

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

DECEMBER 16, 2021
SUMMARY MINUTES

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MEETING WELCOME AND INTRODUCTIONS

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on December 16, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on updates regarding the risk of thrombosis with thrombocytopenia (TTS) related to the Janssen COVID-19 vaccine, a vote on updated recommendations for use of the Janssen COVID-19 vaccine, and an update on the COVID-19 Omicron variant.

THURSDAY: DECEMBER 16, 2021

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the December 16, 2021 ACIP meeting and conducted a roll call, which established that a quorum was present. Dr. Wilbur Chen reported the potential perception of a conflict of interest (COIs) in that his employer, the University of Maryland, receives a grant from Emergent BioSolutions, Inc. for the development of a shigella vaccine. No other COIs were declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session prior to the vote at approximately 2:10 PM Eastern Time (ET). Given that more individuals registered to make oral public comments than could be accommodated, selection was made randomly via a lottery. Those individuals 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-2021-0133. Further information on the written public comment process can be found on the ACIP website.

As noted in the ACIP Policies and Procedures manual, 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 vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but are prohibited from participating in committee votes. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he/she abstains on all votes related to that company. ACIP members state any COIs at the beginning of each meeting.

Welcoming Remarks

Dr. Sam Posner (Acting Director, CDC/NCIRD) thanked everyone for joining another important ACIP meeting. Through collective efforts, the US has made incredible progress with the COVID-19 vaccination program in the past year with more than 200 million Americans fully vaccinated and 55 million having received a booster dose. The ACIP was critical in achieving the success that has been seen, even among the serious continued challenges. The ACIP members have met more frequently than in any other year ever with more than 13 meetings and 40 Work Group (WG) calls just for COVID. While they thought they were finished for the year, everyone is committed to the mission of the ACIP and are ready to respond when important information becomes available to review and discuss in order to ensure vaccine safety. The hard work by the Vaccine Safety Technical WG (VaST) and the COVID-19 Vaccine WG is greatly appreciated. The effectiveness and sustainability of the COVID-19 and routine immunization programs rests on CDC's standard process of transparently reviewing data with expert advisors and soliciting the ACIP's input on how to adjust vaccine recommendations. Dr. Posner expressed gratitude for the ACIP's service and dedication to improving health and well-being for everyone.

Food and Drug Administration Update

Dr. Doran Fink (FDA/CBER) reported that the Food and Drug Administration's (FDA's) action earlier in the week to authorize updates to the contraindications and warnings information in the Janssen COVID-19 vaccine fact sheet for healthcare providers (HCP) and to provide similar updates to the fact sheet for vaccine recipients and caregivers followed a review of updated data on TTS following use of the Janssen COVID-19 vaccine in the US. These data, which would be presented in more detail later in the afternoon, were evaluated as part of FDA's coordinated involvement with the CDC VaST WG in their ongoing safety surveillance for COVID-19 vaccines. Based on these data, FDA determined that revisions to the Emergency Use Authorization (EUA) Fact Sheets were necessary to ensure that HCP, vaccine recipients, and caregivers are adequately informed about the risk of TTS and to ensure that this risk is mitigated to the fullest extent possible. Updates to the fact sheet warning language include additional specificity regarding the definition of TTS, the strength of evidence to support a causal relationship with the vaccine, and the magnitude of the risk. The Fact Sheets now inform that TTS has been reported following use of the Janssen COVID-19 vaccine in both males and females across a wide range of ages, with the greatest risk of TTS among females 30-49 years of age at a rate of approximately 1 case per 100,000 vaccinations as reported through passive surveillance and an overall case fatality rate of approximately 15% or 1 fatal case out of every 7 TTS cases reported. Additionally, data on TTS following the AstraZeneca (AZ) COVID-19 vaccine, which is another adenovirus-vectored COVID-19 vaccine being used exclusively outside of the US, suggests a class effect for a risk of TTS following adenovirus-vectored COVID-19 vaccines in general. With these data in mind, a contraindication against use of the Janssen COVID-19 vaccine has been added for individuals with a history of thrombosis with thrombocytopenia following the Janssen COVID-19 vaccine or any other adenovirus-vectored COVID-19 vaccine.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) noted that the Coronavirus Vaccines WG thought it would be helpful to reflect back on the previous year. On December 11-12, 2020, the ACIP met and discussed Pfizer BioNTech COVID-19 vaccines and voted on its use under EUA. The first COVID-19 vaccine was administered on December 14, 2020 in the US outside of clinical trials. The ACIP met on December 19-20, 2020 for a discussion of Moderna's COVID-19 vaccine and voted on EUA of that vaccine. The ACIP has met 13 times with respect to COVID-19 vaccination in 2021 and there have been 42 ACIP COVID-19 Vaccine WG calls. Critically and most importantly, almost 600 million COVID-19 vaccine doses have been delivered in the US. Of these, at least 486 million COVID-19 vaccine doses have been administered in the US. This represents 202 million people in the US who are fully vaccinated against COVID-19. In addition, 55 million people in the US have received a booster dose. This represents a tremendous achievement on the part of the US healthcare delivery system, including state and local public health systems. It also is a tremendous achievement on the part of vaccine manufacturers. More than that, this represents disease averted and lives saved. There are no data for the counter-factual, meaning that it is unknown how bad the pandemic would have been if not for these vaccines. However, given how effective the currently authorized and licensed vaccines are at preventing hospitalization and death from COVID-19, this certainly represents many thousands of lives saved.

As Dr. Fink has just discussed, a number of FDA updates to the EUA Fact Sheets for the use of the Janssen COVID-19 vaccine were issued on Tuesday, December 14, 2020. Specifically, the updates are as follows:

Contraindication:

Do not administer the Janssen COVID-19 vaccine to individuals with a history of thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine or any other adenovirus-vectored COVID-19 vaccines (e.g., AstraZeneca's COVID-19 vaccine which is not authorized or approved in the United States).

Updated Information:

Cases of TTS following administration of the Janssen COVID-19 vaccine have been reported in males and females, in a wide age range of individuals 18 years and older, with the highest reporting rate (approximately 1 case per 100,000 doses administered) in females ages 30-49 years; overall, approximately 15% of TTS cases have been fatal

To review several ACIP activities with regard to Janssen COVID-19 vaccine, the VaST WG met on December 6, 2021 and the ACIP COVID-19 Vaccines WG met on December 9, 2021 to review and discuss these new data. Prior to the December 16, 2021 ACIP meeting, the ACIP COVID-19 Vaccines WG reviewed an updated benefit/risk analysis with respect to Janssen COVID-19 vaccination, examined the patterns of use of this vaccine since the pause in April 2021, and engaged in detailed discussions about updates to policy options for the use of COVID-19 vaccines in the US. Dr. Daley concluded with a review of the agenda for the day.

Update on Thrombosis with Thrombocytopenia Syndrome (TTS)

Dr. Isaac See (CDC/NCEZID) presented an update on TTS. As a reminder, thrombosis occurs when blood clots block blood vessels. Platelets (thrombocytes) are colorless blood cells that help the body form blood clots. Thrombocytopenia is the medical term for low blood platelet count. A low count is usually considered to be less than 150,000 platelets per microliter (μL) of blood. TTS is a new syndrome that has been recognized to occur after receipt of adenoviral-vectored COVID-19 vaccines. In the US, the only authorized adenoviral-vectored COVID-19 vaccine is the Janssen or Johnson & Johnson COVID-19 vaccine. As the name suggests, TTS is characterized clinically by blood clots with low platelet counts. There are several early reports about TTS, both in the US and abroad.¹

One type of thrombosis is cerebral venous sinus thrombosis (CVST). This is a somewhat rare type of blood clot involving large veins inside the head. CVST can be a very serious condition, and the most severe TTS cases often involve CVST. CVST is often under-diagnosed due to its nonspecific presentation. When patients die from CVST early in the disease course, the immediate mechanism of death is often brain herniation resulting from either a large hemorrhage in the brain, multiple hemorrhages, or diffuse brain edema. Reported prognostic factors for poor short-term outcomes of CVST include anatomical characteristics of disease (brain herniation and hemorrhage) or features of the clinical presentation (seizures, depressed consciousness, altered mental status).

To recap the initial US events concerning TTS, the FDA granted EUA authorization for the Janssen COVID-19 vaccine on February 27, 2021. The first post-authorization doses of Janssen were given March 2nd. On April 13th, CDC and FDA announced a pause in the use of Janssen COVID-19 vaccine after identification of 6 cases of CVST with thrombocytopenia following vaccination. On April 23rd, the ACIP met and reviewed data on TTS following Janssen vaccination and reaffirmed its recommendation for the vaccine. The pause was subsequently lifted. CDC's interim considerations and website and FDA's fact sheets were updated with information about the risk of TTS, particularly in women <50 years of age.² The ACIP reviewed Janssen COVID-19 vaccine benefit/risk data again in light of Guillain-Barré syndrome (GBS), with TTS data included.

Surveillance data for this presentation came from a collaboration between the Vaccine Adverse Event Reporting System (VAERS) and CDC's Clinical Immunization Safety Assessment Project (CISA Project). The initial case findings occurred through searches of the VAERS database. Confirmation required medical records review and cases were presented to CISA experts, including from the fields of hematology and neurology, to confirm that the clinical syndrome was TTS and to rule out other causes of thrombosis and thrombocytopenia. The working case definition for TTS following COVID-19 vaccine differs slightly between Tier 1 and Tier 2 cases. Both require a platelet count of <150,000 cells/ μL . Tier 1 cases are those where there is thrombosis in an unusual location (e.g., CVST, abdominal venous or arterial thrombosis). For these cases, a positive PF4 enzyme-linked immunosorbent assay (ELISA) test is not required. Tier 2 cases are those with thrombosis only in a more typical location (e.g., pulmonary embolism or deep vein thrombosis of extremity). For these, a positive PF4 ELISA test is

¹ <https://www.ema.europa.eu/en/news/astazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>; <https://jamanetwork.com/journals/jama/fullarticle/2779731>; https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e2.htm?s_cid=mm7018e2_w

² <https://www.cdc.gov/media/releases/2021/s0413-JJ-vaccine.html>; <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>; <https://www.fda.gov/media/146304/download>; <https://www.cdc.gov/mmwr/volumes/70/wr/mm7032e4.htm>

required. Reports where the only sites of thrombosis are ischemic stroke or myocardial infarction are excluded. Cases with concurrent COVID-19 infection were excluded, given that COVID-19 is known to be a cause of both thrombosis and thrombocytopenia. Dr. See reviewed descriptive epidemiology and reporting rates for TTS cases receiving Janssen COVID-19 vaccine March 2–August 31, 2021; summarized information about all deaths among TTS cases following Janssen COVID-19 vaccine confirmed by December 9, 2021; and reporting rates for TTS deaths receiving Janssen COVID-19 Vaccine March 2–August 31, 2021.

Regarding the epidemiology of US TTS cases following Janssen COVID-19 vaccination for the time period March 2–August 31, 2021, the median age of patients with TTS was 44.5 years. Most were females and almost half of the cases occurred in women less than 50 years of age. Most patients were reported to be white non-Hispanic. Among the cases, 29 involved a CVST. None of the patients with TTS were pregnant or postpartum and no cases occurred in a patient with diagnosed thrombophilia. Among the cases, 7 were known to have a past SARS-CoV-2 infection. The median time from vaccination to symptom onset was 9 days. The median time from symptom onset to hospital admission was 5 days. A total of 39 of the cases were vaccinated before the pause on April 13th and all cases occurred after a first dose of Janssen vaccine.

For the most part, the specific risk factors for TTS are not known. In terms of general risk factors for venous thrombosis in patients with TTS following Janssen COVID-19 vaccination, the most common venous thrombosis risk factor was obesity, occurring in 46% of patients. However, 39% percent of patients did not have any venous thrombosis risk factors (e.g., obesity, hypertension, diabetes, systemic estrogen therapy, or other venous thrombosis risk factors). Regarding the outcomes of TTS cases all were hospitalized and 36 or 2/3 of those, were in the intensive care unit (ICU). For patients who survived hospitalization, the median length of hospital stay was 9 days, with a range of 1 to 132 days and an interquartile range of 6 to 17 days. Eight patients died during hospitalization, 9 were discharged to a post-acute care facility, and 37 were discharged to home.

Regarding reporting rates for TTS following Janssen COVID-19 vaccination in terms of cases per million doses, the highest rates of TTS were reported in women between 30-39 years of age and women 40-49 years of age, which is a finding that has been seen previously. The current language on the CDC website discusses the increased risk of TTS in women aged less than 50 years. The reporting rate for women 18-29 years of age is similar to the reporting rates for women 50-64 years of age and for men 40-49 years of age at around 4-5 cases per million doses. Comparing the reporting rates that were shown during the previous presentation to ACIP in July 2021, the rates are now slightly higher for all age groups and overall 20% higher. The rates for men 30-49 years of age are now about twice what was presented before. For men 50-64 years of age, there is about a 50% increase, with the overall for men at about a 50% higher rate than what was previously presented.

Transitioning to focus specifically on deaths in patients with TTS following the Janssen COVID-19 vaccine based on all deaths that had been confirmed as of December 9th, there were 8 confirmed TTS deaths in persons vaccinated with Janssen vaccine by August 31st. An additional TTS death was confirmed in a patient who was vaccinated after August 31st, bringing the total to 9 confirmed deaths. All 9 occurred after Dose 1 of Janssen vaccine. The median age of patients who died is 45 years, which is similar to the overall median age of TTS patients of 44.5 years. Of the 9 deaths, 7 were in females and all were reported in non-Hispanic white persons. The most common underlying condition was obesity, which was present in 7 of the 9 deaths. However, 2 of the deaths occurred in patients without any known medical conditions.

