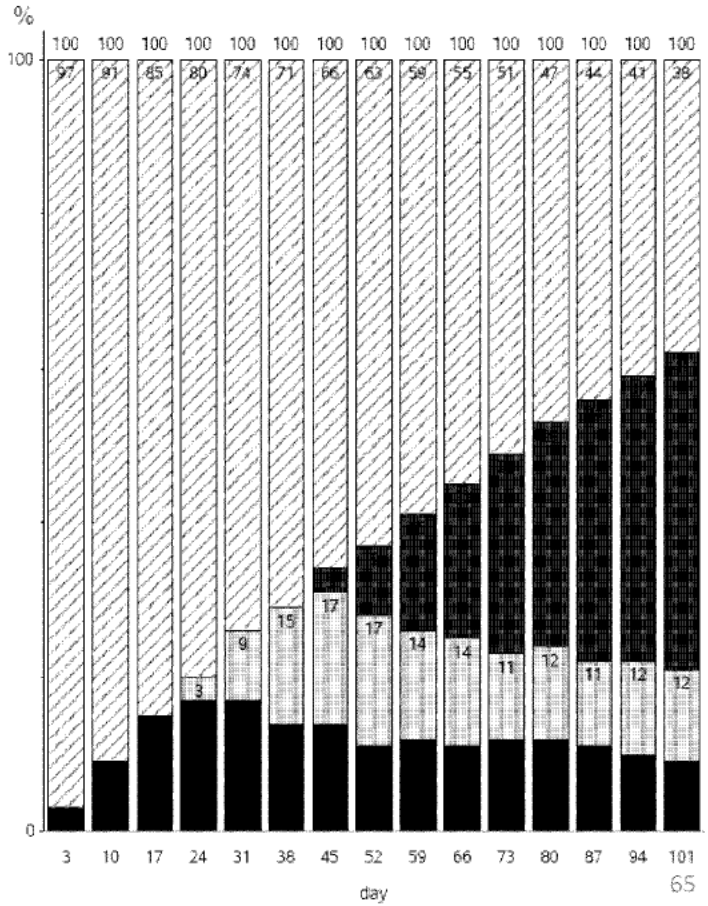
Looking at the data each day in this way, we inherently adjust for variations that occur on different days (e.g., a holiday, every Monday, or a weekend).

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

All AEs in the population on selected days by vaccination status



Distribution of the population on selected days by vaccination status



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.

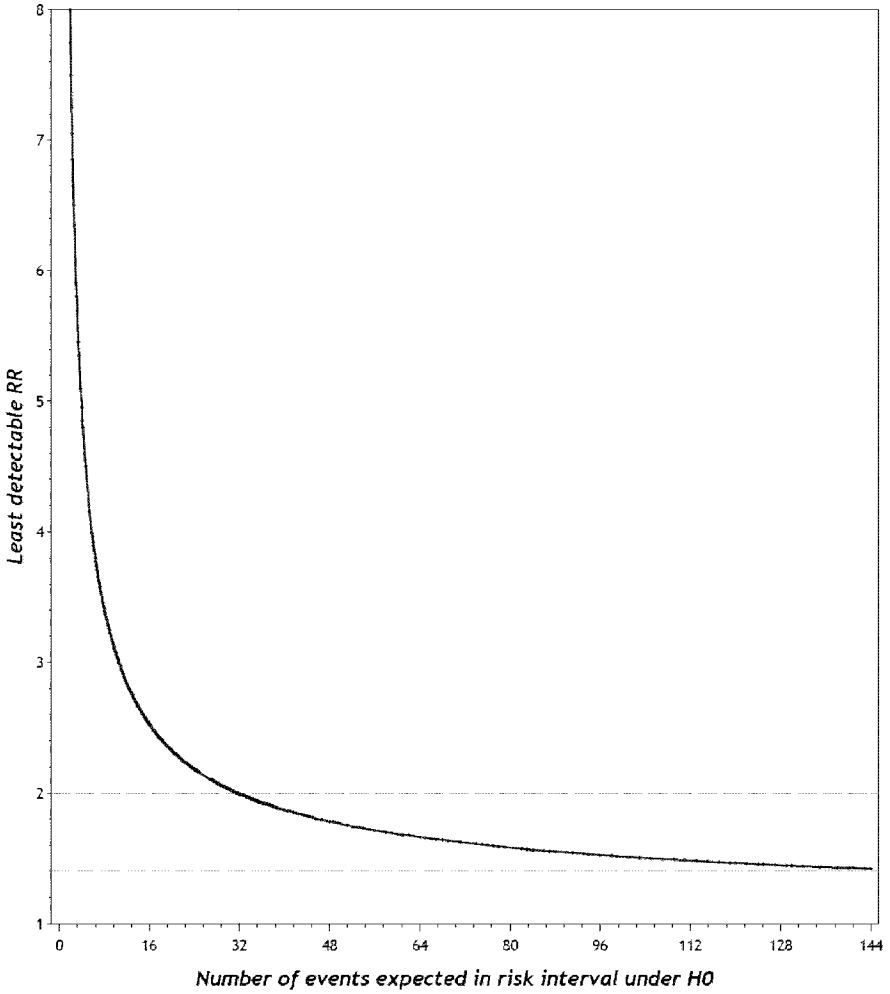
Power (Aim 1)

