MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JULY 22, 2021
SUMMARY MINUTES

TABLE OF CONTENTS

MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on July 22, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on Guillain-Barré Syndrome (GBS) after Janssen COVID-19 vaccine and review of the data and considerations for additional COVID-19 vaccine doses in immunocompromised persons.

THURSDAY: JULY 22, 2021

WELCOME AND INTRODUCTIONS

Dr. José R. Romero (ACIP Chair) called to order and presided over the meeting. He welcomed everyone and thanked them for their attendance and the time they are dedicating to the COVID-19 effort.

Dr. Amanda Cohn (ACIP Executive Secretary) indicated that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session at approximately 1:15 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-2021-0070. 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 conflict of interest (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 stated COIs at the beginning of the meeting. No votes were taken during this emergency meeting.

ACIP is accepting applications and nominations for new members to fill upcoming vacancies. Applications should be submitted by August 1, 2021 for the 4-year term beginning July 1, 2022. The application and additional information can be found on the ACIP website at https://www.cdc.gov/vaccines/acip/apply-for-membership/index.html.

Dr. Romero (ACIP Chair) conducted a roll call, during which one COI was declared by voting member Dr. Sharon Frey, who is the Site Principal Investigator (PI) at St. Louis University for the Moderna and Janssen SARS-CoV-2 vaccine trials in adults. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Introduction

Dr. Matthew Daley (ACIP, WG Chair) introduced the COVID-19 Vaccines WG session, first providing a COVID-19 pandemic update. After a heavy caseload in the winter, there has been a sharp decline with a nadir in early June. However, cases have been rising in the last number of weeks. The current rise has been in parallel with and likely a consequence of the Delta variant. As of July 21, 2021, 339 million vaccine doses have been administered in the United States (US) and more than 161 million individuals in the US are fully vaccinated. This equates to 57% of the population 12 years of age and older.[1]

To place the discussion in some context, Dr. Daley provide an overview of COVID-19 vaccine safety monitoring in the US. It is important to state that COVID-19 vaccines have been monitored under the most intensive vaccine safety monitoring program ever in US history, with ongoing surveillance monitoring through multiple systems from 6 federal agencies. These monitoring systems have demonstrated that hundreds of millions of people in the US have safely received COVID-19 vaccines. As a vaccine researcher, Dr. Daley said it gave him great reassurance to know that this monitoring is ongoing on a daily basis and that this is independent and across multiple federal agencies.[2] Two of these systems are the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

VAERS is the nation's early warning system for vaccine safety, which is jointly managed by the CDC and the Food and Drug Administration (FDA). VAERS accepts all reports from everyone regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event. VAERS has a number of key strengths. It is able to detect potential safety problems rapidly, has the ability to detect rare adverse events (AEs) that cannot be detected in clinical trials, and is national in scope. However, it is also important to highlight some of the key limitations of VAERS. At times, the information reported to VAERS is incomplete or clinically inconsistent. VAERS is also subject to reporting bias, overreporting and underreporting, generally cannot determine cause and effect. However, it can generate signals that are then investigated in other systems.

The VSD is comprised of 9 participating and integrated health care organizations that contribute data on over 12 million persons per year. The VSD is an active surveillance system in that it does not rely on spontaneous reporting from individuals, which is an important distinction. The VSD has rich and detailed clinical data on these 12 million individuals. This includes detailed immunization records, outpatient emergency department (ED) and hospital data, procedure codes, and birth and death certificates. The VSD is able to manually review electronic health records (EHRs), which can be particularly useful in determining whether a case is a true case and that symptoms in fact started after vaccination. The VSD has rich clinical data and can rapidly perform manual review of EHRs when necessary.[3]

[1] https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases; https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total
[2] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/reporting-systems.html
[3] https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html

It is a reflection of this intense vaccine safety monitoring that several rare serious adverse events (SAEs) have been detected following COVID-19 vaccination, such as thrombosis with thrombocytopenia syndrome (TTS) after Janssen COVID-19 vaccine. On April 23, 2021 the ACIP met to review the data and reevaluate benefit/risk in the context of these new data. Additionally, myocarditis had been detected following mRNA COVID-19 vaccines.[4] Consequently, the ACIP met on June 23, 2021, to review the safety data and reevaluate benefit/risk in light of this new data.[5] Reports of GBS following Janssen COVID-19 vaccine prompted the July 22, 2021 meeting to review and reevaluate the benefit/risk in the context of the reports.[6]

To provide some additional context for the day's conversation, GBS is a rare neurologic disorder in which the immune system damages nerves and myelin sheaths around nerves. This causes muscle weakness and can cause paralysis. An estimated 3,000 to 6,000 cases of GBS are reported annually in the US. Typically, these follow several different types of infectious illnesses that are typically triggered by gastrointestinal (GI) and respiratory infection. While most people fully recover from GBS, the recovery period is long and difficult. It is important to note that some people have permanent nerve damage from GBS. The risk for GBS in the US is highest in males and persons over 50 years of age.

GBS has been reported at a higher rate in the 42 days following Janssen COVID-19 vaccination. Due to this, a warning was added to the FDA Emergency Use Authorization (EUA) fact sheets.[7] The warning reads, "Reports of adverse events following use of Janssen COVID-19 vaccine under Emergency Use Authorization suggest an increased risk of Guillain-Barré Syndrome in the 42 days following vaccination. GBS has not been reported following mRNA vaccines."

GBS has been reported following other vaccines. It was reported following the 1976 swine influenza vaccine at an approximate rate of 10 GBS cases per 1 million vaccine doses administered. There have been mixed findings in subsequent influenza seasons, but the magnitude of any potential increased risk appears to be much less than the risk GBS from natural influenza infection. In addition, GBS cases have been reported following the Shingrix zoster vaccine. A causal relationship has not been established, but a warning was added to the package insert due to the approximately 3 to 6 excess cases of GBS per million doses administered in persons 65 years of age and older in the 6 weeks following Shingrix vaccination. No increased risk of GBS has been observed for other vaccines.[8] While over 30 other pre-specified outcomes are being monitored through this intensive vaccine safety surveillance, no other safety signals have been detected.

To highlight how the ACIP responds to reports of AEs following vaccination, the Vaccine Safety Technical Subcommittee (VaST) reviews data from all of the US government vaccine safety surveillance systems and other sources. In addition to comprehensive detailed review by VaST, the COVID-19 Vaccines Work Group (WG) also reviews these data and then puts them into the context of the benefit/risk balance. Following review by VaST and the COVID-19 Vaccines WG, these data are presented in a public ACIP meeting during which the data and benefit/risk assessment are presented to ACIP for review, discussion, and consideration of

[4] https://www.cdc.gov/mmwr/volumes/70/wr/mm7017e4.htm
[5] https://www.cdc.gov/mmwr/volumes/70/wr/mm7017e4.htm
[6] https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm
[7] https://www.fda.gov/media/146305/download; https://www.fda.gov/media/146304/download
[8] DeStefano, F, et al. Clinical Infectious Diseases 69.4 (2019): 726-731; https://www.fda.gov/media/108597/download; Baxter, R, et al. Clinical infectious diseases 57.2 (2013): 197-204

recommendations for use of COVID-19 vaccines. The COVID-19 Vaccines WG meets weekly. Since the June 2021 ACIP meeting, the WG has reviewed the GBS cases after Janssen COVID-19 vaccination, engaged in detailed discussions regarding the benefit/risk balance in light of this new information, and reviewed data and considerations for additional COVID-19 vaccine doses in immunocompromised persons.

As has been stated for many months, immunocompromised people and their close contacts should be vaccinated against COVID-19. While it is important to note that reduced immune responses to vaccination have been observed in some immunocompromised people, serologic testing to assess immune response to vaccination is not recommended for anyone, including for immunocompromised people. It is also important to note that immunocompromised people should be counseled to continue a number of current prevention measures in addition to vaccination. These include wearing a mask, keeping socially distanced, and avoiding crowds. Clinical guidance for additional COVID-19 vaccine doses will be updated pending regulatory allowance from the FDA.[9]

GBS after Janssen COVID-19 Vaccine: VAERS

Dr. Meghna Alimchandani (FDA) provided an overview of GBS after Janssen COVID-19 Vaccine in VAERS. She emphasized that one of the key strengths of VAERS is that it can rapidly detect potential safety issues, including new or rare AEs. Some major limitations of a spontaneous AE reporting system are that some reports have missing or inaccurate data and the reported diagnoses are not verified.

Two methods are used to identify preliminary reports of GBS after Janssen COVID-19 vaccine in VAERS. FDA medical officers review incoming serious reports daily and/or automated queries on the VAERS database using the following Medical Dictionary for Regulatory Activities (MedDRA) coded preferred terms (PT): acute polyneuropathy, autoimmune polyneuropathy, axonal and demyelinating polyneuropathy, demyelinating polyneuropathy, Guillain Barré syndrome, Miller Fisher syndrome. A key limitation of the analysis presented during this session was that the cases had not been adjudicated to determine whether they met the Brighton collaboration case definition for GBS. The diagnosis of GBS is based on clinical features, cerebrospinal fluid (CSF) testing, and nerve conduction studies. It is important to keep in mind that because of the limited availability of medical records, identified cases were not assessed according to the Brighton criteria.

As of June 30th, 100 reports were identified of GBS after the Janssen COVID-19 vaccine in VAERS. Of those, 95% were serious and involved hospitalization, 61% were males, 38% were females, and 1 patient died. The median age was 57 years, with 83% occurring in patients less than 55 years of age. The median time to onset was 13 days. For this assessment, 21-day and 42-day risk windows were used. The majority (98%) of the cases occurred in the 42-day risk window. Two cases were not included in the 42-day risk window given that 1 occurred outside of the 42 days and 1 did not specify time to onset. When the 21-day risk period was applied, 84% of cases were found to have occurred in that window. As a reminder, there were no medical records for the majority of these cases and very limited follow-up information was available at the time of the analysis. However, work is ongoing to collection additional information.

