MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

SEPTEMBER 22-23, 2021
SUMMARY MINUTES

Table of Contents

Meeting Purpose

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on September 22-23, 2021. The meeting took place remotely via Zoom and teleconference. This document provides a summary of the meeting, which focused on the topic of a third dose of the Pfizer/BioNTech BNT162b2 SARS-CoV-2 vaccine.

Wednesday: September 22, 2021

Welcome and Introductions

Dr. Grace Lee (ACIP Chair) called to order and presided over the first day of the 12th ACIP meeting convened in 2021.

Dr. Amanda Cohn (ACIP Executive Secretary, CDC) welcomed everyone and introduced new ACIP member, Dr. Jamie Loehr, from Cayuga Family Medicine in Ithaca, New York. She noted that while the current agenda was for a 2-day meeting, the agenda for the second day remained to be determined and would be finalized if the Food and Drug Administration (FDA) authorized a third dose of the Pfizer product before the opening time scheduled for the second day. She explained that there would be an oral public comment session at approximately 12:20 PM Eastern Time (ET) on September 23, 2021. Given that many 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 were encouraged to submit them through https://www.regulations.gov using Docket Number CDC-2021-0104. Further information on the written public comment process can be found on the ACIP website.

Dr. Cohn reminded everyone that 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. At the beginning of each meeting, ACIP members state any COIs.

Dr. Lee (ACIP Chair) briefly highlighted a few key points about the ACIP's process for recommendations, sharing a figure depicting the vaccine life cycle. She explained that to move from science and Data to recommendations, vaccine manufacturers typically submit clinical trial data to the FDA in their application for licensure or authorization in this instance. The FDA conducts a rigorous and independent review of the data that are submitted to the FDA as part of that application. The previous week, the FDA convened its Vaccine and Related Blood Products Advisory Committee (VRBPAC) to provide advice to the Commissioner of the FDA on the issue of the booster dose application from Pfizer. The FDA then makes a determination on whether to approve a new vaccine or new indication for use of an existing vaccine. After the FDA's regulatory decision, the ACIP typically has the period of time to review the data, GRADE (Grading of Recommendation Assessment, Development and Evaluation) the scientific

evidence, and deliberate on the Evidence to Recommendations (EtR) Framework for the policy question at hand. The ACIP then proceeds with a vote and recommendations for use of the vaccine in the US civilian population. As everyone knows, that cycle has gotten compressed to a very short timeline during the time of COVID.

In addition, Dr. Lee highlighted two key points in the ACIP Charter: 1) the role of the ACIP, which also is a federal advisory committee, is to provide advice and guidance to the Director of the CDC regarding use of vaccines in the civilian population in the US; and 2) recommendations made by the ACIP are reviewed by the CDC Director and, if adopted, are published. She emphasized that the ACIP's process for deliberation would be continued throughout the day and thanked the ACIP Members, *Ex Officios*, and Liaison Representatives for their continued service to the committee. In addition, she thanked the entire CDC team for all of their contributions and for continuing to work around the clock to bring together all of the evidence and data needed to help support a robust decision-making process.

Dr. Lee then conducted the roll call. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. No COIs were declared by any voting members.

Coronavirus Disease 2019 (COVID-19) Vaccines

Introduction

Dr. Matthew Daley (Chair, ACIP COVID Vaccines WG) introduced the Coronavirus Disease 2019 (COVID-19) Vaccines session for the first day of the meeting. He reported that in terms of daily trends in the number of COVID-19 cases in the US,[1] there were more than a 150,000 new cases between January 23, 2020 and September 17, 2021. Over the course of the pandemic, there have been almost 42 million cases in the US. At the most recent date, there were 2087 COVID-19 deaths in the US.[2] This translates to nearly 100 individuals every hour who are dying from COVID-19 in the US. In September 2021 in the US, death from COVID-19 is largely vaccine-preventable with the primary series of any of the three vaccines available in the US.

During August and September of 2021, the COVID-19 Vaccine WG's efforts have focused on review and consideration of booster doses for COVID-19 vaccines in terms of the following topic areas:

- ❑ Real-world vaccine effectiveness (VE) studies in the US and abroad
- ❑ RCT safety and immunogenicity of booster doses
- ❑ Modeling of the impact of booster doses on COVID-19 in nursing homes
- ❑ National Institutes of Health (NIH) booster data
- ❑ Outbreaks among vaccinated people in congregate settings
- ❑ GRADE of booster evidence
- ❑ Benefit/Risk Analysis of COVID-19 vaccine booster doses
- ❑ EtR in terms of implementation, values, acceptability, resource use, and equity

[1] https://COVID.cdc.gov/COVID-data-tracker/#trends_dailycases

[2] https://COVID.cdc.gov/COVID-data-tracker/#trends_dailydeaths (accessed September 19, 2021)

Dr. Daley indicated that during the September 22, 2021 COVID-19 Vaccines session, there would be presentations on the following topics:

- ❑ Safety and immunogenicity of a third dose of BNT162b2 COVID-19 vaccine
- ❑ Immunity and SARS-CoV-2
- ❑ Vaccine effectiveness studies in the US
- ❑ Modeling impact of booster doses in nursing home residents
- ❑ Early safety monitoring for third doses
- ❑ Vaccine Safety Technical (VaST) Work Group summary
- ❑ COVID-19 WG summary
- ❑ Pregnancy: Safety monitoring in v-safe[SM]
- ❑ Pregnancy: Safety monitoring in VSD
- ❑ Updates on COVID-19 and pregnancy

Safety and Immunogenicity for a Third Dose of BNT162b2

Dr. Bill Gruber (Pfizer-BioNTech) began by presenting data of a booster or third dose of BNT162b2 (COMIRNATY®) COVID-19 mRNA vaccine that support vaccine authorization and recommendations that Pfizer anticipates will maximize public health benefit. Data to support the need for a booster dose were presented in some detail the previous week to the VPBPAC. There is a briefing document and slides that speak to the details. The Kaiser Permanente Southern California (KPSC) work was accepted by *Lancet* and is in press. There are additional data in terms of post-hoc analysis, the randomized controlled trial (RCT) itself with the BNT162b2, and Israeli data that support the need, timing, and benefit of the booster dose.

In terms of an overview of the clinical program, the good news is that BNT162b2-elicited sera effectively neutralized a broad range of SARS-CoV-2 spike variants after 2 doses. Pfizer has yet to find a variant that escapes neutralization, including Alpha, Beta, Delta, and Lambda variants. Across the board, the neutralizing titers are well-maintained. Perhaps the lowest is for Beta, for which there are efficacy data from South Africa from Pfizer's pivotal trial. As a reminder, there was a 0/9 split with 8 of the sequences determined to be South Africa and the 9th expected to be as well. These data are very compelling and speak to the fact that if a third dose actually generates sufficient antibody to the wild-type or vaccine virus, there is an expectation that it will restore protection against variants of concern now and into the future.[3]

Regarding how the third dose was evaluated in Phase 1 and Phase 3, participants from the original pivotal trial received 2 doses of vaccine administered 21 days apart. Pfizer took advantage of that population to further study the potential for a booster dose, first in Phase 1 with 23 individuals and then in an expanded group to meet Phase 3 criteria. Reactogenicity and other safety events were captured when sampling was done at the 7 day and 1 month intervals. Immunogenicity data from Phase 1 reveals useful information about the ability to boost response, the nature of maturation of that response, and shows how it bodes well for the potential for the vaccine to work effectively.

[3] Data from Liu et al., 2021, Nature DOI: ; L10.1038/s41586-021-03693-y; Liu et al., 2021 NEJM, DOI: 10.1056/NEJMc2102017; Delta-AY.1, Lambda data submitted for publication

Post-dose 3 vaccine geometric mean titers (GMTs) provide a substantial boost and reduce the gap between wild-type and Beta variant neutralization. As expected after 2 doses, there is a robust immune response that is now known to be associated with 95% at efficacy in the months following vaccination. Especially gratifying is that despite the drop in younger adults and older adults, the drop in neutralizing activity just prior to the third dose was around 7 months after the 2-dose series. There is a robust response of neutralizing antibody to both the wild0type and the Beta variant. The geometric mean ratio (GMR) after Dose 2 compared to after Dose 3 narrows, suggesting a maturation of the response and that antibody continues to rise between 7 days and 1 month, further suggesting broadening and maturation of the response that is likely to provide comparable protection to that seen after 2 doses and perhaps improved projection and greater durability of protection. It also was important to assess the Delta variant since this is the variant of greatest concern at this time. It also is gratifying the post-Dose 3 vaccine GMTs indicate a substantial boost to the Delta variant similar to wild-type. Once again, there is a very robust response to the booster among younger and older groups. Particularly in the older group, there is a narrowing of the ratio between the response to the wild-type and the Delta variant.

The safety profile after the third dose in the Phase 1 trial very closely mimics that seen after the second dose, so the combination of immune response and a satisfactory safety profile encouraged Pfizer to move to Phase 3. The subjects receiving the third dose were representative of 18 to 55 year olds in the parents study. There is good distribution in terms of gender, race, and ethnicity. Over 50% of the individuals had comorbidities by the Charlson Comorbidity Index, which includes risk factors as well as obesity and reflects risk factors seen in the original population that were noticed as part of the 1001 study. The mean age for booster vaccination was 41.3 years and the time from Dose 2 to the booster dose was close to 7 months, with a range of between close to 5 months out to 8 months.

In terms of the immune response as seen in the Phase 3 trial that met criteria for approval, the GMR of neutralizing titers met the non-inferiority criterion specified by the FDA, with titers at least 3-fold higher than those seen after the second dose. The assay was a true neutralization essay in 210 individuals. The nature of the GMT responses one month post-booster dose versus one month after Dose 2 gives a ratio 3.29 and a lower confidence interval of 2.76, so this particular non-inferiority criterion was met. The other non-inferior criterion was a criterion of seroresponse. The non-inferiority of the booster dose was demonstrated based on the proportion of subjects with a seroresponse. There was a 99.5% response one month post-booster dose and there was a 98% response one month after Dose 2, which is well within the specified criteria that required a lower confidence interval greater than -10. This was -0.7, which is well above the criteria required to meet the FDA specification.

It was important to pair this up with safety information. Regarding the follow-up time for the expanded phase, the total exposure from booster vaccination to the cutoff date was 2.7 months with the median of 2.6 months. The total exposure from Dose 2 to the cutoff date, the entire time for which this population had been followed, is 9.4 months with a median of 9.5. Local reactions were comparable between the third dose and the second dose. Particularly informative are the systemic events. Systemic events by maximum severity within 7 days of the third dose were similar to post-Dose 2 in the parent study. In addition to the reactions being similar, fever and chills were somewhat lower after Dose 3 compared to Dose 2. This suggests a lack of enhancement of reactions associated with the third dose and the fact that the safety profile may be even somewhat better.

Unsolicited adverse events (AEs) and AEs by system organ class occurring at ≥1% one month post-Dose 3 overall were less than those post-Dose 2 in the parent study, with the notable exception of blood and lymphatic disorders. The 5.2% is entirely represented by lymphadenopathy, most of which was self-limiting. The investigator reported one individual to have severe lymphadenopathy by virtue of some limitation of arm movement, but this was self-limited and resolved by 4 to 5 days. The 0.6% by comparison post-Dose 2 is also largely represented by lymphadenopathy of 0.5%. Across the board, looking at lymphadenopathy and the nature of the other AEs, these are within an acceptable range for a good tolerability profile for a third dose. One individual had an acute myocardial infarction (MI). This was a 42-year-old who experienced an MI 62 days after Dose 3. This individual had a history of stimulant abuse and the investigator considered this unrelated to the vaccine and more likely related to the stimulant abuse.

As part of the work Pfizer has done with approval, first under Emergency Use Authorization (EUA) and then full approval and licensure for the 2-dose series of vaccine in individuals 16 years of age and above, there continues to be ongoing and active pharmacovigilance and pharmacoepidemiology. That has proven to be particularly useful in identifying rare AEs that are not easily identified during the conduct of a clinical trial, notably events such as anaphylaxis and myocarditis. The rarity of the events associated with the benefit has supported a favorable risk-benefit profile for recommending the vaccine for 2 doses. Pfizer anticipates that this risk profile also will be seen after the third dose. This intensive pharmacovigilance and pharmacoepidemiology will continue to better define risk.

In summary, the safety and immunogenicity data meet the FDA criteria for the booster dose among those ≥16 years of age. The Phase 1 safety profile was satisfactory and notably, the Beta and Delta variants of concern responses after the third dose bode well for the ability to provide broad coverage against variants of concern now and in the future for both younger and older adults. The Phase 3 data revealed a safety profile similar or better than Dose 2. The elicited immune responses against the wild-type virus were non-inferior to responses observed post-Dose 2. The fact that they were statistically greater suggests the potential for not only providing protection equivalent to that seen with two doses of the vaccine, but also perhaps more sustained protections. The Phase 3 data met protocol pre-specified immunobridging success criteria for GMTs and seroresponse rates. BNT162b2 is already demonstrated high efficacy after two doses. The types of immune responses seen and the real-world evidence bode well for the vaccine to provide substantial benefit to those individuals who are boosted. Again, it is known that 2 doses of VE against severe disease and hospitalization remain high in most populations in the US, data from Israel predict that this may not be sustained. Pfizer is eager to maximize the potential for a booster dose to receive an authorization and a recommendation to provide the greatest public health benefit.

Discussion Points

Dr. Poehling expressed appreciation for the diversity of inclusion in the Phase 3 trial. Recognizing that COVID-19 has disparate impact across the nation, this is very important and there is an opportunity to continue to expand the diversity of the population. While Dr. Gruber shared the 1 month post-Dose 3 data, she asked what the plans are to follow the immune response in the future. In addition, she asked whether there were any episodes of myocarditis in these studies.

Dr. Gruber noted that Slide CC-5 represented Pfizer's intentions in terms of follow-up. Active surveillance is ongoing, but that is expected to be challenged. It is expected that once a booster is recommended, the individuals who have not been boosted will need to be. Serum responses will be assessed at 6 and 18 months to get some measure of the persistence of antibody. In the Phase 1 data as shown, that tended to fall off very quickly. Pfizer is hopeful and expects that this may be more sustained. Antibody by itself may not be the basis of protection long-term and certainly memory is important. It was shown early on that cell-mediated immune (CMI) was particularly important in the absence of antibody. Ultimately, real-world evidence is going to provide the most useful information about maintaining protections. Pfizer, CDC, and others will be monitoring that closely. Given the rarity of myocarditis, no cases were experienced in the trial. It is in the label and Pfizer is very keen to ensure that they encourage individuals, investigators, and participants in the trial to be attentive to symptoms or signs that could be associated with myocarditis, so they provide specific guidance in all current protocols and will in those moving forward to alert individuals to report chest pain, palpitations, et cetera that might be associated with myocarditis. In addition, Pfizer routinely engages in pharmacovigilance after general use of the vaccine. While the Israeli data are limited, albeit it limited to not a full month for the full cohort who have now received a third dose, it was reassuring that there was only one episode of myocarditis in an individual over 30 years of age with a denominator of about 1.2 million individuals. No myocarditis cases have been seen, with a fairly sizeable proportion of the Israeli population in the risk groups. That provides some comfort and is expected to be recapitulated with the US data once a large population is vaccinated.

Ms. Bahta asked what proportion of the people in the 18 to 55 years of age group were under 24 years of age.

Dr. Gruber indicated that this information could be obtained and provided to ACIP before the vote the next day.

Dr. Daley asked what Dr. Gruber thought the relationship was between systemic reactogenicity and AEs such as myocarditis and whether anything could be inferred about myocarditis risk from the reactogenicity profile presented during this session. In addition, he requested clarity about whether there were individuals over the age of 55 who were in the Phase 1 study but none in Phase 3, so there was extrapolation to that group from the Phase 3 study findings.

Dr. Gruber observed that it would be useful information if myocarditis risk, as rare as it is, tracked in some way with increased reactogenicity. If that proves to be the case, it could be argued that less reactions would be seen after the third dose. CDC is better equipped to address this because they have a lot more information about how those two may track together, but it occurred to him that one reasonable hypothesis also might be that those people with myocarditis may not be getting a third dose and might drop out. That means that the individuals without risk will not show up. That will have to be part of the decision about recommendations. In terms of individuals 55 years of age and older, the regulatory guidance from the FDA was that it would be possible to study a segment of the population 18 to 55 years of age and extrapolate that both from a safety and an immune response perspective to the group at large for which Pfizer was seeking an indication from 16 years of age and up. That guidance makes sense in terms of the nature of the reactions seen after the second dose among older compared to younger individuals, given that the older individuals had fewer reactions. Coupled with what was observed in Phase 1, which was similar, and the reduction observed after the third dose in reactions, particularly for fever in those 18 to 55 years of age, that provides compelling evidence that the reactions are likely to be less in the older age groups. Likewise for immune response, in addition to the Phase 1 data and although the sample was small, what was seen in the post-

Dose 3 individuals 18 to 55 years of age was predictive in that the responses after the third dose were robust. In Phase 1, the responses among 65 year olds rivaled those seen in the 18 to 55 year olds, so there is every expectation that the same thing would be seen in older individuals. The real-world evidence from Israel is very compelling in that a high proportion of individuals vaccinated have been over 60 years of age have restored efficacy above 95%. In fact, the majority of individuals over 60 years of age in Israel have now been vaccinated with a third dose. This predicts reliably that those 65 to 85 years of age will have a robust protective immune response.

Dr. Sanchez requested clarification whether only groups 18 to 55 and 65 to 85 were included in the studies assessing the third/booster dose and the 16 to 17 and 56 to 54 groups were extrapolations of the other data.

Dr. Gruber indicated that there were no 16 to 17 year olds in the booster study. The study that was submitted for EUA includes the Phase 1 data in those 65 to 85 years of age, but there are no additional data as part of that submission in the older age group. The regulatory guidance when the protocol was first proposed and then approved by the FDA suggested that was sufficient. The rationale that he shared with Dr. Daley supports that guidance.

Referring to slide CC-10, Dr. Kotton observed that about 57% had a co-morbidity of either hypertension, obesity, or meeting the Charleston Comorbidity Index (CCI). She asked how may of these were immunocompromised in the Phase 3 study. Immunocompromised persons comprise about 3% of the US population and she wondered whether that was represented in the cohort and whether anything further could be said about that population.

Dr. Gruber indicated that since these individuals were drawn from the 1001 study, individuals judged by the investigators to be immunocompromised were not included. They could have a past history of cancer or immunocompromising conditions, but if they were on chronic long-term steroids, were receiving other immunosuppressive agents, or the nature of their underlying disease was immunosuppressive, they were not included. Pfizer has reported out the number of individuals who had underlying cancer, with an abstract being presented and a manuscript that carved out that population after 2 doses. He did not know off hand how many were in the Phase 3 cohort of 306. No one was immunocompromised to the extent that now, there is a label indication for individuals who are immunocompromised to receive a 3-dose primary series.

Ms. McNally asked Dr. Gruber to comment on whether Pfizer is conducting trials or plans trials to evaluate the safety and immunogenicity of the Pfizer booster vaccine after the completion of a primary series with either Moderna or J & J vaccine.

Dr. Gruber indicated that Pfizer is not sponsoring trials but welcomes the trials that are being conducted by the National Institutes of Health (NIH) in the US and trial abroad, particularly in the United Kingdom (UK) that are assessing combinations of mRNA vaccines either as priming doses or as a booster dose and vice versa with adenovirus vector vaccines and their competitor’s mRNA vaccine. That information will be useful in informing public health policy. Pfizer’s focus has been on providing as much information as possible about the series of immunizations that they think best provides protection.

Dr. Beigel (NIH) added that the National Institute of Allergy and Infectious Diseases (NIAID) is currently conducting a study evaluating all 3 EUA vaccines as boosters. This is essentially a 3 x 3 study in which people present who have received a primary series with Moderna, Janssen, or Pfizer and are then boosted with Moderna, Janssen, or Pfizer. That study is ongoing and while data are not available to present yet, they hopefully will be available very soon.