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

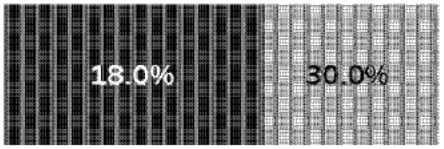
- Near real-time surveillance based on weekly aggregate data
- Sequential analysis to detect signals, but maintaining a pre-defined type I error rate
- Poisson-based MaxSPRT, developed by VSD researchers (Kulldorff, et al.)
- Compare observed number of events to expected number based on the historical 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

VSD COVID-19 Vaccine Totals

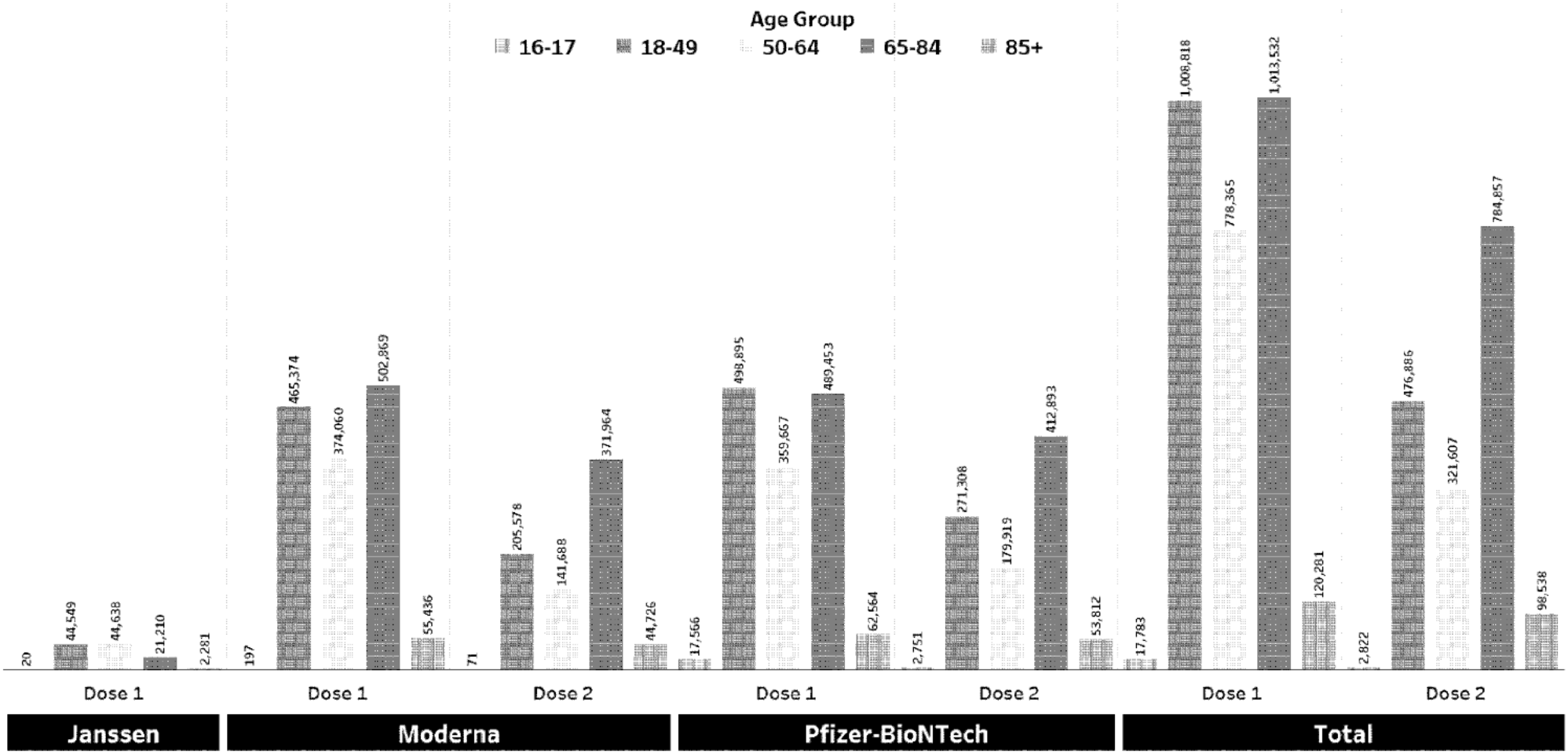
Total Doses Administered	Total Doses Admin per 100K	# People Initiating Vaccination	Completed Series
4,623,489	47,864	2,938,779	1,797,408
+535,177 since last week	+5,530 since last week	+285,436 since last week	+273,499 since last week