[9] https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

To further characterize selected cases among the 95 (95%) patients who were hospitalized, 10 patients were intubated and/or required mechanical ventilation. The 1 death occurred in a 57 year old man with a past medical history of heart failure, stroke, hypertension, and diabetes. He developed pain and weakness 5 days post-vaccination. It was reported that he went to the hospital in an ambulance. Diazepam was prescribed and he was sent home. Several days later, he developed extreme weakness and pain and returned to the hospital. He was hospitalized for 11 days, including 6 days on a ventilator, and he completed a course of intravenous immunoglobulin. He died 25 days after vaccination. There were 24 reports that described bilateral facial paresis. Notably, there have been case reports in the literature of bilateral facial paresis occurring in the context of GBS reported after the AstraZeneca (AZ) COVID-19 vaccine. Also identified in VAERS were 12 reports of unilateral Bell's Palsy and 6 reports mentioned recent illness (e.g., generalized rash, upper respiratory infection, or flu-like symptoms) 1-2 weeks before GBS. No reports listed concomitant vaccines.

In the observed-to-expected (O/E) analysis of the 100 reports in the 42-day risk window, broad age bands were used of 18-29 years, 30-39 years, 40-49 years, 50-64 years, and 65 years and older. As noted earlier, 98 cases occurred in the 42-day risk window, which is why that risk window assumption was used in this analysis. The number of vaccine doses administered was provided by the CDC. The background rate was adjusted for increased incidence of GBS with increasing age based on a systematic review and meta-analysis by Sejvar et al focused on population incidence of GBS.[10] Striking in the O/E analysis is that the number of observed cases exceeded the number of expected cases across age groups. These calculations were repeated using different background rates and using the 21-day risk window. Those additional calculations are provided on the back-up slide 18. While the rate ratio was elevated across age group in the O/E analysis assuming a 42-day risk window, it was highest in the younger age groups under 65 years. An additional O/E analysis was performed that further stratified the age groups under 65 years. The rate ratio was highest at around 7 for persons 40-49 year of age and 50-64 years of age.

As Dr. Daley pointed out earlier, the EUA fact sheets were updated on July 12th, with a new subsection added under Warnings and Precautions in the EUA fact sheet for healthcare providers (HCP) stating, "Reports of adverse events following use of the Janssen COVID-19 vaccine under emergency use authorization suggest an increased risk of Guillain-Barré syndrome during the 42 days following vaccination." The EUA fact sheet for recipients and caregivers also was updated.

In a crude comparison of VAERS GBS reporting rates for mRNA vaccines per million doses administered, the Janssen reporting rate was elevated and slightly different from the mRNA vaccines. There are many limitations to this analysis. First, it looked at doses administered. While there is a 2-dose series for the mRNA vaccines, this analysis looked at cumulative totals rather than by dose. The number of the case counts of the VAERS reports for the mRNA vaccines may include duplicate reports, these reports were not manually reviewed, and the results are from the automated queries using code encoded PTs. Additional analyses were not performed for Moderna or Pfizer and BioNTech because the reporting rate was so low. The number of cases were few and within the expected background rate for the mRNA vaccines.

10 Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33.

The AZ COVID-19 vaccine is not licensed or authorized in the US. It uses the chimpanzee adenoviral vector platform. The FDA and CDC are in close communication with colleagues in European Medicines Agency (EMA) in terms of safety updates for the AZ COVID-19 vaccine. As of the end of June, a total of 227 cases of GBS had been reported to EudraVigilance for the AZ COVID-19 vaccine. These cases were reviewed by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) earlier in July. The PRAC recommended an update to the product information for the AZ vaccine to include a warning for GBS following vaccination with the AZ COVID-19 vaccine.

In summary, 100 preliminary reports of GBS after Janssen COVID-19 vaccine were identified in VAERS as of June 30, 2021. Analyses identified that observed reports were greater than expected across multiple age groups, without respect to Brighton Collaboration criteria. The reporting rate for GBS is higher for Janssen than for mRNA vaccines. On July 12, 2021, the authorized EUA Fact Sheets were updated to include new information about GBS. In terms of next steps, work will continue to obtain follow-up information and medical records. The Janssen reports will continue to be evaluated in order to determine whether they meet the Brighton criteria. Based on the number of confirmed cases after that review and assessment, the O/E analysis for GBS after Janssen will be updated. Follow-up will continue on updates from the FDA Biologics Effectiveness and Safety System (BEST), the Center for Medicare and Medicaid Services (CMS) databases, and the CDC VSD active surveillance system.

GBS after Janssen COVID-19 Vaccine: VSD

Dr. Nicola Klein (Kaiser Permanente Northern California) reported on Rapid Cycle Analysis (RCA) findings to date on a GBS analysis after Janssen COVID-19 vaccine being led by Kaiser Permanente Northern California in close collaboration with the Marshfield Research Clinic and the CDC. She reminded everyone that the VSD is a collaborative project between CDC and 9 integrated healthcare organizations that was established in 1990 and includes EHR information on over 12 million members. The specific aims of this VSD RCA project during the period from September 2020–August 2023 are to: 1) monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members; and 2) describe the uptake of COVID-19 vaccines over time among eligible VSD members and in strata by age, site, and race/ethnicity. As of July 10, 2021, over 12.4 million doses of COVID-19 vaccines have been administered in the VSD. To date, 65.8% of the age-eligible VSD population has received their first dose and 61.5% are fully vaccinated. The vast majority of vaccines given have been the mRNA vaccines. Over 349,000 doses of the Janssen vaccine have been given, among which over 44,000 were administered to those 65 years of age and over.

The primary analyses used vaccinated concurrent comparisons with sequential tests. This involves evaluating vaccinated individuals in the 21 days after vaccination compared to other individuals who also are vaccinated, but are further away from their last vaccine dose by between days 22 and days 42, who are the comparators. In the 21-day risk interval from either dose of any mRNA vaccines, the rate ratios were adjusted for VSD site, age group in 5-year age increments, sex, race/ethnicity, and calendar date. A sequential test required 1-sided P-value of <0.0048 for a signal. This keeps the probability of a false positive signal due to chance alone below 0.05 in 2 years of surveillance. GBS was pre-specified as well as a number of other outcomes that would be included in analysis if they were confirmed. Cases initially underwent a quick review for confirmation, and then they were included in this analysis. However, they were subsequently removed if not confirmed after a chart review and adjudication that takes place later in time. At the time of this analysis, there were no signals for any of the outcomes being followed on the weekly basis, including GBS that had a 1-sided P-value of 0.828 and an

adjusted rate ratio of 0.69. The outcome events in the 21-day risk interval also were compared after Janssen vaccine, again comparing outcome events between the vaccinated individuals with vaccinated comparators. There were no signals after Janssen vaccine for any of the pre-specified outcomes listed. There were 8 cases of GBS in the risk interval for GBS, but the adjusted rate ratio was 1.19 and the 1-sided P value was 0.682.

Turning to the chart review summary as of July 3, 2021, there were 40 GBS cases initially identified within the 1-98 days following any mRNA vaccine. After a quick review, 16 of 39 were ruled, 1 is pending, 23 of the 39 proceeded to full review, 21 of the 23 underwent complete review and adjudication with Brighton level criteria and 2 are pending. Adjudication confirmed 19 of the 21 as GBS following any mRNA vaccine: 1 case was post-vaccination Day 0; 8 cases were post-vaccination Days 1-21; 8 cases were post-vaccination days 22-42; and 2 were case post-vaccination days 43-98. The 8 cases in the post-vaccination Days 1-21 window contributed to the analysis. The chart review of GBS syndrome following the Janssen vaccine as of July 3rd identified 14 cases within the 1-98 days following Janssen and all 14 were quick reviewed. Of these, 2 were ruled out, 12 of the 14 proceeded to full review, 10 of the 12 completed review and adjudication, and 2 are pending. Adjudication confirms 8 of the 10 as GBS following the Janssen vaccine. Of those, 7 were post-vaccination Days 1-21 and 1 was in post-vaccination Days 22-42.

In terms of the characteristics of the confirmed GBS cases in 1-21 days, 75% cases in the mRNA group were over the age of 65 and 100% of the cases after Janssen were 18-64 years of age. Overall, similar proportions in each group had on-going illness at the time of the chart review. In terms of unadjusted incidence rates of chart-confirmed GBS 1-21 days after vaccination, it is important to note that the study was not designed to do a head-to-head comparison of mRNA versus Janssen vaccine. That said, after mRNA vaccines there were the 8 confirmed cases in the 1-21 day interval among just over 11.7 million doses. That translates to an unadjusted rate of 0.7 (0.3 - 1.3) per million doses and an unadjusted rate per 100,000 person years of 1.2 (0.5 – 2.3). In comparison, 7 GBS cases were confirmed in the 1-21 day risk interval out of 345,000 doses for an unadjusted rate per million doses of 20.2 (8.1- 41.7) and an unadjusted rate per 100,000 person years of 35.2 (14.2 - 72.5).

So in summary, the VSD has not identified a signal for any outcome in primary analyses, including GBS after mRNA or Janssen vaccines. The analyses do not include a head-to-head comparison of Janssen to mRNA vaccines. However, the chart-confirmed unadjusted incidence rates of GBS during the 21 days after the Janssen vaccine was much higher than during the 21 days after the mRNA vaccine. The weekly update of Janssen in the VSD has been minimal, in the range of 2,500 to 11,000 doses a week. The investigators strongly believe that continued VSD monitoring of GBS is warranted and will continue to chart review every case of GBS within the 1-98 days following any COVID-19 vaccine.

