

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION**

**Advisory Committee on
Immunization Practices (ACIP)**



**Summary Report
April 14, 2021
Atlanta, Georgia**

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
Atlanta, Georgia 30329
April 14, 2021

<u>AGENDA ITEM</u>	<u>PRESIDER/PRESENTER(s)</u>
Wednesday, April 14, 2021	
1:30 Welcome & Introductions	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
1:45 Coronavirus Disease 2019 (COVID-19) Vaccines	
Introduction	Dr. Beth Bell (ACIP, WG Chair)
Overview of safety with Janssen's COVID-19 vaccine (Ad26.COV2.S)	TBD (Janssen Pharmaceuticals Companies of Johnson & Johnson)
Update on thromboembolic events, COVID-19 vaccines safety surveillance	Dr. Tom Shimabukuro (CDC/NCEZID)
VaST assessment	Dr. Grace Lee (ACIP, VaST Co-chair)
Work Group interpretation	Dr. Sara Oliver (CDC/NCIRD)
3:00 Break	
3:10 Public Comment	
3:30 Discussion	
3:30 VOTE	
Janssen COVID-19 Vaccine: Updated recommendations for use	Dr. Sara Oliver (CDC/NCIRD)
4:30 Adjourn	
Acronyms	
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
COVID-19	Coronavirus disease 2019
ETR	Evidence to Recommendations Framework
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NIAID	National Institute of Allergy and Infectious Diseases
OIDP	Office of Infectious Disease and HIV/AIDS Policy
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WG	Work Group
WHO	World Health Organization
VaST	Vaccine Safety Technical Subgroup
VE	Vaccine Effectiveness

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
Ad.26	Adenovirus 26
AE	Adverse Event
AECI	Adverse Events of Clinical Interest
AESI	Adverse Events of Special Interest
AGS	American Geriatric Society
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
ASTHO	Association of State and Territorial Health Officers
AZ	AstraZeneca
BSH	British Society for Haematology
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CISA	Clinical Immunization Safety Assessment
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CSTE	Council of State and Territorial Epidemiologists
CT	Computed Tomography
CVA	Cerebrovascular Accident
CVST	Cerebral Venous Sinus Thrombosis
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVT	Deep Vein Thrombosis
ED	Emergency Department
EHP	Expert Haematology Panel
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
HAN	Health Alert Network
HCP	Health Care Personnel / Provider / Professional
HCW	Health Care Workers

HHS	(Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin-Induced Thrombocytopenia
HRSA	Health Resources and Services Administration
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
ITP	Immune Thrombocytopenia
ITT	Immune Thrombotic Thrombocytopenia
IVC	Inferior Vena Cava
IVIG	Intravenous Immune Globulin
IV-TPA	Intravenous TPA
J&J	Johnson & Johnson
MedDRA	Medical Dictionary for Regulatory Activities
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NAAT	Nucleic Acid Amplification Test
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	New England Journal of Medicine
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NSAID	Nonsteroidal Anti-Inflammatory Agent
OCP	Oral Contraceptive Pills
PE	Pulmonary Embolism
PF4	Platelet Factor 4
PHAC	Public Health Agency Canada
PhRMA [®]	Pharmaceutical Research and Manufacturers of America [®]
PI	Principal Investigator
PIDS	Pediatric Infectious Disease Society
PRAC	Pharmacovigilance Risk Assessment Committee
PVT	Portal Vein Thrombosis
RCT	Randomized Controlled Trial
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2

SHEA	Society for Healthcare Epidemiology of America
SLUSOM	Saint Louis University School of Medicine
SMEs	Subject Matter Experts
SVT	Splanchnic Vein Thrombosis
tPA	Tissue-Type Plasminogen Activator
TTP	Thrombotic Thrombocytopenic Purpura
UK	United Kingdom
US	United States
UTI	Upper Respiratory Tract Infection
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST	ACIP COVID-19 Vaccine Safety Technical Subgroup
VITT	Vaccine-Induced Immune Thrombotic Thrombocytopenia
VSD	Vaccine Safety Datalink
VSS	Venous Sinus Stenosis
WG	Work Group
WHO	World Health Organization

Opening Session: April 14, 2021

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the April 14, 2021 emergency meeting of the Advisory Committee on Immunization Practices (ACIP), the purpose of which was to discuss the pause of the Janssen Coronavirus Disease 2019 (COVID)-19 vaccine. He welcomed everyone and conducted a roll call, which established quorum. ACIP member, Dr. Sharon Frey, reported that she is a Principal Investigator (PI) for Saint Louis University School of Medicine (SLUSOM) on the Moderna and Janssen COVID-19 vaccine trials. No other no conflicts of interest (COIs) were declared for this meeting. A list of Members, *Ex Officio* Members, and Liaison Representatives is included in the appendixes at the end of the full minutes for the April 14, 2021 ACIP meeting.

Dr. Cohn welcomed everyone and explained that this meeting was arranged within the last 48 hours to ascertain whether ACIP has enough information to make interim age or risk factor-based recommendations for the use of the Janssen vaccine, and what recommendation ACIP feels would be appropriate at this time give currently available information for the use of the Janssen vaccine given the safety signal identified. She acknowledged that while there likely would be numerous important scientific questions, comments and questions from ACIP members, *Ex Officio* members, and Liaison representatives should focus on the question and discussion at hand. She assured everyone that a lot of work is occurring in this space and what is known to date would be presented during this meeting, the goal of which was to determine whether ACIP has enough information to come to a recommendation and vote or if additional information is needed.

A *Federal Register* Docket was opened for oral and written public comments that would remain open through Friday, April 16, 2021. Individuals from the public were randomly selected to present their comments orally during this meeting. Those who were not selected and any other individuals wishing to make written public comments may submit them through <https://www.regulations.gov> using Docket Number CDC-2021-0042. Further information on the written public comment process can be found on the ACIP website.

ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, CDC has issued limited COI waivers. Members who conduct COVID-19 vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines and participate in discussion, but have been asked to withhold participation in discussion after the policy question has been deliberated and to abstain from any committee votes related to COVID-19 vaccine.

Coronavirus Disease 2019 (COVID-19) Vaccines: April 14, 2021

Introduction

Beth Bell, MD, MPH
ACIP, COVID-19 Vaccine WG Chair
Clinical Professor, Department of Global Health
School of Public Health, University of Washington

Dr. Bell introduced the session, indicating that there were some contextual issues the COVID-19 Vaccine Work Group (WG) thought were important for ACIP to be aware of in order to assimilate the information to be presented. She then briefly reviewed adenovirus vector COVID-19 vaccines, described rare clotting events seen after adenoviral vector vaccines following receipt of AstraZeneca (AZ) vaccine in Europe and Janssen vaccine in the US, and ACIP's response.

There are 2 adenovirus vector vaccines, the Janssen/J&J vaccine and the AZ vaccine. The Janssen vaccine is a single-dose vaccine that uses human adenovirus 26 (Ad26) as its vector. An Emergency Use Authorization (EUA) was issued in the United States (US) in February 2021 for the Janssen vaccine and the ACIP subsequently made recommendations. The European Medicines Agency (EMA) has authorized the Janssen vaccine for Europe, but no doses have been delivered to or administered in Europe. The AZ product is a 2-dose vaccine. The vector is a chimp adenovirus. It is awaiting EUA application in the US and is approved in the United Kingdom (UK) and Europe and has been in wide use in those areas and other parts of the world.

Concerns were raised for rare clotting events seen after COVID-19 adenovirus vector vaccines. The clinical syndromes after both vaccines appear similar. However, the extent to which the cases seen after each of these adenovirus vector vaccines represent exactly the same syndrome is not entirely clear at this time. The EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), released a report on April 9, 2021 that concluded that there is a strong association and probable causal link between the AZ vaccine and rare clotting events.

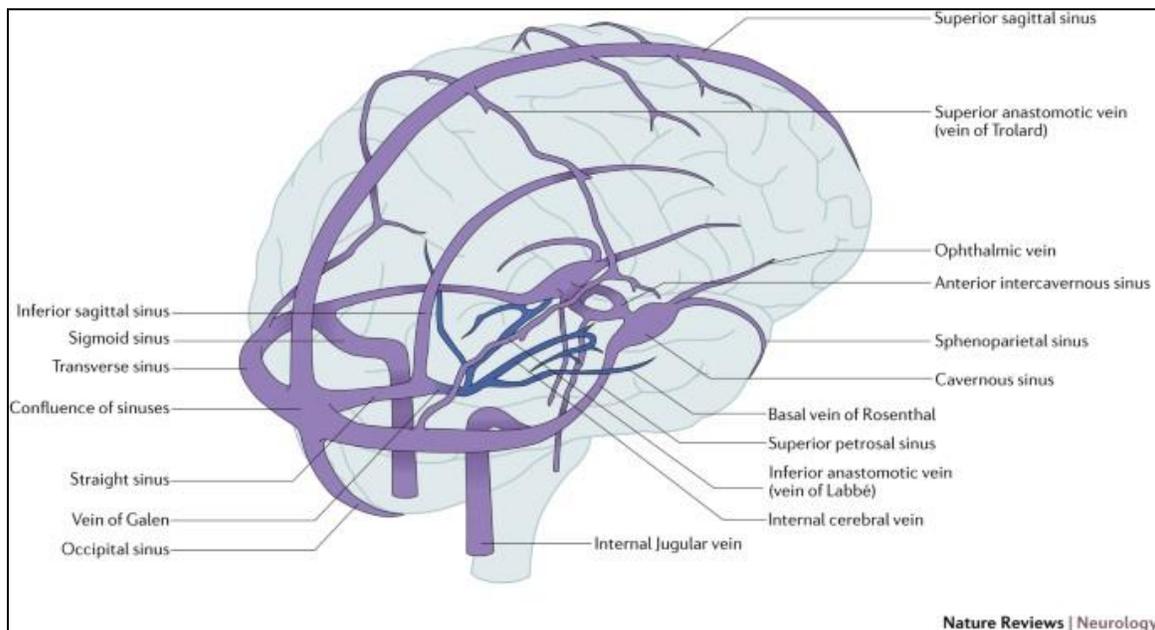
There were press releases from the EU¹ and the UK². From the EU, there have been 62 cases of cerebral venous sinus thrombosis (CVST) and 24 cases of splanchnic vein thrombosis (SVT) with thrombocytopenia. Of these, 18 were fatal. Most occurred in females less than 60 years of age within 2 weeks of AZ vaccine receipt. Due to the different ways the vaccine is used in each country, the EU was not able to exclude age and gender as risk factors. From the UK, 79 cases of thrombosis and thrombocytopenia were reported. Among these, 19 were fatal. There were 44 cases of CVST with 14 fatalities and 35 cases of other clots with 5 fatalities. Of the cases, 51 were female and 28 were male. This is in the context of a denominator of 20.2 million doses of vaccine given in the UK. The press release estimated a risk of approximately 4 per million population, with a comment that there was a "slightly higher incidence" in younger age groups.

¹ <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>

² <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>

Recently, there were reports^{3,4} in the *New England Journal of Medicine (NEJM)* of low platelets (thrombocytopenia) and blood clots (thrombosis) after AZ vaccine in Europe. These cases came from Germany, Austria, and Norway. Many of these cases had platelet activating antibodies directed against platelet factor 4 (PF4), which is a clue to the possible mechanisms. The authors proposed a syndrome entitled “vaccine-induced immune thrombotic thrombocytopenia” (VITT).

Dr. Bell briefly reviewed CVST, given that this is one of the more predominant syndromes or conditions that has been identified. This involves thrombosis within large vessels that are draining blood from the brain as depicted in this figure⁵:



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

CVST occurs primarily among people 20 to 50 years of age and mostly among females. Risks include pregnancy and other identified risks for coagulation such as oral contraceptives. Symptoms typically include headache, nausea, vomiting, other neurologic symptoms. The presentation can be acute or more chronic. This is an overall description of CVST and not specific to CVST with thrombocytopenia, which has been seen in the current situation.

The EMA's PRAC does not make vaccine policy for the EU. Instead, each country weighs the risks and benefits of AZ vaccine individually. In terms of these findings in Europe, many countries have made new policy and have adopted age-based recommendations. On April 7, 2021 in the UK, a recommendation was made to use the AZ vaccine in adults ≥ 50 years of age. On April 8, 2021 in Australia a recommendation was made to use AZ vaccine in adults ≥ 55 years of age. Other European countries have recommended use of the AZ vaccine in adults ≥ 55 to ≥ 70 years of age, depending upon the country.

³ https://www.nejm.org/doi/full/10.1056/NEJMoa2104882?query=featured_home

⁴ https://www.nejm.org/doi/full/10.1056/NEJMoa2104840?query=featured_home

⁵ <http://www.med.umich.edu%2F1libr%2FStroke%2FSinusVeinThrombosis.pdf&usq=AOvVaw3qjvm4UOFcHN-eR4O3Kyf8>

As mentioned earlier, the Janssen vaccine received an EUA from FDA in February 2021 and ACIP made recommendations thereafter. On April 13, 2021, CDC and FDA issues a joint statement on the Janssen COVID-19 vaccine and made several points. As of April 12, 2021, more than 6.8 million doses of the Janssen vaccine have been administered in the US. CDC and FDA are reviewing data involving 6 cases of CVST in combination with low platelets reported among recipients of the Janssen vaccine in the US. The statement said that, “CDC will convene a meeting of the Advisory Committee on Immunization Practices on Wednesday to further review these cases and assess their potential significance.” The statement also indicated that, “Until that process is complete, we are recommending a pause in the use of this vaccine out of an abundance of caution.”