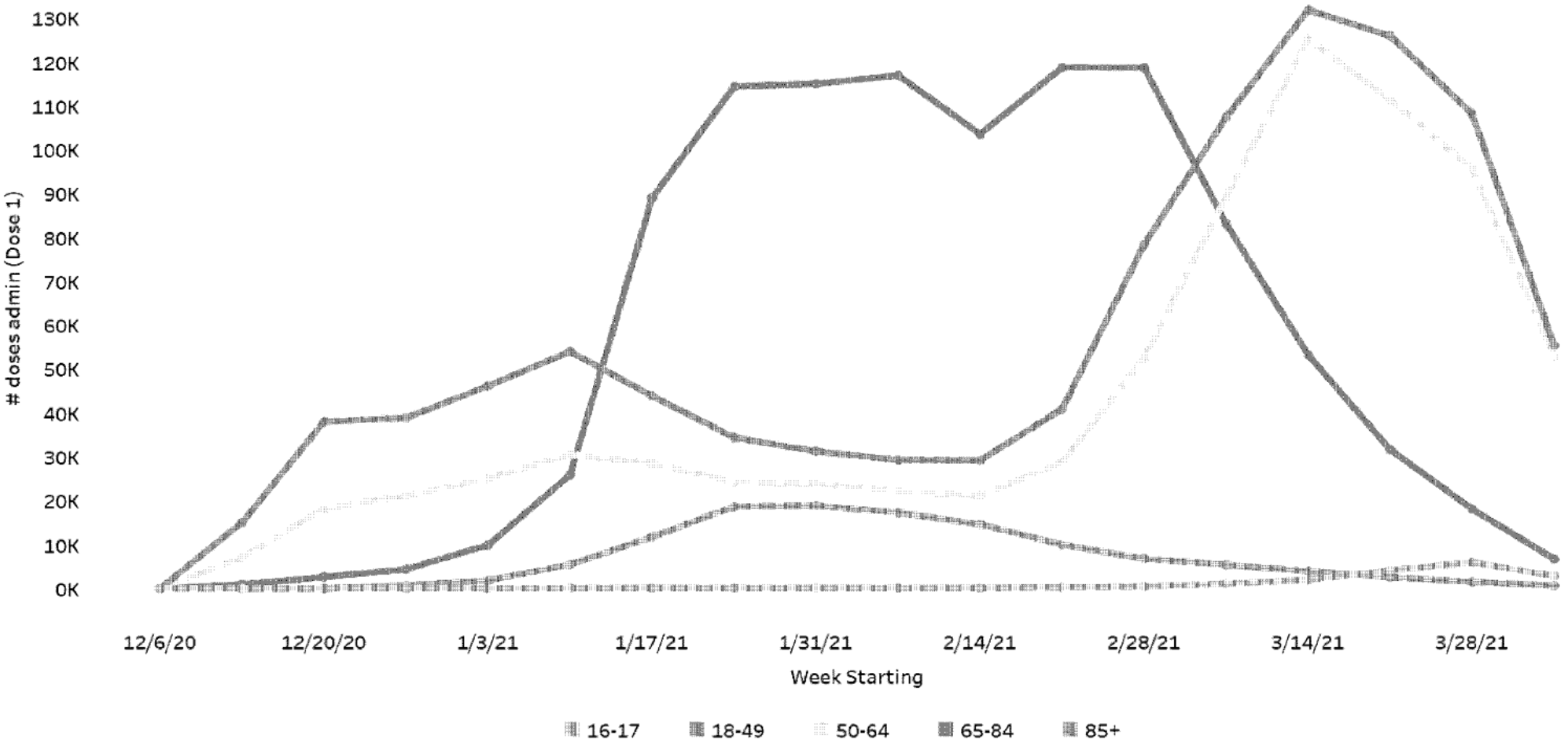
To date, 30.0% of VSD population initiated vaccination and 18.0% is fully vaccinated