VaST assessment of GBS after Janssen COVID-19 Vaccine

Dr. Grace Lee (ACIP, VaST Co-Chair) reported that as of July 21, 2021, there were 339 million doses administered of whom 187 million individuals have received at least 1 dose and 162 million people are fully vaccinated in the US. There is significant variability in vaccination rates by state and by community. The tremendous benefits of COVID-19 vaccines are observed in reducing death rates in states and communities that are highly vaccinated. This also demonstrates the tremendous opportunities there are to continue to protect families and communities against COVID-19 morbidity and mortality.

In terms of the focus of this meeting on the particular AE of GBS and estimating the potential risks associated with vaccination, the role of VaST is to ensure that vaccine safety is being carefully monitored and that any risks are communicated to the ACIP, and hence to the public, in a timely and transparent manner. There is an estimated rate of about 1 in 70,000, which is the midpoint of current estimates for the risk of GBS. This means that 69,999 individuals who receive vaccines do not have this AE.

ACIP's responsibility is to ensure that the best possible recommendations are provided for the for the US population on the use of COVID-19 vaccines, and that its assessments about the benefits and risks of vaccination are placed in the context of the dynamic burden of disease that the US is experiencing, while also recognizing that the US is also a member of the global community and that infections do not respect borders. ACIP members must acknowledge the importance of these AE in individuals, as well as the immense benefits of vaccination in preventing poor health and economic outcomes for the population. ACIP will continue to mitigate these risks whenever possible in close partnership with provider and public health communities.

VaST has had 28 independent meetings to review vaccine safety data since December 21, 2020 and 6 joint meetings with the COVID-19 Vaccine WG to discuss safety issues. Since ACIP's June 23, 2021 meeting, VaST shared a WG report following its meeting on June 28th on GBS following Janssen vaccine. During that meeting, VaST reviewed data from VAERS demonstrating that the observed number of preliminary cases of GBS after a Janssen vaccine was greater than expected in those 18 years and older and in all age groups. No geographic clustering was observed in the VAERS data. At the same time, VaST noted that the observed versus expected recording rates were not elevated for mRNA vaccines. In the VSD and Veteran's Administration RCAs presented that day, no statistical signals for GBS were identified for any COVID-19 vaccines. However, the rate of GBS following the Janssen vaccine was higher than for the mRNA vaccines in the VSD. VaST noted that GBS cases were reported after receipt of AZ COVID-19 vaccine, which is used in other countries. VaST members discussed the need for review and adjudication of VAERS case reports of GBS using Brighton collaboration criteria, and ongoing monitoring of GBS in all persons who receive the Janssen COVID-19 vaccine in the US.[11]

Following that meeting, the EMA announced the addition of a warning for GBS following the AZ COVID-19 vaccine on July 9, 2021. On July 12th, the FDA announced revisions to the Janssen COVID-19 vaccine EUA fact sheets for providers and for patients to include information about an observed increased risk of GBS following vaccination.[12] During its meetings on July 12th and July 19th, the VaST WG reviewed key updates on GBS from the federal safety system, which were shared earlier in this ACIP meeting by Drs. Alimchandani and Klein. As a reminder, GBS can occur following a respiratory or GI illness. Background rates of GBS generally increase with age and risk is greater in males than in females. To summarize the findings regarding GBS cases per million doses of COVID-19 vaccines administered in VAERS and VSD for those 18 years and over, the rate of GBS following the Janssen vaccine ranged from 8-20 per million doses in VAERS and the VSD. In contrast, the rate of GBS following mRNA vaccines ranged from 0.7 to 1.1 per million doses in the two systems, with an expected background rate of approximately 1.6 cases of GBS expected in the 42-day window per million doses given.

[11] https://www.cdc.gov/vaccines/acip/work-groups-vast/index.html; https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-july-2021; https://brightoncollaboration.us/guillain-barre-and-miller-fisher-syndromes-case-definition-companion-guide/

[12] https://www.fda.gov/media/146304/download; https://www.janssenlabels.com/emergency-use-authorization/Janssen+COVID-19+Vaccine-Recipient-fact-sheet.pdf

VaST discussed these findings and felt that the risk for GBS following Janssen COVID-19 vaccine is substantially different than the risk following mRNA vaccines and the expected background rates, with a median onset of 13 days in VAERS and more commonly recorded in males than females. Of note, fewer individuals receive Janssen in the US. It represents less than 4% of all vaccine doses administered in the US. VaST also noted that GBS cases have been reported following SARS-CoV-2 infection in the literature, with a median onset of 12-14 days post-infection.[13] VaST also discussed the importance of medical record review of the VAERS cases in process using Brighton collaboration criteria and the need to confirm the diagnosis of GBS and further characterize the clinical presentation, severity, and outcomes of GBS cases following Janssen vaccine. They also discussed the need to continue to assess benefit/risk balance given the dynamic epidemiology of COVID-19 infection.

The VaST WG will continue to monitor and support the response to safety data in the US. The US safety monitoring systems will continue to track anaphylaxis and myocarditis following mRNA COVID-19 vaccines and TTS and GBS following Janssen COVID-19 vaccines. The VaST WG also will continue to monitor the pre-specified adverse events of special interest (AESI) in each of the federal agencies monitoring safety and is appreciative of the communication and the collaboration among the federal agencies responsible for vaccine safety surveillance in the US, as well as the communication and collaboration with global partners, in monitoring the safety landscape overall. The ACIP will continue to incorporate safety data into decision-making about vaccine use, including ongoing assessments about the benefit/risk balance that are contextualized to real-time data and risk mitigation strategies that support informed discussions with patients and the public about the benefits and risks of available vaccines, as well as clinical guidance to support early detection and appropriate management of potential AEs.

Summary of Discussion (Alimchandani, Klein, & Lee)

- In response to a question regarding whether there was a sense about what proportion of GBS cases tend to be confirmed through adjudication, the Clinical Immunization Safety Assessment (CISA) has started reviewing cases. They have assessed 7 cases so far and have seen a very small number. CISA had good consensus that 3 cases were clearly Brighton Level 2 GBS, with characteristic of GBS regardless of etiology. GBS is reported with Bell's Palsy, which has been seen in some of the cases reviewed so far. Cranial neuropathies in GBS, specifically with a facial nerve, is seen in about 30% to 50% of patients depending upon what series of all-comers is reviewed.

- ACIP members expressed interest in further information on the following topics related to GBS following Janssen COVID-19 vaccination:

    - Breakdown of race/ethnicity and geographic location
    - Further information about the severity of the cases in terms of the number admitted to the Intensive Care Unit (ICU)
    - Rate of GBS cases reported due to COVID-19 infection

[13] Aldawi et al., Can J Neurol Sci 2021; Sheikh et al., J Neuroimmunol 2021; Sriwastava, J Neurol Sci 2021

Johnson & Johnson/Janssen Comments

Dr. Mathai Mammen (J&J/Janssen) reported that Johnson & Johnson/Janssen has been busy at work since the start of the COVID-19 pandemic with a dedication to developing a single-dose vaccine that can be easily distributed and that is safe and effective in helping to combat the pandemic's effects worldwide. They are fully aligned with FDA on the addition of information regarding the cases of GBS that have been observed following vaccination with the Janssen vaccine. They had some recently published data on variant coverage and durability of the immune response that they wanted share with the ACIP to provide additional context for the day's discussion. As everyone is aware, the pandemic is evolving in the US and globally. The Delta variant makes up the large majority of COVID-19 cases in the US at this point whereas just a couple of months ago it was not present at all. Vaccines are needed that cover current and future variants and that are durable in protection.

Importantly, everyone is still learning about the duration of protection and the breadth of coverage against this evolving varied landscape for each of the authorized vaccines. In that context, Dr. Mammen shared some newly evolving data showing that antibody titers against variants continue to rise after Day 29, including against Delta. This suggests further maturation of the immune response. These effects are sustained through Day 239 or approximately 8 months. There is a comparable response to all variants analyzed by 8 months, including the Delta variant. It is critical to understand that there are components to the immune system outside of neutralizing antibodies that play a very important role in preventing infection. As reported in recent publications, the J&J/Janssen vaccine induces very strong CD4-positive and CD8-positive T-cell responses that are comparable across variants. It is important to note that the mutations in the virus seen have not shown up in T-cell epitopes. Therefore, it is not surprising that the T-cells induced by J&J/Janssen vaccine are comparably active against all the variants currently known.

The CD8-positive T-cells in particular are the body's primary mechanism to clear infected cells. Of note, this persistence also has been observed and has a comparable response to variants for non-neutralizing functional antibodies induced by the vaccine. At this stage, J&J/Janssen does not know whether all of these immune data and others recently reported are predictive of clinical efficacy, but do believe that all of these components of the immune response are important and they are all persistent. They will have a better view on clinical efficacy in the coming weeks.

Dr. Joanne Waldstreicher (J&J/Janssen) provided a high-level overview and the J&J/Janssen view on the benefit/risk profile. As noted earlier, there are 100 cases of GBS from VAERS out of the more than 12 million people in the US who have received the Janssen vaccine, giving an overall reporting rate of 8 cases per million people vaccinated. This is in the context of the different published rates of GBS in the US, which have ranged from 1-5 cases per million people. To provide further context in relationship to other vaccines, the estimated risk of GBS reported with the H1N1 vaccine is approximately 3 cases per million, the estimated risk with shingles vaccine is 5-8 cases per million people vaccinated, and the estimated risk with TTS is approximately 3 cases per million people vaccinated. Dr. Waldstreicher emphasized that these cases are not just numbers. They are people and they matter deeply to J&J/Janssen.

