

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

**AUGUST 13, 2021
SUMMARY MINUTES**

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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 August 13, 2021. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on additional doses of messenger ribonucleic acid (mRNA) COVID-19 vaccines as part of a primary series among immunocompromised persons, emerging severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants and COVID-19 vaccines, and considerations for booster doses of COVID-19 vaccines for persons previously vaccinated with a primary series.

THURSDAY: AUGUST 13, 2021

WELCOME AND INTRODUCTIONS

Dr. Grace Lee (ACIP Chair) called to order and presided over her first meeting since assuming the role of ACIP Chair. She welcomed everyone to the 10th ACIP meeting for 2021 and the 20th ACIP meeting since the beginning of the COVID-19 pandemic. She acknowledged outgoing members Dr. Hank Bernstein; Dr. Sharon Frey; and Dr. Jose Romero, ACIP former Chair and expressed gratitude for their service and dedication to the ACIP. In addition, Dr. Lee thanked the current ACIP members for continuing to support the United States (US) on decisions about the use of vaccines and their willingness to make decisions in the face of uncertainty and constantly evolving data.

Dr. Amanda Cohn (ACIP Executive Secretary) added her welcome to those attending the August 13, 2021 virtual ACIP meeting. She indicated that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that there would be an oral public comment session prior to the vote at approximately 12:30 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-2021-0084. 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.

Dr. Cohn announced that the anticipated dates for upcoming emergency ACIP meetings focused on COVID-19 vaccines would be August 24, 2021 and September 29-30, 2021, while the next regularly scheduled meeting focused on non-COVID vaccine related issues would be October 20-21, 2021. She emphasized that there could be additional COVID-19 vaccine meetings at any time, which would be updated on the ACIP website as soon as possible once confirmed.

Dr. Lee (ACIP Chair) conducted a roll call, during which no COIs were declared and quorum was established. 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

FDA Announcement

Dr. Peter Marks (FDA/BCBER) reminded everyone that the immunocompromised is a heterogeneous group in their ability to respond to the available COVID-19 vaccines. While some have relatively modest immune repairment, others may either not respond or respond poorly to the existing COVID-19 vaccines such as those who have received solid organ transplants or who are on medications that are typically used for solid organ transplants. After reviewing recent studies, including one for the Pfizer-BioNTech vaccine and the other for the Moderna vaccine, the Food and Drug Administration (FDA) decided to amend the Emergency Use Authorization (EUA) to allow for a third dose of COVID-19 vaccine to be administered to individuals at least 12 years of age for the Pfizer-BioNTech vaccine or at least 18 years of age for the Moderna vaccine who have undergone solid organ transplantation or who were diagnosed with conditions that are considered to have an equivalent level of immunocompromise. That was caveated with the fact that the administration of these third doses appears to be only moderately effective in increasing antibody titers, so patients should be counseled to maintain physical precautions to help prevent COVID-19 and close contacts of immunocompromised persons should be vaccinated as appropriated for their health status. FDA will continue to evaluate data as they becomes available.

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) introduced the COVID-19 Vaccines WG session, first noting that there had been a 700% increase in the 7-day moving average of COVID-19 cases in the US since July 1, 2021. He reported that for the last 2 months, the COVID-19 Vaccines Work Group (WG) had been meeting at least weekly during which they reviewed vaccines with respect to SARS-CoV-2 variants, reviewed and discussed updates on myocarditis following vaccination, reviewed in detail the Evidence to Recommendations (EtR) Framework for additional doses of mRNA COVID-19 vaccines for immunocompromised individuals, discussed a number of clinical considerations related to these individuals as well as other issues, and talked about considerations for booster doses of COVID-19 vaccines in the broader population. The goal for this ACIP meeting was to discuss and vote on additional doses of mRNA COVID-19 vaccines as part of a primary series in immunocompromised individuals, discuss clinical considerations for mRNA COVID-19 vaccines as part of a primary vaccine series for immunocompromised people, hear an update on emerging SARS-CoV-2 variants and COVID-19 vaccines, and consider booster doses of COVID-19 vaccines in the general population.

EtR Framework: Additional Doses of mRNA COVID-19 Vaccines as Part of a Primary Series for Immunocompromised People

Dr. Kathleen Dooling (CDC/NCIRD) provided a summary of the EtR Framework on additional doses of mRNA COVID-19 vaccines as part of a primary series for immunocompromised people. Before getting into the EtR Framework, she referenced the regulatory allowance upon which they were proceeding during this meeting that was introduced by Dr. Marks. On the night of August 12, 2021, the FDA authorized an additional vaccine dose for certain immunocompromised individuals.¹ It should be noted that the amendment applies only to immunocompromised people. Other fully vaccinated individuals do not need an additional dose at this time. The amendment applies to Pfizer-BioNTech COVID-19 vaccine for individuals ≥ 12 years of age and Moderna COVID-19 vaccine for individuals ≥ 18 years of age. Due to insufficient data, the EUA amendment for an additional dose does not apply to Janssen COVID-19 vaccine or individuals who received Janssen COVID-19 as a primary series. CDC and FDA are actively engaged to ensure that immunocompromised recipients of Janssen COVID-19 vaccine have optimal vaccine protection.

As sanctioned by the ACIP, the EtR Framework provides a structure to describe information considered in moving from evidence to ACIP vaccine recommendations and to provide transparency around the impact of additional factors on deliberations when considering a recommendation. The EtR policy question for this ACIP meeting was, “Should ACIP recommend vaccination with an additional dose of either Pfizer-BioNTech or Moderna COVID-19 (mRNA vaccines) following a primary series in immunocompromised people, under an Emergency Use Authorization?”

This discussion focused on the immunocompromised population, meaning people with medical conditions or people receiving treatments that are associated with moderate to severe immune compromise.² That includes active or recent treatment for a solid tumor or hematologic malignancies; receipt of solid organ or recent hematopoietic stem cell transplants (HSCT); severe primary immunodeficiency; advanced or untreated HIV infection; active treatment with high-dose corticosteroids, alkylating agents, metabolites, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory; and chronic medical conditions such as asplenia and chronic renal disease that may be associated with varying degrees of immune deficit.

The intervention of interest is an additional dose of Pfizer-BioNTech COVID-19 vaccine (BNT162b2) or Moderna COVID-19 vaccine (mRNA-1273), both in people 18 years of age and older after an initial 2-dose primary series of mRNA COVID-19 vaccine in immunocompromised people. The WG interpretations that follow were based on consideration of people 18 years of age and older for both vaccines. However, the FDA EUA amendment provides allowance for the use of an additional dose of Pfizer-BioNTech vaccine in adolescents 12-17 years of age. Attempts should be made to match the additional dose type of the mRNA primary series when

¹ <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised>

² Additional information about the level of immune suppression associated with a range of medical conditions and treatments can be found in general best practices for vaccination of people with altered immunocompetence, the CDC Yellow Book, and the Infectious Diseases Society of America policy statement, 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

possible. However, a heterologous additional dose is permitted when matching is not feasible. The additional dose of mRNA COVID-19 vaccine should be administered at least 28 days after completion of the primary mRNA COVID-19 vaccine series.

Before proceeding with the EtR, Dr. Dooling reiterated that any recommendation for an additional dose would not supplant the importance of infection prevention measures. Immunocompromised people should continue to wear a mask, stay 6 feet apart from others they do not live with, and avoid crowds and poorly ventilated indoor spaces until advised otherwise by their healthcare provider (HCP). Importantly, close contacts of immunocompromised people are strongly encouraged to be vaccinated against COVID-19.³

As a reminder, the EtR domains include the Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity along with related questions for each. In this case, the public health problem refers to COVID-19 among immunocompromised people and the intervention refers to an additional dose of mRNA COVID-19 vaccine in immunocompromised people who already received a primary series of an mRNA COVID-19 vaccine.

First, a description of the public health problem. COVID-19 cases have been increasing since early July. As of August 9th, there have been over 35 million COVID-19 cases reported to CDC with the most recent 7-day average of over 100,000 cases per day.⁴ Hospitalization rates also have been increasing since early July.⁵ Deaths have been increasing as well. The current 7-day moving average is over 600 deaths per day from COVID-19.⁶

According to one national survey, immunocompromised people comprise approximately 2.7% of the US adult population or approximately 7 million adults. Immunocompromised people are more likely to get severely ill from COVID-19. They are at higher risk for prolonged SARS-CoV-2 infection and shedding and viral evolution during the infection and treatment, particularly amongst hospitalized patients. They have lower antibody neutralization titers to SARS-CoV-2 variants compared to non-immunocompromised people and they are more likely to transmit SARS-CoV-2 to household contacts. Immunocompromised people are more likely to have breakthrough infection. In small studies of hospitalized breakthrough cases, 40%-44% were deemed to be immunocompromised. Several observational studies have shown lower vaccine effectiveness (VE) with VE estimates ranging from 59%-72% among immunocompromised versus 90%-94% among non-immunocompromised people after 2 doses of mRNA vaccine.⁷

In terms of the percentage of antibody response after 2 mRNA vaccine doses by different types of immunocompromising conditions, studies among people with cancer showed that the proportion with antibody response ranged from 45%-95%, with lower responses seen among people with hematologic cancers. Studies of people on hemodialysis ranged from 71%-98% response following 2 doses. Studies of people with solid organ transplant have the largest deficits in antibody response, ranging from 0%-79%. Studies of people treated for autoimmune or inflammatory disorders ranged from 40%-94% response to an mRNA primary series. Healthy controls by comparison, where they were included in these studies, ranged from 95%-100% of vaccine response. Almost all studies that assessed response after the first and second doses

³ <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html>

⁴ https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases

⁵ https://gis.cdc.gov/grasp/covidnet/covid19_3.html August 9, 2021

⁶ https://covid.cdc.gov/covid-data-tracker/#trends_dailytrendscases August 9, 2021

⁷ See references list for slides 15 and 16 at the end of Dr. Dooling's slide set

demonstrated a less robust response after only one dose.⁸ Several countries, including France, the United Kingdom (UK), Israel, and Germany, are considering or have announced plans for the use of an additional dose in immunocompromised people.⁹ Based on review of this data, the WG felt that COVID-19 disease among immunocompromised people is of public health importance.