Dr. Brooks asked whether there were any variances by race or ethnicity in response and, if so, whether they were statistically significant.

Dr. Gruber said that based on what they saw with the second dose of vaccination and the more exuberant responses seen after the third dose, there was evidence across racial and ethnic groups that were essentially indistinguishable in terms of efficacy with a much larger database with over 40,000. Given the response observed after the third dose, there is an expectation that the responses are likely to be adequate.

Dr. Czech indicated that they have not yet done subgroup analyses. Regarding an earlier question, about 6.5% of the subjects were 18 to 25 years of age in this population.

Dr. Duchin (NACCHO) asked whether an alternate interval for the primary would enhance the duration and perhaps degree of protection, and whether that would have implications in the future when transmission is lower to have a better response with the primary series.

Dr. Gruber indicated that Pfizer is exploring a number of potential options about how to optimize protection. One of the challenges faced from the beginning that was considered to be an advantage regarded how to protect people as quickly as possible in the midst of the pandemic. After seeing the Phase 1 data following 2 doses, that led them to select the 21-day interval as opposed to waiting even longer to provide protection. As it turns out, there was high protection 12 days after the first dose. Others in Europe have looked at this and Pfizer welcomes that information and will continue to explore whether it makes sense to consider a longer interval. That makes particular sense once out of the pandemic situation. Obviously, they do not want to compromise people between the first and second dose and leave people uncovered.

Dr. Kimberlin (AAP Redbook) pointed out that if there was a correlate of protection, a lot of the considerations about booster doses would be simpler. He asked what Pfizer is doing to identify a correlate of protection in those who have breakthrough infections versus those who do not and when those answers will be available.

Dr. Gruber said that to some extent in terms of the basis for comparisons being made, a reasonable assumption has been made that antibody response comparison can be a basis for approval. In this case, GMTs and seroresponses are being compared. The nature of correlates is tricky because antibody drops off fairly quickly and faster than the efficacy seen for overall COVID-19 and particularly for serious infection. There is more to this than antibody, so it is not so simple to rely on antibody response. It is a useful marker to make the types of comparisons that are being done to meet regulatory criteria. Pfizer is interested ultimately in looking at how this can be considered as a correlate of protection. They will know more about this after the booster dose and observation of what happens with durability in relationship to antibody in terms of real-world evidence—likely into next year.

Dr. Loehr recalled that during the last ACIP meeting, Dr. Stanley Plotkin broached the idea that these should not be called “booster doses” and instead should be considered to be part of the primary series and raising the antibody levels as is done with other vaccines that have a 6-month series process. He asked Dr. Gruber to comment on whether he though that was a reasonable concept.

Dr. Gruber said it was a reasonable hypothesis based on what is known about other vaccines that either require significant spacing between a first and second dose or a 3-dose series in which the third dose is spaced after the second. He has heard two contending positions, one of which is that this could well be a circumstance where after a third dose protection is maintained and perhaps enhanced over a longer period of time. He likes that and thinks that if that proves to be the case, they may come to a realization post-hoc that this is really 3 doses, after which protection may last 1 to 2 years. That is what is great about the information being gathered by Pfizer and real-world evidence to help inform that. He also has heard the other contending view such as from people in the last VRBPAC meeting who said that protection may drop again right after the third dose and it does not cement itself as a 3-dose series. He thinks this will be driven largely by what is found in retrospect as more information is gathered about protection.

Dr. Sanchez emphasized the importance of having a surrogate marker. He asked whether there are any plans to assess the antibody levels at the time of breakthrough cases to ascertain whether there is any association with the antibody level and the serum neutralizing titer with the cases of breakthrough disease. If booster dosing is going to be decided based on the fact that there is waning immunity and lower antibody responses, it is important to know what exactly is occurring in terms of the antibody responses. He emphasized the importance of examining antibody responses and other immune markers.

Dr. Gruber stressed that there is interest in looking at breakthroughs in any case. Pfizer continues to sequence and try to identify the potential that the antibody responses shown and the reassurance that they provide is matched by what is seen. He called upon Dr. Philip Dormitzer, Pfizer’s Chief Science Officer for Vaccines, to comment on future plans for such studies.

Dr. Dormitzer indicated that Pfizer is assessing breakthrough infections and the virus. He did not know whether they had the serum at the time of the breakthrough infection to be able to assess the correlation of the titer at the time of the breakthrough. They are looking at correlates of protection by assessing antibody levels and through modeling work as well. For most vaccines that have been available for decades, there are not reliable correlates of protection. While they will make every attempt to continue to do so, it also is important to set realistic expectations. It is clear that protection is multifactorial. Protection is seen before there are significant neutralizing titers and after neutralizing titers fall to very low levels. Protection against variants does not correlate well with the level of antigenic escape. That is not to say that neutralizing titers are not important. They are probably an overall indicator of overall immune response. However, even when neutralizing titer is seen it is not clear whether it is the neutralizing antibody that is protecting or the associated CD8+ or CD4+ T-cell responses or non-neutralizing antibodies active in antibody-dependent cellular cytotoxicity (ADCC). It is important as a general indicator of immune response, but he does not believe that there is going to be a precise correlate of protection, as is true for almost all current vaccines.

Dr. Lee added that Dr. Thornburg's presentation would go over this particular topic, after which this discussion could continue. She commented that from a safety perspective, the duration of follow-up is less important to her than a sufficient sample size in the clinical trials. Duration is incredibly important from an efficacy perspective, so she understood the need for both. However, she wondered whether it is possible to consider a study that would collect blood approximately 2 to 3 days post-vaccination in the window of myocarditis. She said she asked because a better understanding is needed of the pathophysiology of what might be contributing. Because of the way blood is collected at Day 0 and Day 7, that window is missed. This could capture more information in terms of how that relates to systemic reactogenicity and the potential for understanding risk factors for myocarditis.

Dr. Gruber emphasized that Pfizer is very attentive to trying to figure out how the potential risks can be better identified for even this very rare outcome. They have had discussions with the FDA about how best to do that. One way would be to identify a circumstance where an individual seems to be having symptoms that could be associated with myocarditis. As part of that guidance, they are urging investigators to do a comprehensive work-up that includes getting an appropriate blood specimen at that time with the symptoms. One of the challenges is that across the literature, there is not a lot that offers confidence in terms of the age groups and the specificity of troponins when they are seen and whether it represents a cardiovascular outcome. One study they have referenced indicated that two-thirds of the time, an individual presenting with non-cardiac symptoms were more likely to have a positive troponin in the absence of a cardiovascular finding than in the presence of a cardiovascular finding. The specificity is not particularly good. One thing they are considering is obtaining specimens on the existing samples to get baseline rates across the population before they are vaccinated in order to better define what should be looked for after vaccination. The last thing they want is a non-specific signal that just creates further confusion about that risk. They agree that focused attention on patients experiencing chest pain, palpitations, and fever in association that suggests a cardiac event is important and they are encouraging investigators to do comprehensive work-ups. For the rest, more information is needed to avoid going down a path that leads to more confusion by testing for things that do not have specificity. Pfizer is in a position of working with the FDA about the appropriate obtaining of samples. They do not want to test them prematurely until they know that they have some specificity.

Dr. Gluckman (ACP) asked whether anything can be gleaned from the first two doses of administration regarding anaphylaxis as it applies to the third dose in terms of whether the 15-minute wait period in a provider setting is still necessary for those who did not have an anaphylactic reaction. That will have implications for workflow as vaccines are administered in the provider setting. While it was comforting to see that after a third dose there is still a high level of neutralizing antibody from the Delta variant, he was interested to know whether Pfizer is working to modify their vaccine for variants and how soon they would be able to get something to market if there needs to be a modification of the vaccine to address a variant for which it is less effective.

Dr. Gruber responded that they are reassured that they did not see anything in this sample that would indicate a higher risk of anaphylaxis. He still thinks it is prudent, as with any vaccine, to monitor after the third dose just as is done after the second dose. In terms of potential future variants of concern, as part of this trial though not presented here, they looked at the Beta variant as a basis for a surrogate. Those data are outstanding because the focus was on the current vaccine. Pfizer has had appropriate interactions with the FDA that encourage them that looking at the Beta variant as a surrogate, if they can show that there is an appropriate safety profile and immune responses are generated to that Beta variant that are comparable to those

that are associated with protection from the original 2-dose series with the original vaccine, that would be a basis for approval not only for that vaccine, but also would put them in a position not to have to conduct clinical trials for each new variant. Pfizer has in the works the potential to pivot very quickly if a variant of concern appears in the future that suggests it is escaping protection, and they are setting themselves up to be able to inform that decision based on the current trial and those results are forthcoming.

Dr. Fink (FDA) clarified that FDA has had discussions with vaccine manufacturers about data that eventually could support a seasonal influenza strain change type approach that would not rely on clinical data to support the safety and effectiveness of a strain change. The FDA has not concluded at this time that a single example based on a single modified vaccine would be sufficient to get there.

Adaptive Immunity and SARS-CoV-2

Dr. Natalie Thornburg (CDC/NCIRD) presented on adaptive immunity after SARS-CoV-2 to vaccination with a focus on adaptive cellular and humoral immunity and how they are generated, correlates versus contributors to immunity, immune durability and waning, age-related immunosenescence, and how variant circulation might affect immunity. When one is exposed to a virus or vaccinated, an adaptive immune response is activated. That adaptive response generates T helper cells from a pool of naïve cells. Those T helper cells drive cytotoxic T cells, which kill infected cells and also drives differentiation B cells, which secrete antibodies. All of these cells are considered part of the cellular immune response or CMI, and the antibodies that the B cells secrete are part of the humoral immune response.[4]

There are several different isotypes of immunoglobulins or antibodies. Antibodies are simply proteins and all proteins have half-lives. Each isotope has an approximately different half-life. It is known that serum antibody responses wane according to the half-life of the specific immunoglobulin. Antibody responses are expected to wane at a typical half-life decay curve. Even after antibodies wane, there is still residual adaptive immunity. During the process of driving CMI and antibody secretion, memory B cells and memory T cells are developed that are virus-specific, can be very long-lived, and can actually live for the life of the person. Then if one is re-exposed to antigen either through revaccination or infection, those memory B cells can rapidly expand in a germinal center response called an anamnestic response. As part of that response, antibodies can be freshly secreted to boost the infected or vaccinated person. Those antibodies can be binding antibodies that can be functional neutralizing antibodies, but this process can take a few days or a week. In the process, the lymph nodes swell because that happens in the germinal center reaction, and there may be some symptoms. When one has that amnestic response, the new immune response can then quickly clear of any infection that has established itself. Therefore, it is more self-limiting than a primary exposure or a primary infection.[5]

In terms of correlates to immunity versus a contributor to immunity and what is meant by the word “immunity.” Immunity is not simply a binary protected versus unprotected, especially with regard to upper respiratory infection (URI). There are levels of protection between full sterilizing protection and the full disease process. The top level of protection might mean true sterilizing immunity and no protection might mean very serious infection or death for some individuals. In between those two levels could include asymptomatic infection, symptomatic URI, symptomatic

[4] https://www.virology.ws/2020/11/05/t-cell-responses-to-coronavirus-infection-are-complicated/
[5] Roda et al. Cell

lower respiratory infection (LRI). There might be different immunological contributors within each level that could include, but not be limited to, the level of antibody, antibody isotypes that a person has generated, the functionality of those antibodies (binding versus neutralization), the specific epitopes of those antibodies and their affinity, physical locations in the body (nose, lungs, serum), the number and specificity of the antiviral T cells and B cells, and the ratio of different kinds of T cells that have been generated. Any or all of these contributors could be a correlate if found to be easily measurable and can predict any state of immunity. However, a correlate is not the entire picture. The picture is very complex and dynamic.

Speaking specifically of SARS-CoV-2 and potential correlates, primate models that suggest that very high levels of neutralizing antibodies alone are sterilizing and that lower levels can protect or abrogate lower respiratory tract infection. A manuscript published by Dan Barouch's group shows rhesus macaques that have received passively transferred neutralizing antibodies from previously infected mechanics at high, medium, low, and no neutralizing titers. Transferring very high doses of neutralizing IgG to naïve macaques is enough to protect them from lower respiratory tract infection. An even lower dose partially protects the animal. Similar but less dramatic results are seen in the upper respiratory tract.[6]

There is emerging evidence to suggest that anti-spike and neutralizing antibodies, which are also directed against the spike protein, are correlates of risk. Three studies that are either published or in pre-print all identify neutralizing or spike-binding levels as at least partially protective. The Khourey et al.[7] manuscript compared neutralizing antibody titers after vaccination with a multitude of different products, normalized them to convalescent sera, and then compared the vaccine efficacy (VE) or the protective efficacy of each of these different products and use those normalized values to estimate the level of neutralizing antibodies required for about 50% protection against infection. A Goldblatt et al. pre-print that was recently published looked at both binding and neutralization assays in participants who had received Pfizer BNT162b, Moderna mRNA1272, AstraZeneca AZD1222, or Janssen Ad26Cov2.S and used a population-based method to estimate a protective threshold, which they predicted at 60 BAU/ml anti-spike IgG.[8] Feng et al., AstraZeneca's pre-print, calculated levels of binding and neutralizing antibodies required for 50%, 60%, 70%, 80%, and 90% percent vaccine effectiveness from symptomatic infection after vaccination with their product.[9]

Peter Gilbert and the NIH Study Group also has done a correlates of risk analysis on the Moderna product. They have looked at Day 29 and Day 57 correlates examining inhibitory concentrations with neutralization assays, and they also looked at binding assays. As stated in the previous presentation, they already estimated VE to be about 45% to 60% in vaccine recipients at the early time point—even before they could detect binding or neutralization antibodies. So, there was some protection before antibodies could be detected. VE increased to greater than 98% in the recipients who had the highest neutralization titers, suggesting that very high neutralization titers do contribute to some level of protection. They performed an analysis in which they were able to estimate the proportion of protection they saw from the antibody response and estimated that at the Day 29 timepoint, about 68% of VE against symptomatic infection was mediated through neutralization titers.[10] They have performed similar analyses

[6] https://doi.org/10.1038/s41586-020-03041-6

[7] Khoury, D.S., Cromer, D., Reynaldi, A. et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 27, 1205–1211 (2021). https://doi.org/10.1038/s41591-021-01377-8

[8] Goldblatt et al. A Population-Based Threshold of Protection for COVID-19 Vaccines; NaturePortfolio; under review.

[9] https://www.medrxiv.org/content/10.1101/2021.06.21.21258528v1

[10] Gilbert et al. medRxiv

using influenza vaccines and found that, at least with H3, about 57% can be predicted by hemagglutination inhibition assays. These data suggest that high titers of anti-spike or neutralizing antibodies contribute to immunity. The correlates analysis from the Moderna Phase 3 trial would suggest about 68% of the VE for symptomatic illness is from neutralizing antibody, which would leave about 32% contribution by other immunological factors.

Going back to some of the primate challenge models from the same manuscript shown earlier from the Barouch laboratory, they let the antibodies of previously infected macaques wane or decay to just below what they estimated to be a protective threshold and then re-challenged them. Before they re-challenged them, they left the animals alone so that they had cellular immunity and very low levels of antibodies or depleted their CD8+ T cells. Animals with CD8+ T cells intact had very little viral replication, so CD8+ T cells contributed to protection of those animals. With depleted CD8 T cells, they saw more virus replication. This indicated that both low levels of antibodies and CD8 T cells contributed to protection of these animals.

Given the high level of community transmission being seen for SARS-CoV-2, Dr. Thorburg discussed what happens if a vaccinated person becomes infected with asymptomatic or symptomatic infection. A pre-print looking at 161 infections in vaccinated people was published out of the UK during a time of high Delta transmission, so most of these cases were Delta, compared the recovery of live virus in unvaccinated versus vaccinated health care workers (HCW). These investigators saw lower probability of recovering live virus from vaccinated HCW. However, they did recover a lot of virus from HCW. There are similar data generated locally that corroborate these results, indicating that people who are vaccinated and then have an infection are able to shed live, culturable virus, suggesting that they might be infectious.[11]

Antibodies are expected to wane, which has been confirmed among Pfizer BNT162b2 vaccinated persons. Two different studies examined serum antibody waning in two different populations of individuals. The first by Naber et al published in *The Lancet Regional Health Europe Journal*[12]is a longitudinal cohort of 122 participants comprised of HCW 21 to 69 years of age with a median age of 36 looking at binding antibodies. Those who received the vaccine had significant lower serum antibody titers at 6 months post-boost 2 than they were 1 week after the second dose. These are binding not functional antibodies. Data posted in a pre-print followed participants out to only 3 months, but they did see neutralizing antibody titers. They found waning in both neutralizing and binding antibodies between post-Dose 1 and Dose 2, and more heterogeneity in the neutralizing antibody responses with a similar waning rate. By the last time point, they had several participants who were approaching the limit of detection.[13]

Cellular immunity is expected to be longer lived and there is now emerging evidence to conclude that mRNA vaccine recipients maintain spike-specific memory B cells at 6 months after mRNA vaccination. A pre-print article of Moderna recipients who were vaccinated alone or who were previously infected and then vaccinated, looking out to about 6 months, showed that the vaccine only recipient group had an increase in spike-specific memory B cells at 3 months and 6 months.[14] Another pre-print of memory B cells in Pfizer recipients showed that between 3 months and 6 months post-boost, there was an increase in some individuals and at least maintaining of memory B cells between the 3-month and 6-month time points.[15] These two pre-

[11] Shamier et al. medRxiv

[12] Naber et al; *The Lancet Regional Health*—Europe

[13] Maeda et al., edRxiv

[14] Goel et al. bioRxiv

[15] Ciabattini et al. medRxiv

print studies used different assays and different laboratories, so the results should not be compared to each other. BNT162b2 mRNA vaccine recipients generate spike-specific early memory CD8+ T cells based on a study looking at memory T cells in Pfizer recipients that was published in Nature. This study used three different peptides to detect memory to T cells and collected peripheral blood mononuclear cells (PBMCs) from these individuals after 80 days post-vaccination. In most Pfizer recipients, they were able to detect early memory T cells after vaccination.[16] To summarize durability, serum antibodies decrease over time, memory B cells are maintained out to 6 months post-vaccination, and early memory T cells are generated and detected after vaccination with the Pfizer-BioNTech product.

Given that immune responses in all age groups probably will not be the same, the process of immunosenescence is important to address. At first, people have a large thymus and a very large pool of naive T cells and as immune systems are educated by vaccination and infections, pools of memory T cells are built against antigens to which a person has responded. As people age, the thymus shrinks and the pool of naive T cells dwindles, but the memory B cells and memory T cells of all antigens encountered throughout life are maintained.[17] In terms of what that means for someone who is exposed to a new antigen who has limited naive T cells, this entire process can be abrogated. If someone does not have naïve T cells to differentiate virus-specific T helper cells, they can have abrogated differentiation of cytotoxic T cells to clear infected cells and aggregated differentiation of B cells and secretion of antibodies.[18] There is a publication in *Nature* by Collier et al.[19] looking at age-specific immune responses to Pfizer vaccination. In this, they have assessed both humoral and cellular immunity.

In terms of data from humoral immunity, they looked at neutralizing antibodies after one dose and the probability of having any detecting neutralizing antibody and that plotted against age. Probability starts to decline right around 50 years of age, slowly declines to about 80 years of age, and then drops off very quickly after 80. After a prime and boost, there is a statistically significant difference in the 50% serum neutralization tighter in adults greater than 80 years of age versus those less than 80 years of age. For cellular immunity, Collier et al. found that adults greater than 80 years of age also have less mature antibodies and fewer functional T cells, so abrogated CMI. In terms of mutations in the antibody genes in their B cells, meaning how specific that B cell has been driven to be directed toward the virus, a fewer number of mutations means it is closer to their germline or their own genes and just not as specific. They have a statistically significant fewer number of mutations—so less mature. There is a statistically significant difference between those less than 80 years of age and those older than 80 years of age and the two different T cell secreting cytokines.