They do have some data on the risk of GBS with COVID, one published study and one internal population-based analysis, that they were able to share showing that the risk of developing GBS after COVID is much higher than any of the risks presented during this meeting. That is why it is necessary to consider these risks in the context of the overall benefits of preventing COVID. Looking at estimates of the potential benefit over a 1-year period in terms of hospitalization and death per 1 million people vaccinated with either the Janssen vaccine or no vaccine in the setting of different levels of transmission, for every 1 million people vaccinated, even in the setting of very low transmission, many hospitalizations and deaths are avoided and the benefits outweigh the risk of GBS and TTS. The overall benefit/risk seems favorable even in the very low transmission setting, but particularly so as transmission is higher as seen in various parts of the US and globally. This is especially important as has been seen with the new variant profile emerging, as well as the recent surge in case counts.

There is still a need to vaccinate as many people as possible, both in the US and globally. The pandemic continues to evolve in the presence of many who remain unvaccinated and the variant landscape is changing rapidly and unpredictably. Multiple vaccine options are needed in the global public health toolbox. In this context, the Janssen vaccine offers important benefits. Newly published data that Dr. Mammen just shared demonstrates persistent humoral and cellular immune responses through 8 months, independent of variant. As a single dose with simple storage conditions, the vaccine has particular public health benefits in the US and globally. The global context is critical. As mobility resumes and variants continue to emerge, there is no question that the US population will remain vulnerable so long as large segments of the globe remain unvaccinated. For many parts of the globe, the single dose and easily transportable vaccine is critical. Finally, J&J/Janssen agrees with the FDA's statement that the known and potential benefits clearly outweigh the known and potential risk.

Public Comments

The floor was opened for public comment during the July 22, 2021 ACIP meeting at 1:15 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–2021–0070. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Larry Saltzman, MD
Board Certified Family Physician
Executive Research Director, Leukemia & Lymphoma Society
Blood Cancer Survivor

Thank you for the opportunity to speak to you today. I'm Dr. Larry Saltzman, a Board Certified Family Physician, Executive Research Director for the Leukemia and Lymphoma Society and a blood cancer survivor—now for over 11 years. I'm here today to urge CDC to implement a COVID-19 vaccine booster program. We need a large-scale nationwide clinical trial to assess their safety and effectiveness. As a family physician, I emphasize preventative medicine, including immunizations for all. In my career, I have seen cases of tetanus, measles, and other diseases that are now preventable. In October 2009, I self-diagnosed my lymphoma, confirmed as atypical chronic lymphocytic leukemia and small cell lymphocytic lymphoma. I've been treated on multiple occasions, including chemotherapy, the removal of the right side of my colon due to lymphoma blockage, and years of oral targeted anti-cancer drugs. My most recent

relapse was quite severe. From October 2019 through January 2020, I was hospitalized on five separate occasions and treated with three different courses of chemotherapy. The culmination of these treatments was CAR-T immunotherapy, where my white blood cells were genetically reprogrammed and reinfused so they could act as little Pac-Men, hunting down and destroying my blood cancer. As I returned home in February 2020, I was looking forward to recovery and normal activities until SARS-CoV-2 essentially shut down the world and created a very hostile environment for me and all blood cancer patients to live in. A 2021 publication in *Nature Medicine* by Bange found mortality rates as high as 55% among patients with COVID-19 who also have hematologic cancer. Severe COVID-19 infection is preventable with the available vaccines. I received the COVID-19 mRNA vaccines in January and February 2021. However, I made no detectable antibodies to the spike protein. Based on an ongoing study by the Leukemia and Lymphoma Society published online today in *Cancer Cell*, we estimate 25% of blood cancer patients, or 250,000, in the USA did not have an antibody response to the vaccine. There are estimated to be 5 million immunocompromised patients at risk in America, including any condition that requires chemotherapy or immune suppressive treatments. We have been advised by the CDC that masks are no longer recommended in most settings. Patients like me are left in the lurch. I am in quarantine. I do not trust all unmasked to be vaccinated. I'm hearing too many stories of immunocompromised people like me who are taking matters into their own hands. Thank you for your time and consideration.

Thair Phillips
Healthcare Leadership Council
Seniors Speak Out

Good afternoon. My name is Thair Phillips of Seniors Speak Out. For the 20 years before I became eligible for Medicare and the 8 years since, I have been an advocate for the concerns of older Americans. It is important to remember that well before COVID, pneumococcal diseases were a serious threat to seniors. We know that as we grow older, our protective immune responses are weakened and that increases our vulnerability to infectious diseases such as pneumonia. Each year, about 1.3 million people visit emergency departments with pneumonia and nearly 50,000 people will die from it, many of whom are older Americans. That has not changed and will continue to be our reality post-pandemic. In fact, there is perhaps good reason to be concerned that post-COVID, we may be even more at risk due to lung damage among COVID survivors, deferred medical care for comorbidities, and an increased sedentary lifestyle during pandemic-driven quarantine. I know that this committee has enormous issues before it, but it is a matter of life and death to many seniors who rightfully want to do everything they can to protect themselves as this first post-pandemic flu and pneumonia season approaches. Eighty percent of the deaths during the pandemic were older Americans over the age of 65. We can't let them again bear so heavy a burden. We, and by that I mean we older Americans, lead the country in protecting ourselves from COVID, as those 65 and older have the highest rate of vaccination among all age groups, with 89% having received at least one dose compared with 68% for people ages 18 to 64. We understand the risks and we can and do make carefully thought out decisions to protect ourselves. What we need is access as quickly as possible to preventive measures that make a difference. There are now two FDA-approved vaccines that offer greater protection against pneumonia. We need your help in making them available to us now. This fall, as the normal vaccination period begins, and with a threat of an intense flu season, seniors will need every tool available to keep themselves healthy. It would be disappointing if the availability of these new medicines was hindered in any way. As shown during COVID, we know that when necessary, this committee can move quickly. I think this is one of those times that requires prompt attention. Every scientific advancement in vaccines

saves lives, so I urge the committee to expedite the review and approval of these new vaccines to further empower our generation with the medicines we need to protect ourselves.

Robert Mnookin, LLB
Professor, Harvard Law School

I'm Robert Mnookin, a Law Professor at Harvard. Last December, because I had end-stage kidney disease, my daughter Jennifer Mnookin lovingly donated a kidney for me at UCLA. Her kidney was flown on the red-eye to Boston and was transplanted into me at Mass General. The good news is my kidney function is now in the normal range. The bad news is that the powerful immunosuppressant drugs I take to prevent organ rejection make me not only more susceptible to infections of all kinds, including COVID-19, but less likely to be protected by the standard vaccination protocol. Like many transplant recipients, my two shots of Pfizer provided me with no antibody protection against COVID-19. A spike antibody test shows my antibody level at zero—completely undetectable. I know, and you know, that an additional shot might provide life-saving protection for people like me with little risk, yet I and people in my position currently can't get authorized access to a third shot, even if our physician's clinical judgment favors it. In the broader debate concerning the wisdom of boosters for the general population, your committee must persuade the CDC to stop ignoring the critical special needs of organ transplant patients and others who are immunocompromised and allow access to a third shot now. My situation is not unusual. A Johns Hopkins study of transplant recipients and other immunocompromised individuals showed that nearly half had no immune response to their vaccines. A third shot would likely make a meaningful difference for many of us. A French study reported in the *New England Journal of Medicine* showed that among the 59 patients who lacked antibody response, after two shots, 44%, nearly half, developed antibodies with a third shot with no serious adverse events. An observational study from Johns Hopkins had similar results. Other nations—France, Israel and Great Britain—are taking action now to promote boosters for transplant recipients and the immunocompromised. And, yet, when I asked my doctors about getting a third shot, they told me that they currently lacked any authority to recommend it or provide access. I understand how dangerous COVID could be for me. An Israeli study showed that 40% of severe vaccine breakthrough cases in the hospital were among immunocompromised people, and the Delta variant is making this situation worse. As breakthrough cases become more common, people like me aren't protected, even if we carefully limit our interaction to vaccinated people. This situation needs to change. Your committee must tell the CDC not to ignore the special needs of immunocompromised people. Please show the leadership and the compassion necessary to recognize the scientific and moral imperative allowing a third shot to this group now. Encourage the CDC to follow the French, Israeli, and British example and explicitly recommend that the United States permit a booster for this population.

Mr. Mark Gibbons
President and CEO
RetireSafe

Good afternoon. This is Mark Gibbons. I'm President and CEO of RetireSafe. Thank you, committee, for allowing me to speak. RetireSafe is an organization whose mission is to educate and advocate on behalf of older Americans on issues including Social Security, Medicare, health, safe retirement, and financial well-being. Currently, there are nearly 70 million Americans over the age of 60. Due to immune system decline as part of aging, as well as the prevalence of chronic disease comorbidities, many of them are particularly vulnerable to infectious diseases such as influenza, pneumococcal pneumonia, and of course, COVID-19. Vaccines for these and other conditions can truly be a matter of life or death, and we are

grateful for the continued work by ACIP to evaluate and improve critical vaccines for COVID-19. While we are encouraged by the progress made towards vaccinating older Americans against COVID-19, we are increasingly concerned that experts are predicting the flu and pneumonia season to be more serious than last year now that states across the country are relaxing COVID-19 restrictions. In the US, it is estimated that more than 150,000 hospitalizations from pneumococcal pneumonia occur each year, and about 5% to 7% of those who are hospitalized from it will die. The death rate is even higher in those age 65 years and older due to the strength of the body's immune system declining over time. Given this increased vulnerability and in light of encouraging news that the FDA has recently approved two new and improved vaccines for pneumonia, we are particularly focused on what is being done to ensure we are doing everything possible to protect American seniors. Will seniors have access to the best available vaccines to ensure they are as protected as possible? These new vaccines offer hope and even greater protection against life threatening disease for some of the most vulnerable in our population. They only have to have access to them. We urge ACIP to consider expediting the vote on these vaccines ahead of the upcoming October meeting to ensure the broadest availability possible for America's seniors ahead of this year's flu pneumonia season. Thank you very much.