To summarize some of the clinical features of the 9 deaths, all patients had features consistent with severe CVST (e.g., large or multiple cerebral hemorrhages; evidence of intracranial edema and/or mass effect; depressed consciousness and/or seizure). Of the 9 deaths, 7 had confirmed CVS. While 2 did not have specific brain imaging before death that would be needed to diagnose CVST, the location of the brain hemorrhages was suggestive of CVST. That is, the clinical presentation for all deaths was consistent with what is seen from deaths in CVST in general. None of these patients received IV heparin for treatment and 4 received a craniectomy or craniotomy to try to treat the brain hemorrhage. The median time from symptom onset to admission was 3 days. This is shorter than observed for TTS patients overall of 5 days, meaning that these patients do present for care sooner than the typical TTS patient. In addition, the median time from hospital admission to death was 1 day, with a maximum of 2 days. It has been striking on reviewing these cases how rapidly a patient's status deteriorates and results in death.

To recap the total TTS and dates of death counts previously presented to ACIP and the reasons for those presentations, the purpose of the meeting on April 23rd was to discuss resolution of the Janssen pause at which time 7.98 million doses of Janssen COVID-19 vaccine had been given and there were 15 TTS cases and 3 deaths. The purpose of the meeting on May 12th was for general follow-up on TTS at which time 8.73 million doses had been given and there were 28 TTS cases and 3 deaths. During the July 22nd meeting, there was an updated benefit-risk discussion that included GBS. At that time, 12.5 million doses had been given and there were 38 total TTS cases and 4 deaths. The case counts were revised comparing previously presented data with data as of December 9, 2021. It is now known that there were 39 cases and 5 deaths in persons who were vaccinated by April 23rd. In May, the cases are now known to be 42 and deaths 6. In July, cases are now known to be 50 and deaths 6.

For the calculation of death reporting rates presented during this meeting, there were 54 known total cases and 8 known total deaths among persons vaccinated by August 31st. The highest TTS death reporting rate was for women 30-39 and 40-49 years of age of approximately 2 deaths per million Janssen doses. The 9th death was not used for these calculations because of vaccination after August 31st, which was in a woman under 30 years of age. The proportion of TTS cases resulting in death was 13% for those vaccinated before the pause and 20% for those vaccinated after the pause. In addition to the 9 deaths confirmed to date, 2 additional possible TTS deaths following Janssen COVID-19 vaccination have been identified. Both of these deaths were in persons vaccinated before the pause and they share many clinical and epidemiologic features in common with the 9 confirmed deaths, including symptom onset between 7-14 days after vaccination, large cerebral hemorrhage with mass effect, thrombocytopenia, and rapid progression from admission to death. The difference is that these 2 cases did not have definitive imaging to identify CVST, nor did they have imaging performed that might have identified other thromboses present before the patients expired. These 2 deaths have been reviewed with the CISA Project investigators. They are difficult to confirm as TTS cases because without a documented thrombosis, they do not technically meet the TTS definition. However, the CISA Project investigators were concerned that clinically, it appeared that TTS with CVST could be the underlying cause of hemorrhage.³

³ Source of doses administered: <https://covid.cdc.gov/covid-data-tracker/#vaccinations>; Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

In summary, the US TTS case reporting rate following Janssen COVID-19 vaccination is higher than what was previously presented to ACIP, and the case reporting rate for men 40-49 years of age and women 50-64 years of age is similar to that for women 18-29 years of age. The US TTS deaths following Janssen COVID-19 vaccination have typical features of severe CVST, a clinical course from symptoms to admission, and rapid admission to death. These deaths are more common than what was known when data were previously presented to ACIP, with a TTS death reporting rate following Janssen vaccination of approximately 2 TTS deaths per million doses for women aged 30-49 years of age. The proportion of TTS cases with deaths did not decrease after the Janssen pause. The main limitations of this work are possible under-diagnosis of CVST and the fact that VAERS is a passive surveillance system. Both of these limitations mean that the case and death reporting rates shown might be underestimates of the true incidence rates.

VaST Summary

Dr. Keipp Talbot (VaST Chair) reminded everyone that the objectives of the VaST WG are to: 1) review, evaluate, and interpret post-authorization and approval of COVID-19 vaccination safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization and approval safety monitoring; 3) advise on analyses, interpretation, and presentation of vaccine safety data; and 4) provide updates to the ACIP COVID-19 Vaccines WG and the entire ACIP on COVID-19 vaccine safety.

Since December 21, 2021, the VaST WG has had 45 meetings to review vaccine safety data. On April 12th, the VaST WG met and had the first review of CVST with thrombocytopenia. At that time, 6 cases were identified as rare to very serious adverse events (SAEs) following vaccination with the Janssen vaccine. Risk factors for CVST with thrombocytopenia were not well-understood, and the decision was that timely and transparent communication with HCP and the public was crucial to maintain confidence in the COVID-19 vaccination program. After that meeting, a Health Alert Network (HAN) communication was released on April 13th with recommendations for clinicians regarding diagnosis and treatment of CVST with thrombocytopenia, recommendations for public health regarding case reporting through VAERS, and recommendations for the public concerning clinical signs and symptoms to monitor after vaccination.

The ACIP met again on April 14th and 23rd. On the 14th, the ACIP reviewed cases of CVST with thrombocytopenia after COVID-19 vaccination and discussed the need for additional information to support evidence-based decision-making, including age- and gender-specific risk estimates and evaluation of the benefit/risk balance of using the Janssen vaccine in specific subgroups. On April 23rd, the ACIP discussed the risk of TTS, which appeared to be highest in females less than 50 years of age in which 15 cases were reported that were rare but serious. Other risk factors for TTS were not well-established. Risk mitigation strategies included minimizing exposure in high-risk populations, increasing awareness, ensuring timely diagnosis and management of TTS, and educating patients about the benefits and risks of available vaccines. A decision was made at that time that the VaST WG would continue to monitor TTS or other thromboembolic disease and thrombocytopenia in all available vaccine safety surveillance systems; and would update the ACIP COVID-19 Vaccines WG, the ACIP Secretariat, and the ACIP on a regular basis.

A *Morbidity and Mortality Weekly Report (MMWR)* was published via early release online April 27, 2021 that included updated recommendations on the Janssen COVID-19 vaccine.⁴ Subsequently, the VaST WG continued to review TTS and Janssen COVID-19 vaccination during May through December 2021. The VaST WG heard regular updates on TTS data from VAERS, Vaccine Safety Datalink (VSD), and other safety systems. The VaST WG assessments of Janssen COVID-19 vaccination safety was re-presented to ACIP on May 12th with a focus on TTS and on July 22nd with a focus on GBS.⁵

TTS was again reviewed during a regularly-scheduled VaST WG meeting on December 6, 2021. At that time, 54 TTS cases and 9 deaths had been reported following the Janssen COVID-19 vaccination in the US through August 2021. The TTS case reporting rate following Janssen vaccine was higher than previous estimates in men as well as women and in a wider age range. Follow-up investigations have provided more evidence for the relationship between Janssen COVID-19 vaccination and TTS and associated severe outcomes, including death and neurologic problems. The VaST WG recognizes the public health benefits of the Janssen COVID-19 vaccine. However, the additional TTS cases and reported deaths are concerning. The VaST WG felt that the new data on TTS risk needed to be put into the context of the benefit-risk assessment and presented to the ACIP COVID-19 Vaccines WG and the ACIP.

Discussion Summary (See & Talbot)

- Dr. Poehling requested further information regarding why additional cases from earlier were just now being discovered.
 - Dr. See indicated that there are sometimes lags in reporting and in getting information confirmed. In addition, continued refinement of the search strategy and evaluation process and a better understanding of TTS have resulted in better at detection and evaluation of cases.
 - Dr. Shimabukuro reminded everyone that this was a new condition in Spring 2021. With continued refinement in the search strategies and assessment of cases, retrospective reviews of the data have been done frequently. The additional cases were identified and classified based on these retrospective reviews.
- Ms. Bahta inquired as to whether any neurological sequelae have been identified among the 54 cases.
 - Dr. See indicated that they do not have long-term data at this point. There is some information on the status of the 9 who were discharged to a facility after their hospital stay who were not considered well enough to return home, even with help. Among those 9, it is not clear whether the patients' status at discharge differed from their previous status. Among these 9 patients, 1 had many comorbidities before the TTS diagnosis. While there was not a description of the neurologic status of another patient, the patient was not able to provide their own consent for transfer to the facility. This suggests potentially significant functional impairment. For the other 7,

⁴ MacNeil JR, Su JR, Broder KR, et al. Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:651-656. DOI: <http://dx.doi.org/10.15585/mmwr.mm7017e4>

⁵ TTS, thrombosis with thrombocytopenia syndrome; GBS, Guillain-Barré syndrome; <https://www.cdc.gov/vaccines/acip/work-groups-vast/index.html>

information available was variable. There was significant impairment present for these 7, including 5 with hemiplegia and many additional impairments, 2 who had no movement in some of their extremities, 1 who was still intubated, and 2 with other significant neurological impairments. Notably, only 29 of the identified cases involved CVST. The others involved thrombosis at other locations such as pulmonary embolism or PVT. While they may have sequelae that are not neurologic, they could still be significant.

- Dr. Loehr asked whether any additional information was available regarding the background rate for this syndrome for the general population.
 - Dr. See indicated that the background rate for this syndrome, or for syndromes that look very much like this, are not known exactly. There is a study that is not yet published that tried to estimate the background rate for CVST and thrombocytopenia and hospitalizations. That rate is a couple orders of magnitude lower than seen following vaccination.
- Dr. Poehling asked whether there is any evidence of TTS occurring when the Janssen COVID-19 vaccine is used as a booster dose.
 - Dr. See reported that while no cases of TSS have been observed following the Janssen COVID-19 booster doses, the number of booster doses was somewhat small at this point.
- Ms. McNally inquired as to whether there have been any health literacy assessments completed on the EUA Fact Sheets for the Janssen COVID-19 vaccine, and whether there are any data regarding whether people are reading the Fact Sheets in advance of getting vaccinated with any of the COVID-19 vaccines.
 - Dr. Fink indicated that the FDA strives to ensure that the language in the Fact Sheets for vaccine recipients and caregivers is written at an appropriate level of comprehension. While he did not believe they conducted a formal health literacy evaluation, he will check and will follow up with the ACIP.
 - Regarding whether people are reading the fact sheets, Dr. Wharton indicated that they would check on this and get back to the ACIP.
 - Dr. Lee emphasized that while informed consent is a process that all clinicians try to use every time they interact with patients, the concern that it may be challenging to consistently and reliably implement across the board is an important one in terms of making sure that people have full information about the benefits and the risks.
- Dr. Lee observed that even with the newly presented information, it is potentially challenging for clinicians mitigate the risk of severe complications. Given that early recognition and appropriate management appear to have been done, there remains a challenge.
 - Dr. See said this was his impression as well for the most part. The patients who have TTS and then die present somewhat quickly. When they finally are diagnosed, it appears that progression is too rapid in most cases for much more to be done.

- In terms of the challenges of mitigating risk, Dr. Poehling recalled that when the ACIP heard this information in April, the thought was that receiving heparin was making this condition worse and they wanted people to clearly understand that heparin should not be used. One interpretation is that while none of the patients who died after the pause received heparin, it did not seem to mitigate risk.
- Dr. Duchin asked whether for the Tier 2 category of thrombosis in a typical location that had a negative PF4 ELISA any assessment was done to look for signals for that syndrome.
 - Dr. See responded that this was probably outside the scope of what he has been working on, which has been focused on characterizing the patients who meet the definition and have TTS.
 - Dr. Shimabukuro added that CDC is still actively working with its surveillance partners and the FDA to assess thromboembolic events without thrombocytopenia after COVID-19 vaccination. The ACIP will be provided with updated information when it becomes available.
 - To follow-up, Dr. Daley requested confirmation on whether not only thromboembolic events without thrombocytopenia are being monitored across all the surveillance systems, but also there has not been evidence of elevated risk of those syndromes to date.
 - Dr. Shimabukuro indicated that active surveillance has not shown consistent evidence of an elevated risk. CDC is currently engaged with its FDA colleagues to analyze the passive surveillance data, the results of which they will be happy to present to the ACIP during a future meeting.

Updates to the Benefit/Risk Assessment for Janssen COVID-19 Vaccine: Applying the Evidence to Recommendation (EtR) Framework

Dr. Sara Oliver (CDC/NCIRD) presented updates to the benefit/risk assessment for the Janssen COVID-19 vaccines, applying the EtR to recommend framework similar to what was done in April 2021. The policy question remains the same, “Should vaccination with the Janssen COVID-19 vaccine (1 dose) be recommended for persons 18 years of age and over under an Emergency Use Authorization?”

Regarding the public health domain, the unfortunate milestone of over 50 million cases reported in the US was recently reached. After steady declines in case counts through September and October, there has been an increase in cases reported from November to date in December. The 7-day average as of December 13th reached over 117,000 cases per day.⁶ During the timeframe of August 29-December 11, 2021, the Delta variant has represented nearly all circulating SARS-CoV-2 variants circulating in the US. However, the Omicron variant currently represents an estimated 3% of strains in the US.⁷

⁶ https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed December 14, 2021

⁷ <https://covid.cdc.gov/covid-data-tracker/#variant-proportions> Variant Proportions, August 29 - December 11, 2021

To recap TTS after the Janssen vaccine in the US, through August 31, 2021 there have been 54 cases of TTS identified for an overall reporting rate of 3.8 per million Janssen doses. Rates are the highest among females 30-49 years of age, but the risk is no longer exclusively clustered in this population. Through December 2, 2021, there have been 9 TTS deaths for an overall reporting rate of 0.57 per million doses. The rates of TTS deaths have been highest among females 30-49 years of age.