Antibodies wane, cellular memory is maintained, and older adults are prone to immunosenescence. They have lower neutralizing antibody titers and, as predicted, less robust cellular immunity—probably due to immunosenescence. Therefore, they may need to rely more heavily on humoral immunity. This is a very complex situation for them. In addition, there are variants circulating that may affect immunity overall. Decay of neutralizing antibodies could be confounded by the circulation of variants of concern or variants of interest. Some variants have amino acid changes near the spike receptor binding domain that could result in reduction in neutralization titers. Many groups have tested many different variants and their ability to be neutralized by post-vaccination and convalescent sera and have found that neutralization loss

[16] Oberhardt et al. *Nature*

[17] Candia et al. *Trends in Immunology*

[18] https://www.virology.ws/2020/11/05/t-cell-responses-to-coronavirus-infection-are-complicated/

[19] https://www.nature.com/articles/s41586-021-03739-1

ranges from none, which is an Alpha B.1.1.7 to about 7-fold Beta, which is B.1.351. Delta demonstrates an approximately 1.5 to 2 full reduction in neutralization titers.[20]

Examination of antibody waning in young healthy individuals vaccinated with mRNA over the course of about 6 months is specific to variants rather than PfizerBioNTech-vaccinated individuals. While the kinetics of waning might be different with the Pfizer product, neutralization differences should be approximately the same because the antigen design is very similar. B.1.351 has the most dramatic loss of neutralization. At peak titers, it is significantly lower than the ancestral strain or the vaccine strain (WA1). They all decay at approximately the same rate, but end up with a functionally lower tighter against a variant of concern like Beta just because of the lower initial titers. It is reaching the lower limit of detection by 6 months post-vaccination. Given that older adults have lower antibody titers at peak, they have lower antibody titers against the variants. Older adults have lower neutralization titers against many of the variants. At 6 months looking at three different age groups (18 to 55; 56 to 70; and 71+), there is loss of neutralization against Beta B.1.351 such that several individuals in all age groups drop below the limit of detection.[21] In terms of CMI against variants, the good news is that in three different population of T cells in individuals vaccinated with PfizerBioNTech product there is no statistical difference seen in any variant. Thus, T cell activity is maintained against all of the variant spikes that have emerged so far.[22]

In conclusion, there is a degree of protection from different outcomes based on a person's level of immunity. Multiple components of the immune system are required to prevent infection and illness. These components are complex and dynamic. When a vaccinated person becomes infected, they may shed culturable virus and therefore could be infectious. Antibodies decrease over time as expected in all age groups, but cellular memory is maintained after weaning. Neutralizing antibodies likely confer a majority, but not all, of immunity. Cellular responses likely contribute to protection against severe disease through anamnestic responses even after antibodies wane. Older adults start with lower neutralization titers than younger adults. Because they start at lower titers, they may be faster to fall below the limit of detection. They may have less robust cellular memory generation because of immunosenescence and therefore may be even more dependent on humoral immunity. Reduced neutralization of variant viruses may confound antibody waning in all age groups.

Discussion Points

Dr. Poehling requested additional information about the impact of the lower results with regard to T cells.

Dr. Thornburg indicated that this was from the Collier et al. *Nature* paper testing the function of the T cells in which they found that in the T cells that were activated, there were fewer T cells in the group older than 80 years of age. The T cells that they did generate were not as functional. Individuals who had robust responses seemed to be fairly equivalent in those above and lower than 80 year of age. There did seem to be more people in the group 80 years of age and above who did not have a functional response.

[20] Liu et al. *Nature*

[21] Pegu et al. *Science*

[22] Richardson et al. medRxiv

Dr. Chen noted that some of Dr. Thornburg's slides were impressive because they implied that there was a dropping off effect with age, which looked like about 80 years of age. Another slide implied that there was a drop off of the cell-mediated response around 70 years of age. He asked whether these data or other data would help to better define an age cutoff for a risk-based strategy for vaccine implementation if the population had to be prioritized. Some data suggest that 70 or 80 years of age and above would be the first priority, while some people naturally adopt 65 years of age and older when discussing older adults. However, that is somewhat arbitrary as a cutoff. He also asked whether there are data that Dr. Thornburg did not present that suggest an additional contribution for certain comorbidities (e.g., cancer, kidney patients on dialysis, and other groups) that would help to navigate how to develop a risk-based recommendation.

Dr. Thornburg agreed that finding a cutoff is very challenging in terms of when immunosenescence kicks in. She thinks the answer is that this occurs gradually over time. It seems to be a gradient versus a dramatic cutoff. These studies do not help with that cutoff because they are small by need. These are very difficult, laborious assays that do not allow for population-base studies. These studies also looked at fairly healthy older adults, so there are not a lot of comorbidities. Perhaps a comorbidity is driving this phenomenon because there are a few who just do not respond at all.

Dr. Daley requested a reminder of the difference between binding antibodies and neutralizing antibodies and then a relationship to how that is interpreted in immunogenicity studies from Phase 3 clinical trials that report antibody GMT titers.

Dr. Thornburg replied that neutralizing antibodies are a subset of binding antibodies. Binding assays detect just that process. There is protein stuck on a bead or plastic and any antibody that binds anywhere on the spike protein is binding antibody. The assays detect functional and non-functional antibodies, but these are easier and faster than neutralization assays. Neutralizing antibodies are a subset of binding antibodies, so all of the antibodies have to bind the spike and most of them have to bind the right part of the spike, usually around the receptor binding domains, which bind spike and block the virus from entering a cell. They spherically inhibit the virus from binding and entering the cell. The reality is that the actual contributor to immunity is probably neutralization assays. However, those are difficult and laborious and binding assays are much easier and have less variation between laboratories. If a binding correlate can be found that benefits everyone, studies can be normalized and compared. In terms of the differences being seen in neutralization and binding between different vaccine products, there are also differences in the ways that the antigens have been designed and delivered. There probably is a real difference in the proportion of binding antibodies to neutralizing antibodies that each one of these vaccine products drives.

Dr. Long pointed out that immunology is so complex, she wanted to make a couple of comments so that people might not oversimplify what had been said or apply it maybe hastily. People like to measure antibodies because it is easier to do. While it is known that this is not the full story, it is convenient. The idea that antibodies wane is true and not true in reference to certain vaccinations. As a rule, antibody is not measured 1 or 2 months after vaccine but is measured at 4 months or 6 months because the initial responses are going to wane. However, it depends on what kind of lymphocytes are invited to the vaccine party that determines whether there will be some level of sustained antibody response as there must be without an anamnestic response from seeing an organism again for a lot of vaccines that are not live and that are not latent in the recipient that produce long-term immunity. There are many examples such as Hepatitis A and B and pneumococcus might be another. If there are only antibody responses

that wane, it would be all gone. If there are lymphocytes that are participating that change the immunologic reaction so that there is a sustained or new production of some level of antibodies, that is what one is looking for and for many vaccines that is the case. The fact that these high antibodies wane probably does not have any meaning, except that only very high antibodies administered to a macaque can prevent them from symptomatic disease. In terms of a mucosal infection, which coronavirus is, there is never going to be discussion about sterilizing immunity. They will be talking only about controlling symptoms because an order is being given for spike protein parenterally to prevent an infection. Therefore, instead of caring about whether antibody wanes, more important is the minimum needed to have protection. Even the statement that very high levels of neutralizing antibody are protective is not known except in the macaque model when they had only antibodies. Therefore, it is not clear whether it is the antibodies or is the association that allows one to have high sustained antibodies. She thinks this will become important as they go down the line about boosting.

Dr. Talbot said she thought Slide 8 was critical in terms of moving forward with the pandemic. Coronaviruses often become endemic and it is highly unlikely that all mild or symptomatic respiratory infections will be prevented. Showing the spectrum of disease along with the spectrum of immune responses is incredibly important. It is important to understand that hospitalizations and deaths likely will be prevented, hopefully along with symptomatic respiratory infections. However, it is unlikely that everything will be prevented.

Vaccine Effectiveness Studies in the United States

Dr. Ruth Link-Gelles (CDC/NCIRD) presented a summary of VE data available from CDC platforms or published via CDC's *Morbidity and Mortality Weekly Report (MMWR)*. CDC uses multiple platforms and study designs to monitor COVID-19 VE. These designs monitor both duration of protection and protection against variants by risk groups, outcomes of interest (infection, severe disease, hospitalization), and products. While not every platform has the sample size to cut data by all these categories, CDC has attempted to present data during this session from each platform in a way that will be most meaningful for the questions at hand while not cutting the data too finely.

The first platform, the Increasing Community Access to Testing (ICATT) Partnership, does not specifically focus on any populations of interest. However, with nearly 1 million observations from the general population, it allows the unique opportunity to truly tease apart waning against infection pre-Delta and during Delta. Therefore, it was included in this presentation for background. The ICATT platform includes community-based testing data from pharmacies and partners nationwide. It uses a test-negative design and importantly, vaccine history is self-reported. For this analysis, only individuals reporting symptoms were included. Data are presented here for ages 20 to 64 and adjusted for time, race, ethnicity, gender, HHS region, state, and site census tract Social Vulnerability Index (SVI). No adjustment is available for underlying conditions or prior infection.

Dr. Link-Gelles showed a series of graphs of VE against symptomatic infection by age group for each vaccine. Starting with Pfizer, waning can be seen in both time periods of pre-Delta and Delta, with lower VE and more waiting during the Delta period. The curves look similar for all age groups, with a VE around 65% by 200 days after the second dose. Moderna VE tends to be roughly 5% to 10% percent higher for each age group compared to Pfizer, with VE between 65% and 75% by 200 days after the second dose. The same general pattern is seen with more waning and lower VE during Delta was seen with Pfizer. Again, the patterns are similar across the age groups. For Janssen, VE increases by time since vaccination, which matches the data

from the Janssen RCT. The effect of Delta here is a little murkier and there was less pre-Delta follow-up due to the later rollout of Janssen. The curve for Janssen looks similar across age groups, with VE 200 days after vaccination during Delta up to around 55% or about 10% lower than Pfizer.

As ICATT is such a large dataset, it is important to carefully highlight the limitations, including self-reported vaccine history, which resulted in dropping about 18% of the data. There are no data on co-morbidities, prior infection, or behaviors. Since there are no individual level unique identifiers, analyses are based on text rather than individual people. Finally, there are no genetic sequencing results so time is used to differentiate Delta from non-Delta.

Focusing now on platforms that include data on individuals ≥65 years of age, including residents of long-term care facilities (LTCFs), COVID-19-Associated Hospitalization Surveillance Network (COVID-NET) is a population-based surveillance system that collects data on laboratory-confirmed COVID-19 hospitalizations through a network of over 250 acute care hospitals in 14 states. The case definition is "a resident of the surveillance area with a positive SARS-CoV-2 test within 14 days prior to or during hospitalization." Using immunization registry data, investigators estimated VE against hospitalization during April to August 2021 by age group. VE was calculated using a variation of a screening method through a Poisson regression model that allows control for calendar time. Importantly, this method does not allow for adjustments for other important confounders, including co-morbidities and prior infection.[23]

In terms of VE for the mRNA products by age group over time during April to August 2021 from COVID-NET, these data represent Pfizer and Moderna vaccines combined. However, approximately 71% of the vaccinated cases shown received Pfizer. This may be an artifact in that most residents of LTCFs participating in the federal distribution program received the Pfizer product. VE remained well above 90% and highly overlapping for all ages up to 74 years, but trended lower starting in June for those 75 years and older. VE for this age group was around 88% July and 91% in August.[24]

COVID-NET gets detailed clinical and vaccination status on a representative sample of patients on a monthly basis, excluding partially vaccinated patients and those who are fully vaccinated but had evidence of prior SARS-CoV-2 tests. These included almost 6000 cases, of whom 92% were unvaccinated. In terms of the characteristics of unvaccinated and fully vaccinated hospitalized cases, there were statistically significant differences in demographics and underlying medical conditions. In general, fully vaccinated persons were more likely to be older, with a median age of 72 compared to 59 unvaccinated persons; and 72% of breakthrough cases from January to July 2021 were greater than 65 years of age compared to only 40% among unvaccinated cases. Vaccinated cases also were more likely to be residents of LTCFs and more medically fragile, as evidenced by significantly higher proportions of people who had a Do Not Resuscitate/Do Not Intubate (DNR/DNI) code status on admission and more underlying conditions. Additionally, COVID-NET found that the number of underlying conditions were higher in fully vaccinated persons, with half of the vaccinated persons having cardiovascular disease (CVD) compared to only a third in non-vaccinated persons.

[23] Vaccine effectiveness calculated using previously described methods: Moline et al. Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years — COVID-NET, 13 States, February–April 2021. MMWR, August 13, 2021

[24] Unpublished COVID-NET data, 2021

The New York State Department of Health recently published an *MMWR* using linked laboratory, immunization, and hospitalization records.[25] Dr. Link-Gelles shared an update of their analysis that includes over 150,000 observation. Over 90% of their population received mRNA products. There was a decrease in VE against infection in June and July 2021 for all age groups as Delta surged and then a leveling off of VE against infection in July and August. VE against hospitalization remained relatively stable for all age groups, with a slight decline for the 65 plus age group during the Delta period.

VISION is a multi-state network including electronic health records (EHRs) from 187 hospitals. VE was calculated for adults 18 years of age and up, with the investigators comparing hospitalized individuals with COVID-like illness (CLI) with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection versus virus negative controls. VE was adjusted for propensity to be vaccinated, calendar time, region, local virus circulation, and age. Models for waning used 6 of the 7 total VISION sites. Vaccination is documented in EHRs and jurisdictional immunization registries. Fairly stable VE was seen in the two time periods, pre-Delta versus Delta, with the exception of the 65 plus and a bigger decrease specifically for Pfizer with non-overlapping confidence intervals. While there is a hint of decrease for the Moderna point estimates in this age group, this was not statistically significant. VISION has VE against hospitalization for all adults by time period of January to March, April to May, and June to August and then subsetted by time since vaccination looking at 14 days to less than 2 months since vaccination all the way to 5 plus months since vaccination. Among people recently vaccinated, VE against hospitalization remained high at all three time periods. In the Delta period from June to August, VE has declined among those who have been vaccinated for longer periods of time, with a statistically significant decreasing trend. Waning is expected to be the same or worse in older adults.

Given that there are so little data on Janssen, Dr. Link-Gelles shared a comparison of the pre-Delta and Delta period pulled from previous publications. Due to small numbers, VISION was not able to show a specific 50 plus estimate during Delta. A decrease was seen in the point estimate for VE, although with wide confidence intervals. If anything, the comparison of an older age group in pre-Delta to younger age groups during Delta would bias towards less decline.[26]

The National Healthcare Safety Network (NHSN) is a healthcare data reporting system. For COVID-19, nursing homes report both the number of residents in the facility and the number of COVID-19 cases in residence by vaccination status on a weekly basis. Investigators estimated VE for infection for 3e periods: Pre-Delta (March 1-May 9), Intermediate (May 10–June 20), and Delta (June 20–Aug 1). Reporting to the platform became mandatory in June for the Centers for Medicare and Medicaid (CMS)-certified skilled nursing facilities (SNFs), so the number of facilities reporting rose steadily during the study period.[27] In terms of the results for each of the periods, VE for both, products declined from almost 75% in the pre-Delta period to 53% in the Delta period and did not differ substantially by product.[28]

[25] https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e1.htm

[26] https://www.nejm.org/doi/full/10.1056/NEJMoa2110362 and https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e2.htm

[27] https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm

[28] Adapted from: Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. *MMWR Morbidity and Mortality Weekly Report*. 2021 2021;70. Slide courtesy of Ian Plumb

In summary for individuals 65 plus, large declines were seen for mRNA products against infection. The largest decline was from the platform focused on the LTCF residence, although New York State also reported a decline from 91% to 75% for all adults 65 plus.
Data for VE against hospitalization were more mixed. VE remained relatively high in all platforms, with a larger decline for Pfizer and 65 plus versus the two mRNA products combined or Moderna alone.

Moving to VE estimates in individuals with underlying conditions, including data on individuals 65 plus when included in these platforms, the **SU**rveillance **P**latform for **E**nteric and **R**espiratory i**N**fectious **O**rganisms at the **VA** (SUPERNOVA) Network is a sentinel surveillance network of 5 Veterans Affairs Medical Centers. From February 1-July 31, 2021, investigators conducted a case-control VE assessment using data from these sites. Eligible participants were US Veterans at least 18 years of age who were hospitalized in any of these 5 sites. Cases were defined as "patients with CLI who tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR). Controls also were patients with CLI with negative SARS-CoV-2 test results. Of note, while SUPERNOVA does not specifically target elderly individuals or those with co-morbidities, given the general VA population, this group is skewed in that direction with a median age of 67 years and almost half the CCI above 3. This estimate is included in the group who may be at higher risk of severe COVID-19 due to underlying conditions. For the entire study, not divided by Delta predominance and with Pfizer and Moderna combined, there was a statistically significantly lower VE for older individuals. Pfizer has a more extreme difference between age groups. Neither of the differences in individual products was significant. Estimates broken down by Delta predominance and times since vaccination include all age groups and both mRNA products. Little change is seen in VE and hospitalization by time period or by time since vaccination.[29]

The **I**nfluenza and Other **V**iruses in the Acutel**y** Ill (IVY) Network is an active surveillance network of 21 sentinel hospitals in 18 states. Sites enroll hospitalized adults with and without CLI, rapidly collect in-depth vaccination, critical information, and respiratory samples for central RT-PCR testing and sequencing. PCR-positive cases are matched with PCR-negative controls. For this analysis of VE against hospitalized COVID-19, IVY investigators included adults admitted to IVY sites from March 11-August 15, 2021. For Pfizer, the difference for time since vaccination by time period was both contextually meaningful and statistically significant. Moderna did not show similar waning. There were not enough observations to break out Janssen by time since vaccination, but the overall estimate was included for comparison. With Pfizer and Moderna estimates combined and then separated by age group of under 65 years of age and over 65 years of age, a decline is seen in the 65 plus age group. No similar decline is seen in the younger adults. In the same age groups by pre-Delta versus Delta instead of time since vaccination, there is a less pronounced decline in the 65 plus age group. Finally, the IVY team was able to run some analyses looking specifically at those with co-morbidities in the pre-Delta and Delta periods. This analysis excludes those with immunocompromising conditions and controls for age. Although overall VE for individuals with underlying conditions appears slightly lower than for those with no underlying conditions, no large declines are seen from the pre-Delta versus Delta period in any of the age groups. No estimates were available for VE against infection for individuals specifically with underlying medical conditions. For VE against hospitalization, estimates did not vary substantially by Delta predominance.[30]

[29] https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e3.htm

[30] IVY: CDC unpublished data

Moving to individuals with occupations that put them at higher risk of exposure to SARS-CoV-2 (grocery workers, educators, restaurant workers, et cetera), estimates for most professions are not available. While for this session Dr. Link-Gelles presented data on healthcare personnel (HCP), first responders, and other frontline workers, she noted that there should be no biological difference in VE between these groups and similar individuals in lower risk occupations. Healthcare, Emergency Response, and Other Essential Workers Surveillance Study-Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (HEROES-RECOVER)[31] is a prospective cohort of over 4,000 HCP, first responders, and other frontline workers in 8 US locations. Participants are swabbed weekly and additional specimens are collected if a participant is ill. Vaccination is documented through multiple methods, with 95% of those vaccinated receiving an mRNA product. In the full study period by time since vaccination, although the confidence intervals are wide, some indication is seen in the point estimates of waning immunity over time. A substantial decline is seen in VE against infection from 91% in the pre-Delta period to 66% once Delta was predominant. Importantly, there were not enough hospitalizations in this highly vaccinated population to provide estimates for VE for hospitalization.