Ms. Claire Hannan
Association of Immunization Managers

I'm Claire Hannon, Executive Director of the Association of Immunization Managers. I wanted to take this opportunity to thank the committee for its steadfast commitment to evidence, data, and science. I would also like to recognize and thank the public health workers across the nation and throughout the US territories and Pacific Island nations for their dedication in containing the pandemic and vaccinating the adult population. Today's meeting of the ACIP is just one of 15 special meetings that have been conducted in addition to regularly scheduled meetings conducted in public since the pandemic began. During these committee meetings, members review findings and discuss vaccine research and scientific data. The recommendations of the committee's medical and public health experts guide in the use of COVID vaccine and ensure a vigilant watchful eye on all potential side effects. To the committee and the expert staff and leadership of the CDC, thank you. At the start of this pandemic, our public health workforce was significantly less than previous years. According to data from the Association of State and Territorial Health Officials, the number of public health workers went from 236,000 at the start of the H1N1 pandemic in 2009 to 206,000 workers at the start of the pandemic in COVID-19. Turnover in public health is high. Of the 64 federally funded state, territorial, and large city immunization programs, 32 have experienced turnover with their Program Manager since 2019. The burnout and exhaustion in public health is real. To all the public health workers, and especially the Immunization Program Managers, thank you. They're working long days, nights, and weekends to plan and implement. The vaccination campaign has resulted in much success and impact 68% of adults with at least one shot, 160 million people fully vaccinated, and 336 million doses administered. Epidemiologists at Yale University estimate that New York City's vaccination campaign has prevented 250,000 COVID-19 cases, 44,000 hospitalizations, and 8300 deaths. Between January 1, 2021 and June 15, 2021, 98% of hospitalizations and 98.8% of deaths from COVID-19 were in those who were not fully vaccinated. So, clearly our work is not done. But again, I just want to say thank you to the committee and all those involved in these efforts. The nation is extremely grateful.

Mr. Phillip Canuto
Renal Transplant Recipient
Member, Johns Hopkins Vaccine Study

My name is Phil Canuto and I live in Akron, Ohio. My cousin gave me a kidney 19 years ago. I'm in the Johns Hopkins Vaccine Transplant Study, and I tested negative for COVID antibodies after both of my Pfizer jabs. I appreciate the opportunity to represent immunosuppressed patients today. I urge you, beg you even, to recommend that we be able to receive a third vaccine dose and to allow doctors to make an additional dosing decision on a case-by-case basis. When a friend got her first Pfizer shot, she cried with happiness for the freedom the shot offered her. But those of us who are immunosuppressed have no such freedom. Instead, we exist in an uncertain limbo. We're told to behave as if we are not vaccinated. Continue to mask up, our doctors say. Social distance, avoid crowds, and poorly ventilated spaces. And now the Delta virus variant increases our risk. So what are we to do? Many of us must take risks that could lead to exposure, illness, and death. Hundreds of us lied to pharmacies and immunization sites about our previous vaccinations trying to get an extra unauthorized dose. I know that's what I'll be doing if additional doses are not sanctioned. And we long for a fuller life. For me, it's for family, music, and food. I can't wait to see my stepdaughter's new Colorado home, to hear Lyle Lovett live in concert, to eat a medium rare steak at the Diamond Grill. But I'm retired. I can control my activities. What about transplant patients who must check out groceries or manage an office? They have no safety net. They risk exposure every day. So please, recommend additional shots for us. I know even then there will be uncertainty. I know there is no guarantee that a third or even a fourth dose will provide us with full immunity, but I want that chance. And even if that extra dose doesn't keep me from getting sick, maybe it can help me avoid a ventilator or death. Neither Johns Hopkins nor the French have found meaningful adverse events in patients who have taken a third dose. So the risk of these extra shots, while not nothing, seems very, very small. But the benefit could open up the world to us again. Thank you for this opportunity to speak.

Mrs. Erica DeWald
Director, Strategic Communications and Partnerships
Vaccinate Your Family

Thank you for the opportunity to comment. My name is Erica DeWald. I am Director of Strategic Communications and Partnerships for Vaccinate Your Family, a national nonprofit organization committed to protecting people of all ages from vaccine-preventable diseases. I'm also a mother and a daughter who has celebrated each and every age expansion for the COVID-19 vaccine. I'm hopeful I'll be able to protect my two young children against this really devastating disease, as we've heard in these comments thus far, in the near future. Our organization deeply appreciates the work of this committee. Your careful deliberations this morning show firsthand how carefully you consider even the rarest safety signal for all vaccines, not just COVID-19. Transparency is key in these conversations. As you all know, risk-benefit is a difficult calculation for many of us to make, especially when it's regarding our own health and that of our loved ones. The information you share, particularly in plain terminology, helps all of us better communicate the risk benefit of vaccines versus the diseases they prevent when speaking to the public. And I would like to take this opportunity to remind you that the public overwhelmingly supports vaccines. The proof is in the 160 million people in the US now fully vaccinated against COVID-19. In fact, trust in vaccines increased after the FDA, ACIP, and CDC worked together to investigate concerns about low platelet counts in combination with blood clots following vaccination with the Janssen COVID vaccine. That interagency coordinated communication is key to continuing to increase confidence. But people do want more information and answers to

their questions. It's critical that we direct people with questions to science-based information. My hope is that they will seek out reputable sources such as CDC and a trusted healthcare professional or advocacy organizations like my own, Vaccinate Your Family. Thank you again for your time today and for all you do.

Mr. Gilmore, John
Executive Director
Children's Health Defense New York

My name is John Gilmore. I am the Executive Director of Children's Health Defense New York. We're an advocacy organization working on a wide range of issues affecting the health and well-being of children, including vaccine rights and vaccine policy. I also lost my mother to COVID last year when she contracted it in her nursing home here in New York, so this is an issue I take very seriously. My comment today is that the identification of Guillain-Barré syndrome as an injury associated with the Johnson & Johnson COVID shot following so closely on the discovery of the association with myocarditis after millions of doses have been administered underscores how little we really know about the potential side effects not only of the Johnson & Johnson product, but also the COVID products currently used in the United States. This lack of knowledge is exactly why these products are only available under an Emergency Use Authorization. This lack of knowledge about both immediate and long-term impacts of these products screams for caution and prudence in the use of these products. In light of our lack of information, in combination of the Countermeasures Injury Compensation Program placing the overwhelming burden of risk upon the person receiving the shot, we believe it is incumbent upon the ACIP to reject any measures to coerce compliance with compulsory vaccination measures by both public and private actors. A person receiving the shot should make this decision based on their own evaluation of the risks and benefits of doing so. These decisions should be made for minor children only by their parents and no one else. Now some states on a related issue are citing the lack of knowledge about these products and the lack of guidance from ACIP as a reason to disallow any medical exemptions written by the patient's own treating physicians. I have already encountered personally several instances of these refusals in New York, and I'm sure they are occurring elsewhere. Consequently, I believe the ACIP should issue a policy when it comes to the medical exemptions deferring to the opinion of the treating physician in all instances, especially given our lack of information that we have right now. So, thank you for the opportunity to speak today. Have a good day.

COVID-19 Vaccines: Benefit-Risk Discussion

Dr. Hannah Rosenblum (CDC/NCIRD) reminded everyone that the current COVID-19 mRNA vaccine policy is that COVID-19 vaccines are recommended for persons 12 years of age and older in the US under FDA's EUA. This presentation focused on the risks and benefits of the 3 COVID-19 vaccines recommended for persons aged 18 and older in the US. First to frame this presentation, the goal of this analysis was to assess the benefit/risk balance of the Janssen vaccine given recent reports of GBS in vaccine recipients. The previously presented analyses for TTS and Janssen vaccine and myocarditis and mRNA vaccines were updated so that the benefit/risks of COVID-19 vaccines could be assessed and discussed comprehensively.

Since January 2020, there have been more than 33 million cases of COVID-19. Overall, these have been declining since January 2021. While this past Spring the number of COVID-19 cases was decreasing, the end of June appears to have been a nadir in the US. Over the last few weeks, the number of cases has begun to rise. For the benefit-risk assessment, case incidents and hospitalization rates were used from the week ending June 19th. Because that may represent the trough for COVID-19 cases, these estimates should be interpreted in the context of this trend.[14] The CDC's forecast of new COVID-19 cases through August 14, 2021 and new COVID-19 hospitalizations forecasted through August 16, 2021 predict that the number of daily COVID-19 cases and hospital admissions likely will increase.[15] NOWCAST projections of the proportions of circulating SARS-CoV-2 variants from CDC's COVID Data Tracker provide timely estimates while accounting for limited sequence data availability. Based on recent NOWCAST data for the most recent week through July 17th, the Delta variant comprises the largest proportion at more than 80%.[16]

Turning to the potential harms following COVID-19 vaccine, a greater than expected number of cases of GBS, a rare neurological disorder, have been reported following Janssen vaccine. These have been within 2 weeks of vaccination, mostly in males, and in those aged 50 and older. TTS, a rare but clinically serious AE, also has been observed following Janssen vaccine. Most cases of TTS have been in females 18-49 years of age. ACIP is familiar with the TTS benefit/risk balance assessment, discussions from April after the pause, and the ultimate resumption of vaccine administration when benefits were felt to outweigh risks. Myocarditis is also rare, but has been observed following mRNA vaccination. This has been commonly observed in young males under 30 years of age and more frequently after the second dose. The benefit/risk balance for adolescents and young adults was presented recently to ACIP. The focus of this session's presentation was on adults 18 years of age and older.