Another important point that was made in the press release was that one of the important reasons for the pause was to allow time to provide information to clinicians and the public about specific and unique aspects of diagnosis, treatment, and clinical signs and symptoms to monitor. The first step in that process was the issuance of a Health Alert Network (HAN)⁶ release on April 13, 2021 that provided recommendations for clinicians on diagnosis and treatment, for public health in terms of case reporting through the Vaccine Adverse Event Reporting System (VAERS), and for the public on clinical signs and symptoms to monitor and when to seek medical attention. A few of the details in that report include the following:

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

The ACIP response thus far has included a meeting on April 12, 2021 of the Vaccine Safety Technical Group (VaST); an ACIP COVID-19 Vaccines WG meeting on April 13, 2021; and this emergency ACIP meeting on April 14, 2021 with the purpose of considering the implications of reported cases of thrombosis and thrombocytopenia after the Janssen/J&J vaccine on vaccination policy. Dr. Bell indicated that the day’s agenda would include presentations on the following topics, which would be followed by a public comment session:

- Overview of Safety with Janssen’s COVID-19 Vaccine, Ad26.COV2.S
- CVST with Thrombocytopenia after COVID-19 Vaccines from VAERS for the Period March 2-April 12, 2021
- ACIP COVID-19 VaST Assessment
- COVID-19 Vaccine WG Interpretation
- Public Comment
- Potential Vote: Updated Interim Recommendations for use of Janssen COVID-19 Vaccine

⁶ [HAN Archive - 00442 | Health Alert Network \(HAN\) \(cdc.gov\)](#)

Safety Overview of Janssen's Ad26COV2.S COVID-19 Vaccine & Epidemiology Analysis

Aran Maree, MD
Chief Medical Officer, Pharmaceuticals
Head, Global Safety Organization
Janssen Pharmaceuticals Companies of Johnson & Johnson

Kourtney Davis, PhD, MSPH
Epidemiologist
Senior Director and Head, Therapy Area Matrix
Global Epidemiology at Janssen R&D, LLC

Dr. Maree shared relevant Janssen clinical and post-authorization data on the subject of thrombosis, particularly in terms of CVST with thrombocytopenia, and described the background epidemiological dataset in the context of Janssen's overall evaluation. He emphasized that the safety and well-being of the people who use Janssen's products is their number one priority. While causality has not been fully established between these very rare events and Janssen's vaccine, they recognize that these events could represent an important potential risk with the Janssen vaccine. They are in the process of updating their Company Core Data Sheet (CCDS) and working with health authorities to update labeling appropriately. Johnson & Johnson (J&J) will continue to monitor this potential risk and is committed to efforts to ensure vaccinee and healthcare professional (HCP) awareness of the important signs and symptoms of this event, as well as appropriate diagnosis and management.

To review the vaccine data, Janssen has 2 Phase III pivotal clinical trials in its program. Study 3001 is a 1-dose Phase III trial and Study 3009 is a 2-dose ongoing study that remains blinded. For Study 3001, 43,783 participants have been vaccinated. In the 28 days after vaccination, there have been 4 deep vein thromboses (DVTs) in the active arm and 2 cases in the placebo arm. There are 2 cases of pulmonary embolism (PE) in the active arm and 1 case in the placebo arm. There has been 1 CVST and 1 venous thrombosis of a limb in the active arm and none in the placebo arm. The total number of cases accrued are 11 DVTs in the active arm and 3 in the placebo arm, 9 PEs in the active arm and 4 in the placebo arm, 1 CVST in the active arm and 1 in the placebo arm, 1 venous thrombosis in a limb in the active arm and none in the placebo arm, and 1 venous embolism in the active arm and none in the placebo arm. In Study 3009, the ongoing Phase III 2-dose trial, 28,277 participants have been vaccinated. This study remains blinded and the data are presented as blinded. In this study, there has been 1 PE event up to 28 days after vaccination. There are now 2 DVTs at all time points and 4 PEs beyond 28 days.

There also is an ongoing large, open-label study in South African HCPs that has enrolled 272,438 participants to date out of a total anticipated 500,000 participants. As of April 9, 2021, no CVST cases have been reported. There has been 1 case of PE, but there has been no information on platelet or COVID status with this case. There has been 1 cerebrovascular accident (CVA) in a 38-year-old female 8 days after vaccination. Additional information is being actively sought on this case through the Principal Investigator (PI). There has been 1 case of retinal vein thrombosis in a 68-year-old diabetic whose platelet count was reported as normal.

Dr. Maree reviewed all known cases of CVST and all known cases of thrombosis with thrombocytopenia with Janssen COVID-19 vaccine to date. Per the CDC, the number of vaccinations to date with the Janssen COVID-19 vaccine in the US is 7.2 million as of April 14, 2021. Janssen is aware of 6 post-authorization cases of CVST, 4 of 6 with low platelets and 2

unknown, within these vaccinated individuals. The following table describes all known cases of thrombosis with thrombocytopenia with the Janssen COVID-19 vaccine:

As of 14 April 2021

SOURCE	CA SE	CIOMS#	SERIOUS ADVERSE EVENT	RISK FACTOR(S)	PLATELET COUNT	COVID STATUS	TTO	Treatment	Status
CLINICAL TRIAL CASES									
Study 3001	25 YO Male on Vaccine	2021017267	CVST with hemorrhage	Stenosis of transverse sinus, URI suspected	64,000 (Anti-PF4+)	Negative	8 days	Heparin, tPA and platelets, angioplasty and thrombectomies	Recovered
Study 3001	24 YO female on placebo	20210202793	CVST	Newly prescribed OCP	Normal (Anti-PF4-)	Negative	>50 days	N/A	Recovered
POST-AUTHORIZATION CASES									
VAERS # 1114806	45 YO female	20210354798	CVST with hemorrhage	none	"thrombocytopenia"	Unknown	11 days	Unknown	Fatal
VAERS 1133212	38 YO female	20210408478	CVST	Unknown	Unknown	Unknown	10-14 days	Heparin	Not Recovered at this time
VAERS #1141160-1	59 YO Female	20210407977	Extensive DVTs	Coronary artery disease	15,000	Unknown	7 days	Vena cava filter IVC, thrombectomy	Not Recovered at this time
Janssen SAE Nevada	18 YO female	20210407314	CVST with hemorrhage	unknown	16,000	Unknown	14 days	Heparin then switched to "British guidelines" and thrombectomy	Not Recovered at this time
Janssen SAE (NEJM -editor notification) Nebraska	48 YO female	20210415297	TTP, splanchnic veins thrombosis, CVST, then given heparin and then additional hepatic and splanchnic vein thrombosis	Unknown	<13,000 (hi d-dimer, Anti-PF4+)	Negative	14 days	Heparin first and switched to argatroban then IVIG	Not Recovered at this time
Janssen SAE NJ/PA	26 YO female	20210416236	CVST, PE, portal vein thrombosis	Obesity	120,000 (hi d-dimer, Anti-PF4+)	Negative	7 days	Heparin and then IVIG	Discharged from hospital
VAERS 1182133	28 YO female	In processing	Details pending, FOI requested						

The first 2 rows are the cases already described within the Phase III clinical trial program. The following rows are the post-authorization cases. In Study 3001 in the first row, the case was of a 25-year-old male who received vaccine. The report was of a CVST with hemorrhage. It was noted that the subject had stenosis of his transverse sinus, a suspected upper respiratory tract infection (UTI), and a platelet count of 64,000. It has recently been retrospectively determined that his anti-PF4 antibodies were negative at baseline, but were positive at approximately Day 28 post-vaccination. His COVID status was negative and time to onset was 8 days after vaccination. He was treated with heparin, tissue-type plasminogen activator (tPA), received platelets, had 2 balloon angioplasties and thrombectomies due to the discovery of a venous sinus stenosis (VSS). He has recovered and has been discharged from the hospital. The second participant from the placebo arm of Study 3001 is a 24-year-old female who has recovered from a CVST. She had a normal anti-PF4 antibody test post-vaccination and post-incident. Her COVID status was negative. The time to onset was more than 50 days after vaccination.

Post-authorization phase come to Janssen primarily from 2 sources. The first 3 cases described and the final case came through VAERS, the joint CDC and FDA reporting system. Janssen gains access to these reports when they are refreshed every Friday, so there is a slight lag in reporting to Janssen. Understandably for privacy reasons, there is significant reduction of some of the data fields and it is not possible for Janssen to follow-up for further information or evaluation beyond what is presented to them in the preliminary report. They can attempt to do so through Freedom of Information Act (FOIA) applications, and FDA has been very supportive in helping Janssen to expedite these requests. The other cases come to Janssen directly through their call center, website, or via email. This allows Janssen to acquire further information and result in a richer dataset.

The first case that came through VAERS post-authorization was a 45-year-old female who presented with CVST with hemorrhage. No risk factors were described in the report, the report notes the term “thrombocytopenia,” COVID status was unknown, time to onset after vaccination was reported at 11 days, treatment was not described, and this patient died. The second case that came through VAERS was a 48-year-old female who presented with CVST, risk factors were unknown, platelet count was unknown, COVID status was not described, and time to onset was 10 to 14 days after vaccination. She was treated with heparin and at this time, she is described and reported as not recovered. The third case that came through VAERS was a 59-year-old female who presented with extensive DVT on her left side, had known coronary artery disease, had a platelet count of 15,000, COVID status was unknown, and time to onset after vaccination was 7 days. A vena cava filter was inserted into her inferior vena cava (IVC) and she also underwent a thrombectomy. The day after the procedure to place the IVC, she was reported to have significant thromboses and DVTs on her right side, and it was questioned as to whether this was secondary to the intervention or partially facilitated by the intervention through her right side to place the IVC. She is reported as not recovered at this time.

The next case was reported as a Janssen serious adverse event (SAE) that came from Nevada. This is an 18-year-old female who presented with CVST with hemorrhage, risk factors are unknown, platelet count was 16,000, COVID status was unknown, and time to onset after vaccination was 14 days. She initially was treated with heparin and then switched to what was reported at “treatment according to the British Guidelines,” which Dr. Maree said he took to refer to the Guidance produced by the Expert Haematology Panel (EHP) from the British Society for Haematology (BSH). She underwent a thrombectomy and her status is listed as not recovered at this time.

The next case was reported directly to Janssen through pre-publication by the *New England Journal of Medicine (NEJM)* by an Editor Notification. This case from Nebraska is a 48-year-old female who was reported as presenting with thrombotic thrombocytopenic purpura (TTP), SVT, and CVST. She initially was given heparin and then additional hepatic and SVT was reported. Her risk factors were unknown, her platelet count was 13,000, she was reported to have a high D-Dimer and a positive anit-PF4 antibody test, her COVID status was reported as negative, and time to onset was 14 days after vaccination. She first was treated with heparin but was switched to argatroban after the anit-PF4 antibody test and also was given intravenous immune globulin (IVIG). At this time, her status is reported as not recovered.

The next case is from New Jersey/Pennsylvania and also was reported directly to Janssen. This case is a 26-year-old female who presented with CVST, PE, and portal vein thrombosis (PVT). Risk factors described include obesity, platelet count was 120,000, she had a high D-Dimer, she had a positive anti-PF4 assay, her COVID status was negative, and time to onset after vaccination was 7 days. She was treated with heparin and then with IVIG and has been discharged from the hospital.

The final case was notified to Janssen through VAERS and has very limited details on the company side. This case is of a 28-year-old female and details are pending under an FOIA application via FDA to CDC.

To go into more detail on 3 of the cases, the *NEJM* pre-publication case from the University of Nebraska was reported to Janssen on April 8, 2021. This 48-year-old woman was described as having an unremarkable past medical history who presented to the emergency department (ED) after 3 days of malaise and abdominal pain. The initial evaluation describes mild anemia and severe thrombocytopenia with a platelet count of 13,000. A blood smear confirmed marked reduction in platelet count with occasional schistocytes. She had hypofibrinogenemia, a prolonged aPTT, markedly elevated D-Dimer, and was noted to have extensive SVT on computed tomography (CT). She was transferred to the reporting institution, with further evaluation and progression noted of the thrombosis on heparin. She had a negative reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV2 RNA. A head CT for new-onset headaches reported in her secondary hospital showed CVST. Thrombosis progressed with hemorrhagic stroke despite treatment with heparin. She underwent repeat CT angiography, which showed new thrombus involving right hepatic and splenic veins. Further inquiry revealed that the patient received the Ad26.COV2.S vaccine 14 days before symptom onset. The report describes evidence and management of a possible immune thrombotic thrombocytopenia (ITT). She had positive anti-PF4/heparin antibodies by ELISA. Her latex-enhanced immunoassay was negative. Her heparin was switched in the second hospital to argatroban and she was given IVIG 1 gm/kg of body weight for 2 days. Her platelet count was reported to have increased from 30,000 to 145,000 over 5 days. She remains critically ill as of the last report.

Further details were received on the next case reported directly to Janssen on a follow-up phone call with the physician on April 12, 2021. This is a 26-year-old woman who is described as an overweight but active gym instructor who has no history of clotting disorder and is on no medication. She initially presented to the ED with a severe headache approximately 1 week following vaccination. She was discharged home from ED with paracetamol and Benadryl[®]. However, her headache persisted and she was subsequently admitted to the hospital another week later with abdominal pain and rapid heart rate. COVID-19 infection ruled out, although the exact test is unknown. A laboratory evaluation revealed thrombocytopenia with a platelet count of 120,000, elevated D-Dimer, and normal fibrinogen. The diagnostic scan showed CVST, PVT, and PE. She initially was treated with heparin and is described as having been switched to IVIG after the clinical team became aware of a positive anti-PF4 antibody test result. Her platelet count reportedly started to increase before the IVIG was commenced. This patient has been discharged home on oral anticoagulant after a period of 1 to 1.5 weeks in the hospital.