To summarize the results by risk group, first for the 3 risk groups together to give a sense of magnitude, there are many more data available for adults 65 plus. However, there is not much reason to think there would be a different VE in the other 2 groups than in other adults. For example, a similar decrease is seen in VE against infection for HCP and for 65 plus. Across platforms, VE appears to decrease more for infection than hospitalization, although the VISION platform did see a decrease in VE for adults against hospitalization—a finding that is not generally seen in younger age groups. For individual ≥65 years of age, significant declines were seen in VE against infection during Delta for the mRNA products. Declines also were seen, particularly for Pfizer for ≥65 years of age that were not seen in younger populations. Finally, there is evidence of waning for VE against hospitalization in the Delta period. While an estimate specifically for 65 plus was not available, it is likely that waning for that group would be as bad or worse than in all adults. For individuals with underlying medical conditions, there was no specific data on VE against infection. However, it is likely that VE for this group is similar to that In the general population as shown in the ICATT data. VE against hospitalization for those with underlying medical conditions remained high in the Delta period. For individuals with occupations with high risk of exposure to SARS-CoV-2, there were no data on VE against hospitalization specifically. Again, this is likely to be similar to that in the general population. Similar patterns were seen for VE against infection for this group as were seen in the general adult population.

Discussion Points

Dr. Long suggested not lumping infection and hospitalization, given that there is likely no hope that a vaccine such as the ones currently available will prevent infection after the first couple of weeks with extraordinary immediate responses. She suspects they will end up saying that the ultimate goal of the current program will be to prevent serious symptomatic infections, hospitalizations, and deaths. HCP should not be of concern for transmission to others because they should be masked and practicing appropriate distancing, hygiene, et cetera. She thinks it is confusing for the populous to think that if they can get infected, the vaccine is failing. This vaccine is not going to be more than 80% protective against infection just because the only protection against infection one gets is what leaches out of the parenteral circulation into the mucosa.

[31] https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e4.htm

Dr. Bell emphasized the importance of keeping the age effect in mind when looking at other subgroups.

Dr. Poehling appreciated how many different groups are assessing VE. It appeared to her that the SUPERNOVA population was almost 50% Black and had high co-morbidities, so that VE is very important in terms of thinking about disparities that are seen with race and ethnicity.

Dr. Brooks found this presentation to be important in terms of showing that there is a waning of VE even in the context of T cell protection being high. He asked Dr. Link-Gelles to comment on the decrease in VE in HCP, which he presumed to be generally of a lower age than the general population or senior population. He wondered if HCP experiencing more exposure and therefore more chance of them getting infected might be attributed to the decrease in VE.

Dr. Link-Gelles indicated that in the HEROS-RECOVER data where VE for infection decreased from 91% to 66% and a lot of other studies, there is information to show that most of those infections are actually community-acquired versus acquired on the job. She also pointed back to the ICATT data of the general population in which similar steep declines were observed in VE against infection in particular, regardless of age group and in the general population—not specifically to HCP.

Dr. Duchin (NACCHO) noted that for the COVID-NET hospitalization data, he did not see obesity listed as a risk factor and wondered whether it did not rise to level of increased risk or if it was not assessed. In addition, he asked whether the VE studies accounted for prior COVID-19 in unvaccinated populations. He also asked Dr. Link-Gelles to comment on some of the differences between the data from the US and what has been reported from other countries, in particular from Israel.

Dr. Link-Gelles said that while she did not have the number for obesity in front of her, she could follow up with it. Most of the studies were able to exclude prior COVID-19 infections. Because COVID-NET was using a screening method, the investigators were able to exclude individuals who were hospitalized for prior infection. For the non-hospitalized group, they do not have individualized data for the comparison group on prior infections because they are using an ecological analysis. All of the individual-level platforms (VA, IVY, VISION) exclude individuals with prior infection. In terms of the differences in data reported in the US and other countries, she noted that Dr. Oliver would include some of the international estimates in her presentation later in the day. She emphasized that there are differences between the populations and the methods that are used in the analyses in Israel versus the US, with the biggest on being the difference in how the US defines severe disease. The Israeli data can include outpatient individuals in severe disease based on respiratory rates whereas hospitalization is used almost across the board in the US as the definition for severe disease. That will change the estimate quite a bit and skew the Israeli estimates a little more toward what the US sees for infection.

Dr. Lee observed that it seemed like the Delta variant had a bigger impact in the HCP cohort, while in the IVY cohort it seemed like time since vaccination had a slightly bigger impact. She wondered whether Dr. Link-Gelles could provide an understanding of what might be most relevant in terms of whether it is differences in populations, time variant confounders, or both.

Dr. Link-Gelles said she thought it could be different methodologies and the fact that neither HEROS-RECOVER nor IVY was able to truly tease apart time since vaccination from Delta, so they were not able to do the cross tabulation of looking at time since vaccination in the pre-Delta period and then time since vaccination overall. They looked at time since vaccination in the entire cohort and then separately for pre-Delta versus during Delta. That can skew depending on the cohort. HEROS-RECOVER focuses on HCP, many of whom would have been vaccinated much earlier than the general population included in the IVY analysis. Since pre-Delta versus post-Delta cannot be teased apart, it is hard to parse out. The clearest one for that particular question is the VISION analysis since they actually did have enough observations in the Delta period to look at waning over time since vaccination during Delta, and they did see a significant decrease in trends.

Dr. Weiser (IHS) asked whether any additional data are available for American Indian/Alaskan Native (AI/AN) populations with regard to VE or waning. It is known that during the pre-vaccine era, AI/AN were heavily impacted—especially at younger ages. Hospitalizations and death seemed to peak at a younger age among AI/AN than in the general population.

Dr. Link-Gelles indicated that there is a platform that focuses specifically on VE among AI/AN. However, the population is so small that they have not had enough cases in that platform at this time to provide estimates.

Dr. Lee expressed appreciation on behalf of the ACIP to Dr. Link-Gelles and her team as well as all of the investigators and emphasized that these data are critical to help the ACIP wade through the data and understand it better in support of their decision-making efforts.

Modeling the Potential Impact of Booster Doses in Nursing Home Residents

Dr. Rachel Slayton (CDC/NCEZID) presented mathematical modeling of SARS-CoV-2 transmission in nursing homes. Data on trends in the weekly rate of COVID-19 cases in communities and in nursing homes highlight that outbreaks in the community and nursing homes are linked and that controlling community transmission is important for protecting the vulnerable nursing home resident population. To better understand SARS-CoV-2 transmission in nursing homes, CDC investigators developed a model in collaboration with colleagues at the Harvard T.H. Chan School of Public Health, in particular with Rebecca Khan and Inga Holmdahl, that builds upon previously published work.[32] They modeled an average US nursing homes with 100 residents in 100 staff members. In this analysis, the nursing home is fully occupied, with resident turnover explicitly modeled using resident length of stay data from CMS. Cases are introduced into the nursing home by staff, who have a daily probability of infection from their time in the community that is directly estimated from NHSN data. Transmission within the nursing home is stochastic. It is based on the number of contacts individuals have each day, the probability of transmission given a contact with an infectious person, and the total number of infectious individuals in the nursing home each day. Following guidelines, non-outbreak screening testing of unvaccinated staff is conducted twice per week. One an outbreak is identified, this shifts to twice weekly tests.

[32] https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab517/6292250

The analysis looked at 4 main outcomes over a 2-month period, including the total number of symptomatic cases in residents and in the entire nursing home, including both residents and staff; and the total number of infections in residents and in the entire nursing home. The simulations were repeated 100 times to capture variability. Some key parameters from the model include a basic reproduction number of 6, reflecting estimates for the more transmissible Delta variant. As previously mentioned, the staff have a daily probability of infection from the community, which was varied from moderately high to high. Among residents in the nursing home at the beginning of the simulation and those that enter the nursing homes during the simulation, 80% are vaccinated. Staff vaccination coverage was varied from 40% to 100%. Several values were considered for VE. First, the 2-dose VE against infection for staff was 70%. The 2-dose VE against infection was varied for residents from 50% to 70%, reflecting some data which showed that there is lower VE among older populations. The vaccine also has efficacy against progression to symptoms. It was assumed that VE against symptomatic disease for staff was 90% and varied the same parameter between 80% and 90% for residents. VE against infectiousness or transmission was assumed to be 50% for both residents and staff, which means that infections in vaccinated persons are half as infectious as those occurring in unvaccinated individuals. The introduction of booster doses also was modeled, which take 2 weeks to take effect, and their efficacy was systematically varied from 60% to 90%.

Looking at the cumulative incidence among residents after 2 months by symptom status and vaccination status in simulations with resident vaccination coverage of 80%, staff vaccination coverage of 60%, and no boosters, the distribution of cumulative incidence among residents after 2 months across 100 simulations showed that a majority of cases in vaccinated residents were asymptomatic due to VE against symptomatic disease. While only 20% of residents were unvaccinated in these simulations, they contributed a large share of symptomatic cases. A higher daily importation rate resulted in more nursing home cases. This highlights that an increase in nursing home cases does not necessarily indicate lower or waning VE if a community's transmission is increasing during the same time period. When VE against infection for residents was assumed to be 70%, similar trends were observed. This reflected lower cumulative incidence overall, which would be expected when VE is higher.

Next, Dr. Slayton described simulations assessing the impact of varying levels of staff vaccination coverage and providing all residents a booster dose with varying VE. Investigators began by looking at the number of symptomatic cases among residents showing simulations with a moderate level of staff importation and a higher level of staff importantation—reflecting higher community transmission. In these simulations, no boosters were given and VE against infection in residents was 50%. Staff vaccination coverage was systematically varied from 40% to 100%. As expected, higher staff vaccination coverage resulted in fewer symptomatic cases among residents. The cumulative cases were highly dependent on community transmission. For context, over the 2-month period being modeled in the 100-bed nursing home, there were 217 unique residents on average over the entire time period because the median duration of stay modeled was 27 days. Across nursing homes in the US, NHSN data finds that the average staff vaccination coverage is just above 60%. The impact of increasing staff vaccination coverage from above that national average leads to fewer symptomatic cases.

Moving to simulations that include boosters, VE against infection in residences is 50% after the booster doses were given to all vaccinated residents staff who were not receiving a booster doses in these simulation. As a reminder, 80% of residents were vaccinated and all of them received a booster dose, but the efficacy of that booster was varied. The simulations showed that boosters increased VE against infection from 50% to 60% in residents. Higher staff coverage and higher booster VE against infection leads to fewer symptomatic cases among

residents. Similar to the previous findings, cumulative symptomatic cases among residents were highly dependent on the community transmission. Looking at total symptomatic and asymptomatic COVID-19 infections among residents, there were higher absolute numbers of infections when looking at total infections, but the trends remain largely the same. Once again, higher staff coverage and higher booster VE led to fewer infections.

In terms of symptomatic COVID-19 cases in nursing homes overall, including both residents and staff, similar trends are seen when looking at all symptomatic cases in the nursing home as compared with looking at residents only. Of note, there was a larger impact of increasing staff coverage because this incorporated the direct protection the vaccines provided to the staff in addition to the indirect protection that vaccination provides to nursing home residents. Looking at total infections, including asymptomatic and symptomatic infections in the nursing home overall including both residents and staff, similar trends were seen as when looking at total infections in residents. However, there were higher numbers of infections than previously shown.

This analysis is subject to a number of limitations. The investigators modeled VE against infections, VE against symptomatic disease, and VE against infections as point estimates. These estimates are likely to vary by a number of factors (e.g., vaccine type, age of vaccinated persons, and immunocompromising conditions of vaccinated persons). The analysis shown is most appropriate when we considering the potential impact of providing booster doses for nursing home residents who received an mRNA vaccine. An average nursing home was modeled, which did not capture all facility-level heterogeneity. Additionally, previous COVID-19 infections were not explicitly modeled, which may have underestimated the level of prior immune protection independent of vaccination. In addition, the impact of vaccine supply shortages were not explored in this model.

In summary, maximizing vaccination coverage among nursing home staff remains a critical tool for preventing cases in nursing home residents. Simulations also showed that boosters for nursing home residents can help reduce cases, but the magnitude of their effect depends on their effectiveness and staff vaccine coverage. Even with highly effective boosters, cases in nursing homes will persist when community transmission is high. This highlights the need for continued infection prevention and control strategies and that community transmission remains a key driver of cases in nursing homes.

Discussion Points

Dr. Lee observed that clear to many and made more explicit by the modeling is that community rates can make a major difference. Community rates of transmission have a direct impact on vaccinated and unvaccinated individuals. As community transmission has increased, many healthcare facilities have had to reinstate visitor restriction policies, meaning that family members cannot visit their loved ones. This is similar for nursing home settings and schools. When transmission rates in the community are higher, higher rates of infection are occurring in schools as a reflection of the broader community. The model illustrates this well and supports efforts to achieve individual- and community-level protection.

Dr. Poehling agreed that the impact of community transmission is very important and emphasized that staff vaccination makes a bigger difference than the booster dose among residents.

Dr. Chen wondered whether some of this modeling also could be used for understanding pediatric populations, such as in schools that remain largely unvaccinated because of younger children, or if further modeling exercises already are being conducted internally to help understand this in all segments of populations.

Dr. Slayton emphasized that because nursing home staff vaccination coverage is important and influential, given that staff have contacts in the community and can import COVID-19 into nursing home facilities. Therefore, increasing staff vaccination coverage is incredibly important. Regarding children, CDC is collaborating closely with a consortium of modeling researchers at the COVID-19 Scenario Modeling Hub to assess longer term projections that make different assumptions about whether vaccines become available for children 5 to 11 years of age and what the impact might be on the longer term trajectory. This information can be shared with ACIP in a future discussion.

Dr. Kimberlin (AAP Redbook) commented that looking at CDC's maps by counties reflect the areas of the country that are most red in terms of highest rates of transmission in the community. Arguably, there really are not efforts within most of those communities to enforce or even strongly encourage masking indoors and other efforts that would mitigate transmission within the community. That is probably the reason that they are the most red. He requested that ACIP consider if/how to apply these modeling results. He did not think many communities within the US could be counted on to re-implement masking.

Dr. Zahn (NACCHO) noted that the modeling in nursing homes that Dr. Slayton presented is being lived out in communities around the country for local public health and nursing homes. In the summertime between when the Delta variant arrived, waning immunity, or some combination thereof, it became very clear that even if someone is fully vaccinated, particularly if they have a household exposure, their chance of having breakthrough infection is not trivial. That becomes a difficult calculation for staff, particularly in SNFs where the risk of introducing the virus there is so great. The prevailing thought seems to be that if someone is vaccinated they are immune and if they have a community exposure, it is okay to continue to work. Any measures to assure immunity as optimized in that staff population need to be considered.

Dr. Maldonado (AAP) reinforced what was said about future modeling, particularly in terms of the pediatric population and given what is occurring with return to school and some of the restrictions being placed on masks in some of these populations. It is important to make a case for or against the risks and benefits of vaccination of not only children 5 to 11 years of age, but also for children under 5 years of age for whom there already has been a lot of undercurrent in the lay press and across social media around the necessity or not of vaccinating that population. It is important to have all of those data available when and if ACIP is able to consider the pediatric population and transmission, especially within the school setting and given the high background transmission rates that can occur within some of the high-risk communities where equity may be of particular concern.

Dr. Duchin (NACCHO) agreed with the conclusion that even with highly effective boosters, continued infection prevention and control strategies will be needed. He asked whether consideration was given to assessing testing strategies and what the impact of frequent screening with rapid antigen testing would be on nursing home staff in terms of the incidence of COVID-19 among residents.

Dr. Slayton indicated that they previously considered questions about frequency of testing in their *Clinical Infectious Disease* (*CID*) paper[33] before there were data about what the various VE values would be. They did a wide parameter sweet for the three VE types that she described in the presentation during this session. They looked at trade-offs with time limits of results and sensitivity to try to better understand what that might do to the magnitude of transmission in nursing homes. She pointed out that in the presentation during this session, even with very high staff vaccination coverage and very high VE against infections for residents after boosting, there are still non-zero values. The importations are more frequent when there is more community transmission, which highlights the rationale for increasing the frequency of testing in nursing homes when there is more transmission in the community in order to identify importations early and implement additional infection prevention and control measures to mitigate further spread.

Dr. Zimmerman (APTR) asked whether there had been an opportunity to model various facility sizes to determine differences in large versus small facilities, given the potential for density and effects of infectiousness.

Dr. Slayton indicated that they have not yet explored all of the facility-level heterogeneity, but it is an interesting question to explore in future work.

Dr. Foster (APhA) noted that they often hear that some people do not want to get vaccinated because of herd immunity, so he wondered whether it would be possible to factor herd immunity into these types of models.

Dr. Slayton said she thought that that there would be a way to estimate what the critical vaccination threshold might be based upon what the reproductive number is, but there are also important issues with the emergence of novel variants for which there may be a different level of cross-protection for persons who either were vaccinated or had an infection with a previous variant. There also are issues with the time horizon and questions about waning immunity from either natural infection or vaccination that ought to be incorporated. For an infectious disease with an R naught 6 or higher, which was the estimate for Delta, it is a very high threshold. It is even higher perhaps in terms of heterogeneity.

Dr. Duchin (NACCHO) emphasized the importance of the need to have layered prevention measures with vaccination, infection control strategies, and testing. However, one very important strategy that had not been discussed was ventilation and improving indoor air quality. He wondered whether Dr. Slayton's team considered this. While he knew that there had been some modeling around schools and ventilation, based on what is known about the quality indoor of air in long-term care facilities, he wondered whether it would be possible to understand what type of benefit might be received if 4 to 6 air exchanges per hour could be achieved in addition to the other measures.

Dr. Slayton indicated that indoor air quality was not explicitly included in the modeling she presented during this session because in nursing home with the level of mixing that would be expected (e.g., resident meals, activities, shared rooms, et cetera), this was not explicitly evaluated. However, it is an interesting and perhaps future direction.

[33] https://academic.oup.com/cid/article/73/3/e792/6132104

Dr. Lee asked at what point in the pandemic and in the overall vaccination program for the US, recognizing that there is importation globally, when it might be appropriate to consider modeling to understand the impact of a booster vaccine on decreasing transmission in addition to decreasing the risk of severe disease. She recognized that right now, the greatest opportunity continues to be in insuring that the unvaccinated population is vaccinated. She also took the opportunity to ask their industry colleagues about continued innovation in this space. While she anticipates that boosters will be inevitable, the ability to achieve sterilizing immunity perhaps would be a worthy goal to achieve in order to be able to also address this question in the longer-term.

Dr. Slayton said that by looking at the outcomes of symptomatic COVID-19 cases in total infection was one way they were hoping to provide ACIP with some data to help think through what is occurring with transmission versus disease in the nursing home population. Additionally, if there is a recommendation for booster doses, one could adopt that in some larger scale population models to look at what the impact might be population-wide. If the booster doses will be primarily in older adults, they tend to have less contact than other age groups. Depending on where the US is in the pandemic, her best hypothesis is that the magnitude of that effect may be small to moderate. Additionally, it would be a worthwhile endeavor to think about multi-year time horizons in the model to assess where COVID-19 ends up in the longer-term. Doing that accurately with a novel pathogen that is rapidly changing, such as seen with the novel variants, is a difficult endeavor. They do continue to work on this along with their colleagues in academia and industry to help move this work forward.

Early Safety Monitoring for Third Doses of mRNA Vaccines

Dr. Anne Hause (CDC/NCEZID) presented safety data on reports of additional COVID-19 vaccine doses to the Vaccine Adverse Event Reporting System (VAERS) and v-safe[SM]. COVID-19 vaccines are being administered under the most intensive vaccine safety monitoring effort in US history. CDC is monitoring the safety of these vaccines through 4 complementary systems: v-safe[SM], VAERS, the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA). There are also additional systems in place managed by government partners.[34] During this session, Dr. Hause focused on data from v-safe[SM] and VAERS.

VAERS serves as an early warning system for vaccine safety. It is co-managed by CDC and FDA. Anyone can submit a VAERS report regardless of the possibility of the vaccine causing the event or the critical seriousness of the event. The key strengths of VAERS include rapid detection of safety issues and detection of rare AEs. Limitations of VAERS include inconsistent quality and completeness of information, reporting biases, and that VAERS cannot determine causality of AEs. As of September 17, 2021, there were 2563 reports to VAERS following Dose 3 of mRNA COVID-19 vaccine. The median age was 64 years and 61% of reports were from women. Race or ethnicity was unknown or incomplete for 49% of reports and 39% were from person who identified as White Non-Hispanic. Of the 2563 VAERS reports following Dose 3 of mRNA COVID-19 vaccination, 95% were non-serious. This was regardless of the vaccine manufacturer and is similar to what has been observed for COVID-19 vaccines overall and other vaccines in general.