The benefits and harms domain focused on the primary questions regarding how substantial the anticipated desirable and undesirable effects are for each main outcome, as well as whether the desirable effects outweigh the undesirable effects. Earlier in the week, the first randomized trial of third dose of mRNA vaccine in transplant recipients was published. This study randomized 120 vaccinated people to either a third dose of Moderna vaccine or placebo. The primary outcome was a receptor binding domain (RBD) antibody level of at least 100 U/mL at 1 month post-Dose 3. Antibodies were higher in recipients of the third dose of Moderna vaccine, with 55% of the vaccine group achieving the endpoint versus only 18% of the placebo group. Encouraging improvements in immune response also were observed for neutralizing antibodies and T-cell function.¹⁰

Looking at 5 observational studies looking at seropositivity after a second dose of mRNA, 2 in recipients of solid organ transplants and 3 in patients on hemodialysis, seropositivity after a second dose of mRNA ranged from 20%-89%. A third dose of mRNA was administered among those who had no detectable antibody response to the initial mRNA vaccine primary series, with 33%-50% developing an antibody response to a third dose.¹¹ In the Kamar et al. study¹² of solid organ transplant patients, the proportion of the group who were seropositive increased after each dose at 40% post-Dose 2 and 68% 1 month post-Dose 3. In addition, the average antibody titer increased after each dose. Even those who were already seropositive experienced increases in their antibody levels. In this study of 99 transplant patients, no serious adverse events (SAEs) were reported after administration of the third dose and no acute rejection episodes occurred. The Epsi et al. study¹³ showed the reactogenicity of a third mRNA vaccine in a cohort of patients on hemodialysis. No patients developed side effects that required hospitalization. Symptoms reported were consistent with the previous doses and the intensity of the symptoms was mostly mild or moderate.

To summarize the available evidence regarding possible benefits, emerging experimental and observational data in adults suggests that an additional mRNA COVID vaccine in immunocompromised people enhances antibody response and increases the proportion who respond to COVID-19 vaccine. No efficacy or effectiveness studies of COVID-19 prevention following a third dose exist. With respect to potential harms, in small studies of an additional dose of mRNA vaccine, no SAEs were observed and reactogenicity of a third dose of mRNA was similar to prior doses. It should be noted that mRNA COVID-19 vaccines are associated with rare but serious adverse events, including anaphylaxis, myocarditis, and pericarditis in young adults. The impact of immunocompromising conditions on these rare events is unknown. There are no safety studies published on additional mRNA doses in immunocompromised

⁸ See references list for slide 17 at the end of Dr. Dooling's slide set

⁹ 1) dgs_urgent_n43_vaccination_modalites_d_administration_des_rappels.pdf (solidarites-sante.gouv.fr); 2)

<https://govextra.gov.il/media/30095/meeting-summary-15122020.pdf>; 3)

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009174/COVID-](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009174/COVID-19_vaccination_programme_guidance_for_healthcare_workers_6_August_2021_v3.10.pdf)

[19_vaccination_programme_guidance_for_healthcare_workers_6_August_2021_v3.10.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1009174/COVID-19_vaccination_programme_guidance_for_healthcare_workers_6_August_2021_v3.10.pdf); 4)

<https://www.reuters.com/world/europe/french-president-macron-third-covid-vaccine-doses-likely-elderly-vulnerable-2021-08-05/>

¹⁰ Hall et al. (2021) NEJM. Randomized Trial of a Third Dose of mRNA-1273 Vaccine in Transplant Recipients. DOI: 10.1056/NEJMc2111462

¹¹ See list of references for slide 26 at the end of Dr. Dooling's presentation

¹² Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)

¹³ Epsi et al. (2021) medRxiv doi: <https://doi.org/10.1101/2021.07.02.21259913>

adolescents. The WG felt that the desirable anticipated effects were large, the undesirable anticipated effects were minimal, and that the balance favored the intervention of the use of an additional dose of mRNA COVID vaccine in immunocompromised people.

The domain of values and acceptability addresses how the target population feels about the balance of desirable and undesirable effects, if there is variability in how people value the outcomes, and whether an additional dose of mRNA COVID-19 vaccines is acceptable to stakeholders. The use of additional doses of COVID-19 vaccines in the general US population is not currently recommended by ACIP. Approximately 140 million individuals have completed a 2-dose primary series of either Moderna or Pfizer-BioNTech COVID-19 vaccine. Approximately 1.14 million people (<1%) received one or more additional COVID-19 doses. Approximately 12 million individuals received a 1-dose primary series of Janssen COVID-19 vaccine, with a little over 90,000 (~1%) people in this population receiving one or more additional doses of COVID-19 vaccines.

To focus in on the immunocompromised population under consideration, a large study was conducted among individuals with cancer, autoimmune disease, and other conditions early in the COVID vaccine rollout. At that time, 81% already were vaccinated or intended to become vaccinated and 19% either said that they were unsure, probably would not, or definitely would not receive a COVID-19 vaccine. This was a higher intent to vaccinate than the general adult population. Factors associated with hesitancy among recipients were younger age, female gender, Black, Pacific Island or Native American race or ethnicity, less formal education, anti-vaccine sentiment, and distrust of the media.¹⁴ While the stated reasons for vaccine refusal among immunocompromised people are many and varied, across studies concerns about safety, possible side effects, discomfort, and distrust of vaccines were common.¹⁵

Professional bodies strongly support COVID-19 vaccination and use of an additional dose in immunocompromised populations. In the many letters received from professional associations,¹⁶ two main points emerged. They encouraged study of safety and efficacy/effectiveness of an additional dose of COVID-19 vaccine in immunocompromised people, and they supported swift action on the part of ACIP to recommend use of an additional dose of COVID-19 vaccine in immunocompromised people. The Pediatric Infectious Diseases Society (PIDS) and Children's Oncology Group (COG) supported use of an additional dose in immunocompromised adolescents. Patient advocacy bodies also expressed strong support of COVID-19 vaccination and study of an additional dose. Specifically, the Leukemia & Lymphoma Society (LLS) supports providing access to doses of COVID-19 vaccine for supplemental vaccination in immunocompromised patients and urges that these patients have the opportunity to be among the first to receive these additional doses.

In summary of the available evidence for values overall, the initial intent to vaccinate is high among immunocompromised populations. Concerns about safety and possible side effects are the main reasons for vaccine hesitancy. Younger age, female gender, racial/ethnic minorities, and less formal education are factors associated with vaccine hesitancy. Strong support for an additional dose was expressed by immunocompromised patients via written and oral comments

¹⁴ COVID-19 vaccine hesitancy among individuals with cancer, autoimmune diseases, and other serious comorbid conditions (medrxiv.org)

¹⁵ 1) COVID-19 vaccine hesitancy among individuals with cancer, autoimmune diseases, and other serious comorbid conditions (medrxiv.org); 2) SARS-CoV-2 Vaccine Acceptability in Patients on Hemodialysis: A Nationwide Survey | American Society of Nephrology (asnjournal.org)

¹⁶ Infectious Diseases Society of America, American College of Rheumatology, American Society of Transplantation, American Society of Transplant Surgeons, International Society for Heart and Lung Transplantation, Pediatric Infectious Diseases Society, Children's Oncology Group

to ACIP meeting on July 22, 2021. With regard to acceptability, professionals who provide healthcare to immunocompromised people recognize that their patients are at high risk for severe outcomes from COVID-19 and strongly support a recommendation for an additional dose of COVID-19 vaccine. Societies that advocate for access to the best quality care for patients with immunocompromising conditions support access to an additional dose of COVID-19 vaccine to increase the chances of vaccine protection. The WG concluded that the target group felt the desirable effects were large compared to the undesirable effects and that there was probably no important uncertainty or variability. The WG felt that an additional dose of mRNA COVID vaccine for immunocompromised people was acceptable to key stakeholders.

The primary question regarding the domain of feasibility pertained to whether an additional dose of mRNA COVID vaccine would be feasible to implement among immunocompromised people. In general, there are high levels of interaction between immunocompromised populations and the healthcare system that provide opportunities for an additional dose following the primary series. mRNA COVID-19 vaccine supply in the US is sufficient to make an additional dose for immunocompromised people feasible. Testing for antibodies following vaccination is not recommended, thus reducing the complexity of a recommendation for an additional dose. Therefore, the WG felt that an additional dose of mRNA vaccine would be feasible to implement among immunocompromised people.

The primary question regarding the domain of resource use pertained to whether an additional dose of mRNA vaccine given to immunocompromised people would be a reasonable and efficient allocation of resources. The US Government (USG) purchased 600 million doses of mRNA vaccines,¹⁷ which is available at no cost to the recipient. No studies have evaluated cost-effectiveness regarding the use of COVID-19 vaccines among immunocompromised or a third dose. Immunocompromised patients experience high medical costs at baseline and are at high risk of hospitalization. The cost of an additional dose of COVID-19 vaccine is small relative to these costs. As a reminder, the WG previously concluded that cost-effectiveness may not be the primary driver for decision-making during a pandemic and for vaccines under an EUA. The WG felt that an additional dose of mRNA vaccine given to immunocompromised people would be a reasonable and efficient allocation of resources.

The primary question regarding equity regarded what the impact on health equity would be of an additional dose of mRNA COVID-19 vaccine given to immunocompromised people. As a reminder, health equity is when everyone has the opportunity to be as healthy as possible and no one is disadvantaged from achieving this potential because of a social position or other socially determined circumstances. There are a number of immunocompromised groups in the US who could be disadvantaged with respect to an additional mRNA COVID vaccine dose, such as those who may experience limited access to vaccines because of their place of residence, race/ethnicity, socioeconomic status (SES), personal characteristics associated with discrimination, and/or those who belong to a group for whom vaccine hesitancy is high. In addition, for the time being, those who receive Janssen COVID-19 vaccine will not be eligible for an additional dose of mRNA vaccine.