The case from Study 3001 in the clinical trial program is of a 25-year-old healthy, active male who was vaccinated on September 21, 2020. He began feeling progressively unwell 8 days post-vaccination described as fatigue, faintness, nausea, and a headache for which he took nonsteroidal anti-inflammatory agents (NSAIDs). At 11 days post-vaccination, he had continued fatigue, weakness, and nausea and developed abdominal pain and a headache. A COVID-19 swab taken by the PI on that date was negative. He was then hospitalized 19 days post-vaccination on October 9, 2020 after visual disturbance and collapsing. The laboratory evaluation reported a platelet count of 64,000; PT of 17.7, INR of 1.46; fibrinogen 154, white blood count of 12.4; hemoglobin of 12.7, and hematocrit of 36.1. He underwent CT, magnetic resonance imaging (MRI), and venogram and his diagnosis was CVST and secondary cerebral haemorrhage. He underwent repeated cerebral vascular sinus thrombectomy and balloon venoplasty due to re-occlusion and treatment for stenosed cerebral sinus. He also was treated with low-molecular weight heparin and intravenous TPA (IV-TPA). Extensive haematology and infectious disease laboratory evaluations showed inconclusive results. The patient was discharged on treatment with apixaban. Last week, stored serum tested positive for anti-PF4 antibodies for the post-vaccination phase and a negative baseline laboratory anti-PF4 test. This

gentleman recovered after repeat thrombectomy and balloon angioplasty procedures. He was described as having severe epiglottitis while in the hospital and his discharge medications include apixaban.

Dr. Davis described the epidemiological analysis that Janssen has conducted to assist in this investigation. Janssen conducted a published literature search that resulted in retrieval of articles from the US, EU, Middle East, Asia Pacific. An interim meta-analysis analysis also was conducted across 4 large US healthcare claims databases and 1 US electronic health record (EHR) database. That study design was intended to generate background incidence rates of CVST. The study period 2017 to 2019 was used to generate the incidence of the outcome “cranial venous sinus thrombosis.” The methods used for that analysis are similar to those used in a multi-national network cohort study of 15 adverse events of special interest (AESI). The results of that large network study have been shared with FDA and EMA and are published on a pre-print server. A manuscript of those AESI background is also under review⁷. This table shows CVST background incidence rates from the published literature in the bottom rows along with those from the database analyses conducted by Janssen and by the ACCESS group in Europe:

CVST Background Incidence Rates

Data source	Year of publication	Age group (in years)	IR (95%CI) in 100,000 person-years			
			Male	Female		
US claims and EHR databases (Janssen internal access)	2021	18-34	1.70 (0.02-145.10)	2.64 (0.25- 28.29)		
		35-54	0.92 (0.13- 6.63)	1.90 (0.19-19.43)		
		55-64	0.84 (0.06-11.04)	1.10 (0.06-20.62)		
		65-74	1.58(0.11-21.63)	0.8 (0.11- 5.67)		
		75-84	1.14(0.37-3.45)	1.25 (0.02-65.54)		
		85+	1.26 (0.00-425.37)	1.33 (0.08-23.12)		
		Overall (18-85+)	1.23 (0.1- 56.53)	1.75 (0.16-23.19)		
		ACCESS - FISABIO	2021	All genders		
				0-19	0.12 (0.05-0.29)	
				20-29	0.25 (0.10-0.60)	
		30-39	0.26 (0.12-0.55)			
		40-49	0.42 (0.25-0.71)			
		50-59	0.41 (0.23-0.72)			
		60-69	0.69 (0.42-1.13)			
		70-79	0.60 (0.33-1.08)			
		80+	1.08 (0.63-1.86)			
		Overall (year 2019)	0.48 (0.32-0.71)			
ACCESS – ARS IT	2021	0-19	0.34 (0.15-0.76)			
		20-29	0.64 (0.29-1.42)			
		30-39	1.71 (1.09-2.68)			
		40-49	1.88 (1.32-2.67)			
		50-59	1.00 (0.62-1.61)			
		60-69	1.29 (0.81-2.05)			
		70-79	1.91 (1.28-2.85)			
		80+	1.55 (0.93-2.57)			
				Overall (year 2019)	1.44 (1.08-1.92)	
		Stam, 2005; Bousser, 2007	2005-2007	Overall (adults)	0.2-0.5 (NA)	
Janghorbani, 2008	2008	Overall (adults)	1.23 (NA)			
Coutinho, 2012	2012	Overall (adults)	1.32 (NA)			
Devasagayam, 2016	2016	Overall (adults)	1.57 (NA)			

⁷ Xintong et al., Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across 8 countries: a multinational network cohort study. Manuscript under review: <https://www.medrxiv.org/content/10.1101/2021.03.25.21254315v1>

Beginning with the published literature, the overall adult background incidence rates are shown per 100,000 person years. Those range from 0.2 to 0.5 per or 2 to 5 per million. In the older studies, rates are higher at upwards of about 15 per million in the most recent studies that come from the bottom 2 references on the table. The results of Janssen's claims database are shown in the first row, but are not yet published as they were just generated. Those are displayed by age and sex, which Janssen thought was important as there potentially is a higher risk among younger women. The highest rates are observed in women 18 to 34 years of age at 2.6 per 100,000 or 26 per million, with an overall rate among women 18 to 85 years of age of 17 per million or in men of 12 per million. This provides an understanding of the range of the estimates from more contemporary claims databases. Limitations of the claims databases are that there is no validation of the outcome of CVST, and Janssen did the best they could with the diagnoses that come from hospitalized events. A stratified analyses is underway of CVST incidence by thrombocytopenia.

Dr. Maree pointed out that while ethnicity is not reported in all of the post-authorization reports, it is known that the single case of CVST in the active arm in Study 3001 was in a 25-year-old white male. They also have meta-data on two of the post-market reports indicating that they were 2 white females. However, ethnicity is not described in most case reports. Janssen is conducting an intensive ongoing review of internal and publicly available data including, but not limited to, the following:

- Evolving literature on the relationship between COVID and thrombocytopenic and thrombotic events
- Case reports of association between thromboembolic events, including CVST with ITP and TTP
- US VAERS data on thrombocytopenic and thrombotic events and other AESIs for all available vaccines
- European EUDRAVIGILANCE AE dataset

In conclusion, Dr. Maree reiterated that based on the current data, Janssen believes the overall benefit-risk profile for its COVID-19 vaccine is positive across the population for which it is authorized and strongly supports awareness of the signs and symptoms of this very rare event and the recommendations to ensure the correct diagnosis, treatment, and reporting by HCPs.

Discussion Points

Dr. Romero asked what the significance is of the latex-enhanced negative assay on the first case presented for anti-PF4 antibodies.

Dr. Maree said that it has been represented to him that for the PF4, it is important to use the ELISA test as some of the other assays may not be as sensitive. In the case where both were reported to them, they represented both.

Dr. Bernstein observed that a number of the patients were described as having recovered. He wondered whether the patient who was described as discharged from the hospital was considered recovered, how recovered is defined in terms of whether it means patients are back to normal or are still be treated, and if patients who are considered to be recovered continue to be monitored.

Dr. Maree indicated that the reports to VAERS, which are known as Council for International Organizations of Medical Sciences (CIOMS) reports, have a number of fields. This includes a field for status, with a limited number of options available, so some of what is represented is somewhat clunky form terminology due to the limited options available.

Referring to Slide 15 with the background rates, Dr. Bernstein asked whether these are the cases without thrombocytopenia.

Dr. Davis clarified that this is any CVST and that it is not stratified in this analysis by thrombocytopenia status.

Dr. Sanchez asked whether any of the women had a recent pregnancy, were postpartum, had a history of preeclampsia, and/or had medication listed such as oral contraception.

Dr. Maree said that they did scan all reports and sent questions back to those for whom they had identifiable reporters. They do not have reports of recent pregnancy, being postpartum, or having suffered preeclampsia. He did not believe that any of the participants other than the 24-year-old woman in the placebo on who had a CVST at beyond 50 days was on oral contraceptive pills (OCP), but to the best of his recollection this was not described for any of the cases post-vaccination.

Dr. Cohn indicated that the next presentation by Dr. Shimabukuro would go through the VAERS reports with some specificity and will share any additional information they have about those cases.

Dr. Poehling recalled that the one case from New Jersey/Pennsylvania that was reported directly to Janssen had CVST with PE, and she wondered whether Janssen is aware of any cases of PE without CVST and if they are looking for these, how many cases have been reported, and the timeframe.

Dr. Maree said that while they have had cases of PE, none were reported in the context beyond what has been described with concomitant thrombocytopenia. Referring to Table 18, Dr. Maree indicated that they have interrogated the VAERS database looking for thrombocytopenic, thromboembolic, and hemorrhagic events that have been observed after vaccination. As of April 9, 2021, there have been 55 reports of thromboembolism, 4 reports of thromboembolism with thrombocytopenia, 2 cases of CVST, and other AEs with an exposure of 4.9 million doses administered. In the Phase III program shown on Slide 19, in the summary of total venous thrombosis events up to 28 days, there are 2 PEs in the active arm and 2 in the placebo arm. This again reiterates in a more comprehensive slide venous thrombosis events from the 43,000-person study.

Dr. Ault recalled mention of the Ebola and respiratory syncytial virus (RSV) vaccines that used the same vector and for which there were no cases in those trials. He asked whether there were any thrombotic events or thrombocytopenia events, especially an imbalance in the Ebola trial that included a fair number of pregnant and postpartum women.

Dr. Marnee confirmed that there were not CVST events and called upon Dr. Douoguih from Janssen's Clinical Team to respond as well.

Dr. Douoguih emphasized that they have not seen any CVST events in any of their programs, with the Ebola and RSV programs being the biggest ones. There have been some cases of DVT and PE, but none to their knowledge are associated with thrombocytopenia and there were clear risk factors. There was 1 case of immune thrombocytopenia (ITP) in the RSV program, so they will determine whether there are any stored samples that can be tested. The denominator for this case about 200,000 people or more who received at least 1 dose.

Dr. Long requested that Dr. Davis provide additional information about how the epidemiologic studies were done related to the HCPs under surveillance. She understood that they had to be in the system for a year but was not clear whether they were followed for a year and if these are basically numbers of cases expected in 100,000 people over 1 year. The clustering of these cases around the vaccine is very provocative and compelling, so she also wondered whether any additional analyses were done to estimate the number. If they used some random event such as the anniversary of the person's birthday and asked in 1 month after some random event what then would be the number of cases per 100,000 people in 1 month's time. She is tempted to want to divide by 12 for the background incidence in a month's time unless there is some other reason for these other sporadic cases to be clustered, which would change very much what the dynamic was within the expected range if they occurred within 1 month or even 2 months of vaccination.

Dr. Davis indicated that this is a classic incidence cohort design in which the person had to be observed in the database for a year prior to prove that they did not have a CVST in their history. It is looking for new diagnoses of CVST in a 1-year follow-up period. Regarding picking a random date and looking out 1 month, they did look up to a year. She said she did not have a specific way to answer the question about generating a person month estimate. When they convert this to an expected number when the formal observed to expected analysis is done, they generate it for a 28-day risk period and then divide by 12 in order to create the expected number. That also would be using the age- and sex-specific rates. They apply it to the actual exposure distribution for the vaccinated individuals when they go through this exercise. Simplistically speaking, they want to use these rates to convert them to an expected 28-day observed and divide by 12.

Dr. Cohn emphasized that some of this would be further addressed in Dr. Shimabukuro's upcoming presentation.

Ms. McNally said that as the consumer representative she was trying to understand the reporting process on safety events. She requested that Dr. Marnee explain how Janssen makes FDA and CDA aware of reports directly to Janssen and the extent to which Janssen shares the details of those cases with FDA and CDC.

Dr. Maree replied that when subjects are vaccinated in a Janssen clinical trial, there is an expedited SAE reporting via the clinical trial process to the health authorities. In the post-authorization phase when the vaccine is being given to the public, there are a number of ways in which patients experiences or AEs can be reported. When patients receive a vaccine, they are given a factsheet and information is presented to them on reporting to the FDA and CDC via VAERS. There is the v-safeSM program that sends regular text messages to vaccine recipients who sign up for their experience in the post-authorization first few weeks, which then is sent to VAERS. If any reports of AEs come directly to Janssen, there is an expedited reporting process whereby Janssen processes those cases and sends them immediately to the FDA, EUA, and other global health authorities. There is a continuing, sustained, rapid reporting of events between the companies and the health authorities in the various jurisdictions.

Update on Thromboembolic Events After Janssen COVID-19 Vaccine

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Task Force
Vaccine Safety Team
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro provided a brief background and further detailed the reports of CVST with thrombocytopenia (low platelets) following Janssen COVID-19 vaccine. He explained that platelets, which also are called thrombocytes, are colorless blood cells that help blood clot. A normal platelet count is 150,000–450,000 per microliter. In the medical world that is usually short-handed to 150-450. Platelets are important in that they stop bleeding by clumping and forming plugs in blood vessel injuries. Thrombocytopenia is a condition in which one has a low blood platelet count of <150,000 per microliter of blood. Dangerous internal bleeding can occur when someone's platelet count falls below 10,000 platelets per microliter. Though rare, severe thrombocytopenia can cause bleeding into the brain, which can be fatal⁸. This issue has been in the public view primarily because of the cases of rare and unusual blood clots with low platelets following the AZ COVID-19 vaccine. May of these were CVSTs⁹.