[34] Full list of U.S. COVID-19 vaccine safety monitoring systems: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety.html

The most common AEs reported to VAERS following Dose 3 of mRNA COVID-19 vaccination was extra dose administered. This was true for both serious and non-serious reports. Per federal law, serious reports include hospitalization, prolongation of existing hospitalization, life-threatening condition, permanent disability, congenital deformity or birth defect, or death. No reports of myocarditis in persons less than 65 years of age were identified. There were 18 reports of deaths to VAERS following Dose 3 of mRNA COVID-19 vaccination. The median age was 76 years. Median elapsed from Dose 3 to death was 1 day. A CDC physician reviewed the available documentation, including death certificates, to determine a preliminary impression of cause of death (COD). Most preliminary impressions of COD were cardiac or respiratory arrest. It was not possible to determine COD for 4 reports due to insufficient data.

In terms of v-safe[SM] data, v-safe[SM] is a voluntary, smartphone-based safety surveillance system that allows existing participants to report receiving an additional dose of COVID-19 vaccine and new participants to enter information about all doses of COVID-19 vaccine received. The v-safe[SM] health surveys are sent during the week following each dose of vaccine and include questions about local injection site and systemic reactions and health impact (e.g., inability to perform normal daily activities, missed school or work, or receipt of medical care). Surveys are sent weekly through 6 weeks after vaccination and at 3, 6, and 12 months after vaccination. As of September 19, 2021, 21,935 v-safe[SM] participants had reported an additional dose of COVID-19 vaccine. Of these participants, 63% were female. Approximately one-third were 18 to 49 years of age, 50 to 64 years, and 65 to 74 years. Almost 10% were 85 years or older. Almost 88% of participants identified as non-Hispanic and 82% identified as White.

Regarding the patterns of vaccination for v-safe[SM] participants who reported an additional dose, 98% of participants reported a third dose from the same manufacturer as their primary mRNA vaccine series. Among the most frequently reported reactions at least once during Days 0-7 after Dose 3 of Moderna or Pfizer-BioNTech were vaccine, pain, fatigue, myalgia, and headaches for both vaccines. In terms of reactions and health impact events reported at least once during Days 0-7 after Pfizer-BioNTech vaccination by dose, the odds of reporting an event following Dose 2 and 4 were compared using a multivariable generalized estimating equation (GEE) model that accounted for the correlation between participants and adjusted for demographic variables. p-values less than 0.05 were considered to be statistically significant. Injection site reactions, systemic reaction, and health impacts including inability to perform daily activities and inability to work were all less frequently reported following Dose 3 than Dose 2. While these differences were statistically significant, the magnitude is small. Regarding reactions and health impact events reported at least once during Days 0-7 after Moderna vaccination by dose, like Pfizer-BioNTech injection site reactions, systemic reactions, and health impacts including inability to perform daily activities and inability to work were all less frequent following Dose 3 than Dose 2.

These data are subject to a number of limitations. First, both VAERS and v-safe[SM] are voluntary systems and are likely not representative of the vaccinated US population. Second, during the study period, additional dose recommendations were limited to immunocompromised persons who completed a primary series of mRNA COVID-19 vaccine. However, v-safe[SM] does not include specific information about immune status. Additional dose recipients likely included immunocompromised and non-immunocompromised persons. Immunocompromised persons might have different reactogenicity than immunocompetent persons. Third, insufficient data were available to determine patterns of AEs after receipt of additional doses from a manufacturer different from the primary series. Insufficient data also limited the ability to identify rare AEs. Finally, complete medical review of deaths following vaccination reported VAERS is

dependent on the availability of medical records, death certificates, and autopsy reports that may be delayed or not available.

To summarize, no unexpected patterns of AEs were observed. However, the data are limited at this point to identify rare AEs. Nearly all (95%) of reports to VAERS were non-serious. Most v-safe[SM] participants reported a primary mRNA vaccine series followed by Dose 3 from the same manufacturer. Similar to the Pfizer-BioNTech clinical trial data, local and systemic reactions following Dose 3 were comparable to those following Dose 2. In terms of next steps, VAERS and v-safe[SM] will continue to monitor the safety of additional doses of COVID-19 vaccination. Additionally, the VSD will incorporate near real-time sequential monitoring. CISA will be available to consult on clinically complex AEs. ACIP will be updated as additional data become available.

Discussion Points

Ms. McNally requested additional information on how the safety monitoring systems would capture information regarding mixing of vaccines. She also requested that Dr. Fink comment on how the FDA EUA Fact Sheet would address mixing of vaccines if, in fact, this were to be permitted.

Dr. Hause indicated that participants can enter information in v-safe[SM] about which doses they have received, so there is information about all doses a person might include. That opportunity also is available in VAERS, though sometimes the data are incomplete.

Dr. Shimabukuro added that VSD is an EHR system that has its own immunization registry, so those data are captured and it is possible to identify product-specific doses administered information.

Dr. Fink (FDA) said he would anticipate that the EUA Fact Sheet would not that data are not available to inform the safety or effectiveness of the interchangeability of vaccines.

Dr. Lee highlighted that heterologous boosting is clearly an area of interest, for which they learned earlier in the day that those data are on the way.

Dr. Poehling asked whether any cases of hospitalizations or myocarditis were identified in the v-safe[SM] system among the 21,935 participants.

Dr. Hause indicated that 11 hospitalizations were reported. They do not have the capability to comment on the reasons for hospitalizations, given that v-safe[SM] does not collect information on hospitalizations or myocarditis. This system collects reactogenicity data, although some data are available in free text form about additional symptoms. In addition, v-safe[SM] participants who indicate hospitalization would receive active follow-up and be encouraged to complete a VAERS report with CDC staff, which can be done over the phone.

Dr. Shimabukuro added that in terms of the myocarditis reports to VAERS, there was one preliminary report. They are in the process of obtaining follow-up information, reviewing, and adjudicating this case. This case occurred in a male 73 years of age who experienced symptom onset 22 days after vaccination. Based on the preliminary report, that seems consistent with myocarditis. While they have to confirm this, this is not typical for what would be considered vaccine-associated myocarditis. This individual falls out of the age range for what is considered the age groups of risk. Also, the symptom onset is quite far out compared to most of these

vaccine-associated myocarditis cases. It is outside of the Day 0-7 risk interval and is even outside of the Day 0-21 conservative intervals that is used in other monitoring. Therefore, there is no indication that this would be a vaccine-associated myocarditis case if it turns out to be a confirmed case.

Vaccine Safety Technical Work Group (VaST WG) Assessment of 3rd Dose Safety Data

Dr. Keipp Talbot (VaST Chair) reminded everyone of the objectives of the COVID-19 VaST WG are to: 1) review, evaluate, and interpret post-authorization and approval of COVID-19 vaccine safety data; 2) serve as the central hub for technical subject matter expertise from federal agencies conducting post-authorization and post-approval safety monitoring; 3) advise on analyses, interpretation, and data presentation; and 4) provide updates to the ACIP COVID-19 Vaccines WG and to the ACIP on COVID-19 vaccine safety. VaST has convened 35 independent meetings to review the vaccine safety data, almost all of which have occurred under the purview of Dr. Grace Lee. VaST also has had 8 joint meetings with the COVID-19 Vaccines WG to review a variety of topics.

VaST continues to review data on myocarditis, Guillain-Barre Syndrome (GBS), anaphylaxis, and thrombotic thrombocytopenia syndrome (TTS) following COVID-19 vaccination from passive and active US surveillance systems, including VAERS, VSD, CMS, VA, Indian Health Services (IHS), and the Department of Defense (DoD). This also includes data from outside the US from Israel, Canada, and the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS). Special evaluations are underway, such as follow-up studies of myocarditis cases specifically in VAERS, VSD, and DoD. The focus of this session was on the safety data regarding a third dose of COVID-19 vaccination reviewed by VaST. Regarding third dose safety data on the Pfizer-BioNTech COVID-19 vaccination, VaST reviewed the data presented by Israel to the VRBPAC[35] and the US data from v-safe[SM].

In terms of the safety data regarding the third dose of Pfizer-BioNTech COVID-19 vaccination from Israel, third doses were phased in beginning with persons ≥60 years. Since the end of August 2021, everyone 12 years of age and over has been eligible to receive a third dose. As of September 13th, approximately 2.8 million third doses had been administered to persons ≥12 years of age. Most third doses have been administered to persons ≥60 years. Rates of reported systemic, local, neurologic, allergic, and other reactions were substantially lower after Dose 3 than after Doses 1 or 2. To date, there have been over 1000 non-serious and 19 serious adverse events (SAEs). All hospitalized patients and deaths have been or are being investigated by a work group. Among the serious cases, 7 were possibly associated with vaccination. Data from the Israeli Ministry of Health show the rate of systemic adverse events by dose. There have been many fewer reported AEs after the third dose. VaST suspects that much of this is due to time of follow-up. More data should be following soon. Looking at Israeli data by vaccine dose, age group, and sex, the only observed case of myocarditis following vaccination after a third dose occurred in a male in his 30s.

Turning to v-safe[SM] safety data after the third dose of COVID-19 vaccination, third doses were recorded by over 24,000 participants as of September 11, 2021. While third doses in the US are currently only recommended for persons with an immunocompromising condition, there are no data in v-safe[SM] to support that these 24,000 people were immunocompromised or had indicated other underlying conditions. Compared to the second dose, the original analyses suggested that there may be more local reactions and less systemic reactions following the third

[35] https://www.fda.gov/media/152205/download

dose than after a second dose. However, it now appears based on re-analysis that there are fewer local and systemic reactions following the third dose.

To summarize the VaST assessment of the Israeli and v-safe[SM] safety data after the third dose of COVID-19 vaccination, the assessment of the Israeli data is limited by likely under-reporting of local, systemic, and SAEs. This is likely due to the very short follow-up period. The few SAEs potentially associated with vaccination need further follow-up. VaST noted only a single case of myocarditis in a male age 32-34 after the third dose of e Pfizer-BioNTech. Data from v-safe[SM] show that systemic reactions following third dose are slightly less than following a second assessment. The v-safe[SM] safety data are limited by lack of data on underlying conditions or whether recipients are individuals with immunocompromise. The significance of the v-safe[SM] data is unclear, given that local and systemic reactogenicity do not predict more severe AEs.

In terms of next steps, VaST will continue to review safety data regarding third doses as data become available. In addition, VaST will continue to collaborate with global vaccine safety colleagues and key issues that impact the benefit-risk balance and will continue to provide updates to the ACIP COVID-19 Vaccines WG and the ACIP during future meetings.

Discussion Points

Ms. Bahta requested more information about why there was suspected under-reporting of serious conditions in the Israeli third dose safety data.

Dr. Talbot indicated that the biggest limitation at this point is time. This program was recently begun and is slowly beginning to accumulate data. The second aspect is that many of the questions about myocarditis is an event that would occur in younger adults, while the majority of people who received the third dose were older. It also is unclear how much reporting there is following a third dose, given that this is self-reported information.

Dr. Daley said he was trying to interpret whether the strengths and limitations of the data coming out of Israel were more similar to the strengths and limitations of the VAERS data or the VSD data. It was not clear to him whether the Israeli system misses hospitalizations post-vaccination and/or vaccine doses or if capture of these is likely to be pretty good.

Dr. Shimabukuro said he would have to familiarize himself more with the Israeli data to determine whether it is equivalent to an EHR-based system like VSD, but he thinks it has better capture of information than a purely passive system like VAERS. It is a smaller country and smaller population, so their capture of information may be somewhat better than VAERS.

Dr. Poehling asked whether there has been any observed GBS or anaphylaxis among the 2.8 million doses that have been administered.

Dr. Talbot indicated that there was 1 GBS followed by Bell's Palsy.

Dr. Sanchez found the data to be reassuring for those who decided to receive a third dose, but wondered whether those who had more severe reactions post-Dose 1 or 2 may not have decided to take a third dose. They will have to grapple with this as well if there is a recommendation for a booster dose.

Dr. Talbot agreed that it would be beneficial to have data about how many people decided not to receive a third dose due to having a reaction after Dose 1 and 2.

Ms. Howell (AIM) asked whether there are any data from Israel or the US showing whether people who previously had COVID-19 or had a breakthrough infection after being vaccinated had increased AEs following a third dose.

Dr. Lee reminded everyone that the Israeli data were presented during the VRBPAC meeting the previous Friday and that those slides could be accessed on the FDA website at: https://www.fda.gov/media/152205/download

Dr. Talbot indicated that the booster analysis, shown on Slide 21 of the Israeli data that were presented to the FDA, excluded people who had been infected previously. While this analysis includes data on people 60 years of age and above, it does not include information about AEs.

Dr. Shimabukuro commented on a couple of ongoing studies. There is a fairly large case-control study for the basic series looking at prior infection as a risk factor for more severe reactogenicity using v-safe[SM] data that is in progress for which CDC hopes to have preliminary results soon. He also is aware of another study on which CDC is consulting that is being conducted elsewhere. That does not get at the original question about third dose. It seemed like one would have to have a breakthrough case after the second dose and get a third dose to answer that question, which may be a rare event.

Dr. Long requested clarity about the time interval between Dose 2 and Dose 3, which seemed very relevant if they are trying to assess something like myopericarditis that is happening in younger people—especially teenagers because they are going into their second dose with very high antibody. That might be the case for the third dose in people who had a reason to have a third dose as the primary series and would be much less likely in those who are truly getting a booster if it has been 6 plus months.

Dr. Talbot indicated that everyone in the general population in Israel was eligible for an additional dose, whether called a booster or a third dose, 5 months after the second dose. She did not readily have data on what the average length of time was between Dose 2 and Dose 3.

COVID-19 Work Group Summary

Dr. Sara Oliver (CDC/NCIRD) reminded everyone that as mentioned previously, any policy on booster doses will be coordinated with FDA for regulatory allowance and ACIP for recommendations for use. The COVID-19 WG has reviewed the data and as is the standard process, they await FDA action and then ACIP can make recommendations for use. As a reminder, the data used to inform recommendations for booster doses of COVID-19 vaccines presented during this session included safety and immunogenicity for a third dose of BNT162b2, immunity and SARS-CoV-2, VE in the US, modeling the potential impact of booster doses in nursing home residents, and early safety monitoring for third doses of mRNA vaccines. Dr. Oliver provided a brief summary and WG interpretation of these presentations.

To summarize the safety and immunogenicity for a third dose of BNT162b2 from the Pfizer-BioNTech presentation, the data shown were from 23 individuals from the Phase 1 study who were boosted approximately 8 months after the second dose and 312 individuals from the Phase 3 study who were boosted around 7 months after the second dose. When the immunogenicity data were evaluated 1 month after the booster dose, the GMTs were around 3-fold higher than 1 month after the second dose. To evaluate the proportion with a seroresponse,

99.5% responded after the booster dose compared to 98% after the second dose and reactogenicity was similar after the booster dose and after a second dose.

The WG highlighted the number of individuals included in the evaluation for safety and immunogenicity from the manufacturer. Overall, the immunogenicity data are reassuring, but many unknowns remain. It is unknown what the clinical impact is of lower antibody levels seen pre-booster. In addition, the antibody kinetics over 1 month post-boost, including the rate of waning, is currently unknown. While increasing antibody levels are encouraging, it is unknown how the boost of antibody seen will directly translate to clinical protection. Although the safety data are also reassuring, there is limited size. There were 306 individuals included in the safety population. Based on those numbers, it is not possible to determine the risk of rare side effects such as myocarditis after a booster dose. Finally, the WG anticipates the ability to review additional data from an ongoing trial with around 10,000 individuals in upcoming weeks or months.

Moving to the presentation describing immunity and SARS-CoV-2, Dr. Thornburg described that the immune response generated by COVID vaccines is broad, including both cellular and humoral immune responses. In addition, waning of antibodies likely does not represent the entire picture. Memory B cells are maintained out to 6 months after the primary series. In addition, the immune response may be impacted by both aging and variants. Finally, Dr. Thornburg described data demonstrating that transmission is possible with infections after vaccination. However, the WG discussed that it is unknown how booster doses of COVID-19 vaccines may impact transmission.

As Dr. Link-Gelles mentioned in her presentation, current VE studies in the US will provide additional context around global VE studies in a subsequent presentation. This presentation demonstrated significant declines in VE against infection in individuals ≥65 years of age for mRNA products in the time since Delta. There were smaller declines in VE against hospitalizations in individuals ≥65 years of age, but it was more substantial in this age group than in younger populations. Among adults less than 65 years of age, vaccines remained effective in preventing hospitalization and severe disease. However, the vaccines may be less effective in preventing infection or milder asymptomatic illness due to both waning over time and the predominance of the Delta variant.

In terms of the modeling results from the impact of booster doses in nursing home residents, the results demonstrated that both increasing vaccination coverage of staff and increasing VE in residents can impact cases among these LTCF residents. Community transmission levels also substantially impact cases in LTCF. The WG discussed that these data demonstrate that booster doses are one way to protect the vulnerable LTCF population. However, it is not the only way to protect this population. In addition to including booster doses for LTCF residents, VE can be improved among LTCF residents by increasing vaccination coverage of LTCF staff. Lower rates of community transmission will be important. High rates of community transmission, even with additional vaccines delivered, can lead to COVID importation into facilities.

Given that Dr. Talbot summarized the safety data and the VaST perspective, Dr. Oliver did not-re-summarize it and did express appreciation for VaST's thorough review of the safety data.

In terms of next steps, in accordance with the standard process, FDA is carefully evaluating the data and will issue the regulatory allowance after their review. After FDA regulatory action, ACIP will have additional discussion around recommendations for use. Dr. Oliver invited ACIP to comment on any additional data they may wish to review before discussions around COVID-19 vaccine policy.

Open Discussion

Dr. Lee emphasized that the data presented were the data available at this point, but the COVID-19 Vaccine WG and VaST will continue to review emerging data as they become available. She invited ACIP members to provide input on key areas that might impact the discussion about the use of boosters in the US populations.

Ms. Bahta said she was grappling with what the goal was in terms of whether it was to just prevent disease, which Dr. Long pointed out is not possible. If the goal was to prevent severe disease, consideration must be given to how much would be gained by providing booster doses to certain individuals and how the benefit would weigh against political issues and ethical issues in terms of global partnerships. She also expressed concern that the data are small. Even the data for the 65-75 year old group was an N of 12. It was not clear whether this was a time of urgency for which they have to make a decision despite insufficient or lack of evidence.

Dr. Poehling reiterated the importance of being very clear about the goal if there is a recommendation for a booster. She thought it would be helpful to see the epidemiology on breakthrough infections and the anticipated benefits and potential side effects by age, race, and ethnicity.

Dr. Chen observed that in discussion COVID-19 booster doses, they seemed to be constrained by existing recommendations that seemed to lock a person into whatever primary series of vaccine they received. It would be beneficial for a booster dose to be agnostic to the primary series, allowing for the ability to administer boosters feasibly and in a way that does not require knowledge of the primary series. This would be his preference for the ease of implementation of booster doses.

Dr. Kotton agreed with Dr. Chen regarding making a booster as feasible and available as possible. Currently, there are a lot of combinations of vaccines being given as far as second or third doses depending upon the series. Some flexibility needs to be incorporated, but with an appreciation for the law, licensure, approval, EUA, et cetera. Even with a third dose, many immunocompromised patients (~3% of the US population) still remain not well-protected against COVID-19. The recommendations have been that they should be very carefully following infection control measures, so they still are living such that they cannot have life back yet. Better primary vaccination of the overall population definitely would help curtail the pandemic and would better help protect them. Thinking about the nursing home or LTCF model presented, it was not clear whether booster doses would help protect this population. She would be optimistic that immunocompromised individuals would be better protected if the overall population was better protected.