¹⁷ <https://www.hhs.gov/about/news/2021/02/11/biden-administration-purchases-additional-doses-covid-19-vaccines-from-pfizer-and-moderna.html>

In the general US population, great strides have been made toward equitable uptake of COVID-19 vaccines. However, there is still room for improvement.¹⁸ Similar patterns may be seen with uptake among immunocompromised people. Equitable application of this intervention can be bolstered by a multi-pronged approach to ensure access, making sure that mRNA vaccines are available at primary care provider (PCP) and specialist clinics serving immunocompromised patients, Federally Qualified Health Centers (FQHCs), rural health clinics, community health centers, hospitals, and pharmacies. The WG felt that an additional dose of mRNA COVID-19 vaccine given to immunocompromised people probably would have no impact on health equity.

In summary of the EtR domains, the WG concluded that COVID-19 disease in immunocompromised people is an important public health problem. The anticipated desirable effects of an additional dose of mRNA vaccine are large and undesirable effects are expected to be minimal, favoring the intervention. The certainty of the evidence was not formally graded. The WG felt that the target population valued the intervention and that the intervention was acceptable to stakeholders, feasible to implement, and a reasonable use of resources. The WG thought an additional dose of mRNA vaccine for immunocompromised people probably would not impact health equity. Overall, most WG members felt that the desirable consequences clearly outweighed undesirable consequences in most settings. After reviewing the totality of information presented in the EtR Framework, the WG discussed the type of recommendation to propose to ACIP. Most WG members supported recommending the intervention.

To begin the discussion, the WG posed the following questions for ACIP to consider and deliberate:

1. Does ACIP support the intervention of an additional dose of mRNA COVID-19 vaccine following a primary series in immunocompromised people?
2. Balancing potential benefits and potential harms, what is the optimal lower age threshold for the additional dose intervention in immunocompromised people?

Clinical Considerations for Use of an Additional Dose of mRNA COVID-19 Vaccines as Part of a Primary Vaccine Series for Immunocompromised People

Dr. Neela Goswami (CDC/NCHHSTP) shared the proposed clinical considerations for use of an additional mRNA COVID-19 vaccine dose following a primary COVID-19 vaccine series for immunocompromised people. To respond to a request that was raised during the last ACIP WG meeting regarding COVID vaccines and pregnancy, language strengthening the recommendation for COVID vaccine among child-bearing women and pregnant people was updated and posted by CDC earlier in the week. In summary, COVID-19 vaccination is recommended for all people aged 12 years and older, including people who are pregnant, lactating, trying to get pregnant, or who might become pregnant in the future. It is important to know that CDC and ACIP have never pointed to pregnancy as a contraindication to COVID vaccine, but additional real-world evidence about the safety and effectiveness of COVID-19 vaccination during pregnancy further demonstrates that the benefits of receiving a COVID-19 vaccine outweigh any known or potential risks. This is particularly important given that COVID-19 disease itself increases the risk of severe illness and pregnancy complications.

¹⁸ CDC. <https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic> as of August 8, 2021, and US Census Bureau National Population Estimates

The updated language was posted on August 11, 2021 to the Clinical Considerations site.¹⁹ There is no evidence that any of the COVID-19 vaccines affect current or future fertility. COVID-19 vaccines do not cause infection in the pregnant person or the fetus. There are no safety signals in animal studies. There are reassuring early safety data on mRNA COVID-19 vaccines during pregnancy. Early data suggest mRNA COVID-19 vaccines during pregnancy are effective.

Now moving to the topic at hand. As a reminder, the first step in the process for the consideration of an additional dose of COVID-19 vaccine in immunocompromised people is data review to assess the safety, immunogenicity, and implementation features related to the use of an additional dose of COVID-19 vaccine in this population, which Dr. Dooling just presented. Then there is regulatory allowance by the FDA. At this point, FDA has issued an EUA for both Pfizer-BioNTech and Moderna COVID-19 vaccine that allows ACIP to make recommendations under an EUA. Once there is regulatory allowance, CDC or ACIP can have a clinical update with clinical considerations or recommendations for use. The purpose of this presentation was to review the proposed interim clinical considerations for use of an additional dose of mRNA COVID-19 vaccine in immunocompromised people.

It is important to keep in mind that there are two distinct potential ways an additional vaccine dose can be used. The first way is after but in association with a primary vaccine series. Administration of this additional dose is needed when the initial immune response following a primary vaccine series is likely to be insufficient. In contrast, a booster dose is a dose of vaccine administered when the initial sufficient immune response to a primary vaccine series is likely to have waned over time. The need for and timing of a COVID-19 booster dose have not been established. The focus of the proposed clinical considerations is for people with moderate to severe immunocompromise due to a medical condition or immunosuppressive treatment the potential to increase immune response coupled with an acceptable safety profile support consideration for an additional dose of mRNA COVID-19 vaccine following an initial two-dose primary mRNA COVID-19 vaccine series in this population.

The proposed categories for “moderate” and “severe” immunocompromised people were developed from a combination of resources, including the *ACIP General Best Practice Guidelines for Immunization*, *CDC Yellow Book*, and the *2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host*. The list proposed for inclusion on the CDC Clinical Considerations page includes immunocompromised people who have experienced the following:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of a solid organ transplant and are taking immunosuppressive therapy
- Receipt of chimeric antigen receptor T-cell (CAR-T-cell) or HSCT transplant within 2 years of transplantation or taking immunosuppressive therapy
- Moderate or severe primary immunodeficiency (e.g., DiGeorge, Wiskott-Aldrich syndromes)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (i.e., ≥ 20 mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory

¹⁹ <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#pregnant>

The following additional considerations would be listed:

- There are chronic medical conditions that may be associated with varying degrees of immune deficit.
- The patient's clinical team is best able to assess the degree of altered immunocompetence and optimal timing of vaccination, with specific attention paid to current or planned immunosuppressive therapies.
- Whenever possible, mRNA COVID-19 vaccination doses (including the primary series and additional dose) should be given at least 2 weeks before initiation of immunosuppressive therapies.
- Factors to consider in assessing the general level of immune competence of patients with chronic diseases include disease severity, duration, clinical stability, complications, comorbidities, and any potentially immune-suppressing treatment.
- The utility of serologic testing or cellular immune testing to assess immune response to vaccination and guide clinical care (e.g., need for an additional dose) has not been established and is not recommended at this time.

The following implementation considerations would be listed:

- The additional dose should be the same mRNA vaccine as the primary series.
- An alternate mRNA product can be used if the primary series product is not available.
- Until more data are available, the additional dose would be administered at least 28 days after completion of the initial primary series.
- Currently there are not data to support the use of an additional mRNA COVID-19 vaccine dose after a primary Janssen COVID-19 vaccine in immunocompromised people. FDA and CDC are actively working to provide guidance on this issue.

In response to ACIP feedback, there are plans to emphasize the importance of infection prevention measures, recognizing this additional layer of protection. Here immunocompromised people, including those who receive an additional mRNA dose, should be counseled about their continued potential for reduced immune response to COVID-19 vaccination and their need to follow prevention measures,²⁰ including wearing a mask, staying 6 feet apart from others they do not live with, and avoiding crowds and poorly ventilated indoor spaces until advised otherwise by their HCP. Close contacts of immunocompromised people also should be strongly encouraged to be vaccinated against COVID-19. There also will be updates to the CDC clinical resources regarding administration of the additional dose associated with the primary vaccine series for some immunocompromised patients that will be available on the CDC vaccines website.²¹

Summary of Discussion (Dooling & Goswami)

- Regarding an inquiry pertaining to whether human immunodeficiency viruses (HIV)-positive populations were considered in the 63 studies identified on Slide 14, Dr. Dooling indicated that there was not sufficient information specifically on HIV-positive populations to present the data as a body of evidence.

²⁰ <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html>

²¹ Updates will be posted at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/index.html>

- Children 12-17 years of age have moderate to severe immunocompromised conditions that reflect the full spectrum that occur in adults, leukemia and lymphoma are common cancers in children, and the mechanism creating the immunocompromising conditions are similar for both children and adults:
 - Given that the response to the Pfizer mRNA vaccine, which is the only one with an EUA for children, was similar for children and young adults and that there are data to suggest that breakthrough disease occurs in 40%-44% in persons with immunocompromising conditions, numerous ACIP members felt that it would be very important for children 12-17 years of age to have access to an additional dose. Not only will this be important for health equity, but also some of these children will be in schools making the additional dose of paramount importance.
 - Some ACIP members expressed concern about potential harm for children 12-17 years of age, particularly those who had a robust response to the first 2 doses and potentially would receive a third dose 1 month after the second dose. This could increase the potential for myopericarditis and/or other immune or inflammatory responses. Moreover, there are limited data regarding a rare AE such as myocarditis and giving a third dose. Nevertheless, their risk of severe disease and death also are higher. This raised a request for additional information about the WG's discussions on age and why some members had a dissenting opinion about persons 12-17 years of age.
 - Dr. Cohn noted that when the WG discussed this recommendation, they did not know the specific age indication that would be in the expanded EUA. Therefore, they focused on individuals 18 years of age and older.
 - Dr. O'Leary (PIDS) pointed out that pediatric cardiologists have been integral to the WG's discussions pertaining to myocarditis and pericarditis issues. PIDS also would support the inclusion of children 12-17 years of age.
 - Dr. Maldonado (AAP) commented that the President of the AAP provided an open letter to the FDA underscoring the myopericarditis issue, children 12-17 years of age, and that there needs to be a focus on children under 12 years of age as well. While there is justifiable concern about reported cases of myocarditis, these are extremely rare and the severity of the infections and events seen with vaccines have not shown any evidence of adverse immunologic responses clinically or in laboratory studies. The AAP stands behind any efforts to provide vaccines for children when they are indicated, and the indication for immunocompromised adults would hold true for the pediatric population as well to provide them additional options—of course, with appropriate counseling from their providers and subspecialty providers pertaining to benefits, harms, and potential risks.
 - Dr. Zahn (NACCHO) emphasized that from a public health standpoint, the surge in Delta cases throughout the country is difficult to address in a number of settings. There is probably no setting more difficult than schools. Given the commitment to getting children back in schools and learning, it is especially imperative to protect immunocompromised children in those settings. Therefore, he echoed support for consideration of children 12-17 years of age.