For a summary of what is known about TTS after the AZ vaccine in Europe, the European Union (EU) reported approximately 10 cases per million vaccinated adults in April 2021. Most cases were in women less than 60 years of age within 2 weeks of receiving the first vaccine dose. In an update in September 2021, the European Medicines Agency (EMA) safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC), updated the product information by removing the previous statement reporting that TTS cases occurred mostly in women less than 60 year of age. At this time, they showed that 43% of cases were in males and nearly 40% occurred in vaccinated persons over 60 years of age. In updated data through December from the UK, over 400 cases of blood clots with low platelets were reported, with an overall reporting rate of 15 per million doses. Half of the cases were in women with a broad range of 18-93 years of age. They reported a 17% case fatality. Most cases occurred after the second dose, but 47 cases and 6 deaths were reported after the second dose.⁸

Based on reports of TTS after adenovirus vector vaccines, some countries have updated their COVID-19 vaccine policy. The WG evaluated vaccine policy from 16 countries.⁹ Note these are primarily higher-income countries with broad access to mRNA and adenovirus vector vaccines. This is not meant to be globally representative of all adenovirus vector vaccine policy. All 16 countries with publicly available vaccine policy and broad vaccine access had recommendations for use of the AZ vaccine. Among these 16 countries, 30% (5) halted use of the vaccine; 44% (7) use the vaccine, but have a preferential recommendation for other COVID vaccines; 12% (2) recommend use only in older ages; and 12% (2) recommend use of the vaccine in all ages and populations. Of the 16 countries, 12 also had recommendations for use of the Janssen COVID-19 vaccine. Among these 12 countries, 25% (3) halted use of the vaccine; 33% (4) had a preferential recommendation for other COVID vaccines; 8% (1) does not have a preferential recommendation, but recommended use only in older ages; and 33% (4) recommend use of the vaccine in all ages and populations.

⁸ [https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-\(gacvs\)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-\(vaxzevria-and-covishield\)](https://www.who.int/news/item/16-04-2021-global-advisory-committee-on-vaccine-safety-(gacvs)-review-of-latest-evidence-of-rare-adverse-blood-coagulation-events-with-astrazeneca-covid-19-vaccine-(vaxzevria-and-covishield)); https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant_en.pdf; https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-vaxzevria-previously-covid-19-vaccine-astrazeneca-8-september-2021_en.pdf; <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#yellow-card-reports>

⁹ Australia, Canada, Denmark, Finland, France, Germany, Israel, Japan, Mexico, Netherlands, Norway, Philippines, South Africa, Spain, Sweden, United Kingdom

As an example, this is language from National Advisory Committee on Immunization (NACI) Canada:¹⁰

- ❑ A complete series with an **mRNA COVID-19 vaccine** should be **preferentially offered** to individuals in the authorized age group without contraindications to the vaccine.
- ❑ A viral vector COVID-19 vaccine **may be offered** to individuals in the authorized age group without contraindications to the vaccine to initiate a series when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.
- ❑ A booster dose of an authorized viral vector vaccine should only be considered when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent should include discussion about the risk and symptoms of VITT, as well as the need to seek immediate medical care should symptoms develop.

In summary, there have been recent increases in reported COVID-19 cases and the US is reporting cases of the Omicron variant. Globally, TTS cases have been reported after adenovirus vector vaccines, including both Janssen and AZ COVID-19 vaccines. This has resulted in changes to vaccine policy for adenoviral vector vaccines in many higher-income countries with access to alternative vaccines.¹¹

Moving to the benefit/risk domain, the first Janssen COVID-19 benefit/risk analyses for the US was presented in April 2021¹² when the WG presented a benefit/risk analysis to inform decision-making during the Janssen COVID vaccine pause. In July 2021,¹³ a benefit/risk review was presented of all COVID vaccine-associated events, including TTS, GBS, and myocarditis. The focus of the updated benefit/risk analysis for the Janssen vaccine during this session was in the context of additional data, sufficient vaccine supply, and widely-available mRNA COVID-19 vaccines.

For this assessment of the benefit/risk balance, the benefits were calculated per one million fully vaccinated people and stratified by the age groups 18-49 years, 60-64 years, and 65 years and over. Age- and sex-specific hospitalization rates were used from COVID-NET¹⁴ and age and vaccine-specific VE estimates came from the Influenza and Other Viruses in the Acutely Ill Network (IVY Network).¹⁵ Benefits were calculated over a 180-day period. Harms also were calculated per one million fully vaccinated people. TTS rates came from the previously-reported presentation from VAERS, and previously-presented data on GBS¹⁶ and myocarditis¹⁷ rates from VAERS also were included. In terms of the vaccine-specific estimates of effectiveness against COVID-19 hospitalization from the IVY Network¹⁸ that were used as inputs into the model, the Janssen age-specific estimates ranged from 69% to 76% vaccine effectiveness (VE) and the mRNA age-specific rates ranged from 88% to 92% VE.

¹⁰ <https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization/naci/recommendations-use-covid-19-vaccines.html>

¹¹ Recommendations-use-covid-19-vaccines-en.pdf (canada.ca)

¹² MacNeil et al. <http://dx.doi.org/10.15585/mmwr.mm7017e4>

¹³ Rosenblum et al. <http://dx.doi.org/10.15585/mmwr.mm7032e4>

¹⁴ https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

¹⁵ Self et al. *MMWR* 2021

¹⁶ <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/02-COVID-Alimchandani-508.pdf>

¹⁷ <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/04-COVID-Oster-508.pdf>

¹⁸ <https://www.cdc.gov/mmwr/volumes/70/wr/mm7038e1.htm>; For age strata specific estimates, adjusted for continuous age in years, calendar date (biweekly), HHS region, sex, and race/ethnicity

There have been some notable changes in the methods from the original benefit/risk assessment of the Janssen vaccine that was first presented in April 2021. At that time, it was assumed that all COVID hospitalizations were occurring among unvaccinated. The model now accounts for some COVID hospitalizations occurring among vaccinated persons. In the original model, it was assumed that there were equal sex-specific risks of COVID hospitalization, ICU admission, and death. Now it is possible to use age- and sex-specific rates. In April, it was assumed that VE against hospitalization was 90% for the Janssen vaccine based on the randomized clinical trial (RCT). An age-specific VE between 69%-76% was used in the updated model based on real-world observational data. Hospitalization rates were used in the April model from the week ending March 27th, which had lower rates overall than in the current model that used rates from the week ending November 13th. In the original model, a 30-day time horizon was used, which accounted for a possible expected delay in vaccination that could occur if the Janssen vaccine was no longer available. Now the vaccine supply is sufficient, the time horizon is 180 days and is more in line with what is known about duration of protection. In terms of the reporting rates of TTS following the Janssen COVID-19 vaccination, TTS is most common among women 18-49 years of age who have reporting rates of 8.7 TTS cases per million Janssen doses.

To guide the benefit/risk discussion, this presentation presented the benefits and risks of the Janssen vaccine compared with no vaccine by age and by sex. The differential benefits and risks of the Janssen vaccine were compared with mRNA vaccines, including in the risks of GBS and myocarditis. Looking at COVID-19 associated hospitalizations prevented by Janssen COVID-19 vaccine compared with TTS cases expected per million fully vaccinated people, many more COVID hospitalizations would be expected to be prevented over 6 months than TTS cases expected for all age and sex groups. Focusing only on the benefits and risks among females, many more hospitalizations would be prevented when including other potential risks than TTS and GBS cases expected. Still focusing on females and adding the benefits and risks of the mRNA vaccines compared to the Janssen vaccine, the mRNA vaccines would be expected to prevent more COVID hospitalizations and would have fewer cases of myocarditis expected than of TTS or GBS. Considering the same analysis exclusively among males, comparing the Janssen vaccine with the mRNA vaccine in males, the mRNA vaccines prevent more COVID hospitalizations than the Janssen vaccine in all age groups. In males 18-49 years of age, more cases of myocarditis would be expected from the mRNA vaccines than TTS or GBS cases from the Janssen vaccine. In the older age groups among males, GBS would become the largest vaccine-associated risk.

It is important to note that there are differences in the severity of these vaccine-associated events. For myocarditis after mRNA COVID-19 vaccines,¹⁹ a 3-month follow-up showed that over half reported no symptoms and over 90% are “fully recovered” by a cardiologist or healthcare provider. There have been no confirmed deaths. For TTS after the Janssen COVID-19 vaccines,²⁰ there is an approximately 15% mortality rate and 17% required discharge to a post-acute care or rehabilitation facility. For GBS after the Janssen COVID-19 vaccines,²¹ there is about a 1% mortality rate and 10% required mechanical ventilation.

¹⁹ ACIP Presentation, Dr. Oster: November 2, 2021 <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-11-2-3/04-COVID-Oster-508.pdf>

²⁰ Presentation, Dr. See

²¹ ACIP Presentation, Dr. Alimchandani: July 22, 2021 <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/02-COVID-Alimchandani-508.pdf>

There are several limitations to the benefit/risk analysis. This analysis considers direct benefits and risks over a 180-day period comparing vaccine to no vaccine. The model compares a single-dose Janssen series with a 2-dose mRNA series. The model assumes a static hospitalization rate and VE over a 6-month period and does not account for booster doses or for prior infection. In summary, this was a direct benefit/risk assessment of the Janssen COVID-19 vaccines and TTS, which considered individual benefits of vaccination versus individual risk. Using current VE estimates, the benefit/risk balance of the Janssen COVID-19 vaccine is still favorable for all age and sex groups compared with no vaccine. When compared to the benefit/risk balance for mRNA vaccines, the Janssen vaccine prevents fewer COVID-19 associated hospitalizations, ICU admissions, and deaths and there are more severe health impacts from TTS and GBS after a Janssen vaccine compared to impacts from myocarditis after the mRNA COVID-19 vaccines. In a setting where mRNA and the Janssen vaccines are both widely available, the benefit/risk balance for mRNA COVID-19 vaccines is likely more favorable across all age and sex groups.

Moving to values, acceptability, and feasibility a large-scale nationally-representative survey was conducted to assess individual confidence in each of the COVID-19 vaccines available in the US before, during, and after the temporary pause for the Janssen vaccine. The results show loss of confidence in the Janssen vaccine, which persisted over time even after the halt was lifted.²² In terms of daily reported doses given by the manufacturer,²³ providers are administering about 1.9 million doses per day on average (including first, second, and additional doses). This is approximately 44% decrease from the peak of around 3.4 million doses reported on April 13, 2021. Looking at COVID-19 vaccine administration by vaccine type, over 488 million COVID-19 vaccine doses have been administered in the US, of which 17.2 million Janssen doses have been administered. Approximately 56 million people in the US have received a booster dose, of which about 870,000 were Janssen booster doses. While some vaccine recipients received the same vaccine type of vaccine for their primary and booster dose, others received one type for their primary series and a different type for their booster dose (e.g., heterologous prime boost or the mix-and-match). Among those who received Janssen for their primary series, 40% received a Moderna booster, 30% received a Pfizer booster, and about 28% received a Janssen booster.²⁴

Since the pause, the US has been administering around 110,000 doses of the Janssen COVID-19 vaccine per week since early September. Since authorization in late October, approximately around 100,000 booster doses of the Janssen COVID-19 vaccine have been administered per week. Approximately 65,000 doses of Janssen COVID-19 vaccine have been administered per week since September among males. Since authorization, about 50,000 booster doses per week have been administered to males. About 45,000 primary doses have been administered weekly since early September to females, which is lower than the doses administered among males. However, similar numbers of booster doses have been administered each week among males and females since the booster dose authorization for Janssen COVID-19 vaccine.

²² Rader, et al. Persistent drop in confidence following US recommended pause of Ad26.COV2.S vaccine administration. Data updates as of December 2021.

²³ The New York Times. Covid-19 Vaccinations: County and State Tracker. <https://www.nytimes.com/interactive/2020/us/covid-19-vaccine-doses.html>. Accessed December 15, 2021

²⁴ CDC. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total. Accessed December 15, 2021

Jurisdictions were surveyed for their use of the Janssen vaccine in December 2021²⁵ and reported that overall, the Janssen vaccine is available to nearly all populations and many specific populations. Jurisdictions also highlighted that while being offered widely, the Janssen vaccine is the preferred option in some more transient or transitional settings. Some jurisdictions highlighted that it may be the only option at some settings, such as correctional facilities, homeless shelters, or airport clinics. When asked about a possible impact if the Janssen vaccine was no longer recommended, jurisdictions highlighted issues with access for those who prefer a single-dose vaccine or an alternative to the mRNA vaccines. They also mentioned decreased confidence in COVID-19 vaccines and disruptions to logistics flow.