Dr. Sanchez agreed with clearly establishing the goal for the third/booster dose. With a respiratory virus, the goal really needs to be prevention of severe infection as defined by hospitalization and/or death—not just asymptomatic or mild infection. With hospitalization, it is really hospitalization due to COVID—not just those who are hospitalized for other purposes and found by screening to be positive upon admission. The safety presented thus far has been

somewhat limited, especially for booster doses. For the Pfizer product, there are no data for those less than 18 years of age. He agreed with a recommendation for a third dose for immunocompromised individuals. He would argue more for age rather than just risk of exposure. In addition, there are differences between the Pfizer and Moderna mRNA, which may need to be assessed further for ultimate recommendations. Data are needed on the Janssen product. Patients who have received the Janssen product have been left out not only for the consideration of boosting, but also the consideration for a third dose for immunocompromised persons. Janssen has second dose data now, which ACIP has not yet seen. They do need to comment on those who received the Janssen product and the availability of mRNA vaccine.

Dr. Daley expressed appreciation for the line of discussion that vaccination is not going to eliminate transmission. He also would add that it is possible that booster doses could decrease transmissibility, but that is an unknown and in that case would be the societal benefit of someone getting a booster. In terms of the individual risk-benefit calculus, most people probably have multiple considerations in terms of making a decision about getting a booster, but are likely thinking about their individual risk-benefit. The unknown about transmissibility is difficult to factor in there, because they may not directly benefit from that reduction in transmissibility even though others in their community may.

Regarding Dr. Sanchez's earlier comment, Dr. Loehr indicated that a large number of the hospitalizations with COVID-19 in his community are incidental findings of people getting admitted for something like a knee replacement, but testing positive for COVID upon admission. He asked the WG whether it would be possible to tease out hospitalizations due to COVID versus COVID as an incidental secondary diagnosis, which would help him to make a decision.

Dr. Talbot indicated that the COVID-NET hospitalization network is able to differentiate to some degree, but it is not easy to do and incidental cases tend to be the minority of cases. In addition, she thought the purpose of vaccinating HCP was not to prevent mild disease but to reduce mild disease so that HCP can return to work. There are not enough HCP in some areas to take care of unvaccinated, who just keep coming even though many have to be turned away in areas where there are not enough beds. When there are beds, there often are not enough staff. The idea of vaccinating HCP would be different from vaccines in the general population.

Dr. Duchin (NACCHO) observed that much of the data they saw during this session were categorized by age groups, 50-65 and 65 and older, and asked for additional information about how confident ACIP feels about where the line is drawn in terms of age and putting that in the context of the continuum of risk that exists above 50 years of age for instance.

Dr. Bell agreed that it is extremely important to have clarity about the issue of heterologous boosting and whether they were considering recommendations directed only toward people who received the primary series of the Pfizer vaccine or a much broader population of people with other characteristics as candidates. Second, the point about the objectives is pivotal and she agreed that the objectives here were about preventing serious illness and death. In that context, she reiterated that if they were considering HCP and other occupational groups, they would need to be giving some thought to a different objective of preventing absenteeism and workforce issues. Third, it is extremely important to keep in mind that ACIP would be making recommendations for *now*. Based on the data presented, they were not hearing about major gaps in data at the moment. There remain many data gaps and a huge number of moving parts such that things could change substantively in a relatively short period of time. She emphasized that these are interim recommendations and there may be data forthcoming in the near future that may change those recommendations.

Dr. Long stressed that ACIP had only the Pfizer vaccine data in front of them and it did not appear that they would hear any data on mixing and matching vaccine product, meaning the possibility that ACIP would recommend being boosted with what was received in the primary series. While she did not have a strong opinion about this theoretically, it would leave half of the people immunized in this age group being told that they are at risk for waning immunity and hospitalization but unable to receive a booster. That is a public health panic they would like to avoid. ACIP needs data for the Janssen recipients because it is not clear whether they would need 2 doses if they received a completely different product. She wondered how long it would be before ACIP could expect to see data from NIH and before FDA would see Moderna's information. Given that the dose for the Moderna booster may be different, that will result in further complications in terms of mixing and matching. Therefore, ACIP probably should make a decision about mixing and matching before making a recommendation about Pfizer at all. She asked whether anyone over 65 years of age had been on a ventilator and died because of a breakthrough case of COVID, given that there are many reasons to hospitalize people at this age.

Dr. Link-Gelles indicated that there have been cases of fully vaccinated individuals 65 years of age and older who had a breakthrough case and died. A couple of VE studies are underway, but the numbers are small so it will take a while to get actual VE estimates.

Dr. Sanchez raised the issue of whether individuals who have had symptomatic disease should receive a third dose.

Dr. Lee agreed that goals of the vaccination program and being very clear about it would be very important in helping to explain any ACIP recommendations. She believes the goals of the vaccination program will be dynamic over time depending on the status of the vaccination program. A substantial number of individuals are still unvaccinated, but the hope is to be in a different place in a few months in which case the goals may change or shift accordingly. Second, while ACIP has considered the product-by-product benefit-risk assessment and given dynamics of COVID in the moment the data are being reviewed, at some point ACIP will have to shift to a model like that for influenza to provide overarching recommendations that make sense for the overall population from clinical, population, and public health perspective and then explain any nuances under the overarching recommendations. Third, she feels that some of the struggle she has in terms of a path forward is the balance of ensuring the safety of vaccines in the population, ensuring access to vaccines for individuals, and addressing and maintaining a focus on equity. Specific to equity particular to the Janssen population, they also have to make sure that what they do makes good clinical sense for individuals and that they are not looking at everything in silos.

Dr. Brooks suggested that part of the deliberations should focus on what would cause the ACIP to adjust or revise any recommendations made during the next day of the meeting, given that these would be interim recommendations. They should go on record to state specifically what those parameters would be.

Circling back to the question about hospitalizations and whether they were attributable to COVID-19 or COVID-19 was incidentally diagnosed, Dr. Link-Gelles differentiated between a couple of the platforms. Platforms that have individual-level data have individual clinical information on cases such that they can include CLI as part of their case definition, so it is pretty reasonable to assume that those cases are actually hospitalizations associated with a COVID illness. Surveillance platforms generally do not have that ability and usually require a SARS-CoV-2 test within a certain timeframe of hospitalization.

Dr. Beigel (NIH) indicated that the full dataset for Pfizer, Moderna, and Janssen boosts would not be available until later in the fall. That will include Day 15 and Day 29 immunogenicity and T cell work that is planned, though he did not have a timeline on that. The enrollment was for Moderna boost first, then Janssen, and then Pfizer. The Pfizer data are probably the last that will be available to them. It would be helpful to discuss what datasets would be beneficial, and perhaps it would not be necessary to wait for the full dataset. Discussion might be easier offline or in the WG in terms of timelines, data within those that might be informative to ACIP, and how to present those data.

Dr. Weiser (IHS) asked whether there is a way to obtain more data that would look at other risk factors in addition to age for AI/AN populations, such as race for teasing out the interplay between race and comorbid conditions.

Dr. Cohn reminded everyone that if the FDA issued an EUA, ACIP policy would have to align with the language of the conditions of use. The data presented by Pfizer earlier in the day and the data that the FDA reviewed were all based on the Pfizer primary series with a Pfizer boost. She emphasized the importance of the issues pertaining to equity and not leaving groups of people behind, but this is a rapidly moving issue and data on the other vaccine series are rapidly behind Pfizer. FDA will be deliberating as fast as they can, but people do need to consider all of these as interim policies that will be adapted and responded to as epidemiologic, safety, and effectiveness data emerge on these vaccines. ACIP is fortunate to be able to return anytime there are new data to support changing policy.

Dr. Long requested that Dr. Lee ask Dr. Fink whether there is any timeline for Moderna filing for EUA for a booster. She also expressed an interest in seeing an estimate of what the downside would be of not recommending a booster for those ≥65 years of age at this time and instead waiting if they thought “rapidly emerging” meant that there would be a Moderna authorization within a month.

Regarding the question about Moderna filing for EUA of a booster dose, Dr. Fink (FDA) said he thought that Moderna stated publicly that they filed a submission. FDA is working as rapidly as possible to review that submission. In terms of the question pertaining to heterologous boosting, he reiterated that there are no data from the FDA’s perspective to inform interchangeability of a booster dose of one vaccine with a primary series of another vaccine. However, he appreciated the concerns with regard to flexibility and timing of availability of other authorized vaccines for a booster dose. In order to ensure that he could be as accurate as possible in addressing these concerns, he indicated that he would need to seek input from FDA leadership as to the legal considerations for that question for which he hoped to provide a response the next day.

Ms. McNally requested clarification on whether Dr. Fink was speaking about the Public Readiness and Emergency Preparedness Act (PREP Act) immunity issue, and on whether the Countermeasures Injury Compensation Program (CICP) program also was considering the issue of heterologous boosting.

Dr. Fink (FDA) clarified that he was speaking specifically of the FDA legal interpretation of the condition of an EUA should the Pfizer vaccine be authorized for use of a booster dose following a Pfizer vaccine primary series. There are other considerations such as the PREP Act that also would need to be addressed.

Dr. Rubin (HRSA) added that the PREP Act is very specific in the declaration in terms of countermeasures for COVID-19 vaccines that have FDA EUA or Biologics License Application (BLA) approval. CDC/ACIP recommendations do not affect what is covered under the CICP.

Dr. Loehr asked what the implications would be if the ACIP decided to table the vote for a third dose for a month or two.

Ms. Howell (AIM) commented on the implementation of third doses, especially in terms of going to a number of LTCFs across the US. The vast majority of North Dakota LTCFs administered Moderna and Pfizer products, so it was not clear whether returning with different brands would be feasible. Similar to the recommendation for the additional dose for immunocompromised individuals, she wondered whether either brand could be used for a third dose in a LTCF. She also wondered whether individuals ≥65 years of age could be included with immunocompromised individuals as needing an additional dose, which would give individuals who received either Moderna or Pfizer access to third doses. North Dakota also has a lot of people who already had COVID, so more data would be helpful on how many doses people who have had COVID need to reduce their chance of reinfection.

Dr. Oliver indicated that after FDA had taken a regulatory action on this, they would be able to have an open discussion using the EtR Framework. She reminded everyone that the EtR Framework would include not only an assessment of the public health problem regarding whether booster doses are needed, but also the benefits and harms, values and acceptability, feasibility, resource use, and equity.

Pregnancy: Safety Monitoring in v-safe[SM]

Dr. Christine Olson (CDC/NCEZID) presented results from CDC's results from the v-safe[SM] COVID-19 vaccine pregnancy registry, one of the vaccine safety monitoring systems for COVID-19 vaccination during pregnancy. To provide an overview of the enrollment process, people who use the v-safe[SM] after vaccination health checker indicate whether they are pregnant at the time they received a vaccine or if they become pregnant after vaccination at later check-in points. They are screened for eligibility for the pregnancy registry based on whether they were either pregnant at the time of vaccination or were vaccinated in the pre-conceptual period, defined as the 30 days before the first day of the last menstrual period before the pregnancy. Eligible individuals are then consented for pregnancy registry enrollment and are interviewed at designated time periods. The active follow-up for pregnancy registry participants includes interviews during each trimester after being enrolled, during the postpartum period, and during early infancy. Not all participants will be interviewed during all trimesters of pregnancy, but they may enter the registry at any point in the continuum if they meet eligibility criteria.

The current distribution of the 5096 enrolled pregnancy registry participants by vaccine manufacturer as of September 13, 2021 included 2584 (5.7%) Pfizer-BioNTech, 2236 (43.9%) Moderna, and 276 (5.4%) recipients. In terms of timing of the first COVID-19 vaccination during periconception or pregnancy among v-safe[SM] pregnancy registry participants, there is distribution of vaccination across all pregnancy time periods. About 5% of participants were vaccinated in the peri-conceptual period, 28% in the first trimester, about 42% in the second trimester, and about 25% in the third trimesters. By the end of September 2021, about 75% of the first approximately 1400 women who received vaccination in the first trimester or peri-conception women enrolled in the pregnancy registry will have reached their estimated dates of delivery. These participants will have postpartum follow-up interviews typically conducted between 4 and 8 weeks after delivery and an infant follow-up after infants have reached 3

months of age. Therefore, completed infant follow-up interviews for the majority of these pregnancies are not expected until November 2021 through January 2022.

In terms of the characteristics of the enrolled pregnancy registry participants, the demographics largely reflect the people who were initially prioritized for vaccination when vaccines first became available and those who chose to enroll in v-safe[SM] following vaccination. Most participants were 25 to 35 years of age, with a very low proportion under 25 years of age. For reference, over 20% of live births in the US are to women under 25 years of age. Participants were predominantly non-Hispanic white. Over time, those enrolling in v-safe[SM] have become more racially and ethnically diverse. The v-safe[SM] pregnancy registry participants' occupations were derived from the question asking about vaccination priority group showed that the majority of those who received the mRNA vaccines identified as HCP. That was the least represented group among those who received J&J vaccine. There are several reasons likely contributing to this, including that much of the initial vaccination of HCP occurred before the J&J vaccine received its EUA and that the J&J vaccine with less stringent storage requirements made it more likely to be used outside of large healthcare settings.

A recent v-safe[SM] publication[36] focused on an analysis of early pregnancy losses. The objective in this analysis was to assess among the registry participants the cumulative risk of spontaneous abortion (SAB) for pregnancy loss occurring at less than 20 weeks gestation. The analysis included 2456 pregnant people enrolled in the v-safe[SM] registry who had received at least 1 dose of an mRNA COVID-19 vaccine peri-conceptually or during pregnancy prior to 20 weeks of gestation who had not had a pregnancy loss before 6 weeks of gestation. Lifetable methods were used to examine the cumulative SAB risk by gestational week in this cohort. Recipients of the J&J vaccine were not included in this analysis because as mentioned earlier, only about 5% of registered participants received that vaccine. Results showed an unadjusted cumulative risk of SAB after mRNA COVID-19 vaccination of 14.1%. Because most of the registry participants are over 30 years of age and therefore slightly older than the general US pregnant population, the investigators age standardized using a reference population study on the risks of SAB according to maternal age group and found a slightly lower risk of SAB of 12.8%. As expected, the cumulative risk of SAB increased with maternal age. These risk estimates fall within published baseline estimates of SAB of 11% to 22%. This provides additional evidence that mRNA COVID-19 vaccines in pregnancy are not associated with SABs.

A sensitivity analysis was conducted of the 65 participants who met inclusion criteria for this study, but who could not be reached for the second trimester follow-up and thus for whom it was not possible to ascertain pregnancy status as of 20 weeks gestation. Under the extreme assumption that all 65 of these individuals have had an SAB, the cumulative risk of SAB was 18.8% before and 18.5% after age standardization. In terms of the weekly cumulative risk for 2 published historical cohorts[37] representing the lower and upper ranges of SAB risk, the results for both the primary analysis and the sensitivity analysis fell within the bounds of these 2 historical cohorts representing the expected risk range.

[36] Zauche et al. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. N Engl J Med. 2021 Sep 8. doi: 10.1056/NEJMc2113891

[37] Mukherjee et al., 2013 and Goldhaber and Fireman, 1991

Regarding v-safe[SM] pregnancy registry infant outcomes at birth for which CDC has preliminary information based on participant self-reported data and focusing on results for 1613 pregnancies, this analysis began with the 5096 enrolled participants and was limited to those who had an estimated date of delivery (EDD) before May 15, 2021. This was done to allow enough time for postpartum interviews to be conducted in the typical timeframe after delivery and data to be cleaned, reviewed, and analyzed. Among this group, approximately 500 were still pending follow-up and 63 were determined to be lost to follow-up. The resulting 1613 pregnancies produced 1634 live-born infants, 32 of whom were the results of twin gestations. Of this participant cohort, 70% received COVID-19 vaccine in the third trimester and 30% in the second trimester. Information is included about the participants in the registry who received vaccine earlier than the second trimester of pregnancy, which currently includes 1428 participants. These pregnancies and follow-up are ongoing and therefore data are incomplete at this time. However, the outcomes of these pregnancies will be included in future reports. Infant outcomes of interest among the 1634 live-birth infants included preterm birth, small-for-gestational-age, admission to the Neonatal Intensive Care Unit (NICU) after birth, and neonatal or infant death. The proportions of these outcomes in this birth cohort are consistent with or below the reference background rates.

To provide some context now on registry participant self-reported birth defects, most birth defects arise in the first trimester. However, there are only sufficient data at this time to report on birth defects among participants who were vaccinated in the second and third trimesters. As shown earlier, pregnancies among participants vaccinated in the first trimester are either still ongoing or have not yet had ample time to schedule follow-up interviews and data review. These data will be presented in the future as they become available. Data in the registry are self-reported by participants during the postpartum interview. Participants responded to the question, “Was your baby diagnosed with a birth defect?” Reported birth defects were reviewed by birth defect experts to assess whether they met inclusion criteria and were then categorized. Birth defects were defined as a structural abnormality, chromosomal anomaly, or genetics syndrome. The types of birth defects reported following vaccination in the second and third trimesters are consistent with what would be expected based on population-based birth defect surveillance systems. For example, heart defects are the most common type of birth defect. Among those, septal defects predominate. No unusual birth defect types of clusters of birth defects have been noted. Because pregnancies where vaccination was received in the first trimester were not included in this current cohort and because the reported number of infants with birth defects was small, these current data are not sufficient to assess an association between birth defects and COVID-19 vaccination. However, these reported birth defects by participants do indicate that the registry is identifying this important outcome and the distinct types, which is needed to address the larger question.

In terms of concluding thoughts regarding the information reviewed, there are accumulating data from the pregnancy registry on the safety of COVID-19 vaccination during pregnancy. Specifically, the currently available registry data have been reviewed and no evidence has been found of any increases in spontaneous abortion rates or of any disproportionate negative infant birth outcomes. CDC will continue to closely monitor the safety of COVID-19 vaccination during pregnancy and will provide updates as more data become available. The pregnancy registry is continuing to enroll participants, with the goal of enrolling up to 20,000 participants for each vaccine type.

Discussion Points

Dr. Daley observed that the pandemic has shown that what was thought to be impossible or hard to do is really possible. This is an example in which a surveillance system has been able to recruit and enroll women and then follow them over time. It is known that there are a number of difficulties of enrolling pregnant women in initial Phase 3 clinical trials, but it is very fortunate and important to have these data. He found the Zauche et al. data on Slide 14 to be very reassuring in the sense that the sensitivity analysis is the most conservative and even that is below Muckherjee et al. He wondered whether it would be possible to put the Goldhaber and Fireman data into some context in terms of whether they used very different methods or that SABs have increased in the last 30 years, which is possible given how demographics have changed and other things.

Dr. Olson indicated that interestingly, the data behind the historical reports and reports over time of SABs vary quite a bit—probably more than one might have expected before diving into the literature. There is considerable variability in the populations reported upon and the ascertainment of diagnosis of pregnancies and how losses are identified and confirmed. While it is difficult to compare studies directly to each other, they felt it was important to look at the range of SAB reports, evaluate the methodologies, and select the ones that seemed the most appropriate and similar to what they were trying to do. However, there still are variations among them. They were fortunate to be able to obtain the input of one of the leading subject matter experts (SMEs) in this area who contributed greatly to the methodology and the literature on this assessment.

Dr. Goldman (ACP) noted that a lot of times vaccine-hesitant male patients are concerned about male fertility and there is a lot of disinformation. He wondered whether there are data along that line or if this could be assessed in terms of tackling the social media and disinformation that is occurring regarding this issue.

Dr. Olson acknowledged the concern that has been expressed about fertility and that has taken off within social media. This study did not assess vaccine-hesitant male patients because all of the participants are already pregnant. They have assessed some preliminary data reported into v-safe[SM] at the 3- and 6-month check-in points in the symptom tracker. For individuals who answered the question at the 42-day mark and indicated that they were not pregnant, over 20,000 participants in the v-safe[SM] symptom tracker have reported positive pregnancy tests beyond the point at which this question is asked. They do not have any information that she is aware of about males and fertility issues.