- Given the potential for harm, ACIP members supported the notion that enhanced surveillance in this group would be beneficial. Communication about any expansion of the recommendation should emphasize to providers the importance of having their patients enroll in v-safeSM when they get the vaccine in order to accumulate more robust safety data on these issues of concern.
- Dr. Cohn confirmed that CDC absolutely will be enhancing v-safeSM to capture the third dose, and will ensure that other surveillance methods are monitoring the safety of a third dose.
- Some ACIP members felt that at least some equity issues would be improved with the additional dose among immunocompromised persons, including pediatric patients. Many people already have managed to obtain a third dose, though not under physician guidance. However, this tends to be people who are highly educated, medically savvy, and reside in suburban versus rural areas. Those who may not know how to advocate for their health and live rurally are not equitably receiving an additional dose, which this recommendation is likely to help improve.
- ACIP members expressed concern about the potential consequences for people who received the J&J vaccine as their primary series, who would not be eligible to receive an additional dose under this recommendation:
 - Concern was expressed by some ACIP members that from a health equity standpoint, many African American and Latino populations received the J&J vaccine and immunocompromised persons tend to be higher among these populations. If they are going to make a big push for an additional dose in immunocompromised persons, it would be helpful to be able to recommend that those who received the J&J vaccine could receive an mRNA vaccine as their additional dose since it is unclear how long it will be before J&J data will be available. This seems particularly imperative given the contagiousness of the Delta variant and its rapidly increasing transmission.
 - Dr. Cohn emphasized that while this is recognized as a very important issue, immunocompromised people who received the J&J vaccine as their primary series are not included in the FDA EUA that Dr. Marks announced at the beginning of this session. There were not sufficient data to support that population in the EUA and ACIP and CDC need to keep their recommendations boundaries aligned with the considerations of use to ensure that vaccines are being implemented appropriately under the EUA. Fewer doses of the J&J vaccine have been administered overall, so there is likely to be a very small number of those would fall into the severely immunocompromised based on the timing of when that vaccine became available.
 - Dr. Marks stressed that FDA understands the challenges and will continue to work diligently to try to have solutions. They had to make decisions based on the data they had in hand, which will offer a solution for the large majority of immunocompromised individuals. FDA anticipates having additional data and a solution for the remainder of those individuals in the not too distant future.

- ACIP members requested additional information regarding why antibody testing was not included as an option in the proposed recommendation:
 - Dr. Dooling indicated that there were two primary reasons why the WG agreed with not including an antibody test into a proposed recommendation for a third dose in immunocompromised persons. First, there is insufficient information on a correlative protection. There are many different types of antibody tests (e.g., binding antibody tests, neutralizing antibody tests) and the interpretation of these would be extremely difficult on an individual level, certainly with variability among commercially available tests and between laboratories. Second, no tests are FDA-approved for the purpose of testing antibody levels post-vaccination due to this variability among commercial tests and laboratories. Interpretation would be very difficult and not particularly useful in a population recommendation. While antibody testing is used in studies in various forms to try to characterize the immune response, variability between assays is noted as a limitation of the data.
 - ACIP members pointed out that in Dr. Goswami's presentation, chronic medical conditions and immunocompromised were both mentioned in terms of considering Doses 1, 2, and 3 and that these are different situations. Some members felt that in relation to this, there may be instances in which antibody testing would be prudent. For instance, someone being prepared for/receiving a transplant is likely not to respond adequately to vaccine, especially after receipt of anti-rejection medication. This seems like a case in which antibody testing should be used when considering a third dose.
- From an immunological standpoint, ACIP members suggested that perhaps clinical guidance should be considered in terms of the timing of a third dose for an optimal response. For instance, other vaccine vaccination time periods have been Day 0, 1 Month, and 6 Months:
 - Dr. Dooling pointed out that the EUA was written for at least 1 month after the primary series, though the WG would be happy to hear additional considerations. Some of these individuals will have had time elapse since completing their primary series as individuals with underlying medical conditions, including immunosuppression, were included in the earlier phase of the vaccine rollout. There is concern that these individuals and those who have not responded to the first two doses would be left unprotected if the recommendation was to wait at least 6 months since the second dose before receiving an additional dose.
 - Dr. Kotton, who is a practicing physician caring for immunocompromised patients, confirmed that someone who has not responded adequately to the first 2 doses may not respond to a third dose. Given that this is a heterogeneous population, in the absence of data and presence of an intense worldwide pandemic, she would be reluctant to recommend a Day 0, 1 Month, and 6 month schedule that would require vulnerable patients to wait a long period of time before receiving an additional dose. With that in mind, she supported flexible timing of at least 1 month following completion of the primary series.

- Given that this is a heterogeneous group with very complicated medical needs that will vary by condition and individual, Dr. Dooling emphasized that the WG wanted the clinical considerations to serve as a starting point and understood that the clinical teams caring for such patients would need to adapt the considerations accordingly. The 28 days is intended to serve as a minimum and will need to be adjusted based on individual considerations. Many of the studies presented provided a third dose at an interval of 1, 2, or 3 months beyond completion of the primary series. Perhaps the third bullet stating, “ whenever possible, vaccination should be given at least 2 weeks before initiation of immunosuppressive therapies” could be revised to “at least 2 weeks before initiation or resumption of immunosuppressive therapies.”
- From a clinical standpoint, ACIP members encouraged practitioners to think about patients as individuals in terms of helping them understand the risk/benefit balance as this is highly individualized among immunocompromised patients of all ages.
- Dr. Cohn emphasized that the comments made during this session would be taken into consideration and incorporated into the clinical consideration language before dissemination. She also reminded everyone that ACIP would be voting on whether to make the recommendation as proposed, but would not be voting on the clinical considerations language. The purpose of the clinical considerations was to assist providers who are seeking guidance about their patients.
- Dr. Dooling stressed that the WG was not recommending that any kind of medical sign-off be required to prove immunocompromised eligibility. This is self-attestation that will not require a prescription or physician letter. New patients presenting for a primary series will have to weigh the options of receiving the J&J vaccine or an mRNA vaccine with the vaccine provider to determine which may be the best option depending upon their individual situation.

Public Comments

The floor was opened for public comment during the August 13, 2021 ACIP meeting at 12:30 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–2021–0084. Visit <http://www.regulations.gov> for access to the docket or to submit comments or read background documents and comments received.

Ms. Hanna Kaufman Immunocompromised Individual

Hello. My name is Hannah Kaufman and I am immunocompromised. I live with ankylosing spondylitis and Behcet’s disease. I currently take three different immunosuppressant medications, including an anti-metabolite, a biologic, and corticosteroids. I was hospitalized twice in June for a bad flare of my autoimmune disease, triggered by a relatively mild, non-COVID infection. I’m speaking to you today from the infusion center where I am currently being treated with Remicade®. My doctors are waiting on clearer guidance from you before they can recommend moving forward with any kind of third vaccine dose recommendation for me. My plea is that the guidance that you come up with and vote on today defines “immunocompromised” as broadly as possible. I implore you to leave as much to the discretion

of patients and healthcare providers working collaboratively to determine individual risk/benefit of third doses on a case-by-case basis. I want to stress the importance of recommending the third doses for people in all categories of immunocompromised and immunosuppression. It is horrifying to know that vaccinated solid-organ transplant recipients are 485 times more likely to be hospitalized or die than their healthy, vaccinated peers. Still, many of us don't know our risk level. I haven't had a transplant. Am I 300 times more likely to die? Am I only twice as likely to die, which is still horrifying? What is the threshold where I can get a third dose? Quite honestly, death is not the only thing I fear and not even the thing I fear most. What truly scares me is the possibility of developing long-term COVID complications that will further degrade my quality of life. Something I don't even know the likelihood of because you aren't keeping track of it. I need to do all I can to avoid infection in the first place. The world has become much less safe for people like me since people took their masks off in May. I was unable to even pick up my immunosuppressant medications from the pharmacy yesterday, because there were unmasked people bumping into me from all sides in a ZIP Code that is only 39% vaccinated. For immunocompromised people with less-effective vaccinations, the recommendation has been to build a shield around us of others who are vaccinated and others who wear masks. These are wonderful observations, but not at all in our personal control. Please give all of us who are immunocompromised a fighting chance to protect ourselves in a world where we have to rely on others to make the right choices, and many refuse to do so. Please define "immunocompromised" as broad as possible. Don't just do it for people like me. Do it for the caregivers who are exposed to us. Do it for the children we live with who are too young to be vaccinated and are being thrown back into schools without masks. Do it for the population as a whole. I don't want to be the one who instigates the next variant of concern. Thank you.

Ms. Elizabeth Fashing
Parent of Young Children Too Young for Vaccine
Executive Director, Colorado Immunization Advocates

Hello, my name is Elizabeth Fashing. I'm from Erie, Colorado and I am proud to be the Executive Director of Colorado Immunization Advocates. Today, though, I'm speaking as a parent with two children who are not old enough to receive a COVID vaccination and to urge the approval of the vaccine for those under 12 as quickly as possible. When my children were infants, and too young to receive all of the standard childhood immunizations, I felt some trepidation. I knew there were some members of our community who chose not to vaccinate children and have put my children at risk, but I at least had a light at the end of the tunnel. I knew exactly when each of my children would be fully vaccinated, and once they were, I could breathe a sigh of relief. Today, that trepidation is much different. There is no light at the end of the tunnel. I have no idea when my children will be able to get vaccinated against COVID. Instead of the highly localized outbreaks of vaccine-preventable diseases that are easier to avoid a few years ago, COVID is everywhere and my options to protect my kids from it are limited. They don't come to the store with me. We haven't traveled with them on airplanes or visited the public spaces we used to enjoy like the museum. My husband and I got vaccinated as soon as we could. We wear masks everywhere. Next week, my kids go back to school. I am more worried this year than last year because of the contagiousness of the Delta variant and the number of children currently infected and hospitalized. Although we are fortunate to live in a county which has mandated masking for all students and staff in schools, I still know that the best way to protect my children is to get them vaccinated. Other friends live in districts which don't have mask mandates. Some of my friends have children who are immunocompromised. Only one district in our state is requiring teachers and staff to be vaccinated. We need to get our kids access to the vaccine. Please, on behalf of all parents who are facing such an uncertain

school year and who want to do everything we can to protect our children from COVID, please approve the COVID vaccine for children as soon as possible.