Regarding the equity domain, the patterns of race and ethnicity for the Janssen COVID-19 vaccine are very similar to those for the mRNA vaccines.²⁶ Jurisdictions also were asked about revised recommendations and populations that could be impacted. Based on how doses are currently being used, changes in recommendations may impact various populations such as those experiencing homelessness, incarcerated individuals, home-bound populations, migrant or seasonal populations, rural populations, racial/ethnic minorities, those at higher risk of COVID-19, college students, and those in long-term care facilities.²⁷

In summary, the context of the benefit-risk review in April 2021 was a setting of limited supply of both the mRNA and the Janssen vaccines. It was estimated that if use of the Janssen vaccine was not resumed, it could take nearly 3 months for all vaccine-intending adults to complete a COVID-19 vaccine series based on supply at that time. Within that context, ACIP reaffirmed its recommendations for use of the Janssen vaccine in all persons 18 years of age and over under FDA's EUA that included a warning that rare clotting events might occur after vaccination, primarily among women 18-49 years of age. The *MMWR* that was published shortly thereafter stated, "Education around the risk for TTS with Janssen COVID-19 vaccine, as well as the availability of alternative COVID-19 vaccines, is required to guide vaccine decision-making."

In July 2021, GBS after the Janssen COVID-19 vaccine was identified and the benefit-risk balance was reassessed. ACIP determined that overall, the benefits of COVID-19 vaccination in preventing COVID morbidity and mortality outweigh the risk for these rare SAEs, but acknowledged that the balance of these benefits and risks varied by age and by sex. An additional case review and ongoing safety surveillance have identified previous and newly-occurring TTS cases, including deaths. The context of this presentation of the updated benefit-risk balance of the Janssen COVID-19 vaccine is that the US is no longer in the setting of limited vaccine supply. These data were presented to the COVID-19 Vaccines WG the previous week. The WG discussed several proposed policy updates for use of the Janssen COVID-19 vaccine. The four policy options discussed by the WG were as follows:

- ❑ Policy Option #1: Reaffirm recommendations for all age and sex categories in the setting of FDA's warning on the EUA and guidance in CDC's clinical considerations.
- ❑ Policy Option #2: Recommend the Janssen COVID-19 vaccine only for older adults with a cut-off of either ≥ 50 years or ≥ 65 years of age.
- ❑ Policy Option #3: Recommend against use of the Janssen COVID-19 vaccine for all persons.
- ❑ Policy Option #4: Make a preferential recommendation for mRNA COVID-19 vaccines over the Janssen COVID-19 vaccines.

²⁵ Jurisdictional survey on Janssen vaccine, December 12-15, 2021 (n=46)

²⁶ CDC. Vaccine Task Force. Vaccine Data Section/Data, Analytics & Visualization Task Force. Data updates as of December 15, 2021

²⁷ Jurisdictional survey on Janssen vaccine, December 12-15, 2021 (n=46)

For the first policy option to reaffirm recommendations for everyone, the pros would be that it allows flexibility and choice and would allow for the use of the vaccine in harder-to-reach populations. However, the cons are that it may lead to more cases of TTS and GBS. The burden is on the individual to make decisions for the type of vaccine received and for health departments or providers to convey that risk. At-risk populations for COVID may have limited opportunities for discussions of this risk associated with the vaccine. At-risk populations for COVID may also be at risk for barriers to rapid TTS identification and treatment. For the second policy option to recommend the Janssen vaccine only for older adults, the pros are that it would remove the vaccine from the most at-risk population and hopefully reduce TTS cases. Age-based recommendations can be easier to communicate and implement. Regarding cons, the VE is lower for the Janssen vaccine compared to the mRNA vaccines, so these recommendations may provide less protection in a population that is known to be at risk for severe disease from COVID-19. In the US, most older adults already have initiated a COVID-19 vaccine primary series. This would remove the option of the Janssen vaccine for younger men, who are at higher risk of myocarditis. In addition, it would not remove the vaccine from the population of older adults who are at most at-risk for GBS. If a cut-off ≥ 50 years of age is used, there are still cases and deaths from TTS reported in those 50-64 years of age. There have been 2 deaths in females 50-64 years of age and the TTS rate among females 50-64 years of age is similar to that for women 18-29 years of age.

For the third policy option to recommend against use of the Janssen vaccine for everyone, the pros are that there would be no further cases of TTS or GBS after the Janssen COVID-19 vaccine and no further deaths due to TTS or GBS after the vaccine. For cons, this option would remove choice from individuals for primary series and booster and would limit options for those with contraindications to mRNA vaccines. Importantly, it may have global implications around confidence in the Janssen COVID-19 vaccine that could impact global vaccine supply. For the fourth option of a preferential recommendation for mRNA COVID-19 vaccines over the Janssen COVID-19 vaccine, the WG acknowledged that the benefit-risk balance is more favorable for mRNA in all ages and sexes. This includes higher VE and less SAEs. This option would allow for flexibility and choices and for a vaccine option for someone who may have contraindications to mRNA vaccines. For cons, this option places the burden on the individual to make the decision for the type of vaccine received. At-risk populations may have limited opportunity for discussion of the risk associated with vaccine. While a preferential recommendation does provide more guidance than currently exists, there may be confusion around how to implement a preferential recommendation.

The WG reviewed the data, policy options, and pros and cons and had several conclusions. In the setting where there are no alternative COVID-19 vaccines, the benefits of the Janssen vaccine outweigh the risk. This is important in global situations where there may not be other COVID-19 vaccines available. Due to both higher VE of the mRNA vaccines and the severity of safety issues seen with the Janssen vaccines, in the setting of widely-available mRNA vaccines in the US, the benefit-risk balance of the mRNA COVID-19 vaccines is more favorable than for the Janssen COVID-19 vaccine. Based on reviewing the totality of the data, the WG supported a preferential recommendation for mRNA vaccines. This is similar to many other countries with mRNA and adenovirus-vector vaccines widely available. The WG will continue to review available data on VE and safety. Updates to the recommendations can be made as needed. Education around the risks associated with adenovirus-vector vaccines will be critical for those who may choose to receive a Janssen vaccine. Importantly, ensuring access to mRNA vaccines in all individuals is critical. The jurisdictional survey revealed that there may be some populations and settings where Janssen is being used as the main vaccine offered. If Janssen

COVID-19 vaccine is the only vaccine offered to some harder-to-reach populations, this could result in inequitable distribution of risk for TTS and GBS.

Possible language for a preferential recommendation:

- mRNA COVID-19 vaccines are **preferred** over the Janssen COVID-19 vaccine for the prevention of COVID-19 for those ≥ 18 years of age.
- Janssen COVID-19 vaccines **may be offered** when other authorized COVID-19 vaccines are contraindicated or inaccessible.
- This includes vaccines administered as a part of the primary series and booster doses.

Possible additional guidance if the ACIP votes for a preferential recommendation:

- Education about the risk for adverse events, including TTS or GBS after the Janssen COVID-19 vaccine, is required to guide vaccine decision-making.
- Janssen COVID-19 vaccines **may be offered** to the following populations:
 - Persons with a contraindication to mRNA COVID-19 vaccines (e.g. severe allergic reaction after a previous dose or to a component of an mRNA COVID-19 vaccine)
 - Persons who would otherwise remain unvaccinated for COVID-19 due to limited access to mRNA COVID-19 vaccines
 - Persons who would prefer the Janssen COVID-19 vaccine despite safety concerns identified
- Vaccine providers should start the two-dose mRNA COVID-19 vaccine series, even if there is uncertainty about how the patient will receive their second dose. Two-dose mRNA COVID-19 vaccines can be used in any population or setting.

With all of this in mind, ACIP was asked to discuss the question: “Given the review of benefits and risks, what recommendation does ACIP feel is appropriate for use of the Janssen vaccine?”

Janssen COVID-19 Vaccine Statement

Dr. Penny Heaton (Janssen Pharmaceutical Companies of Johnson & Johnson)

emphasized that based on the data, Janssen is confident in the positive benefit/risk profile of its vaccine. It is saving lives in the US and on every continent around the globe. This vaccine is different in that it is long-lasting, offers high levels of protection, provides breadth of protection, has flexible dosing, and is easy to store and transport. In many low- and middle-income countries, this vaccine is the most important and sometimes only option. Even in the US, given its durable protection, it may be the preferred choice for people who cannot or will not return for multiple vaccinations. The safety and well-being of those who use the Johnson & Johnson vaccine continues to be Janssen’s number one priority. They strongly support education and awareness of rare events, such TTS, and also has several studies underway to help identify factors that may be associated with the development of TTS and the mechanism by which it occurs.

Although rare, Janssen recognizes that the incidence of TTS associated with the Johnson & Johnson vaccine is highest in women 30-49 years of age and that it can be fatal if not treated. While TTS continues to be a rare event, cases of COVID-19 are not. In fact, they are surging in the US and around the world. The pandemic continues to cause high rates of mortality and morbidity, and critically ill patients are at high risk of both venous and thromboembolic complications from COVID-19. A recent study from Oxford showed an estimated 435 cases of CVST and portal vein thrombosis (PVT) occur per million patients with COVID-19. These events occur more commonly in females and the risk post-COVID-19 is much higher than the risk observed post-vaccination. As COVID-19 cases continue to rise during the holiday season, there is a pressing need to protect those at highest risk. Although progress of vaccination coverage has been remarkable, fewer than 1 person in 5 is fully vaccinated and boosted in the US. In the setting where many people do not return for a second dose or a booster, the durability of the single-shot Johnson & Johnson vaccine as a primary regimen could make crucial differences in saving lives in the US and around the world.

There have been several studies of the real-world effectiveness following a single shot of the Johnson & Johnson vaccine. One of those studies that was conducted by Johnson & Johnson was recently posted as a pre-print. These data are unique in that they demonstrate that even a single shot of the Johnson & Johnson vaccine provides durable protection against infections and hospitalizations through at least 6 months. This study also demonstrated a durable benefit across all subgroups of age, sex, and comorbidity. As increasingly more has been learned about the durability of protection of the Janssen COVID-19 vaccine from real-world data across multiple studies, the benefits are being observed in terms of cumulative deaths and hospitalizations avoided. Janssen modeled the benefit/risk over 1 year assuming 75% effectiveness across different transmission intensity scenarios. These data, modeled against being unvaccinated, showed a positive benefit/risk across gender and age groups. This remains important for those who cannot or will not return for follow-up vaccination. Efficacy against severe disease matters and durability matters. A single shot of the Janssen vaccine also generates strong immune responses and long-lasting immune memory. These data are reflected in the immune profile of the Johnson & Johnson vaccine.

Antibody titers peak later than the mRNA vaccines and persist and mature over time, increasing in breadth. There is a 12-fold rise in antibody titer when a booster is given 6 months after the primary vaccination. Janssen is confident in the durability of protection. Further, the Johnson & Johnson COVID-19 vaccine has induced broad antibody responses against a variety of different variants. Data from a clinical study confirm the immune profile of the vaccine, both humoral and cellular. It is unique. Antibody titers peak later than mRNA vaccines. They persist and they mature over time, increasing in breadth as also demonstrated in a recent publication in the *New England Journal of Medicine*.²⁸ T-cell responses also persist at least 8 months post-vaccination, which is important in the prevention of severe disease. The implications of the Janssen vaccine durability data, in contrast to published data on the mRNA vaccines, have not yet been fully evaluated and discussed by this committee in terms of their potential impact on effectiveness. This durability may be crucial in the US setting where less than 20% of the US population are vaccinated and boosted.

²⁸ Barouch et al. *N Engl J Med* 2021; 385:951-953

The committee described the lower level of effectiveness in comparison to the mRNA vaccines. Janssen has seen even higher efficacy post-booster in global clinical trials. In fact, the efficacy after a Johnson & Johnson booster dose was 94% protection against symptomatic COVID-19 in the US and 100% protection against severe or critical COVID-19. Janssen has a global vaccine and the world is depending on them. Janssen is one of the largest suppliers of COVID-19 vaccines to the African Union (AU) and COVAX, which enables equitable distribution of COVID-19 vaccines to the 190 participating countries, including 92 low- and middle-income countries. Janssen already has shipped hundreds of millions of doses of vaccine and is committed to shipping hundreds of millions more in 2022.

The Johnson & Johnson COVID-19 vaccine is a life-saving tool for individuals in high-risk populations and for those where follow-up for multiple vaccinations may be challenging, or where available healthcare resources are low. This week, the US crossed yet another grim milestone in the history of this pandemic. More than 800,000 people in the US have lost their lives to COVID-19. Dr. Heaton has lost loved ones during this pandemic and recognized that many attending the meeting had as well. They must save individuals in the US and facilitate equitable access, both in the US and around the world. In this setting where many people do not return for a second dose or a booster, the durability of this single shot Johnson & Johnson vaccine is a primary regimen to make a crucial difference in saving lives in the US and around the globe.

Discussion Summary (Oliver & Heaton)

- Dr. Long inquired as to whether Janssen is exploring the administration of a second dose soon after the first dose to have a shorter period of time before decreased effectiveness and if so, how much safety data there is on a second dose.
 - Dr. Heaton indicated that Janssen is exploring this. The FDA approved the Janssen COVID-19 Fact Sheet that there is flexibility in giving a second dose. It may be given at least 2 months and up to 6 months after the single dose, or even longer. This is based on Janssen's clinical trial data. Janssen has a large safety database comprised of over 9000 individuals, some of whom received a booster dose in the randomized placebo-controlled trial.
 - Dr. Macaya Douoguih (Janssen) added that a little over 8000 participants from other clinical studies have received the second dose at that interval, which is included in the 9000 individuals in the database.
- Dr. Loehr requested a reference for the number of people that Dr. Heaton reported were getting TTS or CVST from COVID-19 infection. He also pointed out that while the benefit of Janssen's product being a single-dose vaccine had been emphasized, it seemed to him that it was at least a 2-dose vaccine due to the strong recommendation to get a booster dose 2 months later. Even the people who only want to get 1 dose would still need to return for a second dose 2 months later. Therefore, the emphasis that it is a 1-dose vaccine may not be as critical as noted.
 - Dr. Heaton indicated that the information regarding TTS or CVST from COVID-19 infection was published by Oxford a week or two previously and that she would provide the exact citation. This paper looked at thromboembolic events with COVID-19 infection, with a focus on the rare events of CVST and venous thrombosis.