0.0% 50.0% 100.0%

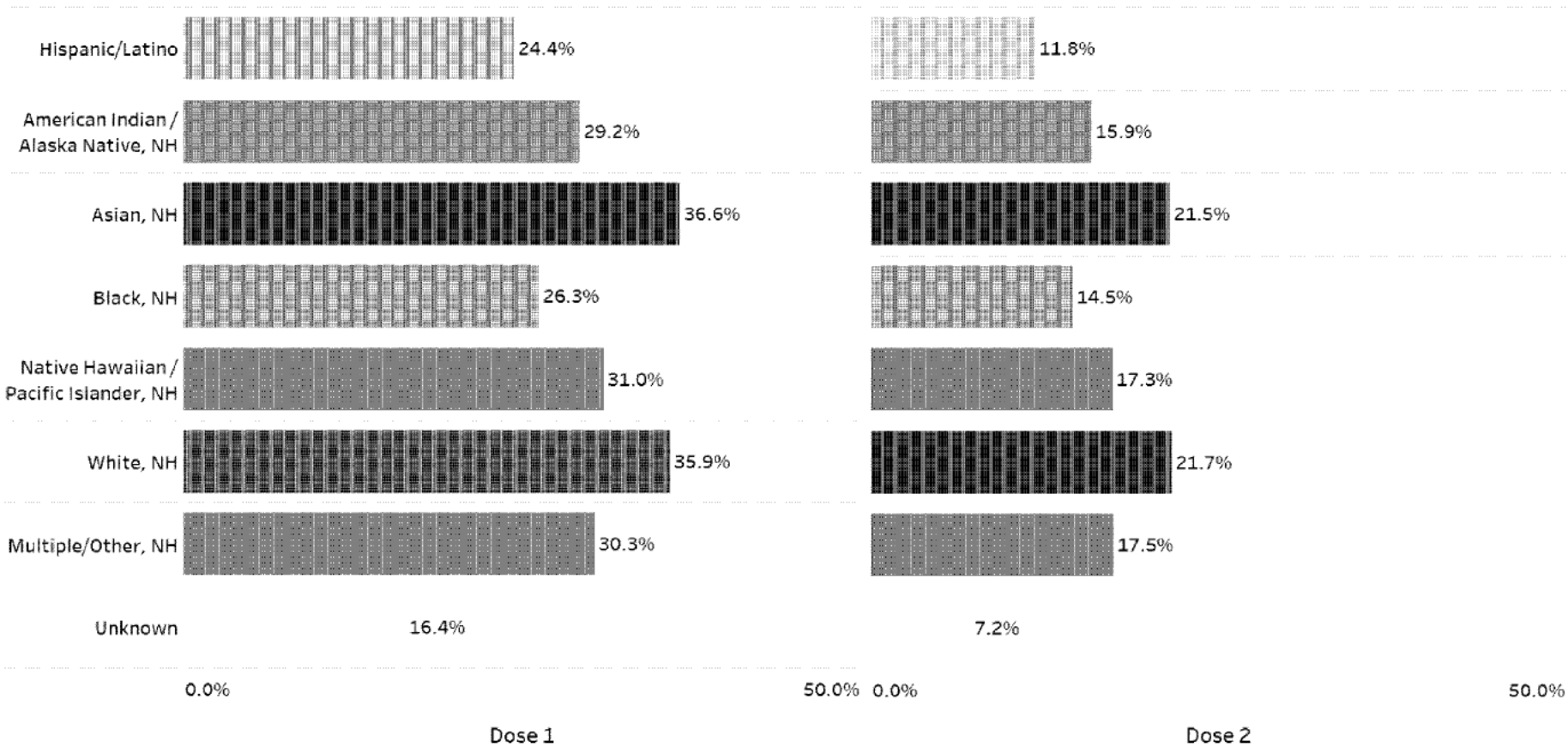
COVID-19 Vaccine Totals by Age Group



Vaccine Totals (Dose 1) by Age Group and Week



COVID-19 Vaccine Coverage by Race