In terms of the Janssen COVID-19 vaccine timeline of key events, Janssen received its EUA on February 27, 2021. ACIP issued an interim recommendation on the following day and vaccination started on March 2, 2021. The first report of CVST with thrombocytopenia was received by VAERS on March 19, 2021. These are serious reports because individuals wind up in the hospital and meet the definition for SAE. That initiates record collection and investigation by CDC and FDA. These reports were received from the period March 19, 2021 through April 8, 2021. An expedited records request was conducted. Physicians at FDA, CDC, and in the Clinical Immunization Safety Assessment (CISA) program conducted detailed reviews of these cases and their accompanying medical records. This investigation is still ongoing, but CDC and FDA recommended a pause in the Janssen vaccine on April 12, 2021. A HAN was issued on April 13, 2021 and the investigation continues. This is a screenshot of the CDC HAN. The second paragraph reflects some of the key points¹⁰:

⁸ <https://www.mayoclinic.org/diseases-conditions/thrombocytopenia/symptoms-causes/syc-20378293>

⁹ <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>

¹⁰ <https://emergency.cdc.gov/han/2021/han00442.asp>

**This is an official
CDC HEALTH ALERT**

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

Summary

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

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

Background

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

Dr. Shimabukuro shared again the Silvis SM et al Figure 1 of the cerebral venous sinus anatomy that Dr. Bell showed in the introduction, emphasizing that the brain is one of the most vascular organs in the body. As such, it requires substantial venous drainage. Fairly large veins drain the blood from the brain. There is quite a lot of redundancy here, so if there is an issue in one area, other parts of the venous drainage can compensate. When these CVSTs become symptomatic, these are significant blood clots that are causing the problems.

The epidemiology and background rates for CVST^{11,12,13} in general are less well-understood because this is such a rare condition. CVST in general occurs at about 0.22–1.57 per 100,000 in the population. It is implicated in about 0.5-1% of all strokes. It is primarily a disease of younger individuals, with a median age of 37 years. Only 8% of patients are >65 years of age. The Female to male ratio is 3:1. Risk factors¹⁴ include genetic or acquired prothrombotic condition, oral contraceptive use, pregnancy and the post-partum period, malignancy, infection, and mechanical precipitants such as lumbar puncture. The most common presentations include isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema, and visual problems), focal syndrome (focal deficits, seizures, or both), and encephalopathy (multifocal signs, mental status changes, stupor, or coma). More rare presentations include cavernous sinus syndrome, subarachnoid hemorrhage, and cranial nerve palsies.

The data for the case reports on which Dr. Shimabukuro presented came from VAERS, which is the nation's early warning system for vaccine safety. It is a spontaneous or passive reporting system. It depends upon astute HCP to recognize and report potential AEs promptly to VAERS. It is designed to detect rare and SAEs that might indicate a safety problem. It is subject to the limitations of passive surveillance in general, but it performed exactly as intended in this case. It has such a wide scope, pretty much anyone in the population who is eligible to receive a vaccine is a potential subject. VAERS is quite robust and rapidly detected these rare, unusual

¹¹ 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.

¹² 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.

¹³ 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.

¹⁴ 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.

thrombotic events in the presence of thrombocytopenia. This is a good example of how robust the US vaccine safety monitoring system is and how in this case, during a large-scale national mass vaccination program, the system worked and functioned exactly as planned. This is an example of a success story for vaccine safety.

To give a high-level overview of what is being seen for all COVID-19 vaccines, Dr. Shimabukuro shared reports of CVST to VAERS after COVID-19 vaccines as of April 12, 2021. For the Janssen COVID-19 vaccine, there are 6 reports of CVST with thrombocytopenia (platelet counts $<150,000/\text{mm}^3$) following 6.86 million doses administered. That comes out to a reporting rate of 0.87 cases per million doses administered, or just under 1 case per million doses administered. By contrast for the Pfizer-BioNTech COVID-19 vaccine, there have been 0 reports following 97.9 million doses administered. For the Moderna COVID-19 vaccine, there are 3 reports following 84.7 million doses administered. All 3 of these reports had normal platelet counts and the onsets occurred at 2, 6, and 12 days after vaccination. For the purpose of this specific condition, these 3 reports are not considered to be cases because they had normal platelet counts. This is considered to be a reporting rate imbalance between the Janssen vaccine and the messenger ribonucleic acid (mRNA) vaccines.

While manufacturers are required to report to VAERS, anyone can report (e.g., HCP, parents, patients, caregivers, et cetera). If reports come in that are classified as “serious” according to the regulatory definition (e.g., death, hospitalization, permanent disability, life-threatening illness, prolongation of hospitalization, congenital anomaly or defect), that information is captured in the VAERS form. For the Janssen vaccines, folks at CDC and FDA are performing what is essentially a pre-screening of these serious reports by pulling them out to look at them before they go through the normal processing. When they began to recognize some of these unusual reports of CVST with thrombocytopenia, which they were looking for because of the information coming out of Europe, they were able to identify potential cases rapidly and conduct an expedited follow-up to obtain medical records and connect with the healthcare facilities. That often was done by people in the Immunization Safety Office (ISO) directly in reaching out to expedite collection of records. Through April 12, 2021, 6 cases have been identified. The median age is 33 years, with a range of 18 to 48 years of age. The median time to symptom onset is 8 days, with a range of 6 to 13 days. This median time to onset differs from what was in the HAN. The analyses are continually being refined as additional data are gathered. In the HAN it was 9 days, with a median range of 6 to 13. All cases occurred in white females, with 1 having a potential risk factor of current estrogen/progesterone use. None of the women were pregnant or post-partum. Pre-existing conditions included Obesity (n=3), Hypothyroidism (n=1), Hypertension (n=1), and Asthma (n=1). There were no known coagulation disorders.

As noted earlier, thrombosis usually does not occur in the presence of low platelets. These case presentations are atypical. Platelets facilitate the clotting of blood. In these cases, clots are forming in large vessels in the presence of low platelets. This is a paradox as it usually does not happen. The Janssen case presentations are consistent with the case presentations observed after receipt of the AZ COVID-19 vaccine. This table lists the initial and late signs and symptoms among CVST patients who received Janssen vaccine, with the list in no particular order:

Initial and late signs and symptoms among CVST patients*, N=6 (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

*All were hospitalized and admitted to the intensive care unit

The important thing to note here is the initial features are largely non-specific symptoms, which may seem mild and not that clinically significant when a patient starts to become symptomatic. In 5 of these 6 cases, headache is the initial presenting feature. Therefore, it is important in the current setting that HCP maintain a high index of suspicion for possible CVST and confirm vaccination history among other things.

This table provides the locations of CVST, intracerebral hemorrhage, and other thromboses in the 6 cases:

Locations of CVST, intracerebral hemorrhage, and other thromboses, N=6

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Location of CVST	Right transverse sinus and right sigmoid sinus	Left transverse sinus, left sigmoid sinus, confluence of sinuses, and straight sinus	Superior sagittal sinus, inferior sagittal sinus, and straight sinus	Right transverse sinus and right sigmoid sinus	Right transverse sinus and right sigmoid sinus	Right transverse sinus
Location of intracerebral hemorrhage	Right temporo-parietal lobe	Left temporal lobe	Bilateral frontal lobes, intraventricular	None	None	Occipital lobe
Locations of other thromboses	None	None	None	Portal vein and right pulmonary artery	Bilateral lower extremity VTE, right internal jugular vein	Portal vein

The important thing to point out is that while these were all 6 cases of CVST, the thromboses were not limited to the cerebral venous drainage system. In 3 of these cases, there were substantial clots in other large vessels in other parts of the body, such as portal vein and right pulmonary artery. Another individual had bilateral lower extremity VTE and right internal jugular vein, while another had portal vein. This is consistent with what was observed in the cases that occurred after the AZ COVID-19 vaccine in Europe. It also has caused CDC to cast a wider net in the future to look for thromboses in the presence of thrombocytopenia. Certainly, most of the cases so far have been CVST. That does not mean that CVST is the only thing to look for. It is important to look for substantial blood clots in individuals with thrombocytopenia regardless of whether they are in the central nervous system (CNS).

While there is some evidence that having COVID-19 may place one at risk for thrombotic events, there is nothing remarkable in the SARS-CoV-2 tests for the 6 CVST patients identified following receipt of Janssen's COVID-19 vaccine. All 6 CVST patients had negative SARS-CoV-2 tests; SARS-CoV-2 serology was not documented for patients 1, 3, and 4; patient 2 had negative nucleocapsid Ab; and patients 5 and 6 had unspecified COVID Ab negative. The hematology test results among the CVST patients showed that all were thrombocytopenic. Patients 1, 3, 5, and 6 were severely thrombocytopenic with platelets less than 50,000 per mm³. Patient 2 was at 69,000 and Patient 4 at 127,000. The PF4 HIT antibody test results were positive for all patients except Patient 1 for whom this test was not done.

In terms of treatment and outcomes among the 6 CVST patients, 4 received heparin. Non-heparin anticoagulants were given in 5 patients, 3 patients got platelets, and 3 patients received intravenous immunoglobulin. There was 1 death and based on the most recent information available, 3 remain hospitalized with 2 of these in intensive care, and 2 have been discharged home.

Regarding some early analyses of observed versus expected CVST cases following Janssen COVID-19 vaccine, estimated annual incidence of CVST is approximately 0.5–2 cases per 100,000 population¹⁵. In collaboration with CDC, FDA is working on a more refined analysis in which they are looking at individuals who were vaccinated, the dates or approximation of the dates of those vaccinations, and calculating individual person time. This should allow them to perform a more sophisticated analysis to get more accurate data on observed versus suspected. In the interim, they wanted to conduct this analysis. Through a review of the literature, the annual incidence of CVST was estimated to be 0.5–2 cases per 100,000 population. This analysis assumed a risk period of 5.6% of a calendar year. The analytic period is from March 2, 2021 through April 12, 2021, which is 41 days. It was assumed that people contributed person time for roughly half of that time. It was not known at this stage when people were vaccinated or came into the cohort. Therefore, the assumption was made to put it at the midpoint and divide the 41 days by 2 to get the person time, which then was divided by 365 days to annualize that. The doses administered among women 20 to 50 years of age where the cases were seen was just over 1.4 million doses. Estimates of reporting ratios were based on and estimated annual incidence of 0.5 to 2.0 per 100,000, splitting that out in increments of 0.5. Expected cases were then calculated in women 25 to 50 years of age for a reporting ratio of low of 3.8 to a high of 15.2. While this is a relatively crude analysis, it demonstrates what is being observed versus expected. It is important to note that the CVST cases are based on CVST rates in general. CVST in the presence of thrombocytopenia is an even more unusual form of

¹⁵ <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/nrneuro1.2017.104>

CVST and there are not enough data to feel very comfortable estimating an incidence for this very specific condition in this very specific age and sex group.

To summarize the findings, CVST is rare, but clinically serious, and can result in substantial morbidity and mortality. It is not usually associated with thrombocytopenia, so this is unusual. The observed cases following Janssen COVID-19 vaccines appear to exceed expected cases based on background rates of CVST among women aged 20–50 years by at least 3-fold or greater. All 6 reports were in women 18–48 years of age and all had thrombocytopenia. No obvious patterns of risk factors have been detected. CVST with thrombocytopenia has not been observed after the 2 authorized mRNA vaccines. Just over 182 million mRNA COVID-19 doses have been administered with no reported cases of this condition to date. Clinical features of Janssen cases are similar to those observed following the AZ COVID-19 vaccine in Europe. Both Janssen and AZ vaccines contain replication-incompetent adenoviral vectors—human (Ad26.COVS.2.S) for Janssen and chimpanzee (ChAdOx1) for AZ. The following recommendations are included in the HAN for clinicians, public health, and the public:

For Clinicians

1. Pause the use of the J&J COVID-19 vaccine until the ACIP is able to further review these CVST cases in the context of thrombocytopenia and assess their potential significance.
2. Maintain a high index of suspicion for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J 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.
3. In patients with a thrombotic event and thrombocytopenia after the J&J 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.
4. Do not treat patients with thrombotic events and thrombocytopenia following receipt of J&J COVID-19 vaccine with heparin, unless HIT testing is negative.
5. If HIT testing is positive or unable to be performed in patient with thrombotic events and thrombocytopenia following receipt of J&J COVID-19 vaccine, non-heparin anticoagulants and high-dose intravenous immune globulin should be strongly considered.
6. 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.

For Public Health

1. Pause the use of the J&J COVID-19 vaccine in public health clinics until the ACIP is able to further review these CVST cases in the context of thrombocytopenia and assess their potential significance.
2. 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.
3. Disseminate this alert to healthcare providers in your jurisdictions.

For the Public

1. If you have received the J&J 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.
2. Report adverse events following receipt of any COVID-19 vaccine to VAERS.
3. If you are scheduled to receive the J&J vaccine, please contact your healthcare provider, vaccination location, or clinic to learn about additional vaccine availability.

Dr. Shimabukuro emphasized the importance of reporting AEs to VAERS, especially these clinical serious and unexpected AEs occurring after vaccine. The information for doing so follows:

- Go to vaers.hhs.gov
- Submit a report online
- For help:
 - Call 1-800-822-7967
 - Email info@VAERS.org
 - video instructions <https://youtu.be/sbCWhcQADFE>

He stressed that CDC values the work of HCP on the frontline as partners in vaccine safety and views them as the “eyes and ears” to help CDC/FDA detect and rapidly assess potential safety problems and make evidence-based public health decisions. It is extremely important for HCP who report AEs if contacted and asked by VAERS or CDC to send records to VAERS as soon as possible. The Health Insurance Portability and Accountability Act (HIPAA) permits reporting of protected health information to public health authorities including CDC and FDA. This is a public health function and there should be no concerns about reporting medical records in order to allow for an in-depth review of these cases and better understand what is going on with vaccine safety.

In terms of next steps, enhanced monitoring will continue in VAERS and other vaccine safety systems, such as the Vaccine Safety Datalink (VSD). The VSD contains approximately 113,000 Janssen doses administered, with 0 cases of CVST in the risk intervals. Potential cases will be investigated through detailed clinical reviews and chart reviews, and CDC is in the process of assisting FDA to refine the analyses to better quantify risk.

VaST Assessment

Grace M. Lee, MD MPH

VaST Co-Chair

Associate Chief Medical Officer for Practice Innovation

Lucile Packard Children’s Hospital

Professor of Pediatrics, Stanford University School of Medicine

Dr. Lee reminded everyone that the objectives of the COVID-19 VaST Subgroup are to: 1) review, evaluate, and interpret post-authorization/approval COVID-19 vaccine safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization/approval safety monitoring; 3) advise on analyses, interpretation, and data

presentation; and 4) provide updates to the ACIP COVID-19 Vaccines WG and the ACIP on COVID-19 vaccine safety.