- In terms of the single-dose emphasis, Dr. Heaton recalled that Dr. Oliver talked about the fact that for people who may not return for boosters, the single-dose regimen can be important. Perhaps even more important than that is the profile of the vaccine. It is likely that that the durability profile seen with a single dose will be seen after a booster dose. Because the booster was just recommended in October, there has not yet been ample time to follow the recipients over 6-8 months. If the same level of durability is seen with the second dose, this would be 94% protection against any symptomatic COVID-19 and 100% protection against severe disease. That is the potential value of a second dose. Janssen's clinical trials were set up to evaluate the single dose and then the booster dose. In thinking about the decision for the day, it is also about the durability profile.
- Ms. Bahta pointed out that while ACIP's role is a commitment to the American public, consideration also must be given to how their decisions impact global equity as well as US national equity. With that in mind, she asked what impact a change in the recommendation for Janssen vaccines in the US might have in distribution globally.
 - Dr. Lee said she thought it would be hard to predict the future and that her perspective was that there may not be a one-to-one correlation. She also recognized that the ACIP has a heavy burden and a great responsibility to both to the US population and the global population.
 - Dr. Heaton said that Janssen is working with the World Health Organization (WHO) and other authorities around the world and has been talking with them over the last couple of days to make sure that they were all well aware of the data. Janssen is committed to providing 900 million doses of vaccine worldwide to continue to address the COVID pandemic.
- Dr. Daley recalled that Dr. Heaton mentioned that the cases of TTS were fatal if not treated and his interpretation of the data presented by Dr. See was that in some cases, TTS could be fatal even if recognized and treated appropriately.
- Thinking about Dr. Oliver's presentation, Dr. Long said she was struck by how Canada handled this and suggested that perhaps another option for the US would be to state something to the effect of, "Janssen COVID-19 vaccine could be limited to use in the following situations . . ." rather than stating that "mRNA vaccines are preferred." Historically, preference has been more nuanced and not quite as concrete. She asked whether the WG believed there would be a difference between limiting under general circumstances and just exerting preference for another vaccine and how this might be interpreted by vaccine givers and public.
 - Dr. Oliver clarified that the NACI language she shared from Canada was just an example from a country that is somewhat similar to the US in the language they have. The WG is happy to adapt and adjust the proposed language based on ACIP discussion. If there is a vote for a preferential recommendation, guidance can be included in the clinical considerations.
 - Dr. Cohn added that they acknowledged that there is a difference in the way that she was describing this. If ACIP was to vote based on the way that the options were set up, it would be a vote against use of the Janssen vaccine except in certain circumstances.

- Dr. Long emphasized that this ultimately would mean recommending a vaccine for the very same people regardless of whether it was preferential or if it was a vote against use except in limited circumstances.
- Dr. Oliver added that there was discussion among the WG members around what limiting would mean for “absolutely cannot be used except in certain circumstances.”
- Dr. Sanchez stressed that this was a very difficult decision-making process and that he could not recommend a vaccine that is associated with a condition that may lead to death such as this with 100,000 women and 30-49 years old potentially having a condition with a case fatality rate of 15%. There are other vaccines available and as noted, the Janssen product is no longer really a single dose vaccine. He thought they should state that the Janssen vaccine would be preferred only for those who have contraindications to the mRNA vaccines. There are also other therapies such as monoclonals and pills that are on the horizon for early disease. The AZ vaccine has seen cases with a second dose, which may occur with booster doses of Janssen vaccine. He is not recommending the Janssen vaccine to any of his patients’ parents and agreed with Dr. Long that if continued use is recommended, it should be limited to certain people.
- Dr. Daley highlighted that it is possible now to better quantify the risk of this adverse event that is very serious, but also continues to be very rare. There is still going to be a need for highly effective COVID vaccines globally across multiple platforms. The WG did not specifically talk about the distinction between “limited” and “preferential.” However, they were very acutely aware of the fact that the language choice is critically important. Thinking about the jurisdictional survey, he wondered whether there was a sense among responders regarding what impact a limited use or preferential recommendation might have on the means by which local and state public health potentially could get mRNA vaccines to difficult-to-reach populations, including multiple doses.
- Dr. Oliver pointed out that because the survey was done within a short turnaround, continued engagement with the jurisdictions would be helpful in order to learn more. There are some advantages now that were not available a year ago, such as improvements in refrigeration, shipping, and handling storage issues with the mRNA vaccines. They also have learned over time in engaging with groups at CDC that directly work with at-risk populations that assurance that it is acceptable to initiate the series even if they cannot guarantee receipt of a second dose in exactly 21 or 28 days later is key.
- Dr. Brooks expressed concern that a strong preferential recommendation against Janssen vaccine may be too restrictive for a vaccine that is likely being disproportionately used among people who are under-represented minorities, homeless, et cetera and could have worldwide implications. Perhaps the preferred language could be more specific and show when mRNA vaccines are preferred versus the Janssen vaccine.

- Dr. Loehr expressed respect for Dr. Sanchez's perspective and recognized the drawbacks of the Janssen vaccine. However, he viewed this as an issue of the trolley problem and ethics in which the trolley driver must decide whether to go down one track and have one person die or go down a different track and have 10 people die. If the Janssen vaccine is taken away and people are choosing to/or cannot get the mRNA vaccine, there will be complications from getting COVID-19 disease. Even though there are significant risks with the Janssen vaccine, he wants that vaccine to be available if it is the only option and was not comfortable saying it should not be an option. He was very comfortable saying it should be a preferential recommendation.
- Dr. Bell said she thought the bottom line pertained to balance and that making a preferential recommendation with additional guidance in the clinical considerations would be the best route. She did not feel comfortable in the context of plenty of mRNA vaccine with the ACIP not making a clear and strong statement that reflects the recognition that there are concerns about the rare but oftentimes fatal side effects. The best way to do that would be to make a preferential recommendation. Informed consent is complex and she was concerned that many people do not have all of the information that they would need to give informed consent, which is another rationale for making a preferential recommendation. Some people may opt for the Janssen vaccine even after being appropriately informed, so it would not be right for ACIP to make that option unavailable to them. Dr. Sanchez's response was precisely the kind of response they hope providers would make when a patient asks them, "What do you think about this?" Perhaps the ACIP being clearer about making a preferential recommendation in favor of mRNA vaccines supports the kind of guidance to individual patients that Dr. Sanchez is providing. While Dr. Bell emphasized that while she would not recommend a Janssen vaccine to her family members, the ACIP has to recognize that different people make different choices. If they are appropriately informed, the Janssen vaccine option should be available to them.
- Dr. Talbot agreed that if the ACIP makes a preferential recommendation, the language would have to be extremely clear and extremely strongly worded. The presentations discussed the advantages of this vaccine in that it is being used in populations that have very little say in their care, possibly lower health literacy, and less access to care such as those in prisons, homeless persons, and those living in rural areas. People in these settings often do not have the same health literacy and access to health care. There is concern that the Janssen vaccine will be used because it is easy, but there are serious risks. Whatever wording is chosen must be incredibly clear and strongly worded in order to protect those who do not have access to as much medical information.
- Dr. Lee added that clearly if people have a contraindication to an mRNA vaccine and wish to have protection, it seemed reasonable to have access to the Janssen vaccine that would provide that protection. The clinical guidance should be clear about this. She was leaning toward the preferential recommendation option to ensure that there is access to the vaccine, while also making clear when it seems appropriate to use. She feels that ACIP's role is to think about not only the benefit-risk balance, but also to implement mitigation as much as possible through its recommendations. She also recognized that it was far harder for the country to implement mitigation by relying on individuals to have equitable access to the full information on benefits and risks, particularly in their preferred language and at an

- appropriate health literacy level. She fully agreed that one population should not bear a disproportionate burden of those risks because that is the only choice that they have.
- As a practicing physician, Dr. Goldman reported that patients presenting for visits are asking which vaccine they should use. This is really not the time for a long and drawn out discussion and 2- to 3-hour review of data to explain to them what the risks and benefits are in as detailed a way as CDC explains. Patients want a clear and concise answer about what vaccine they should get, and they depend upon the physician to tell them this. A preferential clear and concise recommendation from the CDC is key, with the caveat that though there is a risk of the extremely rare side effect of TTS, this vaccine can be used in some populations. It is important not to eliminate this vaccine completely because it is useful in certain populations. Also, the evidence is showing that this is not a 1-dose vaccine and probably should be a 2-dose vaccine. He said he would not necessarily be in favor of age-based, age-restricted, or gender-restricted recommendation.
 - Dr. Zahn observed that from a local public health standpoint, his agency and other agencies around the country had concerns about offering only the Janssen vaccine to disadvantaged populations, homeless populations, and jailed or prison populations for ease once the AEs were identified due to the associated ethical issues. He thought by and large, local public health agencies will be making every effort to offer mRNA vaccines in all of those settings and to try to ensure access to 2 doses. Patients present to public health clinics who say they do not want the mRNA vaccine for variety of reasons other than contraindications, and that they want the Janssen vaccine despite the concerns being conveyed. Public health clinics are administering the Janssen vaccine to people every day who would remain unvaccinated if the vaccine did not continue to be available.
 - Speaking as a practicing physician, Dr. Fryhofer expressed appreciation for convening an emergency ACIP meeting to get data to the public promptly about the rare but deadly TTS risk and the fact that it is not just limited to young women but crosses all ages and both sexes. This whole process should increase confidence in the US vaccine surveillance system. When this vaccine was discussed during earlier ACIP meetings, it was recommended by the ACIP under FDA EUA, and then the CDC clarified in the clinical guidance the increased risk in women 18-49 years of age. She agreed that it is now clear that the Janssen vaccine is not a 1-dose vaccine and that another dose will be needed. Since many patients are missing this point, she expressed her hope that the FDA would approve the Janssen vaccine as a 2-dose series. She agreed that this vaccine needs to be made available for ease of storage and transportation. In addition, a variety of vaccine platforms are needed in that it is unclear what the next variant may be or what twists or turns the COVID-19 pandemic will take.
 - Dr. Duchin agreed with the preferential recommendation strategy that preserves the availability of the Janssen vaccine for those who would not otherwise be immunized or prefer it, with adequate understanding of the risks and benefits. He also was impressed by the discussion around the need to include the second or booster dose in the messaging around what is necessary for full protection, and expressed hope that they could return to the discussion about whether that should be part of the

definition of “fully vaccinated.” It appeared from the conversation that many of the ACIP members felt that the booster dose was essential to being fully protected.

Public Comment

The floor was opened for public comment during the December 16, 2021 ACIP meeting at 2:35 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated during this meeting, selection was 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-2021-0133. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received.

Ms. Elizabeth Ditz Vaccinate California

I would like to thank the committee members for their tireless work over the last 2 years, and the efforts you have made to make the decision factors public and transparent. I am speaking as myself and as an active member of a Facebook group, Vaccine Talk, that has almost 79,000 members worldwide. Some of the Vaccine Talk members are physicians, virologists, and other professionals involved in vaccine safety. We use the experts to volunteer their time to educate other members. I've also learned from people not in the Vaccine Talk groups, such as Kimberly Manning, MD, whose stories from her Grady community have taught me so much about meeting people where they are. Based on the questions posed to Vaccine Talk, I would say that the primary response to all COVID vaccines is anxiety. Many are anxious about the safety and efficacy of the available vaccines. Others are anxious about when they will be able to get the vaccines for their children. For those anxious about vaccine safety, those anxieties can sometimes be relieved. One noticeable feature is the general public, as represented by the members of Vaccine Talk, don't understand or under-value that all vaccinations have improved public health. There is an overemphasis on the direct vaccine effects. In my view, the US government overall has had less than optimal messaging about the safety and value of vaccination to prevent COVID-19 and other diseases. The v-SafeSM program has been generating a vast amount of data, but little has been shared in a timely manner. Likewise, data from the Vaccine Safety Datalink and Rapid Cycle Analysis is almost invisible to the general public. Going forward in public health planning, crafting a more robust and effective public information platform would reduce vaccine hesitancy. As you know, there is a large literature on how to address vaccine hesitancy. I hope the government can recruit and train community-level experts. Also, having a general presentation on v-SafeSM in each meeting would not be a waste of time. Thank you very much.

Dorit Reiss, JD Professor of Law University of California Hastings College of the Law

First of all, thank you committee for giving me a chance to comment again. My name is Dorit Reiss. I'm a Professor of Law at UC Hasting College of the Law and I want to raise three issues. First, I want to reiterate what Ms. Ditz said and thank the committee for its hard and transparent work holding these meetings continuously over the past year. I hope the process continues to be respected because keeping open advisory committee meeting, as happened for example for

the change related to 16- and 17-year-old boosters can undermine trust and legitimacy, especially when there is uncertainty, as here, we really need the committee's input and transparency help. Second, the process points, I realize within the emergency meetings, there are things you cannot do. But although ACIP is likely uniquely able to recommend vaccines, your recommendations need to be explained and communicated to the public and the immunization community by organizations on the ground. These groups need to have an idea about what's coming. I realize it takes time, but it sounds like the VaST committee knew of this at least this December 6th, and the meeting slides were not up until noon Eastern Time today. It would be appropriate to put up information so businesses have to address this beforehand, as early as you can, and as early as you provide these community members, at least in some form, at least shortly. Because communication takes work as well. And I will add that although I do think you should generally consider moving to well-designed written comments instead of "oh, here was an emergency meeting." That's probably impractical, but we need to realize that when people are not afraid of commenting starting the morning of, the value of public comments would be limited. Finally, I appreciate your caution in recommending. I would like to encourage the committee to remember that there are groups for whom mRNA vaccines may be a higher risk than the risk of J&J, or as pointed out by members, that will not use mRNA vaccines. Your language in the slide we've seen before talks about "may be offered mRNA vaccines." I would urge the committee to consider moving to a "should be offered mRNA vaccine" where people who cannot safely take the mRNA vaccine should be offered the J&J vaccine, when people cannot safely take the mRNA vaccine or will not take them, to increase vaccination rates generally. Thank you very much for your time.