Ms. Braaten Heather
Ovarian Cancer Survivor

Thank you for allowing me to speak today. I wrote different versions of my public comments, because I did not know which groups would qualify for additional vaccine doses. It seems that this is still being clarified, but that I will most likely qualify. I am a 44-year-old ovarian cancer survivor. Although I'm grateful to have received my Pfizer vaccination this winter between cycles of chemotherapy, I was also worried because I knew chemotherapy blunts the effects of vaccines. I regretted that I could not wait until after treatment to get my shots. Over the past few months, I have become somewhat obsessive with reading news articles and medical studies. I have become so anxious because research shows that cancer patients like myself, who have solid tumors, only develop a fraction of antibody titers, T-cells and B-cells of healthy controls. I have felt distraught over the situation. My prognosis is poor. I most likely have about two to three years left to live, so everyday counts. My life ambitions are humble. I want to be able to the visit with vaccinated friends and family and not have to worry if I'll become a breakthrough case just because we took off our masks or got too close to each other or dared to actually spend some time inside. I'd like to go grocery shopping again and not panic and leave the store after five minutes. I'd like to travel because that's what people with a diagnosis like mine usually do before our health deteriorates. But this year, catching COVID and knowing that I could become seriously ill and that approximately 10% to 30% of cases become COVID long-haulers, has kept me from being so bold. I don't think I could cope with both the side effects of cancer treatments and debilitating post-COVID symptoms. I'd like to thank the committee for including cancer patients like myself who have recently undergone chemotherapy for solid tumors to potentially receive additional doses of COVID vaccine. I'm not afraid of potential side effects of the third dose. While I understand I will still need to be cautious, I am hopeful for the peace of mind and greater freedom a third shot can provide. Thank you for listening.

Ms. Elizabeth Ann Ditz
Founder Member
Vaccinate California

Good morning. My name is Liz Ditz. Greetings committee members and workgroup members. I am grateful for your tireless work over the last 18 months and in the time before COVID-19 so much. I have been advocating for high vaccine uptake in my community in San Mateo County for over 20 years. I'm a founding member of Vaccinate California, a grassroots volunteer advocacy group. I'm a longtime supporter of Voices of Vaccines, a national parent-led organization advocating for vaccine uptake. I'm a frequent contributor to a Facebook group called Vaccine Talks, an evidence-based discussion forum which has over 67,000 members worldwide. Over the last four-plus years, this group has helped 443 people move from being vaccine-resistant to vaccine-accepting. That's about 1 every 3.5 days. Fact-based social media is having a positive impact. I'm also over 65 with several risk factors for severe COVID if infected. I've been fully vaccinated for 153 days. Eventually, I might be in a group considered for a booster dose. I want to make three points: 1) overreliance on vaccines is a way to end this pandemic; 2) global perspective on vaccine access; and 3) health equity in the US. First, I know you are all not the Advisory Committee on Non-Pharmaceutical Interventions for COVID Prevention, but I must say that the US's hyper focus on immunization over NPIs has harmed our country's response to this crisis. As a nation, we must adopt all the tools at hand to tame this virus. Second, Gavin Yamey, MD tweeted, "For the love of all that is good and holy, we need to

recognize that we are a global community. There's a moral and ethical urgency to ensure that everyone worldwide has the same chance to benefit from the fruits of scientific progress, not just rich people." Finally, here in San Mateo County, we have a very high vaccination rate, with noticeable holes. Many of our agricultural and hospitality-industry workers are not yet vaccinated. When one friend learned, she was bringing in vaccine advocates who are native Spanish speakers. It turns out most of her employees, although from Mexico or Central American nations, were not native Spanish speakers and didn't really have health vocabulary in Spanish. They were native Mixtec or other indigenous languages without health vocabulary in Spanish. So, we need to fine-tune our efforts to increase vaccine uptake. Thank you very much.

Ms. Pam Dixon
Executive Director
World Privacy Forum

Yes, thank you, Chair Lee and members of the committee. Thank you for the opportunity to participate in the ACIP meeting today. I'm Pam Dixon, Executive Director of the World Privacy Forum, a public-interest research group focused on privacy and data governance, including in the health sector. I have two brief points today. First, we support the CDC's prohibition on the use of vaccine-recipient data for commercial and marketing purposes. The CDC's *Vaccination Program Provider Requirements* published in May of this year specifically prohibits the commercial marketing use of COVID-19 vaccination registration information and the vaccine administration data. These prohibitions were warranted and are important for ensuring patient trust in the public health data ecosystem. I note that standard HIPAA rules already prohibit providers from using patient data for commercial purposes. There is now, after many years of HIPAA implementation, a reasonable expectation of some of the same levels of privacy in COVID-19 data ecosystems. Very few individuals understand the rules regarding HIPAA-covered ecosystems and public health ecosystems. Second, we urge the committee to ensure that the same prohibitions that have already been put in place for commercial marketing uses of vaccine-recipient data will also be required when this data is utilized in vaccine-credentialing systems or proof of vaccination systems. We see significant potential risks for the commercial use of patient registration and patient vaccination data due to the sheer number of credentialing systems in development across complex public-private pathways. In conclusion, we support the work that the ACIP committee is doing to protect privacy interests and the integrity of public health data. We can all say a lot about how credential systems should operate, but this the committee has the ability to make the most important statement of all about this ecosystem, which is to ensure that this data of those who have been vaccinated is fully protected in credentialing systems as well. Thank you very much for the opportunity to participate today.

Mr. Edward Nirenberg
Concerned Individual

Hello, and thank you for this time today. I'd like to call attention to several issues. To begin with, I do think it's important to offer consideration to heterologous-boosting strategies in the data suggested inferior responses from the combination of adenovirus vectors and mRNA vaccines, and preliminary effectiveness data suggests non-inferiority. Given how the study has just found 71% effectiveness of the Janssen vaccine against hospitalization, I would request that mRNA boosters be offered for recipients of Janssen, a vaccine that may have been favored in the first place by more vulnerable groups for whom access to vaccination may be an issue. Additionally, immunocompromised patients' infections are especially concerning for their public health implications, because of propensity for antibody escape variants as far as CoV-2. It may be worthwhile to consider prophylactic dosing of monoclonal antibody cocktails for those who have

substantial humoral immunodeficiencies. Pregnancy is also an important, high-risk state for COVID-19. Given that some individuals are becoming pregnant relatively far from their initial immunization, it may be worth considering additional doses during pregnancy, both to bolster their protection and to provide a pathway of immunity to their future children through transfer of antibodies. It remains critical to our mind, everyone, that we have a pretty grave situation with COVID-19 in the pediatric world. Since the beginning of the pandemic, in spite of aggressive mitigation measures in the US, approximately 500 children have died. Hundreds and thousands have been hospitalized, millions have been affected, and hundreds of thousands are additionally likely suffering. Furthermore, as was mentioned during the meeting, the AAP described in a recent letter to the FDA there has been a substantial rise in hospitalization among children recently, and I would urge everyone listening to do everything in their power to vaccinate their children against COVID-19 as quickly as possible. The call for a larger sample size by the FDA in clinical trials for children offers only marginal gains in the way of our pharmacovigilance, but access to vaccination would be substantially delayed and is a limit to the significant surge. The late sequelae of COVID-19 in children are currently unknowable. Many of those cause deaths months to years after initial infection as a complication is both fatal and lacks treatment options. If COVID-19 causes anything analogous, we will not know for some time. A circumspect approach is dominant here, given the substantial cost incurred to address child safety and well-being at the public health scale. Lastly, I would request more frequent updates from v-safeSM and the Vaccine Safety Data link, if possible, because I think that having these references of vaccine safety for the public is extremely valuable. I would additionally like for stronger language regarding recommendations to vaccinate recovering patients now, as the clinical benefits of doing so have been ascertained, in addition to immunological ones.

Vote: Additional Doses of mRNA COVID-19 Vaccines as Part of a Primary Series for Immunocompromised People

Dr. Kathleen Dooling (CDC/NCIRD) presented the following proposed recommendation for an ACIP vote:

An additional dose of Pfizer-BioNTech COVID-19 vaccine (≥12 years) or Moderna COVID-19 vaccine (≥18 years) is recommended following a primary series in immunocompromised people under the FDA's Emergency Use Authorization.

Summary of Discussion

- In response to an observation that Moderna has submitted data to the FDA for expansion to an adolescent indication and the potential to have to quickly revisit this recommendation, Dr. Dooling indicated that the intent for this ACIP meeting was to proceed with the maximum specificity possible under the EUA as it stood at this point. Dr. Cohn added that when there is an FDA authorization for Moderna vaccine down to a different age group, a WG and then ACIP meeting will be convened to review the data and vote on a revised recommendation at that time. It is important to be very careful in voting for each change to ensure that ACIP recommendations are being made in accordance with the EUA as authorized.
- ACIP members expressed how grateful they are for the expanded EUA for persons who are immunocompromised so that more protection can be provided to them, and emphasized the importance of clear communication about who this is for and why it is an additional dose versus a booster dose.