Simultaneous Vaccine Administration with COVID-19 Vaccine

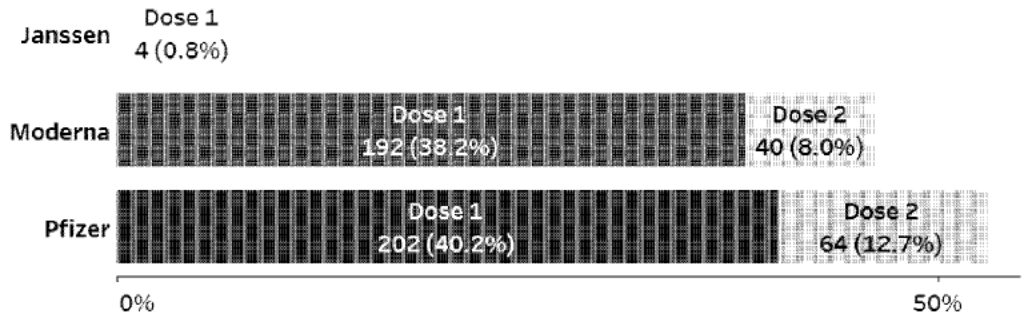
Number of COVID-19 doses admin to date:

4,623,489

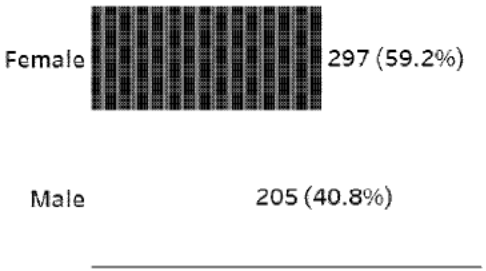
Number of people who received simult vaccs:

502

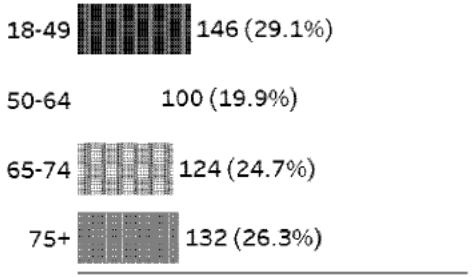
By COVID-19 Vaccine Type and Dose



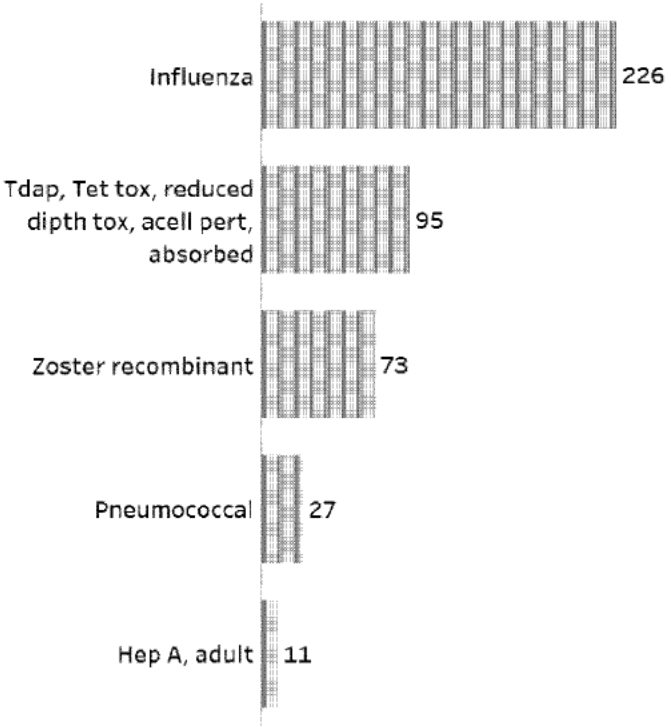
By Sex



By Age Group



Top 5 vaccines administered simultaneously (n=432)



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	793,078	436,514	805,935	534,647	54,102	1,653,115	971,161	2,624,276	5,082,304	32.53	20.17
	Male	596,388	291,934	598,122	368,690	50,179	1,244,689	660,624	1,905,313	4,575,164	27.21	15.54
High Risk	No	698,233	324,309	727,795	419,958	58,947	1,484,975	744,267	2,229,242	6,694,238	22.18	12.00
	Yes	691,233	404,139	676,262	483,379	45,334	1,412,829	887,518	2,300,347	2,963,230	47.68	31.48
History of COVID-19 Disease	**No**	**1,296,271**	**693,232**	**1,319,272**	**854,193**	**96,000**	**2,711,543**	**1,547,425**	**4,258,968**	**8,902,821**	**30.46**	**18.46**
	Yes	**93,195**	**35,216**	**84,785**	**49,144**	**8,281**	**186,261**	**84,360**	**270,621**	**754,647**	**24.68**	**12.28**

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

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

Office of Biostatistics & Epidemiology, CBER

Last Updated: April 16, 2021

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

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

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

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

FDA- CMS
(Center for Medicare & Medicaid Services)

Rapid Cycle Analysis
(Near-Real Time Surveillance)

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

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

AMI and PE

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

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

Crude RR for PE elevated from baseline rates

- Acute Myocardial Infarction (Pfizer)
  - Association met threshold for further QC and sensitivity analyses
  - After seasonality adjustment, relative risk reduced from 1.25 to 1.12 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 1.47 to 1.33 and remained statistically significant.