Ms. Shoshana Fishbein
Families Fighting Flu

Hello. My name is Shoshana Fishbein and I represent Families Fighting Flu. Thank you for your time today. I first want to thank ACIP for all their hard work during this pandemic and beyond for improving recommendations for adult and childhood vaccines. As you make this difficult decision today, Families Fight Flu, a national flu vaccination and education organization, reminds you of the importance of preventing COVID because we're entering a season where flu and COVID-19 are co-circulating. We need to be clear in our messaging that both vaccines are necessary to prevent overwhelming our healthcare system. We know that there are often concerns about side effects from vaccines, and we've heard many of these in the case of flu vaccination. However, in the context of today, we also need to keep in mind that vaccine equity is an issue and other countries look to the US for guidance on vaccines and donations, especially in the case of COVID-19. Viruses don't know geographic boundaries and the US is a leader in vaccination. The recommendations you make today for all vaccines and flu and COVID-19 do matter and we appreciate all of your hard work. Thank you.

Robert Edmonds, PhD
Concerned Individual

Dear committee, today I will again speak about tinnitus and the Johnson & Johnson or Janssen vaccine. COVID-19 vaccine, including Janssen vaccine, has saved many lives. Identification of low-frequency adverse events connected to vaccination are important, not always to discourage vaccination but to encourage patient education to seek timely care and for provider education to apply the appropriate treatment should these low-frequency events occur. We reviewed case studies of tinnitus following vaccination, which potentially suggests a small window of time for treatment of tinnitus after onset utilizing corticosteroids. After this limited window though, management is often the only remaining option available. Janssen at a prior meeting presented

the data that indicates from 3001 an imbalance that has a P value of 0.0096 combined imbalance from all Phase 3 trials of 24 versus 9 that has a P value of 0.007. The EMA recognizes this link after reviewing post-authorization reports. I have asked officials at the CDC and FDA whether they have reached out to the EMA and what made them conclude there is still not sufficient evidence that there is not a link after reviewing the EMA's analysis. I have not gotten a response. Many theories have been floated as to the causal mechanism in peer-review literature and potentially includes a version of micro clotting. No active follow-up is known to have occurred. So for now, these are just ideas that have been postulated. Follow-up is important because it may not just have implications just for Janssen potentially. AstraZeneca has an imbalance with tinnitus, albeit less statistically significant, and while Janssen reported an imbalance the trial data, to Janssen's credit, did capture a measure of the tinnitus background. Nine cases were observed in the nearly 37,000 combined placebo groups with Janssen data. Zero cases were observed within, again, the nearly 37,000 combined placebos of the mRNA's trials to the best of the public's knowledge, thus leading to the question, could the mRNA trials be sensitive to measuring a signal with tinnitus? I never imagined this time last year I would be speaking to a committee like this. I only bring this issue forward, again, this isn't a little ringing in all cases. After developing tinnitus myself and dealing with an amplitude that rang at months 24/7 above a truck radio while driving, this is a place I don't want others to find themselves in. People very often don't notice or care, and when they do, doctors often don't know what to do. Please follow-up with us. Please learn from us. Those with this adverse event include a prior ACIP member. Again, I agree that the public should get vaccinated against COVID. This is simply about providing information about what to do in these rare instances. Thank you for your time.

Ms. Claire Hannan, MPH
Executive Director
Association of Immunization Managers

Good afternoon. I'm Claire Hannan, Executive Director of the Association of Immunization Managers representing state, territorial, and urban area immunization program managers. Thank you to the advisory committee for convening this unscheduled meeting to provide guidance on the use of the Janssen COVID vaccine. It is critical that our nation's immunization experts meet regularly to review and monitor vaccine safety data and in a transparent and open forum. The J&J vaccine plays a unique role in the COVID vaccination response. Frequent populations for use are with individuals experiencing homelessness, residents in corrections facilities, and patients being discharged from hospitals. The 1-dose completion also provides an accessible option for those completing vaccination for travel or employment. Maintaining vaccine options, as well as providing transparent safety data and expert advice, are important to support confidence in vaccines. So, thank you for holding this transparent and open meeting. I also want to take this opportunity to acknowledge the 1-year anniversary of the launch of the COVID vaccine campaign and 486 million doses administered with over 200 million people fully vaccinated. This is absolutely incredible given where we were just one year ago. Sadly, more than 800,000 Americans have lost their life due to COVID, but a Commonwealth Fund analysis estimates that the COVID vaccination program in the United States has prevented over 1,087,000 deaths and over 10 million hospitalizations. Finally, I want to draw attention to a current challenge affecting COVID vaccine program management. COVID vaccine thresholds limit the amount of vaccine that awardees can order and have been put in place to manage inventory and reduce waste. Although vaccine supply is plentiful in the US, awardees are not able to order vaccine above their threshold amounts unless they submit a detailed justification. The threshold and resulting justifications cause delay and cancellation of provider orders and place a heavy burden on public health staff to justify vaccine need on a weekly basis. Share the

goal of reducing waste, but the thresholds and over estimation of inventory at the federal level are limiting operations and the ability to meet demand for vaccines. We look forward to continuing to work with the White House and HHS leadership and the Countermeasures Acceleration Group (CAG) and CDC to resolve this issue. Thank you for the opportunity to make comments today.

Dr. David Wiseman, PhD
Synechion, Inc.

The concluding comments at last meeting advocated for transparency and expression of diversity. I wrote a letter to you then and await the pleasure of your reply. I have submitted additional comments. Given the circumstances of this meeting, concerns about opacity are deepened, having only now seeing the presentations, in particular, Dr. Oliver's, which was only posted around the time she began. Again, I am simply shocked. I'm not a fan of any of the COVID vaccines, but my old employer and sometime client, I believe, is a vehicle here of regular misdirection. You're simply asking the wrong questions. A run analyses suggest a limited window of all-cause mortality benefit of these vaccines, outside of which, at both ends, there appears to be significant detriment. Although TTS is important, there are unexplained safety signals for all vaccines far stronger, including discoagulation, death, and myocardial infarction. We submitted this weeks ago to FDA and CDC at various meetings. According to the founder of BioNTech, the DNA-based vaccines may carry a risk of insertional mutagenesis. Also critical is that some key Pfizer and Janssen analyses have not been verified by FDA. That goes also for . . . [unclear]. How can you make any decisions based on that? In addition to reevaluating the use of all vaccines, you must consider estimates of VE reduction against Omicron to 30% to 48%, toxicity of cumulative dosing, and reduced benefit for greater risk. Attempting to boost our way out of new variants is the immunological equivalent of heroin addiction. What is the subclinical risk of TTS or other discoagulation? These drugs are not classical vaccines but gene therapy drugs. Are you concerned that CDC is not accurately representing the nature of these vaccines, depriving Americans of fully informed consent? Now to children. Additional concerns, other than the unverified data and the full risk-benefit analysis, which is off by 26 times in the wrong direction with at least a 4-time risk over benefit. Pfizer changed their formulation for everyone, and it differs from the one that was used in the clinical study. The change may improve stability and increase the effective dose worse than the safety profile. The change may also affect distribution of the lipid nanoparticles, thereby affecting safety and efficacy. Use of Pfizer's drug in children is akin to using a car seat with poor regulatory oversight. The eyes of the world are on you. Your decisions are being mirrored in other countries. Millions of subject mandates and other harsh measures, including imprisonment and loss of employment. The opacity here deepens mistrust within America and reverberates globally. Would ACIP want to be responsive for long-term detriments, as well as unjust imprisonment based on reliance of flawed data? So, in the spirit of transparency, I'm happy to take questions now or later. Thank you.

Vote: Updated Recommendations for Use of the Janssen COVID-19 Vaccine

Dr. Sara Oliver (CDC/NCIRD) presented the following proposed wording for an ACIP vote:

*“mRNA COVID-19 vaccines are **preferred** over the Janssen COVID-19 vaccine for the prevention of COVID-19 for all ≥ 18 years of age.”*

She reiterated that in the guidance that would accompany this recommendation clarifies that this includes vaccines administered as a part of the primary series and as a booster dose. Because there was a question about specifically saying “for persons with a contraindication to mRNA COVID-19 vaccines,” she clarified that the only firm contraindication is for those with a severe allergic reaction to a previous dose or a component of the mRNA vaccine. That is the contraindication listed in the FDA EUA. There also is some additional guidance around a precaution for those who had myocarditis after a first dose in terms of getting a second dose of an mRNA vaccine. That is all included on the clinical considerations website.

Discussion Summary

- Related to several concerns expressed about the word “preferred” not being strong enough and a request to use the term “strongly preferred,” Dr. Wharton acknowledged the strength of the ACIP’s desire for this to be a preferential recommendation, but reminded everyone that the ACIP does not make “strong” or “weak” recommendations. They make recommendations and this is the language that has been used in the past for preferential recommendations. The comments made during the discussions will be incorporated in CDC’s communications, guidance, and implementation strategies. However, the vote language must be consistent with other ACIP vote language.
 - Dr. Brooks pointed out that they may be under-estimating the strength of “preferred,” especially given how rare it is for ACIP to vote to prefer one vaccine over another.
 - Dr. Lee agreed and emphasized that every preferential vote that ACIP has made has had an impact on the way vaccines have been used.
 - Dr. Fink (FDA) added that the language being shown aligned with the language that was added to the Fact Sheet for vaccination providers in addition to the new contraindication language and new language about reported rates of TTS, which appears in the Warning Statement. The Warning Statement also was updated to be more specific about the clinical case definition for TTS and to further specify that available evidence supports a causal relationship between TTS and this vaccine. The Fact Sheet for vaccine recipients and caregivers was revised to include appropriate language for comprehension by the lay public, including information about reported rates of TTS and the fatality rates for TTS in the section about who should not get the vaccine. These documents are posted to the FDA website and are publicly available.
 - Some apprehension persisted among the ACIP members about not including stronger language within the vote itself, given that not everyone reads the clinical guidelines.

- Ms. McNally inquired as to the status of the Vaccine Injury Table for the Countermeasures Injury Compensation Program (CICP) and if not yet developed, she encouraged accelerating the development of that table due to the TTS and myocarditis issues.
 - Dr. Rubin from the Health Resources and Services Administration (HRSA) indicated that the CICP has not yet developed or published a countermeasures injury table for COVID-19 countermeasures. Pending establishment of a COVID-19 countermeasures injury table, claims are still filed as non-table injuries and eligibility of compensation is being determined on a case-by-case basis. She reminded everyone that other COVID-19 countermeasures outside of COVID 19 vaccine are covered. HRSA is discussing this internally and will take the suggestion into account.
- Regarding implementation of a preferential recommendation, Ms. McNally asked whether someone could address what strategies pharmacies would employ to deal with this. Dr. Lee indicated that they would seek a response to this inquiry and report it back later.

Motion/Vote: Updated Recommendations for Use of the Janssen COVID-19 Vaccine

Dr. Poehling made a motion to approve the proposed language for an ACIP vote on the updated recommendations for use of the Janssen COVID-19 vaccine stating that, “mRNA COVID-19 vaccines are preferred over the Janssen COVID-19 vaccine for the prevention of COVID-19 for all ≥18 years of age.” Dr. Bell seconded the motion. No COIs were declared, with the proviso that Dr. Chen did not believe his declaration of the potential perception of a COI due to his employer, the University of Maryland, receiving a grant from Emergent BioSolutions, Inc. for the development of a shigella vaccine posed an actual COI for this vote on the use of Janssen COVID-19 Vaccine. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Ault, Bahta, Bell, Brooks, Chen, Cineas, Daley, Kotton, Lee, Loehr, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A
0 Absent: N/A

Member Statements

Subsequent to the votes, Dr. Lee invited ACIP members to make a statement about the rationale for their votes and/or to share any additional general comments:

- Ms. Bahta observed that while the discussion regarding education materials and language in the EUA focused on providing a risk assessment of 1 per 100,000 doses administered, she thought the bigger issue was the consequence of this event. While there is a higher frequency of myocarditis with mRNA COVID-19 vaccines, the ACIP voted to prefer the mRNA vaccines over the Janssen vaccine. With that in mind, she stressed the importance of including the severity of the side effect that is a driving factor for this recommendation.