VaST has met 30 times in total, including 14 meetings pre-authorization between June 2020-December 2020 to prepare for vaccine safety surveillance in the US and 16 times between December 21, 2020 and the present to review vaccine safety data across multiple surveillance systems. As a reminder, ACIP recommended use of the Pfizer/BioNTech mRNA vaccine on December 12, 2020; the Moderna mRNA vaccine on December 19, 2020; and the Janssen vaccine, the first adenovector vaccine in the US, on February 28, 2021 with the first doses being shipped to jurisdictions on March 29, 2021.

To recount the events of the last 48 hours, VaST met to review the data on CVST on April 12, 2021 from VAERS through April 10, 2021. There were 3 cases following Moderna vaccine at that time without thrombocytopenia among 82.6 million doses administered, 0 cases following Pfizer-BioNTech vaccine out of 94.7 million doses administered, and 6 cases following the Janssen vaccine *with* thrombocytopenia out of 5.9 million doses administered.

VaST noted that the characteristics of the cases following the Janssen vaccine were similar to those following the AZ COVID-19 adenovirus vector vaccine reported from Europe, including evidence of thrombosis with thrombocytopenia, elevated D-dimer, and antibodies to PF4 where those data were available. These cases also were similar in terms of age group, female predominance, and timing of onset within 2 weeks of vaccine receipt. All of the Janssen cases occurred in White, non-Hispanic individuals. VaST does not yet have any specific information about race/ethnicity in the AZ cases. Other items to note are that the data that VaST reviewed focused on the cases, which is numerator only data in order to estimate risks and factors associated with CVST with thrombocytopenia. It also is important to understand the denominator data, which is forthcoming. This is a quickly evolving situation. It has been only 48 hours and new details continue to be learned, even during this meeting. Dr. Lee expressed gratitude for everyone's continued vigilance and work in rapidly investigating this potential safety signal.

After the April 12, 2021 meeting, the VaST Subgroup discussed these findings in their usual independent fashion and expressed several observations based on the review of the data. CVST is a rare but SAE following vaccination. The risk factors are not yet well-understood based on these case reports. VaST members expressed their concern about delayed recognition of this new entity. CVST with thrombocytopenia is fairly unusual. VaST felt strongly that early recognition is critical for timely and approach management, including the use of IVIG and anticoagulation with non-heparin-based therapies. Vaccine safety is paramount for everyone. Global safety monitoring efforts and VAERS enabled the CDC and FDA to rapidly detect AEs, which is greatly appreciated in this situation. VaST felt that information about this potential life-threatening AE should be provided to clinicians promptly in order to enhance early recognition and appropriate treatment of persons who develop thrombosis with thrombocytopenia following vaccination. VaST also discussed that further evaluation of the benefit-risk balance of using J&J/Janssen vaccine in specific subgroups would be warranted. Other vaccines are currently available for use in the US for the prevention of COVID-19. VaST recognized that timely and transparent communication with HCP and the public is crucial to maintain confidence in the vaccination program. Within 24 hours of that VaST discussion, their colleagues at CDC and FDA communicated these findings to providers and the public.

Going forward, VaST plans to focus on enhanced case identification via public health, clinicians, and patients, including recent vaccine recipients. Patients will continue to be encouraged to enroll in v-safeSM and providers and patients will be encouraged to report to VAERS. VaST will continue with its typical investigation process that includes 3 phases. The first phase is signal identification, which already has occurred. The second phase is signal refinement, which includes a series of steps to evaluate the magnitude and clinical significance of a suspected association. The third phase is signal evaluation, which often consists of formal epidemiologic analyses to more definitively establish or review causality. The signal refinement phase for CVST with thrombocytopenia will include a review of findings in other vaccine safety surveillance systems and an assessment of the risk of developing CVST in various subgroups in order to inform risk mitigation strategies and support decision-making. VaST will continue to review all safety data from the US COVID-19 vaccination program and any data that also are made available to them for review outside of the US. VaST also will continue to update the ACIP COVID-19 Vaccines WG, ACIP Secretariat, and the full ACIP on a regular basis.

Discussion Points (Lee & Shimabukuro)

Dr. Ault pointed out that ACIP usually does not interact with ED physicians, hematologists, inpatient hospitalists, and several other groups. He asked what was being done to get the word out to these types of groups.

Dr. Lee responded that they look to their CDC and partner organization colleagues around the table, many of whom communicate with provider communities, as well as their public health colleagues who have also issued state HANs to insure that this information expeditiously gets to all individuals. She expressed her hope that this open meeting also would help to stimulate the necessary attention to ensure that there is timely diagnosis and management of these cases.

Dr. Cohn added that CDC has a Clinician Outreach and Communication Activity (COCA) call planned for the next day to do some additional outreach to clinical providers. They also will continue to send alerts in CDC's many emergency response ways to ED providers, primary care doctors, and other HCP about what to look for and how to immediately manage any potential cases.

Ms. Bahta asked whether the death was associated with and could be attributed to heparin treatment, and how widely available the PF4 ELISA test.

Dr. Broder (CISA, ISO) said that they are trying to learn about the unfortunate patient who died. They are not in situation where they are looking specifically at the cause of death (COD), which they defer to the jurisdictions. In reviewing the cases in general, it does appear that a number of cases were initially treated with heparin. That is one of the reasons why the HAN message and communication has gone out to ensure that people are aware of this condition and that heparin is not to be used unless the HIT testing is negative. Regarding the second question, HIT testing is an available test in hospitals, though she was not aware of the nature of the availability in all of the regions.

Dr. Bernstein recalled from Dr. Shimabukuro's presentation that 4 of the 6 CVST patients received heparin, but PF4 HIT test results were positive for 5 of the 6 patients.

Dr. Shimabukuro said he thought that this phenomenon occurred prior to the patients being treated with heparin. He called upon Dr. Broder to speak more about the mechanism or pathophysiology of this condition.

Dr. Broder said it was her understanding that the use of heparin would not trigger a test positive immediately. The idea is that this may be a similar mechanism to what Dr. Bell described earlier in which the test is positive due to the effects of the vaccine, and that giving heparin may exacerbate the situation and make it worse.

Given the effort to study children and de-escalate by age, Dr. Bernstein wondered whether there are background rates for CVST in children.

Dr. Shimabukuro said he thinks there are background rates for children, though they were not included in his presentation. He would have to get back to the committee on what the rates are by age and by sex.

Dr. Bernstein asked whether the 106 AZ cases so far and 6 Janssen cases are attributable to the overall number of doses administered, or if there is a difference between chimp and human adenovirus.

Dr. Lee the mechanism of action and making sure there is clarity on the denominators in terms of who is receiving vaccines are important. The allocation strategies in the US and in other countries may mean that the denominators might differ for the individuals who are exposed to these vaccines. This is an area for which additional information will be helpful. She emphasized that if someone has an anti-PF4 antibody, heparin would not be an appropriate treatment for use and other anticoagulation therapies would be indicated if they have the presence of this particular antibody. It is not necessarily the exposure to heparin during the admission that is creating the positivity. It is an indicator or marker of a potential immune response that is facilitating the thrombocytopenia and associated thrombosis. The main point to get across is that the diagnostic test is helpful to know whether it is safe to use heparin.

Dr. Long did not think they wanted people to think that the thrombocytopenia is causing the clots. It is a risk for bleeding associated with the clots. The part of it that is CVST is seemingly special to her with this vaccine. Many people have lots of clots who have platelet antibodies and not CVST. With the number of doses administered so far of the Janssen product, it seems unlikely that enough time has passed to have reporting of the AEs from the majority or almost all of those doses. It is likely that more will be learned in the next 2 to 4 weeks, as well as people recognizing that they have cases who did not associate it with the vaccine. The inference of white women might also infer that people of color are not at risk, so she wondered whether anything is known about the distribution of the vaccine to white women versus non-white women.

Dr. Oliver indicated that she would be discussing both of those points during her presentation.

ACIP COVID-19 WG Interpretation

Sara Oliver, MD

LCDR, U.S. Public Health Service

**Co-lead, Advisory Committee for Immunization Practices COVID-19 Vaccines WG
COVID-19 Response**

Centers for Disease Control and Prevention

Dr. Oliver indicated that in this presentation, she was going to walk through the overall risk-benefit balance for the use of the Janssen COVID-19 vaccine that has been discussed by the WG. This includes a review of the CVST cases, the risk of COVID-19 disease by sex and age, COVID-19 vaccines administered by age, Janssen vaccine doses administered to date, and projected supply of COVID-19 vaccines in the US. The WG also discussed policy options for updated recommendations for use of the Janssen COVID-19 vaccine.

The WG reviewed 6 cases of CVST reported to VAERS¹⁶, all of which were among women 18-48 years of age. The interval from vaccine receipt to symptom onset ranged from 6-13 days. These cases were described in detail earlier. The WG also discussed the case of CVST reported in the Janssen Phase 3 clinical trial in a 25-year-old male. The Janssen presentation described these case details as well. The symptoms developed 9 days after vaccination and on Day 21 after vaccination, the patient was diagnosed with CVST was ultimately found to be anti-PF4 positive.

In terms of overall COVID-19 epidemiology, the exact risk factors for CVST are unknown. Therefore, it is difficult to highlight the epidemiology among the specific population at risk for CVST with thrombocytopenia. Therefore, Dr. Oliver discussed the epidemiology by several possible factors that could be associated with these cases. Overall for COVID-19 cases by sex from January 22, 2020 through April 12, 2021, females represent a slightly higher proportion of overall cases and a slightly smaller portion of COVID-19 deaths. The younger age group of 18 to 29 years represents a higher proportion of COVID-19 cases relative to the percent of the US population¹⁷. Regarding COVID-19 associated hospitalizations throughout the pandemic, the oldest population has represented a larger proportion of hospitalizations throughout the year compared to the younger population¹⁸. As everyone is aware at this point, the oldest population represents a substantial proportion of deaths from COVID-19 relative to the younger population¹⁹.

Moving to COVID-19 coverage by age, nearly 80% of the oldest population of those 65 years of age and older have received at least 1 dose, 40% to 50% of adults 40 to 65 years of age have received at least 1 dose, and 25% to 30% of those 18 to 39 years of age have received at least 1 dose. This highlights the proportion of the population who have yet to be vaccinated with any of the COVID-19 vaccinations and to be most impacted by future recommendations²⁰. This graphic shows the numbers in millions of doses of adults who are fully, partially, and not vaccinated by age group:

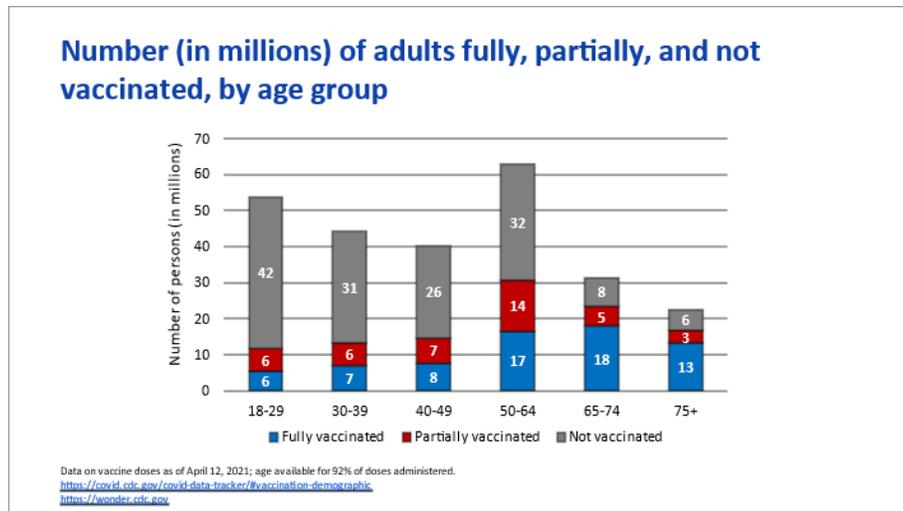
¹⁶ HAN Archive - 00442 | Health Alert Network (HAN) (cdc.gov)

¹⁷ <https://covid.cdc.gov/covid-data-tracker/#demographics> (Data from 24,349,551 cases. Age group was available for 24,176,192)

¹⁸ https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

¹⁹ <https://covid.cdc.gov/covid-data-tracker/#demographics> (Data from 433,171 deaths. Sex was available for 433,132)

²⁰ <https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic> (Data as of April 13, 2021; age available for 92% of doses administered)



Over 7.2 million doses of the Janssen vaccine have been administered to date. Of those, approximately 1.5 million Janssen doses have been administered to females 18-50 years of age to date²¹. To answer one of the questions posed earlier, this table breaks down Janssen vaccine doses administered by various populations, from male to female there has been a relatively even split by age. Given the time that this vaccine rolled out, only 18% of doses were administered to those 65 years of age and older. The majority of doses have been given to adults 18 to 50 or 50 to 64 years of age. Race and ethnicity are listed here as well. There is a proportion for whom race and ethnicity are not available, but of the doses for which this is known, about 60% of doses were administered to White, non-Hispanic individuals.