***Data through observation week 16, 3/27/2021**

Quality Assurance and Signal Characterization

Signal Assessment Summary

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

Quality Assurance

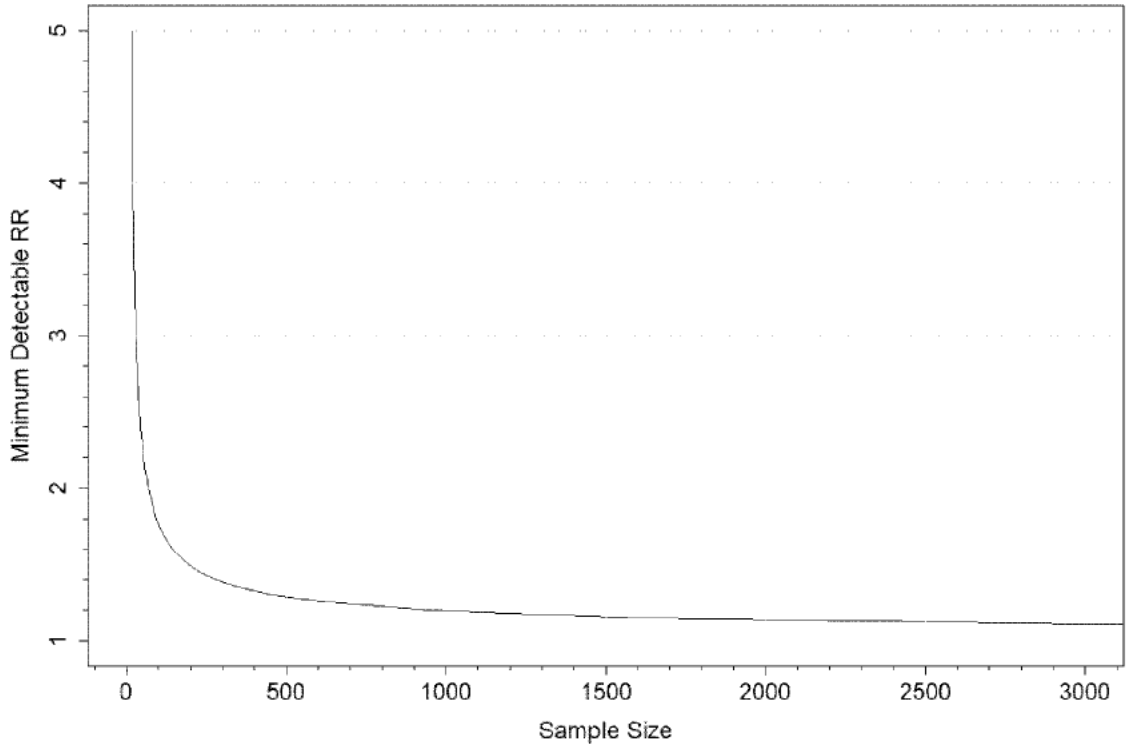
- Several analyses were performed to evaluate data quality, including:
  - Seasonality through stratification
    - PMaxSPRT sensitivity analysis using Jan-Mar background rates resulted in no association for AMI and delayed observed association for PE post-Pfizer.
  - Potential duplication of vaccines, 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

Signal Characterization

- Analyses were performed to verify findings from the RCA, including:
  - Outcome definitions
    - Proportion of specific claims-based codes to identify AMI and PE events were lower in COVID-19 vaccinees in RCA ('observed') than in historical period used to calculate background rates ('expected').
  - Temporal scan statistics
    - Temporal scan statistic did not identify significant clustering for AMI or PE post Pfizer first dose
  - Patient claim profiles
    - Majority of AMI cases were NSTEMI or Type 2 AMI, and approximately 25-40% were deemed unlikely to be true cases. For PE, 40-50% of cases were considered unlikely to be true cases due to use of anticoagulants or lack of diagnostic scans or treatment
  - Prior COVID Diagnosis
    - Proportion of AMI and PE cases post Pfizer vaccination that had a prior COVID diagnosis was 18% and 19%, respectively
- Additional analyses are in progress
  - Residual confounding

Next steps: Inferential Studies

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



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

Next steps: Inferential Studies

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

Conclusions

- Rates are elevated but below RR > 1.5
- Continuing to run RCA on remaining outcomes

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- Manette Niu
- CBER OBE Colleagues
- Federal Colleagues: CMS, VA, CDC
- FDA Partners: Acumen, IBM Watson – and new partners in FY2021

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Thank you!

Questions?