- Regarding an ACIP inquiry about the language in the clinical considerations regarding not including the J&J vaccine in this recommendation, Dr. Cohn indicated that the language would be clear that there are no data at this time to support the use of an additional dose of mRNA vaccine after the J&J vaccine. Efforts are in place to address this as soon as possible and it is anticipated that data will soon be available on this matter. CDC also will have a communications package for HCP and the public to ensure that people understand who needs an additional dose at this time and who does not.
- ACIP members commended the CDC for their incredible efforts to develop and prioritize education and communications materials in the midst of ever-evolving contexts and data.
- Regarding an ACIP inquiry about whether CDC has any guidance for dealing with persons who are obtaining additional doses of their own accord in a variety of places, CDC is working on clinical guidance about this matter based on the feedback provided by ACIP that was anticipated to be published later in the day. In addition, CDC anticipated having a COCA call with partners early the next week and already had been working over the last 24 to 48 hours with pharmacy groups and jurisdictions to prepare for implementation of this anticipated recommendation. While pharmacy groups ask some questions about potential contraindications and/or compromising conditions, there will be no requirement for a prescription or other proof from a person's HCP.
- Regarding whether v-safeSM will be updated to include a third dose, Dr. Broder from CDC's Immunization Safety Office (ISO) indicated that v-safeSM is being updated to capture third dose information for new registrants and those who have entered previous doses.
- ACIP members emphasized the importance of the clinical guidance being as specific as possible from clinicians in the field in terms of coded diagnoses, specific drugs, medication names, et cetera in electronic health records (EHR). "Immunosuppressive therapies" and "severe primary immune deficiencies" are too broad to be used in EHRs. It is important to ensure that people who have been diagnosed with conditions that are considered to have an equivalent level of immunocompromise be permitted to receive a third dose. The proposed recommendation seemed like too broad a swath of what appeared to be all persons who are immunocompromised. With that in mind, it was suggested that the language be amended to reflect something to the effect of "an additional dose following a primary series in those who have moderate or severe immunocompromise" to avoid confusion.
- Dr. Coyle, American Immunization Registry Association, pointed out that there is a technological component in terms of clinical support capabilities for EHRs and immunization registries. For immunization registries, it will be important to note that "immunocompromised" is a very broad category as most Immunization Information Systems (IISs) will not have the ability to identify individuals who would fall into this category due to the types of risk factors. EHRs and IISs will have to work together on this. It may be challenging with booster doses when systems reflect that a series is complete at 2 or 3 doses.
- In response to several comments, Dr. Dooling emphasized that this recommendation is for moderately and severely immunocompromised people. This is very clearly spelled out with specific reference to conditions that would constitute that category in the clinical considerations document that will be posted on the CDC website as soon after the vote as is humanly possible. She fully supported all of the statements made about registries' ability to

collect a third dose. The more that EHRs and IISs can link and add specificity around immunocompromised and a third dose, the better.

- Regarding concerns expressed about the potential for confusion with regard to mandates and whether immunocompromised persons will be considered fully vaccinated with 2 or 3 doses, Dr. Dooling stressed that for the purpose of meeting the definition of “fully vaccinated,” it is 2 doses of mRNA or 1 dose of Janssen. That has not changed and will be spelled out explicitly in the clinical considerations.

**Motion/Vote: Additional Doses of mRNA COVID-19 Vaccines
as Part of a Primary Series for Immunocompromised People**

Dr. Ault made a motion and Dr. Poehling seconded to approve the recommended language for additional doses of mRNA COVID-19 vaccines as part of a primary series for immunocompromised people as presented. The motion carried with 11 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

11 Favored: Ault, Bahta, Chen, Daley, Kotton, Lee, Long, McNally, Poehling, Sanchez, Talbot
0 Opposed: N/A
0 Abstained: N/A

Following the vote, ACIP members were invited to make a statement on the rationale for their vote or provide additional comments:

Dr. Talbot: I just wanted to say how much I appreciated how ACIP, and the WG and the CDC have really delineated the idea of a third dose in a series, for a primary series versus a booster. I think that’s incredibly important. I think we’re looking at a very specific population of the US that was not able to mount an appropriate immune response to the normal two doses. This is a very specific population and it’s not meant for the entire US population. We are all very worried about the Delta variant, but that may be the least of our problems if COVID-19 continues to circulate across the US and the world. So, I think it’s incredibly important that we remember that we need to begin sharing more and more vaccines across the world and encouraging those pockets of low vaccination rates to immunize, or the Delta variant may be the least of our concerns.

Dr. Poehling: I do want to express my sincere thanks to everybody at the ACIP, the WG, and the FDA for making this data available so we could have this vote. I voted “yes” for an additional dose of mRNA vaccine for all children and adults over 12 years of age with moderate and severe immunocompromising conditions to maximize their chance of protection from vaccines. These persons have increased risk of hospitalization, breakthrough disease, and death from COVID-19. In addition, the VE among immunocompromised is lower than those without immunocompromising conditions. Recent studies demonstrate that 33%-50% of persons with immunocompromising conditions who did not initially respond, did respond with a third dose in the primary series. This vote enables all persons 12 and older to obtain a third dose in the primary care series to increase their protection from the vaccine. It is critical to highlight to persons with immunocompromising conditions and their families the importance of wearing masks, maintaining social distance, avoiding crowded locations indoors, and cocooning by having close contacts vaccinated. It’s equally important to share and highlight the importance

that all schools create plans so that all children, including those with moderate-to-severe immunocompromising conditions can safely attend school.

Update on Emerging SARS-CoV-2 Variants and COVID-19 Vaccines

Dr. Heather Scobie (CDC/CGH) first shared an example one of the new ways that CDC is visualizing the impact of COVID vaccination in the COVID Data Tracker website. The graphs display weekly trends by age group for the cumulative percent of people fully vaccinated and the average rate of new cases per 100,000 population. In the three age groups greater than 50 years of age, there were higher coverage rates and lower case rates compared with the younger age groups between December 28, 2020—August 11, 2021.²² The county-level map from Data Tracker shows that counties with low vaccination coverage have had high coverage rates. Counties with greater than 50% coverage and high incidence were relatively few and reflected the recent increases in Delta variant transmission occurring largely among unvaccinated persons.²³

A lot of public concern has been raised about the Delta variant and breakthrough transmission, which Dr. Scobie contextualized with 2 example state scenarios each with 1 million population and different coverage levels. State A had 70% coverage and State B had 30% coverage. The COVID data used for this example are actual data from the COVID Data Tracker website for states with similar coverage levels. In State A, 130 cases were occurring per week compared to over 5000 cases occurring weekly in State B. Using VE estimates from the UK, the number and proportion of unvaccinated cases and vaccinated cases. Proportionally, there were more vaccinated cases in State A at 22% of cases vaccinated, compared with just 5% vaccinated in State B. This is expected because the proportion of cases vaccinated increases with increasing vaccination coverage. At the extreme of 100% vaccination coverage, all cases would be vaccinated because no vaccine is 100% effective. Similar trends were observed with hospitalizations. Just 1.4 hospitalizations would occur weekly in State A compared to 18.8 hospitalizations in State B. In both states, the majority of cases and hospitalizations would occur among unvaccinated people.

In terms of what is currently known about emerging SARS-CoV-2 variants and vaccines, 4 variants are considered Variants of Concern (VOCs): Alpha (B.1.1.7) first detected in the UK, Beta (B.1.351) first detected in South Africa, Gamma (P.1) first detected in Brazil and Japan, and Delta (B.1.617.2) first detected in India. Of note, all of the VOCs have mutations in the receptor binding domain that have variably impacted VE, with the cluster of mutation shared by Beta and Gamma having the largest known impact. Another class of variants under monitoring are the Variants of Interest (VOIs), which have similar mutations but less current evidence of public health impact.²⁴

Regarding the latest national NOWCAST projections²⁵ of the proportions of circulating SARS-CoV-2 variants from CDC's COVID Data Tracker for the 2 weeks ending July 31, 2021, Alpha decreased to a projected prevalence of 2%, Gamma decreased to 1%, and Beta remained at 0%. However, the Delta variant increased to 94%. The Delta sub-lineage AY.3 increased to 13%. This lineage does not contain the so-called Delta plus mutation, formally known as AY.4.2.

²² <https://covid.cdc.gov/covid-data-tracker/#vaccinations-cases-trends>

²³ <https://covid.cdc.gov/covid-data-tracker/#vaccination-case-rate>

²⁴ <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html>

²⁵ <https://covid.cdc.gov/covid-data-tracker/#variant-proportions> as of 8/10/21

CDC monitors several types of evidence to assess the impact of variants on vaccines, including antibody neutralization generated in the laboratory.²⁶ Though a correlative protection has not yet been established, good correlation has been observed between VE and neutralizing antibody levels from different vaccines. This likely will be the first type of evidence obtained on the impact of new variants on vaccines. CDC also monitors VE data from clinical trials and real-world VE. Notably, greater protection is usually observed against severe disease and symptomatic illness and confirmed infection, which includes asymptomatic cases. This is because protection against severe disease requires lower antibody levels and is less affected by differences in efficacy across vaccines. In addition, CDC monitors breakthrough infection.

A review was conducted of available studies on vaccines authorized or intending to be authorized in the US (mRNA, AstraZeneca, Novavax, Janssen) and containing data on the ability of post-vaccination sera to neutralize SARS-CoV-2 variants. Beta had the largest median reduction at 7.5-fold, Delta had a median reduction of 2.8-fold, Gamma was reduced 3.1-fold, and Alpha was reduced 1.9-fold. While an alpha variant with an E484K change, which has been detected in the UK, US, and other countries, had a further reduction in neutralization compared to Alpha alone.²⁷

In terms of what is known about duration of immunity to date, available data demonstrate antibody persistence for at least 8 months after COVID infection and at least 6 months after the second mRNA vaccine dose, with some evidence at 8 months for the Janssen vaccine. Studies suggest that individuals may maintain long-term protection from severe illness caused by antigenically similar strains, even if they become susceptible to mild infection. Two studies have shown a combined impact of waning antibody levels and reduced neutralization of variants. At 6 months after receiving the Moderna vaccine, neutralizing antibody levels were reduced but sufficient to protect against the ancestral strain, while about 50% of people had undetectable neutralizing titers against the Beta and Gamma variants. A small study at 8 months after receipt of the Janssen vaccine observed minimal decline in neutralizing titers and improved protection against Beta, Gamma, and Delta variants compared with 1 month after vaccination, which was suggested to be related to antibody maturation. It is unclear if there are differences in the kinetics of antibody response by vaccine platform and more data are needed.²⁸

Pfizer recently published their 6-month clinical efficacy data.²⁹ VE against infection out to 6 months was 91%. They performed an additional analysis looking at different time intervals after receiving the second vaccine dose and observed a gradual decline in VE against infection of 6 percentage points every 2 months. The confidence intervals around the estimates were overlapping. At 4 to 6 months post-vaccination, VE was 84% compared with 96% at less than 2 months after vaccination. VE against severe illness during the period was 97%. Moderna³⁰ has not yet published their extended efficacy results, but announced in a press release that VE was 93% for up to 6 months.