- Dr. Chen expressed appreciation for how hard their CDC colleagues had been working behind the scenes to provide much more precise estimates of the rates, determine the risks, et cetera. There were no real surprises to him. He thought they continued to grapple with the fact that TTS is a serious disease that has that 15% fatality rate, which sounds scary. Even though the numbers are small numbers, this is a rare event. He was happy that they wrangled over this preference, tackled it together, and came to a unanimous vote. He emphasized the importance of the clinical consideration section being crystal clear. He deals with the yellow fever (YF) vaccine on a daily basis in his travel clinic, which also has a serious but very rare AE that can be fatal. There is some nice language in the precaution section of the YF vaccine recommendations that communicates risk clearly, because there is no other alternative for YF vaccine. This language could serve as an example for communicating the highest risk for Janssen vaccine.
- Dr. Poehling thanked the VaST team, CDC team, FDA, and the many people behind them all who are working so hard to identify both the benefits and the risks of all of these vaccines. She believed this meeting demonstrated the benefit and the strength of all the work that is being done, and she appreciated coming together and sharing this discussion and recommendation openly and transparently. It was interesting that this occurred in the week that the US crossed the milestone of more than 800,000 people in the US having lost their lives to COVID-19. COVID-19 death is now vaccine-preventable in the vast majority of persons. She hoped that as people looked at the discussion from throughout the day, they would recognize the strength of the vaccine recommendation, the encouragement that all persons who are eligible for vaccines and boosters receive them, and that other precautions (e.g., masking, social distancing, hand sanitizing) continue to be used as the holidays approached and Omicron was coming.
- Dr. Daley reminded everybody that this recommendation was, in part, a reflection of the strength of the US's vaccine safety surveillance system. Safety surveillance continues daily and includes surveillance of all vaccine platforms and booster doses. He also expressed appreciation for the transparency of this process. These new data were immediately brought to the VaST WG. The VaST WG then immediately presented the data to the COVID-19 Vaccine WG, and the ACIP was convened quickly. He reiterated that these are interim recommendations that would be revisited if the circumstances change with respect to effectiveness, durability of the immune response, effectiveness against variants, and/or safety. While the ACIP makes vaccine recommendations for the US, there are global implications. There may be settings in which there may be just a single vaccine available. The best COVID-19 vaccine one can get is the one that is available immediately. In the global circumstance, if only the Janssen COVID-19 vaccine available—the benefits of vaccinating at that moment in time strongly outweigh the risks.
- Ms. McNally echoed the sentiments regarding the strength of the US safety monitoring system and the action based on the resulting data. However, monitoring is only one component. Communication to the public is an important element of this as well. The better the patient education around this issue and other issues, the more beneficial it will be in terms of vaccine confidence. Everyone must continue to be focused on this effort and the fact that this is a shared responsibility.

- Dr. Lee highlighted that the scientific deliberations on this topic were critical for the vote during this meeting, but some of the points that were brought to the forefront by various members were not just about the vote language in this instance. The underlying concern was one that they all shared with regard to the importance of how the risk information is communicated to the public. The committee members made a strong request that there be full transparency about the fact that the balance of benefits and risks, vaccine safety, access to vaccines, and equity drove the recommendation decision. There is a need for strong language around the importance of all of those aspects in how this information and decision are communicated to the public. This is shared responsibility. The ACIP's CDC colleagues will work hard to ensure that this is reflected in the clinical considerations. The provider community, public health community, public, and the media can help communicate the importance of this information. There continue to be gaps in equity and access to full information about COVID-19 vaccines. This recommendation highlights that gaps continue to exist.

COVID-19 Vaccine Safety Surveillance in Children 5-11 Years of Age

Dr. John Su (CDC/NCEZID) presented an update on COVID-19 vaccine safety surveillance data for children 5-11 years of age. First to review v-safeSM data. v-safeSM is a voluntary CDC smartphone based monitoring program. Participants receive a daily text message for the first weeks after vaccination, after which they receive text messages on a more periodic basis to find out whether they have experienced any health outcomes. As of December 12th, v-safeSM includes 41,232 participants 5-11 years of age. All of them have received Dose 1 and 23,583 have had Dose 2 of the Pfizer COVID-19 vaccine. For context, 7.1 million doses have been administered to children 5-11 years of age across the US. This population is roughly equal in male and female distribution and most are of white and non-Hispanic race and ethnicity.

Looking at reactions and health impact events reported by children 5-11 years of age at least once 0-7 days after Pfizer-BioNTech vaccine by dose as of Dec 12, 2021, there was generally a slightly greater proportion of participants reporting outcomes after Dose 2 relative to Dose 1. The outcome categories included any injection site reaction, any systemic reaction, any health impact, unable to perform daily activities, unable to attend schools, and needed medical care. Regardless of dose, very few (~1%) reported needing to seek medical care and most of those were for outpatient clinic visits. For participants reporting any systemic reaction during the week after vaccination by days since vaccination, most people reported systemic reactions within the first day or two after vaccination, but systemic reactions drop off considerably after that. Most of the systemic reactions reported tended to be transient in nature. The top 5 solicited reactions included pain, fever, fatigue, headache, and myalgia—all of which were observed during pre-authorization clinical trials. Fever was determined by temperature (mild = 38.0–38.4 C; moderate = 38.5–38.9 C; severe = 40.0+ C). A slightly greater proportion of participants reported these symptoms after Dose 2 relative to Dose 1. That said, the proportion within each dose reporting severity tended to be comparable between doses.

To briefly summarize, most reported reactions were mild to moderate in severity. Most were reported the day of vaccination, slightly more frequently after Dose 2, and transient in nature. For both Dose 1 and Dose 2, missing school was infrequently reported and around 1% reported seeking medical care—mostly outpatient in nature. The local and systemic reactions were reported at a similar frequency as per clinical trials. Some limitations of the v-safeSM data include that the v-safeSM population likely does not represent all of the vaccinated US population. It is a voluntary opt-in program, so this is a selected population that might have some reporting bias.

In addition, data describing the second dose of Pfizer's vaccine is limited at this time. Updates can be provided in the future as the data mature.

Now to review some data from VAERS. As a reminder, VAERS is the nation's passive early warning system for vaccine safety. As of December 10th, there were 3,233 reports to VAERS among children 5-11 years of age after COVID-19 vaccination. That is in the context of 7.1 million doses administered, of which 5.1 million doses were Dose 1 and 2 million were Dose 2. The median age was 9 years, with a roughly even distribution between males and females. The counts of reports tend to increase by age. Within age, the distribution by sex is comparable. Most reported children were non-Hispanic white or race/ethnicity data were unknown or not reported. The median time from COVID-19 vaccination to symptom onset in children 5-11 years of age was the day of or the day after vaccination. The most frequent AEs among 3,152 (97%) non-serious reports were either a vaccination error of some sort or symptoms that were observed during pre-authorization clinical trials, including fever, headache, and fatigue. When a vaccine error was reported, frequently the reports specified that no AEs occurred as a result of that error. That would explain why no AE is reported very frequently either. The most frequently reported AE among the 81 serious reports included fever, vomiting, and chest pain. "Serious" means fulfilling federal criteria such as hospitalization, prolongation of existing hospitalization, et cetera. Many of the 81 serious reports reflected potential myocarditis, such as elevated troponin or chest pain. Some might reflect potential multisystem inflammatory syndrome (MIS), such as fever or C-reactive protein increase.

There were 2 reported deaths, both of which are still under review. Both involved children with complicated medical histories and frail health. One female was 5 years of age who had a history of twin-to-twin transfusions, spastic cerebral palsy, seizure disorder, and continuous positive air pressure (CPAP) at night. She was admitted to the pediatric intensive care unit (PICU) because of respiratory failure due to infection with rhinovirus and *mycoplasma*. To stabilize and transfer her to the floor and because of her history, she was observed overnight after vaccination and was found to have an uneventful evening. She was discharged home and the night prior to death she was at her baseline state of health, but the following morning was found pulseless and not breathing. Unfortunately, they were unable to resuscitate her. The second child was a female 6 years of age who suffered a near drowning incident that led to severe hypoxic encephalopathy, spastic cerebral palsy, dysautonomia, neurogenic bladder, and frequent urinary tract infections (UTIs). The extent of the dysautonomia was such that the pain from a distended bladder would be enough to affect her vital signs. Though she was vaccinated without issue, 10 days afterwards she developed fever and lactic acidosis, progressive weakness, flaccid paralysis, and loss of her gag reflex. Notably, those particular functions remained preserved with past stressors. This was new for her, and unfortunately she continued to decompensate. She ultimately experienced respiratory failure, hypotension, and died. The autopsy was unrevealing.

There were 10 reports to VAERS of myocarditis in the context of 7.1 million doses administered. Of the 3,233 reports, 14 were of myocarditis. Of those, 5 are pending follow-up information. Follow-up information was obtained on the other 9, with 8 meeting the CDC working case definition for myocarditis and 1 still under review. Of the 8 reports that met the case definition, 4 were male, 4 were female, 6 were after Dose 2, and 2 were after Dose 1. Based on the data obtained on the 8 confirmed cases that met the case definition, the clinical picture looks very much like the presentations seen in older children. There are outcomes for 6 of these 8 children. For 5 of the 6, the patient's symptoms were resolved at the time of the report. The 6th was recovering at the time of the report, but that was a couple of months ago. It seems that for many

of these, the symptoms were mild. Notably, 1 of these children had a fairly long onset. The onset range is from 0-4, but was almost 2 weeks for one patient. This patient had a headache and gastrointestinal symptoms 3-4 days before presenting with chest pain, which actually represents viral myocarditis.

Now to review some data from the VSD. As a reminder, the VSD is a collaboration of 9 integrated healthcare organizations across the US that share data (e.g., immunization records, outpatient visits, vital statistics, and other data) on over 12 million persons per year all linked by study identifications (IDs). This provides an easy means of identifying people with potential AEs of interest who can then be followed up by chart review or electronic health record (EHR) review to get a good idea of what happened to identified people. Because of that robust organization, the VSD is able to perform near real-time monitoring as data become available. Myocarditis is one of the numerous conditions that the VSD is actively monitoring. As of December 14th, there were 333,000 doses of COVID-19 vaccine administered to children 5-11 years of age. Of those, 226,000 were of Dose 1 and 107,000 were of Dose 2. There were no confirmed reports with myocarditis in either the 0-7 or 7-21-day risk windows. Data are being monitored as they evolve.

To summarize, during November 2-December 10, 2021 VAERS received 3,233 reports among children 5-11 years of age. Over 7.1 million doses of the vaccine had been administered as of December 9th. The median age was 9 years, most children were of non-Hispanic white race and ethnicity. The median time to onset was the day of vaccination. While the majority (97%) of the reports were non-serious, there were 2 reports of death in children with complicated medical histories. There were 8 reports meeting the case definition for myocarditis, but the clinical course appeared mild. The most common AEs were vaccination errors or symptoms observed in pre-authorization clinical trials. Between v-safeSM and VAERS, the reported race and ethnicity was comparable. For v-safeSM, reactions following Dose 2 were slightly more frequent. Most reactions were mild to moderate in severity and transient in nature. Regardless of dose, no more than 10% of children reported missing school and few (~1%) reported seeking medical care. There have been no reports of myocarditis in the 0-7 or 0-21-day risk windows in VSD to date.

Discussion Summary

- Dr. Daly emphasized that it was good to see these early data for this age group. He observed that the 2 cases mentioned in which individuals died following vaccination would be investigated carefully by VAERS. As a pediatrician, he stressed that these were children with special health care needs who were medically fragile and at greatly increased risk of respiratory disease. If such children get a respiratory disease, it is often severe and puts them at significantly increased risk of severe outcomes if they develop COVID-19. While people may be concerned by these reports, he reiterated that these children were medically fragile at baseline and were likely to have increased risk from COVID-19 as well.

Update on the COVID-19 Omicron Variant

Dr. Heather Scobie (CDC/NCIRD) provided an update on the COVID-19 Omicron variant. A new variant of SARS-CoV-2 (B.1.1.529) was reported to the WHO on November 24, 2021. This new variant was first detected in specimens collected on November 11, 2021 in Botswana and November 14, 2021 in South Africa. B.1.1.529 was classified as a variant of concern (VOC) named Omicron by WHO on November 26, 2021 and by the US SARS-CoV-2 Interagency Group (SIG) on November 30, 2021. On December 1, 2021, the first case of Omicron was confirmed in the US.