Janssen Doses Administered to Date by Sex, Age Group, and Combined Race and Ethnicity – United States

Characteristic	Doses Administered	Percentage
Sex		
Male	3,539,227	49.5%
Female	3,400,989	50.5%
Age Group		
Under 18	9,299	0.1%
18-49	3,400,989	47.0%
50-64	2,508,374	34.7%
65+	1,314,359	18.2%
Combined Race and Ethnicity		
Hispanic	696,395	15.7%
NH, AI/AN	25,874	0.6%
NH, Asian	206,743	4.7%
NH, Black	429,091	9.7%
NH, Multi/Other	245,033	5.5%
NH, White	2,828,538	63.8%
Total		

NH = Non-Hispanic
 AI/AN = American Indian / Alaska Native
 Sex available for 99% of vaccination records; Age available for 99.9% of vaccination records; Combined race and ethnicity available for 61% of vaccination records
 Source: CDC Immunization Data Lake; Includes data reported to CDC as of 4/13/2021 at 6:00 am

There was another way that the WG thought through the doses administered. From currently available data, the thrombocytopenic thrombotic events developed 6 to 13 days after vaccine receipt. It is known that approximately 7.2 doses have been administered to date. Thinking through doses since the beginning of the Janssen program in early March through March 30, 2021, about 3.4 million doses (48%) were administered. With a risk window of up to 2 weeks after doses were administered, it is likely that if these vaccine recipients were to develop thrombocytopenic thrombotic events post-vaccine, they likely would have already occurred. In

²¹ CDC Immunization Data Lake; Includes data reported to CDC as of 4/13/2021 at 6:00 am

terms of doses administered within the last 2 weeks between March 30 to April 13, 2021, about 3.7 million doses (52%) had been administered. Therefore, thrombocytopenic thrombotic events post-vaccine may still occur after these doses as these individuals still remain within the risk window²².

Moving to overall COVID-19 vaccine supply considerations, approximately 14 million first doses are expected of Pfizer and Moderna vaccines each week without any substantial interruptions anticipated. To date, Janssen COVID-19 vaccine comprises <5% of the vaccines administered. However, Janssen vaccine administration began in March 2021 compared to December 2020 for the mRNA vaccines. Approximately 13 million doses of Janssen vaccines are currently available, about 3.6 million doses are available to order, and an estimated 9.2 million doses are currently available at administration sites. There may be an additional 11 million doses by the end of April 2021. While doses for the Janssen vaccine may be less than for the mRNA vaccines overall, the Janssen vaccine occasionally has been used in populations that may be difficult to reach with mRNA vaccines that require freezer temperatures or 2 doses.

To summarize what is known so far, thrombocytopenic thrombotic events have occurred after receipt of the AZ vaccine. In the US, 6 cases of CVST have been reported after authorization and receipt of the Janssen COVID-19 vaccine. No cases of CVST with thrombocytopenia have been reported after receipt of either Pfizer and Moderna COVID-19 vaccines. The CVST cases have occurred primarily in younger adults and females. CVST can be clinically devastating or fatal. In the US, alternative mRNA COVID-19 vaccines are available. Based on current projections, supplies of both mRNA vaccines are expected to be relatively stable in the near future. Therefore, the decision is not necessarily receipt of the Janssen vaccine versus remaining at risk of COVID-19. Instead, the decision may be receipt of a Janssen vaccine versus receipt of another mRNA vaccine.

Regarding what is not known, the true background incidence of CVST with thrombocytopenia is not known. The specific risk factors for these thrombocytopenic thrombotic events are unknown. Also not known is the incidence of other thrombotic, non-CVST cases with thrombocytopenia after receipt of the Janssen vaccine. The ability to compare or generalize thrombotic cases after the AZ vaccine to Janssen vaccine is unknown. The true incidence of thrombocytopenic thrombotic events/CVST after a Janssen COVID-19 vaccine is unknown, and more cases may be identified in the coming days to weeks.

Moving to the policy options for use of the Janssen vaccine, the WG had several discussion points overall. First, while the reported CVST cases are rare, once limited to doses administered to the age and sex of CVST cases seen, the observed cases exceed expected cases. Given the timing of doses administered (52% of doses administered in the previous 2 weeks), additional cases may be identified over the next 1 to 2 weeks. Finally, the WG emphasized that robust safety surveillance is critical. The fact that they are having these discussions so quickly after the cases demonstrates that signal detection and evaluation of cases occurred as planned, moving to public discussion of these safety issues and policy implications as soon as possible.

There is a spectrum of policy options available for the Janssen vaccine. ACIP could decide that the risks outweigh the benefits and vote not to recommend use of the Janssen vaccine due to these safety concerns. ACIP also could decide that the benefits outweigh the risks overall and recommend use of the vaccine in all adults 18 years of age and older. The WG also discussed

²² CDC Immunization Data Lake; Includes data reported to CDC as of 4/13/2021 at 6:00 am (Data stratified by age and sex does not include Texas)

something in the middle of this spectrum as well, which would be to recommend use of the Janssen vaccine in some populations with age- or gender-specific recommendations such as adults 50 years of age and older only or males only.

The WG was concerned that sex/gender-based recommendations would be difficult to implement and were not very supportive of this policy option. For age-based recommendations, there was concern that there may not be sufficient data at this time to inform a specific age cut-off. However, the WG acknowledged that many countries in Europe have used an age-based approach for the AZ vaccine recommendations. Overall, this would allow for the additional options of a choice of an mRNA or Ad-vector vaccine in an older population who is at risk for COVID-19.

The WG also discussed the possibility of extending the pause while awaiting additional information. This potentially could allow for a more informed, specific recommendations for the use of the Janssen vaccine. The risk by age could be evaluated to inform a possible age-based recommendation. An extended pause also would allow for further assessment to determine whether the thrombocytopenic thrombosis risk extends beyond CVST cases. However, extension of the pause could have broad consequences. Individuals may want to receive the Janssen vaccine. In addition, a pause could have global implications such as pausing clinical trials or limiting the availability of Janssen vaccine in other countries with more limited vaccine supply.

The WG had a full discussion around these policy options the previous day and favored extending the pause for a limited period of time while awaiting additional information. To move to specific recommendations, the previous vote to recommend the Janssen vaccine was as follows:

The Janssen COVID-19 vaccine is recommended for persons 18 years of age and older in the US population under the FDA's Emergency Use Authorization.

The WG posed the following questions for ACIP to discuss during this meeting:

- Does ACIP have enough information to make interim age- or risk factor-based recommendations for use of the Janssen vaccine?
- What recommendation does ACIP feel is appropriate today given current available information for use of the Janssen vaccine?

The WG acknowledged that any recommendations made would be interim and could be updated as needed, and that the pause issued by FDA and CDC was only until ACIP had the opportunity for discussion during this emergency ACIP meeting. Dr. Oliver thanked the many people who helped assemble information for the WG's meeting the previous day and for this emergency ACIP meeting in just a matter of hours. She called upon Dr. Fink from FDA to present FDA's thoughts on this matter prior to opening the discussion to ACIP members.

FDA Perspective

Doran Fink, MD, PhD
Deputy Director, Clinical, Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

Dr. Fink said that on behalf of FDA, he wanted to thank the ACIP and the COVID-19 Vaccines WG for the presentations and for what he was sure would be a thoughtful discussion of this safety signal and considerations for that moving forward. As they work to understand the nature of this signal, including potential mechanisms and risk factors, FDA will continue to collaborate closely with CDC to collect and evaluate information as it becomes available. FDA also will continue to collaborate closely with its regulatory and public health counterparts outside of the US to leverage their experience with a similar safety signal observed with the AZ vaccine. The pause recommended the morning of April 13, 2021 out of an abundance of caution has raised national awareness of the safety concern, and has provided time and opportunity to carefully and collectively evaluate the information at hand and to formulate questions that remain to be addressed.

In FDA's ongoing assessment of these rare but serious thromboembolic events with thrombocytopenia, the current thinking is that this risk could be managed by inclusion of warning statements in the EUA Fact Sheets along with coordinated communications from FDA, CDC, and others to inform HCP and vaccine recipients of the potential risk and symptoms that should warrant medical evaluation, as well as advice to ensure proper diagnosis and management of the condition and reporting of any additional cases. With such information available, FDA appreciates that individuals, in consultation with their HCP or vaccination providers, may arrive at a conclusion of favorable benefit/risk after taking into account demographic factors, risk of exposure to SARS-CoV-2, severe outcomes from COVID-19, and access to other authorized COVID-19 vaccines. Consequently, this risk management approach could be considered to allow for further assessment of the safety signal concurrent with resuming use of the Janssen COVID-19 vaccine in individuals or populations for whom the benefits of the vaccine continue to outweigh the risks.

Discussion Points

Dr. Duchin (NACCHO) asked Dr. Shimabukuro if it is possible to have a ballpark estimate of the timeframe in which more could be learned about the potential safety signal from non-CVST thromboses associated with low platelets to get a better picture of what a potential syndrome might be that is associated with this vaccine. Secondly, he wondered if there would be any role for v-safeSM in providing any information about this potential issue.

Dr. Shimabukuro said that a timeframe may be difficult to determine because this is such a rare condition in general. CDC is reviewing every potential case that comes in. One of the things they are looking for in the report and medical records is low platelets. They are able to identify cases with and without thrombocytopenia. There also are other AESIs that they plan to assess differently, such as PE and VTE. He thinks that now that they are aware of this unusual condition of thrombotic events in the presence of thrombocytopenia, they will re-evaluate how surveillance will be done to try to get a better idea of what is occurring with these reports. The main benefit from v-safeSM may be to get these reports into VAERS. The individuals for these specific case reports are quite ill and in the hospital, so they probably are not able to submit a

report for themselves. The initial presenting symptoms like headache and fatigue are quite common and may be less useful. For a rare serious condition like this, VAERS has been demonstrated as the system that is going to be able to rapidly detect and evaluate these initial reports. He emphasized that their partnership with HCP seeing patients, recognizing potential events, reporting, and working with CDC and FDA to access medical records will allow for further evaluation of these rare and serious AEs. He stressed that as others had said, this is a good example of the system working, how robust the system is, and how the US vaccine safety system is able to rapidly detect rare serious events and assess them.

Dr. Drees (SHEA) endorsed what Dr. Lee said earlier that the distribution system for the HAN alert is pretty robust and they certainly has communicated that information out to the EDs, hematologists, et cetera. Even before the HAN was released, they already were getting questions from physicians, patients, EDs, et cetera. They appreciate how quickly the HAN was released and the level of clinical detail that was in the HAN. In terms of the availability of the heparin-induced antibody testing, her first task when the HAN was received was to figure out what this test is and whether they have it in her own institution. While they are a large clinical laboratory that is fairly sophisticated, they do not have this test onsite. They send it out, with a minimum of a 48-hour turnaround time. She would anticipate that the majority of hospitals in the country would have to send out.

Dr. Romero asked whether reference laboratories are able to scale up testing for this if there is a surge in requests for it.

Dr. Drees (SHEA) said she did not have the answer for that and did not know how many different reference laboratories are typically used by community hospitals, and it is a fairly specialized test. She imagines that demand is going to increase quickly.

Dr. Kimberlin (AAP Redbook) noted that there was a key summary on Dr. Shimabukuro's Slide 24 that the observed rate was 3-fold or great than the expected rate and requested further information about that.

Referring to Slide 22, Dr. Shimabukuro pointed out that observed in this instance is 6 for everything because 6 cases have been observed in the analytic period. The calculations involved were then done to estimate the number of expected cases among women 20 to 50 years of age in the same analytic period. For example, that is basically $6 \div 1.58 = 3.8$ reporting ratio. They did this for different estimated annual instances because there is a range. There are at least 3 and possibly up to 15.

Recognizing that CDC and FDA are refining this analysis, Dr. Nirav Shah (ASTHO; State of Maine CDC) questioned the choice of denominator for the observed versus expected cases to doses among women 20 to 50 years of age. Realizing that epidemiologists often disagree on denominator choice, he suggested that it was implausible that the denominator could have been all recipients of the vaccine regardless of their age given that there was 1 male with CVST in the clinical trials. To the extent the mechanism of action with AZ in Europe is plausibly similar, there have been men there who also were affected. Including that and doubling the denominator would greatly affect the ratios, so he wondered how they should think about that.

Dr. Shimabukuro said he did not disagree, but they had observed that all cases were in women ages 18 to 48 years. Because it appeared to be concentrated in that age group, the decision was made that the best analysis would be to look at that denominator. Certainly, they can expand on this for future analyses.

Dr. Sanchez commented that there is a positive message that there are 2 vaccines currently available in the US that have not been associated with these thrombotic episodes and accompanying disorders. He asked whether the cases are being investigated further in terms of the adenovirus vector and if there is something unique about this not being seen with the mRNA vaccines because of not having the adenovirus vector. For instance, he wondered whether the adenovirus vector is being found within the thrombi and/or if there is something different within these clots that is different from other cases. He urged further investigation, more autopsy specimens, and looking at the thrombi to see if anything can be found that may have been triggered by the adenovirus or something else in the vaccine.

Dr. Goldman (ACP) commented that as a practicing internist, he is reassured that the VAERS system works and reiterated how important it is for his colleagues on the frontline to be utilizing it. He thanked CDC for the HAN as these clinical guidelines help clinicians on the frontline treat the patients. Regarding the policy question, as a practicing internist, he favors a pause for the immediate future to determine whether more cases are reported. The true incidence of this condition may be revealed now that so many doses have been administered. Now that he and his colleagues are aware of this issue, he suspects that more cases will be reported as it is recognized. He also suggested that they consider the risk/benefit of the vaccine compared to the risk of getting COVID-19 itself and the potential of deaths from the disease. They may lend themselves more toward individuals' decisions on which vaccine an individual may choose to get, although this could be complicated logistically. In the long-term, he is hopeful that they can see if this is an issue with the vaccine adenovirus platform or an issue with this vaccine specifically. Regardless, he stressed to the public that they need to remain confident in the process and science regarding vaccines in general, and that vaccination against COVID-19 and many other diseases should continue and not let this sour their decision on getting vaccinated in general.