²⁶ <https://www.nature.com/articles/s41591-021-01377-8>

²⁷ See references for Slide 11 at the end of Dr. Scobie's slide set

²⁸ Gaebler, C. et al. *Nature* 591, 639–644 (2021); Dan, J. M. et al. *Science* 371, (2021); Choe et al. *Emerg Infect Dis.* 2021;27(3):928-931.; Doria-Rose et al. *N Engl J Med* 2021; 384:2259-226; Khoury et al. *Nat Med* (2021).; Pegu et al. *bioRxiv* preprint; Wu et al. *medRxiv* preprint (2021); Luo, Hu, Letterio, *medRxiv* preprint (2021); Barouch et al. *medRxiv* preprint (2021); Thomas et al. *medRxiv* preprint

²⁹ Thomas et al. *medRxiv* preprint <https://doi.org/10.1101/2021.07.28.21261159>

³⁰ Moderna. <https://investors.modernatx.com/news-releases/news-release-details/moderna-reports-second-quarter-fiscal-year-2021-financial>

In terms of VE against the variants,³¹ for the Alpha (B.1.1.7) variant, mRNA vaccines have been shown to have greater than 85% real-world VE against confirmed infection in the US and multiple countries. For Gamma (P.1), mRNA vaccines have 84% to 88% real-world VE against symptomatic infection and 79% VE against confirmed infection when Gamma was widely circulating in Canada. For Beta (B.1.351), Moderna vaccine had 96% real-world VE and Pfizer vaccine had 75% VE against confirmed infection in a study from Qatar, while Janssen vaccine had 52% VE against moderate or severe disease in their clinical trial in South Africa. Importantly, all studies observed high VE against severe disease.

Regarding what is known about the Delta variant,³² it is nearly twice as contagious as previous variants. There is some evidence of increased illness severity compared with previous strains and unvaccinated persons. The greatest risk of transmission is still among unvaccinated people, and fully vaccinated people with Delta breakthrough infections can spread virus to others. However, vaccinated people with Delta may be infectious for shorter periods than unvaccinated persons with Delta.

VE studies³³ have been published from several countries for the Delta variant, mostly for the Pfizer vaccine. In England and Scotland, reduced Pfizer VE was observed at 70% for infection and 88% for illness, compared to 92% and 93% for the Alpha variant. Protection against hospitalization from Delta was 96%, which was similar to that observed with Alpha. In Canada, Delta VE estimates were similar to the UK, but with smaller differences in VE for Alpha and Delta. Israel has observed a progressive decline in VE during the period after Delta predominance, with the most recent VE estimates of around 40% against infection and illness, while VE against severe disease has remained above 90%. Qatar was the only country that assessed Delta VE for both Pfizer and Moderna. VE against symptomatic illness was 54% for Pfizer compared with 85% for the Moderna vaccine. While VE against severe illness was above 90% for both, it is important to note that the comparison shown for the Alpha and Delta VE in Israel and Qatar are for different studies that were separated by 2 to 5 months during the time periods when Alpha and Delta circulated. Other methodologic differences may explain some of the variation observed in the study results across countries.

Other potential differences in VE results relate to differences in the vaccine programs by country.³⁴ The US uses the Pfizer, Moderna, and Janssen vaccines, which have followed the manufacturers' recommended intervals of 3 and 4 weeks between mRNA doses. Israel has used Pfizer vaccine only, though they also authorized Moderna, and follow the 3-week interval between doses. Israel also had a very tight cohort with more than 50% of the country vaccinated in the first 3 to 4 months. Qatar is the most similar country to the US in terms of using both

³¹ CDC Science Brief : <https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html> Abu-Radad and Butt. NEJM (2021); Andrejko et al. medRxiv preprint (Apr 10 2021); Chemaitelly et al. Nature Med (2021); <https://doi.org/10.1038/s41591-021-01446-y>; Sandoff et al. NEJM (2021); Chung et al. medRxiv preprint (May 28 2021); Yassi et al. medRxiv preprint (May 25 2021); Nasreen et al. medRxiv preprint: <https://doi.org/10.1101/2021.06.28.21259420>

³² <https://www.cdc.gov/coronavirus/2019-ncov/variants/delta-variant.html>; Fisman & Tuite. medRxiv; Ong et al. SSRN Journal. 2021; Sheikh et al. Lancet (2021); Daggpunar J. medRxiv.; Li et al. medRxiv; Lopez Bernal et al. NEJM (2021); Stowe et al. PHE preprint; Riley et al.; medRxiv : Micochova et al. Research Square preprint ; Musser et al medRxiv; Brown et al. MMWR (2021); Riemersma et al. medRxiv; Chia et al. medRxiv

³³ Sheikh et al. Lancet (2021): [https://doi.org/10.1016/S0140-6736\(21\)01358-1](https://doi.org/10.1016/S0140-6736(21)01358-1); Lopez Bernal et al. medRxiv preprint; <https://doi.org/10.1101/2021.05.22.21257658>; Stowe et al. PHE preprint: https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZIEig/view/479607266; Nasreen et al. medRxiv preprint: <https://doi.org/10.1101/2021.06.28.21259420>; Haas et al Lancet (2021): [https://doi.org/10.1016/S0140-6736\(21\)00947-8](https://doi.org/10.1016/S0140-6736(21)00947-8) ; Israel MOH: https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf; Abu-Radad and Butt. NEJM (2021); Chemaitelly et al. Nature Med (2021); Tang et al medRxiv

³⁴ Parry et al. <https://www.medrxiv.org/content/10.1101/2021.05.15.21257017v1>; Flaxman et al. Lancet (2021); https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3873839; Amirthalingam et al. <https://www.medrxiv.org/content/10.1101/2021.07.26.21261140v1>; Carazo et al. : <https://doi.org/10.1101/2021.07.19.21260445>

Moderna and Pfizer at the same dosing intervals. Finally, the UK and Canada are the most similar to each other in that they both use mRNA and the AstraZeneca (AZ) vaccines. As part of a dose-sparing strategy, they also adopted extended dose intervals of up to 12-16 weeks, which were later shown to improve immunogenicity and VE compared with standard intervals, including for ages greater than 80 years. The countries also support mixing and matching between vaccines, which has been shown to increase VE. The Pfizer vaccine has a lower mRNA dosage and accelerated schedule of 3 weeks compared to 4 weeks for Moderna, which has the potential to impact the robustness and duration of immunity, as has been generally observed for other vaccines.

In public data from Israel,³⁵ the Ministry of Health (MoH) has observed higher breakthrough rates and lower Pfizer VE against infection for persons vaccinated during January to February. Then in more recent months for persons 16-59 years of age and 60 years of age and older and older. Two retrospective cohort studies of persons vaccinated with Pfizer in large healthcare systems observed increasing breakthrough infections among persons vaccinated in January versus April, and higher breakthrough infection rates among those who received the second mRNA dose more than 5 months ago compared with less than 5 months ago. All age groups were impacted, but one study observed higher magnitude of differences with increasing age.

Delta only rose to predominance in the US at the end of June. This week, the first study assessing potential VE changes in July was posted from the Mayo Clinic Healthcare System.³⁶ For patients in Minnesota, the authors observed that VE against infection was significantly lower for both Moderna and Pfizer vaccines in July when the Delta variant was more than 70% prevalent compared with previous months and insignificantly lower for Pfizer at 42% compared with Moderna at 76%. Importantly, the effectiveness of both vaccines against COVID-associated hospitalization remained consistently high during the same timeframe. More information is needed in this area and will be forthcoming.

Despite high efficacy, vaccine breakthrough cases are still expected to occur, including those caused by circulating variants. CDC conducts nationwide monitoring of vaccine breakthrough cases resulting in hospitalization or death. As of August 2nd among more than 164 million fully vaccinated in the US, there have been 7101 hospitalizations and 1507 deaths with vaccine breakthrough cases reported through national passive surveillance. Among hospitalized or fatal breakthrough cases, 75% were 65 years of age or older. In addition to national passive surveillance, CDC has a number of other ways to monitor breakthrough infection, including a population-based service surveillance system called COVID-NET, which represents 10% of the US population. The most recent COVID-NET data on COVID-associated hospitalizations among adults estimated that 32% of all vaccinated cases are immunocompromised versus 11% of unvaccinated cases.³⁷

To summarize, Alpha, Beta, and Gamma variants have low prevalence in the US. Alpha has minimal impact on VE, while Beta and Gamma have moderate impact and the vaccines appear likely to protect against severe disease. Delta has high prevalence in the US and has moderate impact on VE. The vaccines are likely to still provide protection against severe disease. More

³⁵ Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study | medRxiv; Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort | medRxiv; https://www.gov.il/BlobFolder/reports/vaccine-efficacy-safety-follow-up-committee/he/files_publications_corona_two-dose-vaccination-data.pdf

³⁶ Puranik et al. medRxiv: <https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v2>

³⁷ CDC website as of 8/5/21; 1,816 hospitalizations and 316 fatal cases reported as asymptomatic or not related to COVID-19; CDC. MMWR (2021); COVID-NET: <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html>

data are needed on the impact of Delta, especially for the Janssen vaccine and the potential for waning immunity.

Manufacturers are conducting booster studies of current vaccines and or second-generation vaccines against the Beta variant. Moderna has posted preliminary results of the Phase 2 trial of a single booster dose of the previously authorized and a Beta variant-specific vaccine. Both vaccines had acceptable safety and boosted immunity to the wild-type strain, as well as to the Beta and Gamma variants. Pfizer has also submitted preliminary data on a booster of their original vaccine to the FDA. No Delta-specific booster vaccine studies have been shared to date.³⁸

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

Summary of Discussion

- Referring to Slide 3 from the COVID Data Tracker, a breakdown of vaccine breakthrough cases by race and ethnicity would be beneficial. In terms of understanding the overlapping pockets of unvaccinated persons, the age category is just one part of the problem. Understanding how race and ethnicity are affecting both vaccination levels and case counts would be extremely helpful.
- It would be beneficial to have additional information on the duration of immunity for those who had the vaccine and COVID-19 infection in terms of how long their immunity antibody persistence lasted.

Considerations for Booster Doses of COVID-19 Vaccines

Dr. Sara Oliver (CDC/NCIRD) presented considerations for COVID-19 vaccine booster doses. In thinking through recommendations for booster doses of COVID-19 vaccines, the primary policy question is, “Are booster doses needed for those previously vaccinated with the primary series?” Policies on boosters will be coordinated with FDA for regulatory allowance and ACIP for recommendations around use in specific populations. There are two distinct potential uses for an additional dose of COVID-19 vaccine: 1) An additional COVID-19 dose after receipt of a primary series is one way to provide protection for those who may not have mounted an appropriate immune response to the initially recommended series. This is not considered a booster dose and is what was described for the first part of the meeting; and 2) An actual booster dose, which is a dose administered when the initial sufficient immune response to a primary series may have waned over time. This presentation focused on booster doses.