Given that more than 80% of participants were HCP and do not reflect the general population, Dr. Cineas asked whether any subgroup analyses were performed in the non-HCP participants.

Dr. Olson indicated that this has not been done to date. As they are continuing to enroll, the proportion of HCP will decrease. They are aware that the study population demographics are in the process of shifting because of the time course. They are following the pregnancies as they move along, with the initial group being followed being comprised of those who received vaccine when it was first available and prioritized for HCP. Additional steps are being taken to ensure that they have a better balanced study population in addition to the fact that the population pool from which they are drawing for interviews has changed over time.

Pregnancy: Safety Monitoring in the Vaccine Safety Data Link (VSD)

Dr. Elyse Kharbanda (HealthPartners Institute) presented VSD data on the safety of COVID-19 vaccines before and during pregnancy, spontaneous abortion following COVID-19 vaccination, and stillbirth surveillance. As a reminder, the VSD is comprised of 9 integrated health systems working in collaboration with CDC. Of these health systems, 8 are data contributing sites. These sites create standardized files using data from EMR, claims, and administrative databases with weekly updates. Sites also create more comprehensive data files, which include birth records. These are updated on an annual basis.

Before presenting the data, Dr. Kharbanda described the algorithms that are the critical underpinnings of this work. Previously, the VSD developed and validated the pregnancy episode algorithm (PEA). This algorithm is applied to the VSD annual data files and is used to identify completed pregnancies. The PEA is the algorithm that was used in prior VSD studies of maternal Tdap and maternal influenza vaccine safety. Recently, an enhanced pregnancy algorithm was developed and validated known as the dynamic pregnancy algorithm (DPA). The DPA incorporates data from the standardized VSD files with weekly updates and is used for identifying ongoing pregnancies.

The DPA has made work on the safety of COVID-19 vaccine and pregnancy possible. Using the DPA, it is now possible to track receipt of COVID-19 vaccines before and during pregnancy in the VSD in near real-time. Data on COVID-19 vaccines administered between December 14, 2020 and July 31, 2021 showed that there were 122,998 pregnancies in the VSD. There were 10,178 pregnancies in women who received ≥1 COVID-19 vaccine dose prior to pregnancy and 6,792 pregnancies with 2 vaccine doses prior to pregnancy. As of July 31, 2021, there have been 31,080 pregnancies with ≥1 vaccine during pregnancy and 23,310 pregnancies with 2 vaccine doses during pregnancy.

Turning to current data from a recently published study on SABs following COVID-19 vaccination during pregnancy[38], SABs and ongoing pregnancy were identified for 6-19 weeks gestation. SABs were assigned to a single 4-week surveillance period. Ongoing pregnancies, including pregnancy time before SAB, was assigned to one or more surveillance periods. For these SAB cases and ongoing pregnancy period controls, GEE was used to calculate the odds of exposure to a COVID-19 vaccine in the 28 days prior to the SAB compared to the odds of exposure to a COVID-19 vaccine in the 20 days prior to an index date in the ongoing pregnancies, while adjusting for gestational age groups, maternal age groups, receipt of prenatal care, race, ethnicity, and VSD site.

For COVID-19 vaccines received before 20 weeks, data were available for 105,446 unique pregnancies included in the cohort from December 15, 2020 to June, 28, 2021 and were stratified by ongoing pregnancy versus SABs. Most vaccines received were mRNA. Ongoing pregnancies could contribute data to more than one surveillance period so during that same timeframe, there were 264,104 pregnancy-periods. Receipt of COVID-19 vaccines in the prior 28 days was stratified by ongoing pregnancies versus SABs. Across all pregnancy-periods and strata, 8.0% of ongoing pregnancies and 8.6% of spontaneous abortions received a COVID-19 vaccine in the prior 28 days. These same comparisons were assessed by gestational age groups, maternal age groups, race/ethnicity, number of antenatal, and by surveillance period. Most vaccinations occurred between March and May. For the full population, the adjusted odds

[38] Kharbanda et al. Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. *JAMA*. 2021 Sep 8. doi: 10.1001/jama.2021.15494.

of COVID-19 vaccination in the 20 days prior to SABs as compared to ongoing pregnancy controls was 1.02 with a 95% confidence interval of 0.96 to 1.08. Odds ratios varied slightly when stratified by gestational age. There was no difference in the odds ratios when stratified by vaccine manufacturer. Adjusted odds ratios were not calculated for the Jansen vaccine due to the small number of exposures.

A few limitations should be noted. First, SAB cases were not chart-confirmed and dating may be inaccurate early in pregnancy. Second, it was not possible to adjust for some potential confounders, including prior pregnancy history. Nevertheless, in summary the investigators found that among women with SABs, the adjusted odds of a COVID-19 vaccine exposure were not increased in the prior 28 days as compared to women with ongoing pregnancies. Next, they are planning to conduct an individually matched case-control study with all SAB cases chart-confirmed.

In terms of updates on monthly surveillance for stillbirths following COVID-19 vaccination, potential stillbirths with COVID-19 vaccine exposures are identified monthly from the DPA. To increase sensitivity for finding stillbirths, late SABs also were identified. All potential cases were chart-reviewed by sites and then adjudicated by the Yale Obstetrics Team. The goals of chart review and adjudication were to confirm the outcome, estimate the date and gestational age at fetal demise, and identify possible etiology for the stillbirth. For confirmed stillbirths using the adjudicated date and gestational age at fetal demise, timing of any COVID-19 vaccine exposures were then reviewed.

During the surveillance period from December 2020 through July 2021, there were 11,300 live births in the VSD who received at least one COVID-19 vaccine dose during pregnancy. Among those, 670 possible stillbirths were identified to date using the DPA. Of these, 92 had a possible COVID-19 vaccine exposure during pregnancy. These 92 cases were chart-reviewed and adjudicated, with 66 for excluded for the following reasons: SAB (n=41) ongoing pregnancy (n=2), live birth (n=10), ectopic pregnancy (n=1) therapeutic abortion (n=9), and records not available (n=3). The majority were SABs rather than stillbirths, with 26 cases confirmed as stillbirths with one or more COVID-19 vaccine received during pregnancy.

To provide additional information on these 26 cases, the mean gestational was 29.5 weeks with a standard deviation of 6.6 weeks and the range of 20 to 40 weeks gestation. Of the 26 stillbirths after chart review and adjudication by the Yale Obstetrics Team, 25 had at least one complication associated with stillbirth. Most common among these were umbilical cord or placental complications, obstetric complications, and maternal comorbidities. In terms of timing between vaccinations and stillbirths for the full 26 cases, stillbirths occurred between 8 and 140 days following Dose 1. For the 16 cases who received 2 vaccine doses in pregnancy, the timing between Dose 2 and stillbirth ranged from 3 to 112 days. In terms of the distribution of timing between vaccinations and stillbirths by manufacturer, 4 cases occurred following the J&J vaccine, 17 following Moderna, and 21 following Pfizer.

Of note, stillbirth surveillance is descriptive and there is no comparison group. In summary, monthly stillbirth surveillance was chart-reviewed and adjudication identified 26 stillbirths following COVID-19 vaccination from December 2020 through July 2021. Nearly all cases had one or more stillbirth risk factors. No concerning patterns were identified related to the timing of vaccine exposures or stillbirth etiology. A future case-control study is planned.

Open Discussion

Ms. Hayes (ACNM) observed that having the racial diversity in VSD that is not available in v-safe[SM] is reassuring. In terms of the stillbirths that occurred with the Janssen vaccine, she asked whether there were any data on the links and if any clots formed among the women who received this vaccine.

Dr. Kharbanda indicated that she did not have the etiology in front of her for the stillbirths associated with the Janssen vaccines, but will follow-up with this information.

Dr. Ault recalled that there were data from the last pandemic showing that influenza vaccination actually protected against stillbirths. Therefore, he would be curious to see data in the future pertaining to whether COVID-19 vaccine also protects against stillbirths. In the news the week before, public health officials in Mississippi noticed a spike in stillbirths over the summer correlating with pregnant women getting COVID-19 disease. Rather than looking for negative associations, he would be interested in seeing positive associations in future research.

Dr. Poehling noted that as she is taking care of newborns, she is seeing an increase in maternal infections. The gestalt is that they seem to be more severe than they were earlier in the pandemic. She asked whether there are analyses underway about the impact of COVID-19 infection in pregnant women in the VSD.

Dr. Olson indicated that Dr. Meaney-Delman would be presenting on some of the current epidemiology of pregnancy related to COVID-19 infections, which might help to answer this question.

Dr. Kharbanda added that as part of VSD's safety work, they will be assessing infant outcomes. Specifically, there are some studies looking at infant infections in the first 6 months of life.

Dr. Sanchez commented that they always have allowed rooming in with mothers and babies and anecdotally, it appears that slightly more of their newborns are testing positive at 24 to 48 hours.

VaST WG Summary on Pregnancy

Dr. Keipp Talbot (VaST Chair) indicated that since February 2021, VaST initiated monthly and bi-monthly sessions with additional experts to review data on vaccine safety and pregnancy. This is especially important as pregnant women were excluded from the original vaccine studies. There have been 6 maternal immunization-focused sessions during the VaST calls to date. VaST has reviewed data from VAERS, v-safe[SM], v-safe[SM] pregnancy registry, VSD special studies, manufacturer data, and plans for further study.

VaST first reviewed data on vaccination of pregnant women from v-safe[SM] and the v-safe[SM] pregnancy registry, and VAERS. VaST assessments conclude that a large number of pregnant women have chosen to receive COVID-19 vaccines in the US. A novel pregnancy registry in v-safe[SM] was established to monitor pregnancy and birth outcomes. Similar to non-pregnant adults, pregnant women commonly report local and systemic reactogenicity, pain, fatigue, and headache. Pregnancy and birth outcomes following COVID-19 vaccination appear similar to rates reported in the literature. In April, May, and June 2021, VaST reviewed data from VSD that contributed to data from v-safe[SM] and VAERS showing no safety concerns. Specifically, SAB is from near real-time surveillance, stillbirth surveillance, and acute event surveillance.

Maternal vaccination safety data from multiple sources are regularly reviewed in collaboration with pregnancy experts. VaSt is reassured about safety and maternal immunization. More data are emerging on the risk of COVID-19 for pregnant women, which can further inform the assessment of the risk and benefit of vaccination of this population. VaST will continue to review data on maternal vaccination and update the ACIP COVID-19 Vaccines WG, the ACIP Secretariat, and ACIP on a regular basis.

Updates on COVID-19 and Pregnancy

Dr. Dana Meaney Delman (CDC/NCBDDD) provided updates on COVID-19 disease and pregnancy, including recent epidemiologic trends, VE, and CDC's vaccine recommendations. She noted that the term "pregnant people" would be used in this presentation as much as possible, but would maintain the term "pregnant women" for publications in which that term is used.

Beginning with recent trends in the epidemiology of COVID-19 among pregnant people, the epidemic curve of pregnant people with laboratory-confirmed SARS-CoV-2 infection reported through the National Notifiable Diseases Surveillance System (NNDSS) as of September 20, 2021 reflects that 123,633 laboratory-confirmed SARS-CoV-2 infections had been reported among pregnant people. These case counts are likely an under-estimate of the true number of SARS-CoV-2 infections because pregnancy status is not known for all cases reported to CDC. Several things to note are that the case trend mirrors that of the non-pregnant population shown earlier in the day, with a clear fourth wave of infection associated with the Delta variant. The recent peak in pregnant cases began at the end of June and was higher than the Spring peak in cases seen in March. More than 1000 cases were reported among pregnant people weekly during the month of June. Case data does not routinely capture vaccination status. However, clinical partners have shared anecdotally that the majority of cases receiving care are unvaccinated pregnant persons. CDC hopes to have the vaccination status of cases in the future. It is important to note that there is a 2- to 4-week data delay. Therefore, the decrease in cases at the tail end should be interpreted with caution.[39]

Overlaying the number of Intensive Care Unit (ICU) admissions and deaths among pregnant people on the epidemic curve, two very concerning trends have been observed and highlighted in recent news reports and in some of the conversations earlier. The first is the recent increase in ICU admissions. While the number of pregnant people admitted to the ICU was highest early in the pandemic and subsequently declined, there was an increased number of pregnant people admitted to the ICU in July and August. CDC is hearing from clinical partners that this trend in ICU admissions is continuing through September. Second, the number of deaths among the pregnant people has increased. The deaths reported in August represented the highest number of deaths reported in any month since the start of the pandemic. While CDC does not have the vaccination status for pregnant persons admitted to the ICU or for those who have died at this time, they do have preliminary data from other sources suggesting that these are predominantly unvaccinated person. For example, data in COVID-NET from 2021 indicate that approximately 97% of pregnant women hospitalized with confirmed SARS-CoV-2 infection are unvaccinated. These data may be under-estimates due to lag time in death reporting.

[39] https://covid.cdc.gov/covid-data-tracker/#pregnant-population

Increased ICU admissions and deaths are not entirely unexpected. It is known that pregnancy is associated with severe COVID-19 illness and that COVID-19 is associated with adverse maternal, pregnancy, and neonatal outcomes. Based on forest plots from the living systematic review (LSR) by Allotey et al. and some additional data from a systematic review by Wei et al., pregnant women with COVID have statistically significant higher odds of ICU admission, ventilation, and extracorporeal membrane oxygenation (ECMO) compared with non-pregnant women of reproductive age with covid-19. Pregnant women with COVID-19 have a higher risk of maternal death, preeclampsia, preterm birth, and stillbirth than pregnant women without COVID. Neonates born to pregnant women with COVID-19 have higher risks of neonatal ICU admission when compared to those born to women without COVID-19. Of note, the absolute numbers of maternal deaths and stillbirths were low so the findings should be interpreted with caution.

In a CDC publication that assessed the risk of severe illness among symptomatic pregnant women with COVID-19 compared to symptomatic non-pregnant women with COVID-19 among approximately 400,000 women of reproductive age with laboratory-confirmed SARS-CoV-2 infection approximately, approximately 5.7% were pregnant. This analysis, which adjusted for age, race, ethnicity, and underlying medical conditions found a statistically significant increased risk of death for symptomatic pregnant women with COVID-19 compared to non-pregnant symptomatic persons with COVID.[40] In addition to these findings, perinatal infection is another outcome of interest for pregnancies affected by SARS-CoV-2 infection. A recent analysis examined the results of SARS-CoV-2 PCR testing among approximately 26,000 neonates. Among these, 30% of neonates underwent testing and 4% of neonates born to women with SARS-CoV-2 infection were positive.[41] Other cohorts have estimated perinatal infection rates at approximately 1% to 2%.[42] While perinatal infection among neonates appears to be a rare outcome, it is yet another outcome to consider in the risk-benefit analysis of vaccination during pregnancy.

In terms of recent data on COVID-19 VE and pregnancy, there have been two published reports on VE and pregnant people from Israel.[43] Both assess receipt of the Pfizer-BioNTech vaccine and matched vaccinated pregnant people 1:1 to unvaccinated pregnant people by demographics and clinical characteristics. The first study by Goldshtein et al. examines the cumulative incidence of infection over time. This is a retrospective cohort study from a large state-mandated Health Care Organization (HCO) in Israel. There were 202 SARS-CoV-2 infections in the unvaccinated group and 118 in the vaccinated group. The authors concluded that mRNA vaccination compared with no vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among pregnant people. The second study by Dagan et al. was an observational cohort study of pregnant women aged 16 years or older with no history of SARS-CoV-2 infection. Approximately 10,800 vaccinated pregnant women were matched 1:1 to unvaccinated pregnant controls. Looking at cumulative incidence of infection curves of SARS-CoV-2 infection over time, the vaccinated and unvaccinated groups are similar until about Day 14 post-vaccination when the incidence of infection in the vaccinated group begins to decline. In total, there were 235 infections in the unvaccinated group compared to 131 infections in the vaccinated group. The authors estimated that VE after the second dose 7 to 56 days later was

[40] Zambrano LD, Ellington S, Strid P, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep. ePub: 2 November 2020. DOI: http://dx.doi.org/10.15585/mmwr.mm6944e3external icon.

[41] Data from Surveillance for Emerging Threats to Mothers and Babies Network https://www.researchsquare.com/article/rs-491688/v1

[42] Mullins E, Hudak ML, Banerjee J, et al. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. Ultrasound Obstet Gynecol. 2021;57(4):573-581. doi:10.1002/uog.23619

[43] https://jamanetwork.com/journals/jama/fullarticle/2782047; https://www.nature.com/articles/s41591-021-01490-8

96% for any documented infection, 97% for symptomatic infection, and 89% for COVID-19 related hospitalizations. Overall, the VE estimate for pregnant women was not lower than that for the general population. More data are forthcoming on VE during pregnancy from CDC.

In addition to examining VE for preventing maternal infection, there is great interest in understanding if maternal vaccination confers immunity to the fetus or neonate. Current data from Gray et al.[44] indicate that for pregnant people who have received an mRNA COVID-19 vaccine during pregnancy, immunogenicity is similar to that observed in non-pregnant women. In addition, antibodies have been identified in umbilical cord blood and breast milk. These findings are encouraging, but not unexpected. More data are needed to determine whether maternal vaccination at different points during pregnancy can provide immune protection to neonates. NIH is beginning a multi-site study on this topic in which researchers will evaluate antibody responses in vaccinated participants and their infants among 750 pregnant individuals and 250 postpartum individuals. Participants and their infants will be followed through the first year after delivery. Antibody testing will be done on umbilical cord blood, breast milk, and blood from infants at 2 and 6 months after delivery. While immune protection to the neonate conferred by maternal immunization is an important area of study, it is important not to lose sight of the importance of protecting pregnant persons themselves. It is known that a healthy mother is critical for a healthy pregnancy and a healthy infant.

With respect to CDC's updated clinical considerations for COVID-19 vaccine in pregnancy released on August 11, 2021[45], CDC made a strong recommendation for COVID-19 vaccination in pregnancy:

- COVID-19 vaccination is recommended for all people aged 12 years and older, including people who are pregnant, breastfeeding, or who trying to get pregnant now or might become pregnant in the future.
- Consistent with recommendations from professional medical organizations

This recommendation aligns with recommendations recently released from several clinical organizations, including the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), and over 20 clinical professional organizations that have signed on to indicate medical consensus. These recommendations are based on the evidence to date on the safety, effectiveness, and health benefits of vaccination. It is known that pregnancy increases the risk for severe illness from COVID-19 and that COVID-19 is associated with adverse maternal, pregnancy, and neonatal outcomes.

To summarize, there is evidence on the safety of mRNA COVID-19 vaccines during pregnancy, and the information to date has been reassuring. There are recent studies on vaccine VE demonstrating that vaccination during pregnancy reduces the risk of infection and hospitalizations. There also are studies that have identified vaccine antibodies in cord blood and breast milk, which are promising signs with regard to the potential for immune protection for the neonate. Despite all this information, current coverage with COVID-19 vaccination among pregnant people is very low.[46] Based on coverage of COVID-19 vaccination among pregnant people reported to CDC's VSD described earlier, only 30% of pregnant people were fully vaccinated against COVID-19 prior to and during pregnancy as of September 11, 2021. While the overall trend in vaccination is upward, vaccination coverage both before and during

[44] https://pubmed.ncbi.nlm.nih.gov/33775692/

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

[46] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/planning-for-pregnancy.htm

pregnancy is far lower than hoped would be achieved. These low coverage rates are particularly concerning in light of the recent increases in cases, ICU admissions, and deaths among pregnant people.[47]

CDC and its clinical partners are committed to improving vaccine coverage for pregnant people, including encouraging vaccinations prior to, during, and after pregnancy. To highlight a few concrete efforts, CDC is assessing the reasons for vaccine hesitancy and planning to share personal stories of families. One of the most common reasons for vaccine hesitancy is concern about safety and theoretical risks of the vaccines. As evident from the presentations during this session, CDC is making every effort to disseminate information rapidly and broadly at ACIP, on the CDC website, through social media, and through CDC partners. The agency continues to address vaccine access issues and is working with clinical partners to encourage more clinicians caring for women to become vaccine providers. In addition, CDC is continuing to develop and provide resources to assist HCP and others who are having conversations with pregnant people about vaccines. Finally, the agency is working closely with clinical and public health partners to ensure consistent messaging about the need for COVID-19 vaccinations and to dispel myths about vaccines.