Dr. Romero observed that the data on race and ethnicity is notably weak. As of 3 to 4 weeks ago, only 50% of those individuals receiving the vaccine provided information regarding race and ethnicity. He cautioned against making any extrapolations based on the data available at this time. He pointed out to the voting members of ACIP that they did not have to arrive at a recommendation and vote during this meeting. If more information and time are needed to think about this, ACIP can reconvene later in the week or during the weekend if necessary. This should be a considered vote based on the data ACIP needs. To the general public watching this meeting and listening to these presentations, Dr. Romero stressed that it had been stated multiple times throughout the meeting that safety has been a paramount issue in ACIP's deliberations for this vaccine recommendation and in following the vaccine. When the deliberations on this vaccine began in April 2020, that was foremost on the list of things that must be kept in mind and ACIP is doing that at this time. The FDA, CDC, and the pharmaceutical companies have stated that safety is the ultimate goal with the vaccine. The fact that these very rare clotting incidents have been identified points to the robust safety systems that are in place and demonstrates that the US vaccine safety systems are some of the strongest in the world. It is important for the public to understand that moving forward with new vaccines, there continue to be ongoing safety checks. Regarding the issue of vaccines in general and the public, everyone knows there is vaccine hesitancy or reluctance regarding the use of these vaccines for the prevention of disease. ACIP needs to come to a decision regarding recommendations in a timely manner and ask that if they extend the pause, that the pause be sufficient to address the question. This is an issue of safety and risk/benefit analysis. All of the questions may not be answered at this time, but a decision must be made in an appropriate timeframe. This reminded him of the talk that Dr. Frieden gave when ACIP was

discussing pneumococcal vaccine. They have the data before them and need to act on those data as appropriate and add to those data going forward to modify or strengthen it.

Dr. Frey asked what the WG discussed regarding clotting, DVTs, PEs, et cetera in general with or without thrombocytopenia; whether that was taken into consideration; if there is increased incidence in clotting without thrombocytopenia; and how that factors into the overall picture. Dr. Bell responded that the WG did not focus on that.

Dr. Long stressed that the thrombocytopenia that is so telling here may be only the very severe that impacts the cerebral sinuses. The others are much harder to figure out because the underlying occurrence is so much higher. It seemed to her that they should be ready to make an interim decision to continue the pause for at least a month until they see what else transpires, such as whether it occurs in men. In the most recent weeks, increasingly younger individuals have been immunized. They might be able to make risk-related, more definitive potential use of the vaccine in about a month. It is possible that many more instances will occur in the coming month that will help with a more definitive recommendation. She very much favored a continued pause and would be opposed to continued use at this time.

Dr. Bernstein requested clarification about Dr. Fink's statements representing the FDA in terms of whether they are suggesting a risk management approach, which includes warning statements. He also wondered what is meant by "warning statements" and how that actually would be operationalized in the real world.

Dr. Fink (FDA) indicated that the warning statements he mentioned would be warnings in the EUA Fact Sheets for HCP and recipients that are given to vaccine recipients before the vaccine is administered. The risk management approach would be in the warning statement in combination with other communications from FDA and others.

Dr. Bernstein pointed out that the EUA Fact Sheet is multiple pages as it is and many of the people receiving vaccines are not having an opportunity to talk with their own provider about it, so there might be a disconnect in some way.

Ms. Bahta said that in reviewing the data, understanding how rare this event is, and based on what she had heard in the conversations over the last 24 hours, there are 2 sides to this. One is that there is over-reacting and the other is that vaccination should be stopped. There has been consideration of a provider risk-based discussion about continuing to use the Janssen vaccine for those who would feel comfortable. She thought she was coming down on the side of Drs. Long and Frey that it would be helpful to have some additional information and that by having more robust information, ACIP could be much more confident in how they talk about the safety of this vaccine. Right now the confidence for COVID-19 vaccines is right at a precipice. There are people who cannot wait to get it and there are others who are waiting and seeing. This will contribute to the confidence that people have, so she would be in favor of getting more information.

Dr. Ault asked whether the WG discussed how much longer they would need to acquire this information. There is another emergency ACIP meeting scheduled for May 5, 2021. That is 3 weeks rather than a month from now.

Dr. Bell indicated that there was not a final conclusion about how long would be necessary. There was a general sense that there needs to be enough time to provide the kind of data the WG felt was necessary, but also that it is extremely important to do this as expeditiously as possible because of all of the potential unintended consequences of a prolonged pause.

Dr. Talbot emphasized that fortunately, there are very good, well-proven alternative vaccines in the US for which safety signals have not been seen. This puts them in a position to be much more cautious and thoughtful and use the old model of “first do no harm.” They should have the time to review data on other thrombotic events such as stroke, DVT, and PE. This also is a setting in which the usual treatment may be harmful, so they cannot say this is treatable and let it go. In addition, insufficient information is known about age at this point. Her suspicion is that events like strokes may be under-reported or not flagged and usually occur more often in older adults. Therefore, she is hesitant to say that this does not occur in anyone over 50 years of age. They should strongly encourage people to continue using the mRNA vaccines that have proven to be safe and effective until more is known. If ACIP can say that the Janssen vaccine is incredibly safe and they are not worried about risk, they will come back and say that. If not, then they have done no harm and have been able to continue vaccinating at this time.

Dr. Sanchez agreed and favored/recommended a continued pause as he was not comfortable continuing vaccination with the Janssen product.

Dr. Bell said that to be very frank, she did not want to vote on this issue during this meeting. While she also did not want to vote not to recommend the vaccine. They have been looking at this issue for less than 2 days and she did not feel that there was sufficient information to make an evidence-based decision. While they will not have all of the information, there are some things that can be gathered relatively quickly that all have to do with the benefit/risk balance. They do need to better understand the risk, which is going to be very low and rare. However, they do not know exactly how low, how to characterize it, what the denominator should be, what the numerator is, how many cases there are with thrombocytopenia that is not CVST, et cetera. In addition, the risk needs to be understood in some kind of context with other things that might cause thrombosis for example. It is important for the public to understand what “rare” means with respect to other risks that people might take every day. There needs to be a formal risk/benefit analysis that allows ACIP to very clearly point out to the American people why ACIP thinks that the risk/benefit favors whatever the recommendation is that is made. She wants to feel comfortable with her family members and herself to receive this vaccine. Nothing is risk-free and as people have said, they are ahead of themselves because this issue was so quickly identified and because of what has been going on in Europe. Because she did not want to send the message that they were recommending not to take the Janssen vaccine, she thought they should not vote and should gather the necessary information to make an evidence-based decision.

Dr. Cohn pointed out that while there is a scheduled ACIP meeting for May 5, 2021, if information can be assembled before that period, it is not necessary to wait until then to have a follow-up discussion.

Dr. Romero emphasized that one option would be to continue the pause until the next meeting on May 5, 2021 or ACIP could meet sooner if more information becomes available that allows them to make a more concrete vote prior to that time. The meeting in 3 weeks would fall within the period of a pause and would allow them to gather more data and see if more cases come forward.

Ms. McNally agreed that it seemed reasonable to try to collect more data. From the cases that were reported directly to Janssen, ultimately those cases were reported to VAERS. She wondered if Dr. Shimabukuro could comment on what might be a reasonable period of time to gather more data and reevaluate this.

Dr. Shimabukuro indicated that the median onset was 8 days, with a range of 6 to 13 days. Individuals have been vaccinated who they would want to follow out for what they think is perhaps a reasonable risk window and allow time to actually capture and evaluate any cases that might be identified in that risk window of about 1 to 2 weeks. There may be cases that have not but might come to CDC's attention now that this information is known, which is known as a reporting bias or stimulated reporting. In the coming weeks, he thinks they will continue to gather better and more information as they get access to the medical records. They will refine the observed versus expected analysis and will have more and better information to assess the signal and possibly characterize the risk.

Dr. Frey asked what the delay is on average for the physician to report information to VAERS after an event.

Dr. Shimabukuro indicated that the decision to report occurs at the HCP level. There are reporting requirements in EUA, and this would constitute an SAE because the 6 known individuals are hospitalized. This would fall under the EUA reporting requirements. CDC's recommendation is to report an AE as soon as possible after the onset of symptoms or after a person or HCP becomes aware of the symptoms. They want these reported to VAERS as quickly as possible. The other part pertains to how quickly these reports are processed and followed-up. Because CDC was following these types of reports closely because of what was happening in Europe, CDC is reviewing these events in collaboration with FDA in fairly close to real time. The categorization of serious or non-serious is made known to them quickly, so they can review the serious reports and identify CVST or other thrombotic events, and expedite records collection such that they direct the contractor to expedite collection on a specific report or simply do it themselves. They have ways of compressing that timeline and the current focus is to make sure that they identify, follow-up, and assess these reports as quickly as possible. On CDC's end, the process is fairly quick and based on the reports that are coming in, providers are reporting them in a timely manner as well.

Dr. Lee said that having had only about 48 hours to think about this, she wanted to make a few statements and put out a few requests. Everyone acknowledges that risk is an inherent part of life. They would not be vaccinating anyone if there were not a COVID-19 panic right now. There is a population level benefit/risk balance and an individual risk/benefit balance that need to be considered at this point. She thinks the role of ACIP in this instance is to focus on mitigating that risk and to better understand the benefits. She also has seen patients admitted with clotting disorders and thrombocytopenia—some type of immune-mediated thrombocytopenia associated with COVID-19 disease. From the ACIP perspective, she thinks there are 3 things they can do to mitigate risk. One is to identify populations at the highest risk for this potential complication and adapt the recommendations to minimize exposures for them. The second is to educate patients about the benefits and risks of different vaccines, and to ensure that patients seek care in a timely manner. The third is ensuring that healthcare systems are able to diagnose and manage these cases in an incredibly timely way. If these cases can be managed early and well similar to anaphylaxis, it may be possible to employ strategies that change the outcomes that are seen with these patients. That said, this is challenging because ACIP decisions have to be based on the global stage. This is clear to her given their past experience with rotavirus vaccines. The benefit risk/balance may be very different in other countries where

vaccines are either not available or are not feasible for widespread implementation. She recognized that ACIP's responsibilities are to individuals in the US, but she also feels the weight of the burden of the global responsibility that they also have and the impact that their decision-making potentially could worsen inequities. Regardless of the decision they make on this particular safety signal, it is important to ensure that they are collaborating with partners outside the US to address those inequities in whatever ways they can. In terms of thinking about what information is needed before she thinks a vote can be taken, she did not think they had enough information at this point and need to go through the signal refinement phase in order to capture age and gender stratified rates of CVST and the associated outcomes among both vaccinees and those with COVID-19 disease so they have a better understanding of risk factors associated with CVST and those who have poor outcomes associated with CVST. They need to review the data across multiple vaccine safety surveillance systems. She wholeheartedly agreed that a formal benefit/risk assessment is needed to make well-informed decisions. They need to move through the safety signal refinement phase as quickly as possible in order to be able to support evidence-based decision-making. They also need strong collaboration across federal agencies and with global partners in order to make the best possible decision in as timely a manner as possible. She continues to feel that they are in a race against time and the variants, but that they need to do so in the safest possible way.

Dr. Kotton very much agreed with Dr. Lee and added that putting this vaccine on pause for those who are frontline healthcare workers (HCW) has been devastating. She agreed in general that there is not enough data to make a decision at this time, but the State of Massachusetts was planning to use this vaccine for people who are homebound and otherwise not able to get a vaccine, vulnerable inpatient populations who often have multiple comorbidities and are often at high risk of disease but have not been able to get vaccinated, otherwise under-served populations, and populations who are not able to get mRNA vaccines. She definitely wants them to be cautious and careful with their decision-making, but also emphasized that loss of this one-and-done vaccine that did not require the cold-chain that the mRNA vaccines do is significant.

Dr. Cohn summarized what she had heard thus far and offered some potential options moving forward. They certainly heard that there is a need for more refinement of the risk and of the risk/benefit analyses. She reminded everyone that the goal for this meeting was for CDC to be as transparent as possible and communicate information as rapidly as it was available to ACIP members, liaison organizations, and the public knowing that they will be doing some of this work around the clock over the next several days. They are working on these analyses. The question at this time pertained to whether ACIP is comfortable continuing the pause and not making any decisions at this time, or if the committee preferred to make a recommendation around shifting the pause for a short basis just in a certain population versus the entire population that is currently paused. The interim shift can be for just a week or two as they try to refine. Typically when ACIP makes interim recommendations they are thinking for longer periods of time, but there are various options including just waiting for more information. The critical question regards whether the pause should continue for the whole population versus refining that.

Speaking in his capacity as President of ASTHO and Director of the State of Maine CDC, Dr. Shah (ASTHO) expressed concern about the direction he feared the committee may be going. They are in a situation where not making a decision is tantamount to making a decision. Any extension of the pause will invariably result in the fact that the most vulnerable individuals in the US who are prime candidates for the Janssen vaccine will remain vulnerable, the most at risk will remain at risk, and those who would benefit immediately from vaccination will remain unvaccinated for an unknown period of time that would occur during a period when the US

logged 5000 deaths and 489,000 new cases across the country in the past 7 days. The initial reason for the pause among others was to ensure that HCP and recipients were apprised of the possible risks as well as to be on the lookout for them so appropriate treatment could be given. It is always possible to get more data and, indeed, in the history of pharmaceuticals, the understanding of risk is always being refined. There are also tools available to better evaluate and mitigate that risk while continuing provision of the Janssen vaccine. He urged that any pause be counterbalanced by consideration of the equity consideration that would befall from any lengthening of the pause.

Dr. Fryhofer (AMA) said that speaking as an individual practicing physician, the whole process during this meeting increased her confidence in vaccine safety. She greatly appreciated the honesty, transparency, and quick action that the FDA and CDC have taken. She listened to the comments from their esteemed group of ACIP members and expressed her personal hope that they would support a pause sufficient to determine whether this is a “needle in a haystack” or the “tip of an iceberg.” Other vaccines are available and there is a supply of them. She is sensitive to the equity of vaccine distribution and knows that many patients have not been able to get vaccinated, but they want to make sure the vaccines are safe. A short pause will give them a chance to collect this information and give physicians and patients time to understand the issues. She emphasized that she respects the process and is proud to be a part of it.