In summary, while overall COVID-19 incidence has been decreasing, the US may have reached a low point in June. The US has begun to see cases and hospitalizations rising in recent weeks. Variants of concern (VOC) continue to spread, with the Delta variant currently found in more than 80% of US cases. The rare AEs of TTS and GBS for Janssen vaccine and myocarditis for m/RNA vaccines have been observed after COVID-19 vaccination.

Moving to the benefits and harms analysis for Janssen COVID-19 vaccine, a similar direct estimation approach was used as the one used in April for TTS and recently for myocarditis to estimate the direct benefits and risks of Janssen vaccination. The benefits included estimation of COVID-19 cases, hospitalizations, ICU admissions, and deaths prevented per 1 million doses of Janssen vaccine. These calculations were based on the most recent age- and sex-specific incidence of hospitalizations from COVID-NET ending the week of June 19th, vaccine efficacy (VE) against hospitalization, and symptomatic COVID-19 from the Phase 3 trial and assumed a 120-day period of not being vaccinated. The potential harms of the Janssen vaccine also were estimated per 1 million doses by age and sex using GBS cases from VAERS through June 30, 2021. The same was estimated for TTS using VAERS data through July 8, 2021.

[14] https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases from July 21, 2021
[15] https://www.cdc.gov/coronavirus/2019-ncov/science/forecasting/forecasts-cases.html; https://www.cdc.gov/coronavirus/2019-ncov/science/forecasting/hospitalizations-forecasts.html
[16] https://covid.cdc.gov/covid-data-tracker/#variant-proportions

For benefits, in the Phase 3 clinical trial, the Janssen vaccine was found to have an overall efficacy of 66% against symptomatic laboratory-confirmed COVID-19. VE against hospitalization was 93%. VE against deaths due to COVID-19 was 100%. Both persistence of antibody response following vaccination and activity against a variety of variants, including the Delta variant, have recently been shown.[17] In terms of the cases of GBS reported to VAERS following Janssen vaccine by sex and age group, over 12 million doses had been administered and 98 cases with age and sex information had been reported to VAERS as of June 30, 2021. Cases were greatest among males 50-64 years of age, with a reporting rate of 15.6 per million doses.[18] As of July 8, 2021, there have been 38 cases of confirmed TTS reported following receipt of Janssen COVID-19 vaccine. Cases were greatest among females 30-49 years of age, with a reporting rate of 8.8 per million doses.

Now turning to the predicted cases of COVID-19 hospitalizations, ICU admissions, and deaths that are prevented compared to the estimated number of GBS and TTF cases for every million Janssen doses over 120 days by age group and sex. For females 18 to 29 years of age, it is estimated that for every million doses, 8900 cases of COVID-19, 700 hospitalizations, 50 ICU admissions, and 5 deaths would be prevented and 1 GBS case cases might be seen. For males aged 18 to 29 years, it is estimated that 6600 cases of COVID-19, 300 hospitalizations, 60 ICU admissions, and 3 deaths would be prevented and 2 GBS cases might be seen. For females 30-49 years of age, it is estimated that 10,100 COVID-19 cases, 900 hospitalizations, 140 ICU admissions, and 20 deaths would be prevented and 6-7 GBS cases and 8-10 TTS cases might be seen. For males 30-49 years of age, it is estimated that 7600 COVID-19 cases, 650 hospitalizations, 150 ICU admissions, and 25 deaths would be prevented and 7-8 GBS cases and 1-2 TTS cases might be seen.

For individuals 50-64 years of age, the benefit risk balance is even more favorable with still more COVID-19 outcomes prevented compared to GBS and TTS cases. For females in this age group, it is estimated that 29,000 COVID-19 cases, 5900 hospitalizations, 1250 ICU admissions, and 840 deaths would be prevented and 8-10 GBS cases and 0 TTS cases might be seen. For males in this group, it is estimated that 36,600 COVID-19 cases, 11,800 hospitalizations, 3300 ICU admissions, and 2300 deaths would be prevented and 7-8 GBS cases and 0 TTS cases might be seen.

The same direct estimation approach is used to estimate the benefits and risks per million doses of mRNA vaccine. Benefits were again estimated to include COVID-19 cases, hospitalizations, ICU admissions, and deaths prevented. Calculations were based on the most recent age- and sex-specific incidence of hospitalizations from COVID-NET ending the week of June 19th, as well as mRNA vaccine efficacy observed in Phase 3 trials, and also using a 120-day period. Potential harms of the mRNA vaccines have been estimated per million doses by age and sex using various data through June 30th. The Phase 3 clinical trials for Pfizer and Moderna mRNA vaccines showed overall efficacy of 94%-95%, with VE against COVID-19 hospitalization of 89%-100%.[19] Persistence of antibody response and activity against a variety of variants were also noted for mRNA vaccines and were demonstrated for several months.[20]

[17] https://www.nejm.org/doi/full/10.1056/NEJMc2108829?query=featured_home
[18] Source of doses administered: FDA, through June 30, 2021
[19] Polack FP et al. N Engl J Med 2020; DOI: 10.1056/NEJMoa2034577; Frenck RW et al. N Engl J Med 2021; DOI: 10.1056/NEJMoa2107456; Baden LR et al. N Engl J Med 2021; DOI: 10.1056/NEJMoa2035389
[20] https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html

As of June 30th, there have been about 141 million second mRNA vaccine doses administered[21] and 497 cases of myocarditis reported following the second dose. The greatest number of cases has been observed in persons 18-29 years of age, with a reporting rate of 24.3 per million doses. For females 18-29 years of age it was estimated that 12,800 COVID-19 cases, 750 hospitalizations, 50 ICU admissions, and 5 deaths would be prevented and 3-4 myocarditis cases might be seen. For males 18-29 year of age it was estimated that 9600 COVID-19 cases, 300 hospitalizations, 60 ICU admissions, and 3 deaths would be prevented and 22-27 myocarditis cases might be seen. For females 30-49 years of age it was estimated that 14,600 COVID-19 cases, 950 hospitalizations, 140 ICU admissions, and 20 deaths would be prevented and 1-2 myocarditis cases might be seen. For males 30-49 years of age it was estimated that 11,000 COVID-19 cases, 700 hospitalizations, 160 ICU admissions, and 24 deaths would be prevented and 5-6 myocarditis cases might be seen.

For females 50-64 years of age, it is estimated that 17,500 COVID-19 cases, 1700 hospitalizations, 375 ICU admissions, and 125 deaths would be prevented and 1 myocarditis case might be seen. For males in this group, it is estimated that 14,700 COVID-19 cases, 1900 hospitalizations, 500 ICU admissions, and 150 deaths would be prevented and 1 case of myocarditis might be seen. For females 65+ years of age, it is estimated that 32,000 COVID-19 cases, 6200 hospitalizations, 1300 ICU admissions, and 900 deaths would be prevented and less than 1 myocarditis case might be seen. For males in this group, it is estimated that 52,700 COVID-19 cases, 12,500 hospitalizations, 3500 ICU admissions, and 2400 deaths would be prevented and less than 1 case of myocarditis might be seen.

To summarize the overall reporting rates for these rare AEs, 3 cases of TTS have been observed per million Jensen doses among all adults. For GBS, 7.8 cases per million doses of Janssen vaccine have been reported. For myocarditis, 3.5 cases per million doses of mRNA vaccine have been reported. There are some limitations of the benefit-risk estimates. The model likely underestimates benefits for a few reasons. First, cases in general may be underreported and COVID-NET might not capture all COVID-19-associated hospitalizations. The model uses case incidence and hospitalizations from a snapshot in time and does not account for rising case counts. Second, these benefits are estimated over 120 days following vaccination, but protection from vaccination likely lasts longer. Third, the prevention of post-COVID-19 conditions is not accounted for. A few additional limitations to mention are that some of the hospitalizations used might be related to diagnoses other than COVID-19. The VE used was from clinical trials because there are limited data about real-world efficacy for input. Certain estimates for harms were from crude numbers of AEs reported to VAERS, which is a passive surveillance system. Not all events that are reported following vaccination have been confirmed to meet case definitions.

In terms of the benefit-risk interpretation and summary, this direct approach benefit-risk assessment for Janssen vaccine and similar direct benefit-risk assessment for mRNA vaccines each considers individual benefits of vaccination versus individual risks, which can help inform policy. Each shows a balance of benefits that far outweighs potential risks. As described, this relative balance of benefits and risks for individuals varies by age and by sex.

[21] Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; some age- and sex-specific doses administered data were imputed

Work Group Interpretation and Next Steps

Dr. Sarah Mbaeyi (CDC/NCIRD) presented the COVID-19 Vaccine WG's interpretation of the benefits and risks of COVID-19 vaccines. After a period of decline, COVID-19 cases are rising again. This is fueled by the spread of the highly transmissible Delta variant, which now accounts for 83% of US cases. Over two-thirds of US adults have received at least one COVID-19 vaccine dose, and approximately 60% are fully vaccinated.[22] However, coverage varies in the population by age, geographic location, race, and ethnicity, among other factors. At the local level, low vaccination coverage places individuals and communities at risk. Hotspots have emerged in areas where vaccination coverage is lagging.[23] mRNA vaccines account for the majority of the over 338 million COVID-19 vaccine doses administered in the US to date. Janssen accounts for 4% of doses administered, which remained consistent before the April pause.[24]

However, willingness to receive Janssen vaccine remains lower since the April pause. Among people who have not yet received a COVID-19 vaccine but plan to get one, 26% said they would be willing to get a Janssen vaccine. To inform ACIP discussions, CDC conducted a survey of jurisdictions to better understand the current use of Janssen vaccine and how it relates to patient choice, access, and vaccine equity at the state and local levels. Eighty-three percent of jurisdictions reported that most vaccination sites offer more than one type of vaccine at that site, which helps to ensure that patients have a choice in vaccine product. In addition, Janssen vaccine is used in a variety of populations and settings including in rural populations, mobile clinics, corrections populations, persons experiencing homelessness, primary care provider offices, among college students, and among other groups.[25] Thus, Janssen vaccine likely remains important for reaching disproportionately affected populations and for achieving vaccine equity.