³⁸ Wu et al. medRxiv preprint (May 6, 2021): <https://doi.org/10.1101/2021.05.05.21256716>; <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-initial-booster-data-against-sars-cov-2>; <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development>; <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/06-COVID-Oliver-508.pdf>

Recommendations for booster doses would apply only to those who have completed a primary series. To date, over 350 million vaccine doses have been administered in the US. Over 60% of those 18 years of age and over are fully vaccinated. This increases to over 80% among those 65 years of age and over. The timing of when individuals became fully vaccinated is important to this discussion as well. Looking at the daily count of fully vaccinated people, the COVID vaccination program began in December of 2020. As only 2-dose series were available at that time, individuals began to become fully vaccinated in January 2021. Through Spring vaccination rates increased such that between 1 to 2 million individuals were fully vaccinated each day. Through the past month, approximately 200,000 fully vaccinated individuals have been added each day. However, it is known that due to the way the vaccine was recommended and rolled out initially, age groups are not evenly distributed across the last 8 months. Looking at the weekly count of fully vaccinated people in the US by age group, those 65 years of age and over were among the earliest vaccinated. In the Spring, vaccination moved into larger populations of those 18-39 years of age and 40-64 years of age. Since vaccination was recommended recently for adolescents, persons 12-17 years of age were added. This varying age distribution will be important in thinking through recommendations for boosters in a variety of populations and ages.³⁹

The plan for how ACIP will approach booster doses over the next several weeks will involve thinking through the key considerations for decision-making, evaluating what data are available for decision-making, and addressing whether ACIP recommends booster doses for COVID-19 vaccines in any populations. This presentation focused on key considerations for decision-making. During the June ACIP meeting, the data were laid out that would be needed to inform recommendations for booster doses in terms of the risk of COVID complications, exposures, risk of waning immunity, and risk of COVID variants.

Moving into preparations for a possible vote in the future, the WG restructured the questions slightly into two main questions that need to be addressed in terms of whether they are needed (public health problem) and whether they work (benefits and harms). The WG can use these questions to think through aspects of the EtR Framework. In terms of the public health problem, the WG will need to specifically address whether VE is waning over time, if VE is reduced for the Delta variant, and whether the data vary by sub-population. Regarding benefits and harms, the WG will need to consider whether booster doses of COVID-19 vaccines are safe and immunogenic; will reduce COVID-19 incidence, hospitalization, and mortality; and if they improve VE against the Delta variant. Dr. Oliver walked through each of these questions in more detail, outlining the data that will be collected to address these overall questions.

Regarding whether VE is waning over time in terms of the public health problem, VE will need to be assessed at 6 and 8 months similar to what was noted at 2 months after vaccination that ACIP reviewed at the time of the EUA. Consideration will have to be given to how these data vary by severity of disease. It may be that VE wanes for asymptomatic or mild disease, but remains high for severe disease, hospitalization, and death. In addition, the WG would need to consider what data on waning VE would identify a need for booster doses of COVID-19 vaccines. Consideration would have to be given to whether VE is reduced for the Delta variant, how this varies by severity of disease, how this information would impact VE for future variants. The final question for the public health problem pertains to whether the data vary by sub-population. During previous ACIP meetings, the WG discussed that boosters may be recommended for the entire population or they could only be needed among specific sub-populations. Groups identified as needing close monitoring and additional data collection

³⁹ <https://covid.cdc.gov/covid-data-tracker/#datatracker-home>

include residents of long-term care facilities (LTCF), adults 65 years of age and over, and HCP. Persons in LTCF and older adults were vaccinated in the earlier phases of the COVID-19 vaccine rollout. In addition, this is a population that has needed special considerations for other vaccines, including additional boosters or higher dose vaccines. In addition, HCP were vaccinated in the early phase of the vaccine rollout. They will have continued exposure to SARS-CoV-2. Another point that clearly could be an issue in the future is that there could be a need for additional considerations for HCP to include the continuity of healthcare systems, given that there may be a very specific need to prevent asymptomatic or mild infections in HCP if there are COVID-19 surges straining the healthcare infrastructure.

Moving to the benefits and harms, it will be important to address whether booster doses of COVID-19 vaccines are safe and immunogenic. Assuring COVID-19 vaccine safety has been a critical element of the entire COVID-19 vaccine program and will continue into this phase as well. It is important to know if COVID-19 vaccines provide a boost in neutralizing antibody response. While it is likely that this information will be available, it also will be necessary to address how neutralizing antibodies correlate to clinical protection from COVID-19. It will be necessary to evaluate if booster doses of COVID-19 vaccines will reduce COVID-19 incidence, hospitalization, and mortality. There are not to be data from long-term efficacy studies with booster doses, but thought must be given to other ways to address whether booster doses will reduce COVID-19 morbidity and mortality. Additionally, consideration will have to be given to whether booster doses improve VE against the Delta variant and other VOCs. While Delta is the current VOC, it is unlikely to be the only variant that will have to be addressed in the future.

Now moving to the WG's interpretation of these considerations and the framework around booster doses. In terms of the public health problem, receipt of a COVID-19 vaccine primary series will continue to have the largest public health impact. Decisions for boosters need to focus on prevention of severe disease, hospitalization, and death. It is known that the vast majority of cases, especially cases requiring medical attention now, are among unvaccinated individuals. The WG emphasized the importance of ensuring global vaccine availability, given that new variants could emerge from regions with low vaccine coverage and high community transmission. One of the best ways to protect the US population from the next variant threat is to ensure that the remainder of the global population has access to a safe and effective COVID-19 vaccines.

Turning to the WG's interpretation of the benefits and harms, neutralizing antibody data will be important for booster dose discussions, but may not represent the entire immune response to COVID-19 vaccines. Decisions around boosters cannot be based solely on detectable neutralizing antibodies. The cellular immune response can be difficult to measure in a broad population, but is important in the ability to fight COVID-19. Commercial antibody testing is not authorized or recommended to evaluate post-vaccination immune response. Based on the available data and the timing of vaccine rollout, the initial booster vaccine policy will be focused on the at-risk adult population. Adolescents are only just now receiving their primary series. The at-risk individuals on whom the WG will focus will include adults 65 years of age and over, LTCF residents, and HCP as mentioned earlier.

Returning to the roadmap for booster doses, key considerations for decision-making were just addressed. The plan moving forward is to have another ACIP meeting in the next several weeks to fill in this framework and identify what data are available for decision-making. Once the available data have been evaluated and there is regulatory allowance for booster doses, the WG can address whether the ACIP recommends booster doses of COVID-19 vaccines in any populations. There will be some questions for which the amount of data desired may not be

available as the ACIP moves into these decisions. For instance, there may not be detailed information around how VE varies for each specific COVID-19 vaccine in each specific sub-population; what the VE is for booster doses of COVID-19 vaccines and how that varies by sub-population; and or how the need for booster doses of COVID-19 vaccines may evolve as the pandemic evolves. By continuing to present and discuss the available data during public ACIP meetings, the WG can highlight what is known and not known and how that information can inform possible future recommendations.

The following questions were posed for ACIP consideration and deliberation:

1. Does ACIP agree with the framework laid out to address booster dose recommendations and the WG's interpretations?
2. Are there other questions that would be important for ACIP to address?

Summary of Discussion

- ACIP members suggested the following topic areas of interest related to booster doses:
 - Identification of areas in the US with low vaccination rates
 - Assessment of whether giving a third dose to people already willing to take it and to mask will help to overcome the large pockets of unvaccinated individuals
 - Effectiveness of booster doses and duration, particularly with regard to whether this varies depending on race/ethnicity and type of chronic underlying medical conditions such as diabetes and HIV, which are higher among some populations (e.g., African Americans, Latinx, Native Americans)
 - Identification of a better correlative of immunity
 - A better understanding of the gaps in data and what is being pursued by the CDC, the FDA, and/or the National Institutes of Health (NIH)
 - More information about individuals living in congregate settings
 - At well beyond a year since the clinical trials started and many thousands of individuals volunteered for them and provided blood samples and extensive detailed follow-up information, the vaccine companies owe it to the public health infrastructure of the US and elsewhere to share those data
 - Plan ahead relative to children and do not wait to finish one set of studies before starting studies among children pertaining to booster doses
 - The overwhelming driver of current disease, particularly severe disease, is people who are unvaccinated—an important distinction that needs to be communicated to the general public and providers

CERTIFICATION

Upon reviewing the foregoing version of the August 13, 2021 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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ACRONYMS USED IN 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
CMS	Center for Medicare and Medicaid Services
COG	Children's Oncology Group
COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CSTE	Council of State and Territorial Epidemiologists
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
DVRPA	Division of Vaccines and Related Product Applications
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
EIP	Emerging Infections Program
EMA	European Medicines Agency
EtR Framework	Evidence to Recommendations Framework
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHCs	Federally Qualified Health Center
HCP	Health Care Personnel / Provider / Professional
HHS	(Department of) Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Viruses
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplantation
IAC	Immunization Action Coalition
ID	Identifier
IDSA	Infectious Disease Society of America

IHS	Indian Health Service
IM	Intramuscular
ISO	Immunization Safety Office
ISTM	International Society for Travel Medicine
J&J	Johnson & Johnson
LLS	Leukemia & Lymphoma Society
LTFC	Long-Term Care Facilities
MASO	Management Analysis and Services Office
MMWR	<i>Morbidity and Mortality Weekly Report</i>
MoH	Ministry of Health
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
PCP	Primary Care Provider
PHAC	Public Health Agency Canada
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PIDS	Pediatric Infectious Disease Society
RBD	Receptor Binding Domain
RCT	Randomized Controlled Trial
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
TNF	Tumor-Necrosis Factor Blockers
UK	United Kingdom
US	United States
USG	United States Government
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
VOI	Variant of Interest
VSD	Vaccine Safety Datalink
WG	Work Group