Dr. Talbot said she appreciates the comments about giving vaccine to those who are homebound and difficult to find. However, she also is worried that those who cannot get to medical care and those who are difficult to find also may be at risk for severe clotting if they do develop this and do not get to care in sufficient time. It is a double-edged sword, which is why the risk/benefit analysis will help figure this out.

Dr. Duchin (IDSA) emphasized for the public that what they are talking about is a very rare albeit serious event that is associated with a vaccine that was detected through the vaccine safety systems. If the ACIP elects to pause further, it should not be interpreted as a signal that there is an increased concern about vaccine safety at this point beyond which was evident initially. Instead, this is a desire to better characterize the risk in order to make the best possible guidance going forward.

Dr. Long said that they did not really answer Dr. Cohn’s question about whether any less/more at risk groups could be parsed out rather than a universal pause. She thought ACIP would be uncomfortable with that due to the lack of specific and large data that would help them decide what person is more or less at risk. While the risk is very small, it is very serious. There could be severe consequences for people’s lives, so she thought they could live with the unintended consequences of extending the pause because of the amount of vaccine that is available. It would be sending the wrong message to the people who would be getting this. She favored continuing the pause until better data are available.

Dr. Lee stressed that they all care very much about safety and individual and population risk/balance. She did not think an indefinite pause would be good and as Dr. Shah pointed out is functionally a decision. The main question regards whether they can assess where they are in a week or two. Even in the last 24 hours, a tremendous amount of data have come out.

Dr. Cohn completely agreed that they did not want for it to feel like an indefinite pause. From a process perspective, if ACIP did not have a motion or desire to vote on a recommendation during this meeting, that would result in going back to work as quickly as possible and

scheduling an additional emergency meeting in a week to 10 days at which time as much information as possible would be presented.

Dr. Bell stressed that she did not want to send the message that there is some huge concern of a different order of magnitude than any other vaccine safety signals they evaluate, or that there is something fundamentally wrong with this vaccine. Whatever the process is that would allow them to have enough information as expeditiously and quickly as possible, which is never all of the information, but hopefully will be some of the items mentioned as important and necessary, she would support. This is a very rare event, nothing in life is free, but she wants to be able to understand and defend the decision that she has made based on a reasonable amount of data.

Dr. Ault agreed that there should not be an indefinite pause and was reassured hearing that this could be a relatively short amount of time.

Dr. Bernstein agreed that this should not be an indefinite pause. He expressed interest in knowing how many Janssen vaccinees they could expect to have data from and in what time looking forward over the next 1 to 3 weeks.

Dr. Oliver indicated that 3.8 million doses were administered in the last 2 weeks, but did not have a further breakdown on each week. They expect some stimulated reporting as Dr. Shimabukuro noted now that the information has been communicated and they are highlighting cases and asking for reports. They would expect a much faster turnaround between presentation and diagnosis and then diagnosis to reporting to VAERS now that the HAN and other educational messages have been disseminated.

Dr. Shah (ASTHO) expressed concern on this line of discussion. While he understood the rationale behind the pause but thought that they also should have a theory of lifting the pause. If the concept of operations right now is simply to accrue more data without a theory of what those data may mean and how they might be evaluated, it is just as possible that the committee may continue the pause in the 3 weeks to wait for even more data. If they are going to continue the pause, they should at least couple that with a theory of what lifting the pause may look like and under what criteria they would do so.

Dr. Lee said that to her, it was not about having perfect data because they will never have this and there always will be uncertainty. Instead, it was about getting better risk estimates and understanding how to minimize exposure to those who may be at highest risk for this particular AE. It is possible there may not be any further information, in which case ACIP will still have to make a decision or recommendation at that time. Her hope is that in the next week or two, this can be captured in a more robust way. The benefit/risk balance to her remains unclear without having a risk estimate of this particular potential AE by age, gender, and other risk factors that may contribute. She agreed that ACIP needs to make a recommendation soon.

Dr. Romero summarized that ACIP was not ready to vote at this time. Dr. Cohn added that she was hearing from the ACIP members and liaisons is that there is a strong desire to reconvene as quickly as possible after a risk/benefit analysis and risk refinement have been done, which CDC committed to doing as rapidly as possible. At this time, ACIP does not wish to vote or put any motions on the table to vote for a change in the current recommendation. Instead, the pause would continue on the current recommendation. That is, ACIP would be providing no recommendation to the CDC Director until they meet again in a week to 10 days. There was no ACIP opposition to this. CDC will try to identify the next meeting date by Friday, April 16, 2021.

Public Comments

José Romero, MD, FAAP ACIP Chair

Dr. Romero opened the floor for public comment during the April 14, 2021 ACIP emergency meeting at 4:20 PM ET. He welcomed and thanked the public speakers for addressing ACIP and emphasized that ACIP takes public comments very seriously. Given the limited timeframe available, speakers were requested to limit their remarks to the 3 minutes allotted. All speakers submitted a request in advance of the meeting, with the final selection of public commenters made randomly via a lottery. The comments made during the meeting are included here. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2021-0042. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received.

Richard Junghans, MD, PhD Associate Professor Boston University School of Medicine President, IT Bio, LLC

My name is Dr. Richard Junghans. I am an Immunotherapist and Hematologist-Oncologist who trained with Thomas Waldmann at the National Cancer Institute (NCI). I am an Associate Professor at Boston University School of Medicine (BUSM) and President of IT Bio, LLC, an immunotherapy company in Cambridge. A start-up I should say. I have a technical comment about the anti-platelet antibody, so if I have time at the end, I'll move to that. But I want to jump into what I consider the "elephant in the room." That is, prior infectees, people who have been infected previously, I contend have a superior immunity than any conferred by these very good vaccines. If I'm right, then we're subjecting patients to risk unnecessarily, however small these risks are which are being addressed today, and also wastes drugs that could have been used to save other people's lives already who waited in line for those who didn't need it. The policies I'd like to see changed would be to accord infectees the same status as vaccinees officially by CDC, which serves as an example around the world. This would be for so-called immunity passports, jobs, travel, et cetera. Exempt them from vaccination requirements at some jobs that have been put in place. Any prior test by polymerase chain reaction (PCR), antigen, or antibody would be accepted. Antibody waning doesn't concern me because neutralizing antibodies are not judged by this assay as proven in the initial Chinese study that focused on total antibody waning, but was the wrong focus—neutralizing antibodies predicted to persist for years. Antibodies aren't critical anyway. T-cells are the main bullwork of the immunity. This is seen in agammaglobulinemia where patients don't get sick from bad viral infections. They get sick from bacterial infections. Proof that infection is better is quickly available. Look at the Pfizer vaccine study: 20,000 patients per arm; 160 in the control arm got infected; 8 in the vaccine arm got infected. To compare that 20,000 to 20 million patients who are documented to have recovered from COVID—that would predict 8000 second infections. It's been hard for people to find even a dozen such cases. CDC estimates a 4.6:1 ratio of people infected to those who actually have tested positive. That would mean 138 million people have been infected out of 210 million. I would like to say that I'll be posting this material.

Del Bigtree
CEO, Informed Consent Action Network
Host, The HighWire

My name is Del Bigtree. I am the CEO of the Informed Consent Action Network (ICAN). I'm the host of the internet talk show, The HighWire. I am formerly Producer of the CBS talk show, The Doctors, where I won an Emmy Award celebrating the best that science and medicine have to offer. I have been attending the meetings of the Advisory Committee on Immunization Practices for over 3 years now. I have spoken many, many times during public comment. I have done several of these now over the computer. I have been saying and trying to make the same point for some time now. You at the CDC and the Advisory Committee need to start taking much more seriously the visibility of the work that you're doing and the promotion and the PR around it. I have been warning you that you cannot continue to keep promoting products like vaccines made by Johnson & Johnson that have not been properly tested for long-term issues or even short-term issues in the clinical trials. We are talking about a company that has paid out billions of dollars for lying about safety. They lied about the oxycontin epidemic and yet you at the Advisory Committee and at the CDC now find yourselves in an incredible situation, and it's something that I have been warning you about. Confidence in this vaccine program and now the CDC is in grave, grave danger. We now have a vaccine that is just like the AstraZeneca vaccine in Europe and I'm honestly questioning the CDC. Are you going to make the same mistake that the European Medicines Agency (EMA) in Europe made and try to cover this up and say, "Oh, it's gonna be just fine" only to have to retract that a couple of weeks later. Now we have nations like Denmark withdrawing the AstraZeneca vaccine because their own science shows that this issue is happening in 1 in 40,000 people. What will be the plan? The CDC, if it wants to hold on to any credibility right now, you know, and risk not only a loss of confidence in our healthcare system and the CDC, but maybe the science as we know it. I urge you, please withdraw Johnson & Johnson completely. Europe is now overwhelmed. The United Kingdom's (UK's) hospitals are overwhelmed by people that are panicking even from mild symptoms. Our hospitals can't afford this. This mistake is only going to get worse and worse. We have a few other vaccine options. Please, do the CDC a favor. Do the nation a favor and lead by erring on the side of caution for the citizens and not the pharmaceutical industry and pull Johnson & Johnson immediately or we could seriously see the disruption of confidence in all vaccine programs and science as we know it. This is what is now sitting in your hands. Thanks. I hope this time you will finally hear my plea.

Marla Dalton, PE, CAE
Executive Director & CEO
National Foundation for Infectious Diseases

Thank you and good afternoon. I am Marla Dalton, Executive Director & CEO of the National Foundation for Infectious Diseases (NFID). On behalf of NFID as a longstanding partner of CDC, we appreciate the valuable work of ACIP and the robust United States (US) vaccine safety surveillance systems in place. Monitoring the safety of vaccines is an ongoing process. The decision by the Food and Drug Administration (FDA) and CDC to review reports of a rare blood clotting condition among some recipients of COVID-19 vaccines demonstrates the strong US commitment to vaccine safety. To date, there have been 6 reported cases of blood clotting among the approximately 7 million doses of the Johnson & Johnson COVID-19 vaccine administered in the US, clearly demonstrating the sensitivity of the vaccine safety system in place. The fact that public health officials have paused administration of the vaccine to investigate these reports is reassuring to all of us who are committed to vaccine safety. We at NFID stand ready to help communicate the results of the data analysis and any implications for

public policy. The actions taken by CDC and FDA also illustrate some of the core principles of communicating about COVID-19, which are outlined in a new NFID report²³, “COVID-19 Communications: Promoting Prevention Measures and Vaccine Confidence.” The report, which was developed with input from more than 50 leading organizations and multidisciplinary experts is now available on the NFID website at [nfid.org](https://www.nfid.org). As the science and knowledge around COVID-19 continue to evolve, being open and transparent about what we know and what we do not yet know helps all to manage expectations and reduce anxiety and confusion about vaccines and other COVID-19 prevention measures. The work of ACIP in guiding US immunization policy and overseeing vaccine safety is vital to protecting public health. On behalf of NFID, thank you all for your dedicated service.

²³ <https://www.nfid.org/infectious-diseases/covid-19-communications/>



Certification

Upon reviewing the foregoing version of the April 14, 2021 ACIP meeting minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP Membership Roster

**Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
December 23, 2020 – June 30, 2021**

CHAIR

ROMERO, José R, MD, FAAP
Arkansas Secretary of Health
Director, Arkansas Department of Health
Professor of Pediatrics, Pediatric Infectious Diseases
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Term: 10/30/2018-06/30/2021

EXECUTIVE SECRETARY

COHN, Amanda, MD
Senior Advisor for Vaccines
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS

AULT, Kevin A, MD, FACOG, FIDSA
Professor and Division Director
Department of Obstetrics and Gynecology University of
Kansas Medical Center
Kansas City, KS
Term: 10/26/2018 – 6/30/2022

BAHTA, Lynn, RN, MPH, CPH
Immunization Program Clinical Consultant
Infectious Disease, Epidemiology, Prevention & Control Division
Minnesota Department of Health
Saint Paul, Minnesota
Term: 7/1/2019 – 6/30/2023

BELL, Beth P, MD, MPH
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University of Washington
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Term: 7/1/2019 – 6/30/2023

BERNSTEIN, Henry, DO, MHCM, FAAP
Professor of Pediatrics
Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center
New Hyde Park, NY
Term: 11/27/2017-06/30/2021

CHEN, Wilbur H, MD, MS, FACP, FIDSA
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Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, MD
Term: 12/23/2020 – 6/30/2024

DALEY, Matthew F, MD
Senior Investigator
Institute for Health Research, Kaiser Permanente Colorado
Associate Professor of Pediatrics
University of Colorado School of Medicine
Aurora, CO
Term: 1/4/2021 – 6/30/2024

FREY, Sharon E, MD
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Clinical Director, Center for Vaccine Development
Division of Infectious Diseases, Allergy and Immunology
Saint Louis University Medical School
Saint Louis, MO
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KOTTON, Camille Nelson, MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School
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Term: 12/23/2020 – 6/30/2024

LEE, Grace M, MD, MPH
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Professor of Pediatrics, Stanford University School of Medicine
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Term: 7/1/2016 – 6/30/2021

LONG, Sarah S, MD
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Section of Infectious Diseases
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MCNALLY, Veronica V, JD
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POEHLING, Katherine A, MD, MPH
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Term: 10/29/2018 – 6/30/2022

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)

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Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification Centers
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Food and Drug Administration (FDA)

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Office of Vaccines Research and Review

Center for Biologics Evaluation and Research

Food and Drug Administration

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Health Resources and Services Administration (HRSA)

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Division of Injury Compensation Programs

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Indian Health Service (IHS)

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Office of Infectious Disease and HIV/AIDS Policy (OIDP)

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Office of the Assistant Secretary for Health

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National Institutes of Health (NIH)

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America's Health Insurance Plans (AHIP)

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American Immunization Registry Association (AIRA)

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American Nurses Association (ANA)

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Infectious Diseases Society of America (IDSA)

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