Omicron was classified as a VOC based on its detection in multiple countries, including in people with no travel history; its potential increased transmissibility; and the presence of a large number of mutations in the spike gene (S-gene), including 15 mutations in the receptor binding domain. These mutations may lead to reduction in the efficacy of some antibody treatment and a reduction in neutralization by sera from vaccinated or convalescent individuals. In terms of what is currently known about Omicron, it is likely to be more transmissible than the original SARS-CoV-2. It is likely that vaccinated people with breakthrough infection or people without symptoms can spread the virus to others. However, more data are needed to know if Omicron causes more severe disease or death than infection with other known variants. Vaccines are expected to protect against severe illness, hospitalization, and death. However, breakthrough infections in people who are fully vaccinated are expected to occur. Scientists are still working to determine how well existing treatments for COVID-19 work, but some treatments are likely to be less effective.²⁹

In the United Kingdom (UK), Omicron cases are growing rapidly despite Delta. The Delta variant and one of its sub-lineages, AY.4.2, had higher growth rates than other variants. This resulted in Delta's success in dominating the viral landscape. Omicron has an even steeper slope than Delta. With its calculated growth rate of 0.35 per day, or an inferred doubling time of every 2 days, Omicron is predicted to surpass Delta by mid-December in the UK.³⁰ South Africa has documented Omicron spread, with a doubling time of every 3.4 days in a province with high population immunity. The country has also shown an increased risk of reinfection associated with Omicron. Norway documented a large Christmas party outbreak, with an attack rate of over 70% where most of the people infected were vaccinated with two mRNA doses. There were no hospitalizations associated with the outbreak.³¹

As of December 15th, 37 US jurisdictions had reported an Omicron case.³² Details of early Omicron cases were recently reported in the *MMWR* by CDC co-authors. As of December 8th, 43 cases with full case details have been identified in 22 states in the US, 33% of which have an international travel history. Others had exposure to domestic travel, large public events, and household transmission. Of the cases, 79% were fully vaccinated. Overall, 32% had a booster dose, but a portion of these had recently received their additional dose within 14 days before symptom onset. A limitation of initial Omicron case descriptions is that people with recent international travel or participation in large public events might be more likely to be vaccinated. Finally, 14% of cases were previously infected.³³

As part of the response to Omicron, CDC is monitoring genomic surveillance and vaccine breakthrough. CDC works with partners on scientific experiments to answer important questions about the Omicron variant and also monitors vaccine administration and VE. CDC continues to support state, local, tribal, and territorial health departments in their responses. CDC also

²⁹ <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html>; <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html>

³⁰ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040076/Technical_Briefing_31.pdf

³¹ Grabowski et al. <https://www.medrxiv.org/content/10.1101/2021.12.08.21267494v1>; Pulliam et al. <https://www.medrxiv.org/content/10.1101/2021.11.11.21266068v2>; NIPH. <https://www.fhi.no/en/news/2021/preliminary-findings-from-outbreak-investigation-after-christmas-party-in-o/>

³² <https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html>

³³ MMWR: SARS-CoV-2 Omicron Variant —United States, December 1–8, 2021 https://www.cdc.gov/mmwr/volumes/70/wr/mm7050e1.htm?s_cid=mm7050e1_w

continues to update recommendations related to travel, prevention strategies, and holiday activities based on the most recent evidence.³⁴

There is a multifaceted genomic surveillance system for analyzing SARS-CoV-2 variants circulating in the US. This includes the national SARS-CoV-2 strain surveillance, CDC-supported contracts with several commercial diagnostic laboratories, and sequences that partners randomly sampled, deposited, and tagged in public repositories (e.g., GISAID and NCBI). CDC estimates that if a variant is circulating at 0.1% frequency, there is a greater than 99% chance that it will be detected in the national genomic surveillance. To further increase the surveillance sensitivity, enhanced genomic surveillance for S-gene target failure (SGTF) was conducted during November 28-December 10, 2021. This consisted of rapid sequencing for SGTF by PCR-based-type diagnostic tests, which were then referred for further confirmation by genomic sequencing. This approach was successful at identifying many of the early Omicron cases. Voluntary airport-based genomic surveillance programs were expanded in Atlanta, New York City, Newark, and San Francisco.³⁵

Based on the latest national Nowcast productions of the proportions of leading SARS-CoV-2 variants from CDC's COVID Data Tracker, the Delta VOC has maintained its dominance at 98% to 99% since August and over 50% since late June. Omicron was first detected and specimens collected during the week ending November 27th, resulting in less than 0.1% proportion during that week. Nowcast projections for Omicron increased to 0.4% for the week ending December 4th and 2.9% for the week ending December 11th. Delta is now at 96.7%. Only three weeks after Omicron was first reported to the WHO, preliminary results have been posted from 15 laboratory neutralization studies with vaccinee sera using both pseudoviruses and live viruses. All studies show large reductions in neutralization of Omicron viruses of 15- to 127-fold compared with wild-type viruses. One study showed an 11-fold reduction compared with Delta, which is known to be further reduced compared to wild-type.

The actual reduction may be underestimated because Omicron neutralization was below the limit of assay detection for most individuals who received 2 doses of mRNA or 1 dose of the Janssen vaccine. These values had to be imputed or ignored to calculate a full deduction. The impact of the Omicron variant on neutralization with vaccinee serum is greater than previously reported with any other variant, including the Beta variant that had previously the had the greatest observed impact. In more positive news, neutralization of Omicron was above the limit of detection in many vaccinated people who had either received a booster dose or vaccinated people that had been previously infected. Given the limits of detection in these types of assays, it is difficult to evaluate whether people have the minimal levels of antibodies thought to be needed to protect against severe disease. T-cell response also appears to be largely preserved against Omicron, with the exception of a few HLA types.

Within the last few days, preliminary results posted from South Africa have observed 70% protection for Pfizer vaccine against COVID-19 hospitalization and 33% protection against infection during the current Omicron wave. This is reduced compared with the Delta variant which had 93% protection against hospitalization and 80% protection against infection. Booster vaccination was not evaluated in this study. The authors also noted that the risk

³⁴ <https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html>; <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html>

³⁵ https://www.cdc.gov/mmwr/volumes/70/wr/mm7050e1.htm?s_cid=mm7050e1_w; <https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html>

of hospital admissions among [inaudible] COVID-19 was 29% lower for the Omicron variant compared with the ancestral lineage after adjusting for vaccination status.³⁶ A study by Andrews et al looking at Pfizer VE against infections with Delta and Omicron versus time since vaccination for 2 and 3 vaccine doses in the UK, study investigators observed decreased protection against Omicron with increasing times since receipt of the second dose at 35% VE against infection observed for Omicron versus 64% for Delta at 25-plus weeks. Two weeks after the Pfizer booster dose, VE against hospitalization increased to 76% against Omicron compared with 73% for Delta.³⁷

The prevention strategies to slow the spread of the Omicron variant in the US include vaccination, which is recommended for everyone 5 years of age and older; and booster doses, which are recommended for all persons 18 years of age and older. Other prevention strategies include increased use of masking, improved ventilation, wider and more frequent testing (including self-testing), and adherence to guidance on quarantine and isolation.³⁸ Vaccine manufacturers are conducting booster studies of current vaccines and second generation vaccines against the Omicron variant. Moderna is testing a higher dosage of their existing vaccine against the Omicron variant. They are also evaluating 2 multivalent vaccines for the Beta and Delta variants against Omicron and developing an Omicron-specific vaccine. Pfizer is evaluating Alpha, Beta, and Delta boosters against Omicron, as well as developing an Omicron-specific vaccine. No Omicron-specific booster vaccine study results have been shared to date.³⁹

In summary, the currently authorized vaccines work against known variants. Given the increased risks related to the Delta and Omicron variants, it is important to increase uptake of primary vaccination in booster doses in all eligible populations. CDC is closely monitoring real-world VE and breakthrough infections using multiple methods, populations, and outcomes. CDC continues to monitor emerging variants including their prevalence and impact on disease incidence, severity, and vaccine breakthrough. The ACIP will continue to review evidence submitted for boosters in any next-generation vaccines to address evidence of diminished VE related to variants or waning immunity. This is a changing landscape and CDC will communicate promptly about emerging evidence.

Discussion Summary

- Dr. Fryhofer asked whether there were any specifics on how the Moderna and Janssen COVID-19 vaccines were reacting against Omicron, and whether she had any details about the NIH study mentioned in the news.
 - Dr. Scobie emphasized that it is still very early. A nice study was completed by Moderna using a neutralization assay, which showed that the booster doses appear to protect well or at least was less defective against Omicron. VE data are still needed for the other authorized US vaccines. They planned to meet with the NIH the next day and would have more details to provide to the ACIP in the future.

³⁶ [covery-holdings-ltd.mynewsdesk.com/pressreleases/discovery-health-south-africas-largest-private-health-insurance-administrator-releases-at-scale-real-world-analysis-of-omicron-outbreak-based-dot-dot-dot-3150697.pdf](https://www.coverly-holdings-ltd.mynewsdesk.com/pressreleases/discovery-health-south-africas-largest-private-health-insurance-administrator-releases-at-scale-real-world-analysis-of-omicron-outbreak-based-dot-dot-dot-3150697.pdf)

³⁷ Andrews et al. <https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+variant+of+concern.pdf/f423c9f4-91cb-0274-c8c5-70e8fad50074>

³⁸ https://www.cdc.gov/mmwr/volumes/70/wr/mm7050e1.htm?s_cid=mm7050e1_w_15

³⁹ <https://investors.modernatx.com/news/news-details/2021/Moderna-Announces-Strategy-to-Address-Omicron-B.1.1.529-SARS-CoV-2-Variant/default.aspx>; Pfizer investor brief: <https://investors.biontech.de/static-files/47b4131a-0545-4a0b-a353-49b3a1d01789>

- Given the need for boosters for better protection against Omicron, Dr. Kotton wondered whether ACIP might need to make a recommendation for boosters for immunocompromised persons sooner than 6 months after their third dose of mRNA vaccine.
 - Dr. Scobie replied that she had not assessed this question in terms of how neutralization studies would evaluate specific populations, and did not know whether the early studies had looked into this.
 - Dr. Oliver added that the ACIP would be updated as additional information becomes available.
 - Dr. Drees stressed that answering whether a booster is needed earlier for the general population due to Omicron also should be considered.
 - Dr. Scobie encouraged the ACIP to think about earlier booster doses based on what was being seen with the Omicron variant. Neutralization is not very good after 2 doses and is better with boosters, especially for vulnerable immunocompromised patients who may be much more vulnerable to Omicron in the next few months and represent approximately 3% of the US population.
- Dr. Maldonado noted that reports were being made by large health centers in South Africa, for example, that children are less likely to have transmission of Omicron but are more likely to be hospitalized if they are infected with it. In addition, it was not clear whether mention that there was a 50% increased risk of hospitalization with infection regarded incidental infection or was separate from incidental infections in children being hospitalized for other reasons. She wondered if anyone had information about the health system study conducted on this.
 - Dr. Scobie replied that this study was referenced in her slides, there is a booklet about it, and she heard that these data were to be published the previous day in the *New England Journal of Medicine (NEJM)*.⁴⁰ While she had not yet seen the publication, the presentations she had seen cited a 20% increased risk in younger children. Given that there were no 95% confidence intervals, she was hesitant to talk about the 20% during this presentation. Once the publication is released, they can review the details and clarify the information regarding severity in children.
- Dr. Gluckman wondered whether there were any clinical trials with a third dose being given shortly after the second dose within 1 to 2 months or at some interval other than 6 months to address this issue of when a third dose may be needed. He pointed out that while there should be information within 3 to 4 months about the effectiveness of an Omicron booster, they need to be prepared for the fact that people who have a third dose may have waning immunity to Omicron as time goes on and might need another booster at some point before a year.
 - Dr. Oliver indicated that while they were not aware of any specific manufacturer-conducted clinical trials to evaluate this, they could follow global real-world VE data and would be happy to review and bring to ACIP what is available.

⁴⁰ Preliminary results for Omicron from South Africa: <https://discovery-holdings-ltd.mynewsdesk.com/pressreleases/discovery-health-south-africas-largest-private-health-insurance-administrator-releases-at-scale-real-world-analysis-of-omicron-outbreak-based-dot-dot-dot-3150697.pdf>

- Dr. Fink reported that a couple of clinical trials already have been conducted to assess booster dose intervals shorter than 6 months for mRNA vaccines, which have been published. One is the NIH mix-and-match trial and the second is the trial conducted in the UK. Those trials evaluated the safety and immunogenicity of a booster dose and included intervals shorter than 6 months, but they do not speak to the need for a booster dose at those decreased intervals.

CLOSING REMARKS

Dr. Grace Lee (ACIP Chair) took a moment to express her sincere gratitude to her ACIP and CDC colleagues for their time, knowledge, and commitment to struggling mightily through these issues as individuals and as a group. Many of them have not had a break since the pandemic started. Though perhaps they originally thought the pandemic was going to be a sprint, it has turned out to be a marathon. While it seemed like a year later things would get easier for the ACIP, the pandemic continues and the deliberations are getting harder and more complex. On behalf of herself and Dr. Wharton, she expressed gratitude and hope that the ACIP members, CDC team members, federal partners, and liaisons all would have an opportunity to rest and recharge during the holiday season. With that, she said she was calling this the last meeting of 2021.

CERTIFICATION

Upon reviewing the foregoing version of the December 16, 2021 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN THIS DOCUMENT

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
AE	Adverse Event
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
ASTHO	Association of State and Territorial Health Officers
AZ	AstraZeneca
CAG	Countermeasures Acceleration Group
CDC	Centers for Disease Control and Prevention
CICP	Countermeasures Injury Compensation Program
CISA Project	Clinical Immunization Safety Assessment Project
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
COVID-NET	COVID-19-Associated Hospitalization Surveillance Network
CPAP	Continuous Positive Air Pressure
CSTE	Council of State and Territorial Epidemiologists
CVST	Cerebral Venous Sinus Thrombosis
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
ED	Emergency Department
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers

GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HCW	Health Care Workers
HHS	(Department of) Health and Human Services
HRSA	Health Resources and Services Administration
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information Systems
IM	Intramuscular
ISD	Immunization Services Division
ISO	Immunization Safety Office
IVY Network	Influenza and Other Viruses in the Acutely Ill Network
LTCF	Long-Term Care Facilities
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MI	Myocardial Infarction
MIS	Multisystem Inflammatory Syndrome
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
<i>NEJM</i>	<i>New England Journal of Medicine</i>
NFID	National Foundation for Infectious Diseases
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NMA	National Medical Association
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency Canada
PICO	Population, Intervention, Comparison, Outcomes
PICU	Pediatric Intensive Care Unit
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RN	Registered Nurse
RNA	Ribonucleic Acid
ROA	Route of Administration
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine

SDOH	Social Determinants of Health
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
URI	Upper Respiratory Infection
US	United States
USG	United States Government
UTI	Urinary Tract Infections
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST WG	Vaccine Safety Technical Work Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VOC	Variant of Concern
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group
WHO	World Health Organization