The benefits of the currently authorized COVID-19 vaccines are unequivocal. All of the vaccines are effective against COVID-19, including serious outcomes like severe disease, hospitalization, and death. Available evidence also suggests that currently authorized vaccines offer protection against known circulating variants, including the Delta variant. A growing body of evidence indicates that people fully vaccinated with an mRNA vaccine are less likely to have symptomatic infection or to transmit SARS-CoV-2 to others.[26] However, rare SAEs have been reported after vaccination, including TTS and GBS after Janssen vaccination and myocarditis after mRNA vaccination. While rare but potentially serious risks of COVID-19 vaccines have been reported, the updated benefits/risk evaluation that Dr. Rosenblum presented continues to show that the benefits of vaccination outweigh these risks across vaccine types, age, and sex. The model demonstrates that for every million doses of vaccine administered, thousands of hospitalizations, ICU admissions, and deaths can be prevented.

[22] As of July 21, 2021 https://covid.cdc.gov/covid-data-tracker/#vaccinations
[23] https://www.cdc.gov/coronavirus/2019-ncov/images/communication/covid-data tracker/Vaccinations_By_Case_Rate_FINAL_07072021.pdf
[24] As of July 21, 2021. https://covid.cdc.gov/covid-data-tracker/#vaccinations
[25] Source: CDC Jurisdictional Pulse Survey 07/16-2021 1700, N=40
[26] https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html; Nasreen S, et al. "Effectiveness of COVID-19 vaccines against variants of concern, Canada." medRxiv (2021); Stowe J, et al. "Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant." Public Health England. 2021; Sheikh A, et al. "SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness." The Lancet (2021).

Taken together, the WG's interpretation was that vaccination continues to be critical during this period of rapidly increasing cases and spread of variants of concern. The reported AEs of TTS, GBS, and myocarditis are potentially serious and should be communicated transparently with the public. Even with the new GBS safety signal, the benefits of vaccination of Janssen vaccination continue to outweigh the risks. In addition to the benefit-risk profile, the WG discussed the importance of patient choice in vaccine product, access to vaccines for disproportionately affected populations, confidence in patients and providers to understand the benefits and risks of vaccines and to make informed decisions, the need for communication and educational materials around these rare risks, and the implications of any change in vaccine recommendations on global vaccine confidence and use.

The WG reaffirmed that all eligible persons should receive a COVID-19 vaccine. Patients and providers should be aware of both the benefits and risks of COVID-19 vaccination when choosing a vaccine product. The WG expressed strong support for the continued use of Janssen vaccine according to the current recommendations. The WG also emphasized the importance of clinical education and communication materials to help support patient-provider decision-making. CDC will be updating its clinical considerations[27] to state that persons with a prior history of GBS can receive any of the authorized vaccines. However, given the possible association between Janssen vaccine and GBS, patients with a history of GBS and their clinical team should discuss the availability of mRNA vaccines to offer protection against COVID-19. The clinical considerations also will provide information on GBS signs and symptoms and when to seek care. CDC also will be updating other clinical resources and tools, such as the standing orders and pre-vaccination checklists. In addition, CDC will be updating some of its communication materials, including information for providers on talking to patients about Janssen vaccine safety and updated frequently asked questions.

The following questions were posed for ACIP consideration and deliberation:

1. What is the ACIP's interpretation of the benefits and risks of COVID-19 vaccines?
2. Does ACIP agree with the WG's interpretation that Janssen COVID-19 Vaccine should continue to be used according to the current recommendations?

Data and Clinical Considerations for Additional Doses in Immunocompromised

Dr. Sara Oliver (CDC/NCIR) reviewed the COVID19 Vaccine WG's response to COVID-19 vaccine response among immunocompromised people, response to an additional dose of COVID-19 vaccine among immunocompromised people, and frequently asked questions about vaccination in this population. In terms of the process for additional doses in any population, there first would be a review of the data to assess the safety, immunogenicity, and implementation of any updated guidance or recommendation. Then there would be regulatory allowance by FDA. There are a variety of mechanisms by which this could occur. For example, one way is an EUA amendment that would allow for recommendations under EUA. Another possibility is a Biologics License Application (BLA), which would allow for ACIP to make off-label recommendations as is done for a variety of other vaccines. Once there is regulatory allowance, CDC or ACIP could have a clinical update with clinical considerations or recommendations for use.

[27] Updates will be posted at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

It has been estimated that immunocompromised people comprise approximately 2.7% of US adults.[28] This includes people with solid tumor and hematologic malignancies; receipt of solid-organ or hematopoietic stem cell transplantation (HSCT); severe primary immunodeficiencies; persons living with human immunodeficiency viruses (HIV); and treatment with immunosuppressive medications such as cancer chemotherapeuticagents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids.

Data from the pandemic also show that immunocompromised persons are more likely to get severely ill from COVID. They also are at higher risk for prolonged SARS-CoV-2 infection and shedding, viral evolution during infection and treatment, and low antibody titers to SARS-CoV-2 variants. In addition, they may be more likely to transmit SARS-CoV-2 to household contacts. Recent studies have demonstrated a higher proportion of vaccine breakthrough cases that occur among immunocompromised people. In one US study, 44% of hospitalized breakthrough cases were immunocompromised. This was 40% in an Israeli study.[29]

To summarize the VE studies among immunocompromised persons for mRNA vaccines, one study[30] evaluated VE 7-27 days after a second dose of the Pfizer-BioNTech vaccine. This study found 71% VE against SARS-CoV-2 infection compared to 90% overall. VE was slightly higher at 75% protection against symptomatic COVID. Another study[31] at least 7 days after a second mRNA dose found 80% VE against SARS-CoV-2 infection among people with inflammatory bowel disease (IBD) on immunosuppressive medications. This study also found that VE was quite low at 25% after the first dose. Another study[32] evaluating VE at least 14 days after the second mRNA vaccine dose found 59% VE against COVID hospitalization from 14 days after the second dose among immunocompromised persons compared to 91% among those without a documented immunocompromising condition. It was this specific hospitalized cohort where 44% of breakthrough cases had a solid or hematologic malignancy or a history of a solid-organ transplant. The percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study was updated with additional studies since the last ACIP meeting. Hemodialysis patients have the highest proportion with an antibody response, while those who have a history of organ transplant have the lowest percent response. In general, studies that were able to compare response after Dose 1 and Dose 2 compared poor response to Dose 1.[33]

Moving to the emerging data on response to an additional dose of a COVID-19 vaccine in immunocompromised people, 4 studies looked at the antibody response in immunocompromised populations. The optimal data in this situation would be to have clinical VE documenting protection against infection or illness. However, in many circumstances there are data only on antibody response. While it may not tell the full story, something can be learned from these data. While many of these studies have small numbers, among those who had no antibody response to an initial mRNA series, 33%-50% did develop a detectible antibody response to an additional dose.[34]

[28] Harpaz et al. Prevalence of Immunosuppression Among U.S. Adults, 2013. JAMA 2016
[29] See references for slide 7 at the end of Dr. Oliver's slide set
[30] Chodick et al. Clinical Infectious Diseases, ciab438, https://doi.org/10.1093/cid/ciab438
[31] Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf
[32] Tenforde et al. medRxiv preprint: https://doi.org/10.1101/2021.07.08.21259776
[33] See reference list for slide 9 at the end of Dr. Oliver's slide set
[34] See references list for slide 11 at the end of Dr. Oliver's slide set

Looking more closely at the Kamar study[35] of Anti-SARS-CoV-2 antibodies before each dose and one month after the third dose in a study population of solid-organ transplant recipients, the prevalence of Anti-SARS-CoV-2 antibodies was 40% before the third dose and 68% overall 4 weeks after the third dose. Looking only at patients who had been seronegative before the third dose, 44% were seropositive at four weeks after the third dose. In addition, no SAEs were reported after the administration of the third dose and no acute rejection episodes occurred. Looking more closely at the Maxime study[36] on the reactogenicity of a third mRNA vaccine dose in a cohort of patients on hemodialysis, no patients developed side effects that required hospitalization. Symptoms reported after the third dose were consistent with what has been seen after the second dose. Most symptoms were mild or moderate.

Internationally, several countries have commented on policies for additional doses for immunocompromised individuals. France[37] has recommended that a third dose 4 weeks after the second dose be given for patients who are severely immunocompromised. The UK[38] has a proposal for additional doses of COVID vaccine for immunocompromised people 16 years and older, but a formal recommendation and decision are pending. Israel[39] announced a policy recently for an additional dose for people living with organ or stem cell transplants, blood cancer, autoimmune disease, and treatment with specific immunosuppressive medications.

In summary, immunocompromised people are at an increased risk of poor outcomes from COVID. Studies indicate a reduced antibody response in immunocompromised people following a primary vaccine series compared to healthy vaccine recipients. Emerging data suggest that an additional COVID-19 vaccine dose in immunocompromised people may enhance antibody response in some and increase the proportion who respond. In small studies, the reactogenicity of a third dose of mRNA vaccine was similar to prior doses.

Now moving to frequently asked questions about vaccination of immunocompromised people. In terms of which immunocompromised groups should be considered for an additional dose once allowed by regulatory mechanisms, it is likely that the most benefit would be focusing on conditions and treatment associated with moderate to severe immunocompromise. This would include those on active or recent treatment for solid tumor and hematologic malignancies; receipt of a solid-organ or recent stem cell transplant; severe primary immunodeficiency; advanced or untreated HIV; and treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids. There are chronic conditions associated with varying degrees of immune deficit, such as asplenia and chronic renal disease. Different medical conditions and treatments can result in varying degrees of immunosuppression. A patient's clinical team may be able to assess the degree of altered immunocompetence and optimal timing of vaccination.

In terms of whether immunocompromised people should undergo antibody testing following COVID-19 vaccination, the utility of serologic testing or cellular immune testing to assess immune response to COVID vaccination has not been established. The exact correlation between antibody level and protection from COVID remains unclear. In addition, commercial antibody and cellular immune testing may not be consistent across laboratories. For all of these reasons, serologic (antibody) testing or cellular immune testing to assess response to

[35] Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)
[36] Maxime et al. (2021) medRxiv doi: https://doi.org/10.1101/2021.07.02.21259913
[37] dgs_urgent_n43_vaccination_modalites_d_administration_des_rappels.pdf (solidarites-sante.gouv.fr)
[38] C1327-covid-19-vaccination-autumn-winter-phadvicease-3-planning.pdf
[39] https://govextra.gov.il/media/30095/meeting-summary-15122020.pdf

vaccination outside of the context of research studies is not recommended in the US at this time.

Regarding whether there are data to support a mixed-dose series in immunocompromised people, such as a Janssen vaccine followed by an mRNA COVID vaccine, studies in Europe[40] have assessed heterologous primary series, specifically an AZ and a Pfizer vaccine, in the general adult population and found immunogenicity to be at least equivalent to a homologous series. A large UK trial, the Com-COV study, found that 1 dose of AZ plus 1 dose of Pfizer resulted in superior immunogenicity compared with 2 doses of an AZ vaccine, but lower antibodies than 2 doses of Pfizer. In addition, an increase in systemic reactogenicity was observed with heterologous schedules. However, evidence is needed regarding the safety and immunogenicity using a mixed-dose approach with mRNA vaccines and a Janssen vaccine in immunocompromised persons.

With regard to what infection prevention measures should be maintained following COVID vaccination, immunocompromised people should be counselled about the potential for a reduced immune response to COVID vaccination and the need to continue to follow prevention measures,[41] such as wearing a mask, social distancing, and avoiding crowds. Given that less than half of the immunocompromised persons had a detectible antibody response after an additional dose, these measures should be maintained for immunocompromised persons even if additional doses are given. Close contacts of immunocompromised people should be encouraged to be vaccinated against COVID.

With respect to whether there is a role for monoclonal antibody use in immunocompromised people, monoclonal antibodies are currently authorized by FDA for emergency use in persons with SARS-CoV-2 infection who are at high risk for progressing to severe COVID and hospitalization. While monoclonal antibodies are not yet authorized for SARS-CoV-2 infection, studies are underway.

With regard to the implications for an EUA of the COVID vaccines with respect to considerations for additional doses in immunocompromised persons, the FDA has authorized mRNA vaccines as a 2-dose series and Janssen COVID vaccines as a single dose. At this time, no data have been submitted to the FDA to support amendments to the EUA for this population. However, CDC and ACIP will closely monitor for any updates to the data and to regulatory mechanisms. Meanwhile, immunocompromised people should continue to follow infection prevention measures. Close contacts who are of age to be vaccinated should be vaccinated against COVID-19 to protect their immunocompromised friends and family. Early treatment with monoclonal antibodies may be beneficial in this population as well.

In terms of next steps, the WG will continue to assess additional studies of safety and immunogenicity of additional doses in immunocompromised people; assess additional studies and expert opinion regarding subpopulations of immunocompromised people who may benefit the most from an additional dose; determine acceptable intervals, as well as mix-and-match schedules; and await all of the data that can support a regulatory allowance, which could

[40] 1) Borobia et al. Reactogenicity and Immunogenicity of BNT162b2 in Subjects Having Received a First Dose of ChAdOx1s: Initial Results of a Randomized, Adaptive, Phase 2 Trial (CombiVacS). Available at SSRN: https://ssrn.com/abstract=3854768; 2) Shaw et al. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(21)01115-6; 3) Hillus et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunization with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. medRxiv; 2021. DOI: 10.1101/2021.05.19.21257334; 4) Schmidt et al. medRxiv preprint (June 15 2021): https://doi.org/10.1101/2021.06.13.21258859 Click to add text; 5) Liu et al. Lancet preprint (June 25, 2021): http://dx.doi.org/10.2139/ssrn.3874014

[41] https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

possibly include an FDA amendment of the EUA or a BLA for additional doses of COVID-19 vaccines.

The WG posed the following questions for ACIP to consider and deliberate:

1. What additional data does ACIP need to inform these discussions?
2. Thoughts on the focus of "moderate to severe" immunocompromised populations, once authorized/approved?

Summary of Discussion (Rosenblum, Mbaeyi, & Oliver)

- ACIP expressed interest in information on the following with respect to additional data needed and the focus of "moderate to severe" immunocompromised populations:
    - Whether immune compromised people who do not respond to the initial 2-dose series followed by a third dose should receive a fourth dose
    - Length of time after receipt of monoclonal antibody administration before receipt of a vaccine, with the understanding that the type of immunocompromise, degree, and underpinnings differ
    - Potential implications of giving a third dose to people who have high antibody levels (e.g., perhaps myopericarditis is the result of making too much spike protein antibody, maybe hemodialysis patients do not need a third dose given their robust antibody response)
    - The possibility of offering a third dose to immunocompromised individuals through a study or Investigational New Drug (IND) route for this population in order to provide earlier access
    - Whether large datasets such as the VSD could be queried to find potential breakthrough cases among vaccinated immunocompromised individuals, understanding that a complicating factor is that many people seem to have gotten vaccinated outside of the healthcare system and that a lot of work would be required to ensure that the data are of high enough quality to analyze
    - Possible safety signals for those who have obtained additional doses of vaccine in an unsupervised fashion
    - Equity and the potential for some people to be left behind, in that patients who tend to be more educated and more empowered to take care of their own healthcare are likely the ones getting additional doses
    - Determining a target level antibody among immunocompromised persons
    - Immunocompromised people are not vaccine-hesitant and already are having their antibodies measured on a regular basis, so this seems like a potential place for shared decision-making with their clinician(s), though this could prove difficult because the immunocompromised population is heterogenous
    - More information on studies being planned for persons 12 to 18 years of age
    - A better understanding of what could be done to expedite the BLA process

- In response to potential recommendation for antibody testing prior to a third dose, Dr. Oliver pointed out that many of the assays for COVID and spike antibody are under EUA by FDA as well. There is concern with the variety of cut points and thresholds across the assays. Without a correlative protection, it is not clear what testing positive on one test and negative on another test necessarily means as it relates to vaccine response, clinical protection against disease, or vulnerability to COVID-19.

- Dr. Fink, FDA, assured the ACIP voting and liaison members and the public that FDA is working as rapidly as possible to conduct a thorough and comprehensive review of all regulatory submissions for COVID-19 vaccines with the goal of ultimately approving safe and effective COVID-19 vaccines for use in the US. They appreciate the comments that have been made by committee members, liaisons, and the public about the need for better protection amongst immunocompromised populations. This is truly an important scientific issue and an important public health issue. And FDA is actively exploring all regulatory options for providing access to additional doses of authorized vaccines in situations where the data suggest that the benefits would outweigh the risks. Ultimately, FDA is a data-driven agency such that any regulatory action or regulatory mechanism for access would rely upon submission supportive data to the FDA for consideration.

- Several ACIP members and liaisons emphasized the critical importance of getting the unvaccinated vaccinated in order to protect those who are immunocompromised, and stressed that boosters alone are not likely to be sufficiently effective. While boosters are important, so is creating a circle of protection for individuals, their families, their friends, their neighbors, and their loved ones. It has been reported that 13 million doses of COVID vaccine are about to expire. Every day, vaccine doses are being wasted because there are not enough people taking advantage of getting vaccinated. Now the Delta variant is rampant and there are increasing rates of infection. This is a great opportunity for those who are not vaccinated to get vaccinated.

CERTIFICATION

Upon reviewing the foregoing version of the July 22, 2021 ACIP meeting minutes, Dr. Jose Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN THE DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACC	American College of Cardiology
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
AESI	Adverse Events of Special Interest
AGS	American Geriatric Society
AHA	American Heart Association
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
ASTHO	Association of State and Territorial Health Officers
AZ	AstraZeneca
BEST	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CAR-T	Chimeric Antigen Receptor T-Cell Therapy
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CSTE	Council of State and Territorial Epidemiologists
CVST	Cerebral Venous Sinus Thrombosis
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVRPA	Division of Vaccines and Related Product Applications
ED	Emergency Department
EHR	Electronic Health Record
ELISA	Enzyme-Linked Immunosorbent
EMA	European Medicines Agency
EtR Framework	Evidence to Recommendations Framework
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations

HAN	Health Alert Network
HCP	Health Care Personnel / Provider / Professional
HCW	Health Care Workers
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Viruses
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplantation
IBD	Inflammatory Bowel Disease
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
IVIG	Intravenous Immune Globulin
J&J	Johnson & Johnson
MASO	Management Analysis and Services Office
MedDRA	Medical Dictionary for Regulatory Activities
MIS-C	Multisystem Inflammatory Syndrome in Children
MMWR	*Morbidity and Mortality Weekly Report*
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NMA	National Medical Association
NSAIDS	Nonsteroidal Anti-Inflammatory Agents
O/E	Observed-to-Expected
PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PI	Principal Investigator
PIDS	Pediatric Infectious Disease Society
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Terms
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SHEA	Society for Healthcare Epidemiology of America
SMEs	Subject Matter Experts

TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST	ACIP COVID-19 Vaccine Safety Technical Work Group
VE	Vaccine Effectiveness
VOC	Variant of Concern
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolism
WG	Work Group
WHO	World Health Organization