Taking off her CDC hat and putting on her clinical OBGYN hat, Dr. Meaney-Delman said she wanted to speak directly to the public listening during this meeting. It is known that pregnant people with COVID-19 can become very sick, some will die, and many will experience pregnancy and neonatal complications. It also is known that because of COVID, some children will grow up without their mothers. COVID-19 vaccines are known to be safe and effective. Dr. Meaney-Delman implored those who are pregnant, postpartum, breastfeeding, trying to get pregnant now, or might become pregnant in the future to please get vaccinated.

Summary of Discussion

Dr. Ault noted that vaccine uptake in Black communities is about half of what Dr. Meaney-Delmand showed, so specific outreach is needed to this group who suffers from very high morbidity and mortality already at a baseline—specifically for subgroups of women who are under-vaccinated.

Dr. Meaney-Delman indicated that the highest uptake observed among pregnant people was among those who are Asian Non-Hispanic at 35.7%, the lowest uptake was observed among Black Non-Hispanic at 13.5%, uptake among Non-Hispanic Whites was 27.2%, and uptake among Hispanics was 21%. Everyone is interested in whether the Delta variant is associated with more severe disease in pregnancy. The only data she is aware of is from the UK, which does not have genomic sequencing and is basically time-series. The question remains regarding whether the Delta variant is associated with more severe illness or higher rates of perinatal infection. Right now the message is that people absolutely must be encouraged to get vaccinated.

Dr. Kotton noted that in general for the VSD and the v-safe[SM] registry, Black women were under-represented and she asked whether there are any plans to try to enhance that given how much the community has been impacted.

[47] https://covid.cdc.gov/covid-data-tracker/#vaccinations-pregnant-women

Dr. Olson responded that this is recognized as a deficiency of the current population pool on which they present data for the pregnancy registry. There are active plans to try to prioritize some groups who are significantly under-represented by the nature of how people enrolled and became participants of v-safe[SM].

Dr. Kharbanda commented that for VSD, the data are based on members of the integrated health systems. The VSD as a whole has worked to increase diversity in the population. Denver Health was added as a VSD site and other sites that may be joining would increase diversity, but their data are yet to be included in the VSD work.

Dr. Sanchez observed that the adverse outcomes such as low stillbirths remained somewhat controversial in terms of the relationship, given that some of the studies have not shown that association in pregnant women with COVID-19 infection. If a booster dose is recommended for high-risk individuals, he wondered whether pregnant women would be included in that category.

In terms of stillbirths, Dr. Meaney-Delman indicated that they assessed the studies that were included in the Allotey systematic review. Many of those studies are from countries that have much better stillbirth surveillance than the US. She agreed that this question still remains, but the studies conducted in countries with better stillbirth surveillance are interesting albeit small numbers. Nevertheless, there are some concerns. She does not see a clear and compelling reason for this to be different than it is for the primary vaccine series, but she thought they would have to see what ACIP recommended. At this point it seemed premature to make specific recommendations for pregnant women.

Dr. Kharbanda added that in the VSD early in the pandemic CDC published some data in the *MMWR* on COVID infection and outcomes in pregnant women. One of the issues that has been discussed was assessed in a very small sample of women admitted for delivery who were found to have COVID infection versus women who showed symptomatic. In that sample, the proportion of women with stillbirths was higher than the VSD background rate. The VSD is again looking at continuing that surveillance and those data are currently being collected. It is important to be careful in these evaluations during pregnancy to understand the right comparison group, because some of these observational systems are missing COVID infections that are asymptomatic during the course of pregnancy, but are capturing the more severe infections very well. They will continue to learn from that data, which continue to evolve.

Dr. Poehling reiterated that COVID infection during pregnancy is associated with increased negative maternal outcomes (ICU admissions, maternal deaths, stillbirths, increased NICU admissions for newborns, increased prematurity, increased preeclampsia). The data shown previously indicate that vaccine does not increase any of these outcomes. As Dr. Ault noted, there are data from influenza showing that vaccine actually reduces these. That highlights the importance of equitable access to COVID vaccines, encouraging persons who have increased risks for these negative outcomes to get vaccinated, and making sure everybody is captured.

Dr. Sanchez added that the data presented are very important and concerning, and pointed out that some of the consequences of prematurity actually may be unrelated to fetal or perinatal infant infection. Even the inflammatory changes that occur secondary to a COVID infection may result in placental inflammation, fetal inflammation, and prematurity leading to adverse consequences beyond some of the pregnancy outcomes that also should be evaluated.

Dr. Meaney-Delman agreed and pointed out that the other thing they have to keep in mind is that if moms are really sick, sometimes delivering them is necessary to improve the ability to treat them. There is an element of iatrogenic preterm birth as well.

Dr. Fyhofer (AMA) said that speaking as a mom who hopes to be a grandmother very soon, she is very disappointed by the 30% uptake of the vaccine by pregnant women. Dispelling the myth that COVID vaccines are related to infertility has been one of the major challenges she has had in trying to overcome vaccine hesitancy. Many people do not understand that these vaccines actually protect moms during pregnancy. She greatly appreciates the outreach and consistent messaging and also thinks that a strong recommendation from CDC, ACOG, SMFM, and the other medical organizations has been very powerful.

Dr. Meaney-Delman agreed that it is incredibly important to continue with outreach and consistent messaging to address the myths. “Infertility” is defined as a year of trying to get pregnant unsuccessfully. It is hard to dispel that myth when there has not been sufficient time to conduct longitudinal studies on fertility, but it is known than many women have gotten pregnant subsequent to vaccination. There is not a biologically plausible reason to expect there to be an infertility concern associated with these vaccines, yet the myth has taken off.

Dr. Poehling highlighted the point that an increasing number of people have received vaccine before pregnancy. She emphasized that they all have a role in the effort to increase equitable distribution of vaccine, which will have a huge impact.

Dr. Cohn indicated that if there was an FDA authorization by noon the next day, the second day of the ACIP meeting would be convened as scheduled. If not, rescheduling information would be posted on the ACIP website. With no further business on the agenda, ACIP stood in recess for the day.

Thursday: September 23, 2021

Welcome, Roll Call, Opening Remarks by Drs. Fink and Walensky

Dr. Cohn (ACIP Executive Secretary, CDC) welcomed everyone to the second day of the September 22-23, 2021 ACIP meeting and noted that the updated agenda had been posted to the ACIP website.

Dr. Grace Lee (ACIP Chair) called to order and presided over the second day of the 12th ACIP meeting convened in 2021. She called the roll and established that no new COIs were identified/declared.

Dr. Dorin Fink (FDA Ex Officio ACIP Member) announced that late the previous day, FDA amended the EUA for the Pfizer-BioNTech COVID-19 vaccine to include use of a single booster dose administered at least 6 months after the primary series in the following populations: Individuals 65 years of age and older, individuals 18 through 64 years of age at high risk of severe COVID-19, and individuals 18 through 64 years of age whose frequent institutional or occupational exposure to the SARS-CoV-2 virus puts them at high risk of serious complications of COVID-19, including severe COVID-19. This was a regulatory action that followed FDA’s comprehensive and independent review of clinical trial data submitted by the vaccine manufacturer, as well as additional information concerning VE from real-world evidence and observational studies inside and outside of the US presented and discussed at the VRBPAC

meeting the previous Friday. Additionally, the FDA decision and construction of the authorized population for the booster dose took into account the feedback and recommendations that FDA received from the members of the VRBPAC.

Dr. Rochelle Walensky (CDC Director) made the following remarks: Good afternoon, everyone. Let me start with just a huge thank you to all of you. Over the past year, you have met 18 times, mostly focused on COVID-19 and recommendations for vaccination. This is a tremendous amount of work, a tremendous amount of data to review, and in truth, a tremendous service. So, thank you. You're tasked with difficult decisions, weighing the risks and benefits, extrapolating from sometimes a wealth and sometimes a paucity of data available, applying an equity lens to your actions, and doing all of this while reflecting on your own experiences on the pandemic frontline. What's been your North Star and what drives my own thinking every day is a commitment to follow the science to improve the health of as many Americans as possible. Like you, I'm approaching this decision with an interest in doing what's right for the public health and like you, I can't close my eyes to my experience as a clinician. Collectively, we want to do what is right for the millions of Americans over the age of 65 and in LTCF who are at high risk of severe complications of COVID-19. Like you, I am also thinking about the 25-year-old man with cystic fibrosis who may walk into our clinic nervous about his risk for one more hospitalization and also of the 35-year-old pregnant resident physician working in a Tennessee emergency room with a 1-year-old at home. It is in these complicated decisions where ACIP has always led, evaluating safety, equity, and access for those at risk. It is here where I am most grateful for your guidance.

I appreciate your meticulous review of the data available from CDC's own cohort studies, from FDA's review of Pfizer studies, and from public health partners and institutions around the world. These data are not perfect, yet collectively they form a picture for us and they are what we have in this moment to make a decision about the next stage in this pandemic. Thank you for leaning into this complexity, trying to fit the pieces together, and to come to the best conclusions. I've spoken with you previously and I hope some of you have heard some of my other public remarks. What you're doing today is an essential part of the process. A thorough evaluation of data by this full committee is how we maintain a system that maximizes safety, ensures effectiveness, lets data drive our decisions, and provides confidence to the American people. It is also how we strive to implement interventions that are equitable. Back in December before I was even here, you created a blueprint for the country and the world—one that makes sure those at greatest risk for disease whether because of their age, underlying conditions, or occupational exposure had access to the most effective intervention we have to prevent symptomatic disease, severe disease, illness, and death from COVID-19.

Now, you have an opportunity to again lead our public health response with recommendations on how we can best utilize the tools we have to protect those at greatest risk. As you continue your discussion today, I make three commitments to you. First, as we move into a new stage of this pandemic and our vaccination program, I will not lose sight of our collective goal to protect as many people as possible from COVID-19 infection, hospitalization, and death. That means that as we operationalize a plan to provide booster doses to Americans, we remain committed to continuing our robust efforts to vaccinate as many people as possible here in America and around the world, and to continue to support and disseminate the public health interventions that we know work best to prevent disease. I see these as complementary. One can simply not replace the others. Second, we all recognize that the science and data of COVID-19 are moving faster than any data we have ever seen before. While I recognize the tremendously heavy lift of the past year, we all know that the pace is unlikely to let up anytime soon. We will continue this dialogue. You will have more data to review and more recommendations to make, and I will be

here with you. Third, the discussion of the data is critical. My clinical experience reminds me that in my most challenging cases, I learn more and make better clinical decisions by discussing with my colleagues and by hearing their points of view from their own clinical experience and review of the medical literature that I might not have considered. My academic experience reminds me that in every research conference, I was enriched by hearing diverse perspectives. While we all plan to provide clear and aligned recommendations, the underlying discussion of diverse opinions and interpretations of the data only serves to strengthen our ultimate guidance.

You have a busy afternoon ahead of you, a lot of data to review, and a robust discussion to ensue. I will let you get to it and I will be watching and listening. Know that I am grateful for your efforts and that I so appreciate your expertise, your counsel, and your partnership.

Coronavirus Disease 2019 (COVID-19) Vaccines

Introduction

Dr. Matthew Daley (Chair, ACIP COVID Vaccines WG) indicated that during the September 23, 2021 COVID-19 Vaccines session, there would be presentations on the following topics:

- ❑ Public Comment
- ❑ Benefit/Risk Analysis of COVID-19 Vaccine Booster Doses
- ❑ EtR Framework
- ❑ Clinical Considerations
- ❑ Policy Options
- ❑ Votes on a BNT162b2 COVID-19 Vaccine Booster Dose

Public Comments

The floor was opened for public comment on September 23, 2021 at 12:20 PM ET. Given that many more individuals registered to make oral public comments than could be accommodated, 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–2021–0104. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Mr. Kermit Kubitz
Individual

Good afternoon. Thank you. My name is Kermit Kubitz. I look at things from the point of view of a scientifically trained graduate of Cal Tech a long time ago. I believe booster shots of mRNA vaccines are valuable, safe, and justified relying principally, for example, today on Gruber's September 22nd slides CC7 and CC8 showing a large increase in protection after the third dose within seven days and a further increase one month after the third, including against the Delta variant as shown on slide CC8. I previously testified in support of EUA of the Pfizer vaccine in December 2020 and subsequently received the Moderna vaccine at a San Francisco VA hospital facility in Ft. Miley in February 2020. I have two sisters in their late 80s who have been vaccinated. One, immunocompromised with rheumatoid arthritis (RA), received a booster dose with no significant adverse effects, so I also rely on that personal experience. My friend Chuck Wolf from Caltech (California Institute of Technology) pointed out to me that we need to plan for

the logistics of boosters with three priorities: 1) the unvaccinated, 2) children 6 to 11, and 3) boosters for other people. Approval of phased boosters for those over 65 and high risk, including from occupational exposure is not inconsistent with President Biden's goal of boosters for all Americans because HCW, the elderly, first line essential workers, and those who are at high risk easily exceed 150 million people, which will take time to roll out. So we should plan, and the CDC and FDA should plan for vaccination of HCW in groups, long-term care facilities in groups, and other rollouts. That is the most expeditious way of getting a boosters out there, including, for example, to my veteran friends at the veterans clinics across the country. I want to thank the ACIP for their work and suggest that it is important to also approve the Moderna mRNA vaccine as soon as possible so that the logistics of boosters can be easily accomplished for the maximum number of at risk people at the earliest possible date. Thank you very much.

Mr. Edward Nirenberg
Individual

Good afternoon, everyone. I have had the honor of addressing you before and I am grateful to be able to speak to you again. I want to thank every member of ACIP once more for their stalwart efforts in leading us through these trying times, but I would like to draw attention to how those who wish to keep a pandemic burning through the US are exploiting public comments. There are deceptive videos and papers featuring overconfident, undereducated, well-funded charlatans who use the opportunity of public comments to advance arguments that ACIP and VRBPAC meetings as those of authority. Some of the videos in particular use FDA or CDC logos to provide the similitude of authenticity. All use the docket number format of bringing comment submissions and provide the .gov URL as a way to convince their acolytes that their counterfactual presentations are bombshell revelations from the government rather than the sophomoric meanderings of desperate hucksters that they actually are. It is heartbreaking to me that in my outreach for vaccination I've yet to encounter someone who has refused vaccination on the basis of a true premise. With the remainder of my time, I'd like to address some of these. The misuse of VAERS reports is salient. VAERS is a critical component of our vaccine safety network and they do a solid job of flagging adverse events for investigation in more robust systems like the VSD. But evidently that giant disclaimer that one must assent to have read before accessing VAERS is falling on deaf ears. VAERS is primarily for hypothesis generation, early warnings, potential safety signals, and not a tool to investigate something in and of itself as reports may be incomplete, coincidental, or even reflect phenomena which never occurred. The "Incredible Hulk Vaccine Side Effect" is a famous example. On a less lighthearted note, a VAERS report was issued months ago describing the death of a 3-year-old girl in Virginia following an mRNA vaccine for COVID-19 after a prolonged hospitalization. However, the vaccination in question could not record because it was done before clinical trials were even initiated for age groups. Similarly, many coincidental events will occur. Follow any random group of 10 million Americans for 2 months and you will see 4,000 heart attacks; 4,000 strokes; 60 diagnoses of multiple sclerosis; 9,500 diagnoses of cancer; and 14,000 deaths. We have now vaccined 182.4 million Americans—a number that is still far too low. A great many coincidences will occur and seeking a causal link is best left to the experts. The spike protein is not toxic at concentrations in which is induced by vaccination. It would need to be roughly 10,000 to 100,000 times greater in concentration than has been found in the plasma of vaccinated people to start to reproduce the toxicities associated with it. Similarly, the mRNA vaccines are not associated with blood clots. The Johnson & Johnson vaccine is associated with what we are calling the disorder TTS at a frequency of about 7 per million doses and being greatest in the females younger age groups. There is no biological plausibility by which these vaccines can spontaneously exert or adverse effects months to years after vaccination. The lifetime of any vaccine component is a number measured in hours to days and the adverse effects should be

apparent by then. But out of an abundance of caution, EUA required immediate and 8 weeks of follow-up. Despite the first individuals receiving their vaccinations in March in the clinical trials, there are no credible reports of spontaneous adverse events outside that 8-week window, nor in anyone else, because this is a fantasy invented by anti-vaccine activist to scare people, because when the facts don't support your agenda and you're an amoral narcissist, you lie. Thank you for this time. Please be safe. Please get vaccinated.

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

Thank you so much. Good afternoon. I'm Erica DeWald, Director of Strategic Communications and Partnerships of Vaccinate Your Family (VYF). Thank you for the opportunity to address this committee today. Vaccinate Your Family watches each of your meetings with deep interest as it is our organization's policy to follow ACIP recommendations. They're the basis for our communications to both the public and our immunization partners. Throughout the development of the COVID-19 vaccines, the ACIP and FDA's VRBPAC members have remained true to the science. That's no small feat given the many pressures to move quickly and exercise every possible tool to end this devastating pandemic. Once again as pressure and confusion mount about the need for a booster dose of COVID vaccine, the VRBPAC and ACIP have proven the independence to science by not getting ahead of the data available to us. In order to make an informed decision about boosters, however, we need to understand the goals of a booster program in the US. We appreciate that Dr. Walensky, the CDC, and this committee are focused on that very issue. Setting a goal can help us better understand the role of a booster program, both for Pfizer and new future recommendations for Moderna or Janssen vaccines. It can also help us better design studies to identify whether our vaccination programs are moving us toward that goal. Additionally, clearly defined goals will help organizations, institutions, and health care providers combat misinformation around COVID-19 vaccines and all vaccines for that matter. We also need to encourage politicians to support, not direct, public health. When the Administration announced boosters, the data to support or reject a booster was not yet publicly available and neither FDA nor CDC had even scheduled meetings of their independent advisory committees. That led to a lot of confusion and some communities' mistrust. It further hurt our efforts to promote science-based public health recommendations, including vaccination. Confusion among the public will continue with announcements from political leaders perceived as independent bodies of the FDA and CDC. It also makes our work communicating clearly about the safety and necessity of vaccines even more difficult because it makes room for division and politicization of a critical public health issue. Now, to avert this confusion, we need ACIP to provide us clear direction around the definitions of those who are considered high risk and high occupational risk. We're going to need very clear guidelines on who should receive a booster to prevent further confusion among the public and ensure an efficient, timely rollout of these boosters. It's on ACIP's recommendations to uphold rigorous processes and communicate the science clearly. This will ensure that the public continues to have faith in the overall vaccination program. Thank you for your careful deliberations and transparency. I appreciate your time.

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

My name is Dorit Reiss. I'm a Professor of Law at the University of California, Hastings College of the Law and a vaccine advocate. First, thank you for your thorough, transparent, and careful work on vaccines generally and COVID-19 vaccines specifically. I want to echo what my colleague Erica said that sticking to the science is not an easy thing these days. Your presentations provide substantial insight, a lot of information, and I know I always learn a lot as a lay person—even if most days like today you insist on having them at unreasonable East Coast times. I want to reiterate the point made to you by my friend and colleague Dr. Eve Switzer's about 2 years ago. It's when the science is uncertain that we need your guidance even more when the evidence can go either way. We are hearing experts disagree on the booster question, but a decision is needed one way or the other. I appreciate your willingness to face the hard decision and make recommendations. I hope that you consider equity at home and abroad when you do that and not just effectiveness. I want to follow up both on yesterday's pregnancy data and on Erica's point about the need for a clear definition by asking you to consider whether pregnant women should be considered high risk when you make your booster recommendation, even if they don't really fit clearly into other categories. Two suggestions that are not about boosters: 1) If you're looking for a place to increase transparency, the online advocates could use a more comprehensive discussion on VAERS on the back end. What happens to reports after they are submitted? How are they investigated? How do you avoid duplicates? Because that comes up quite a bit in questions from the vaccine-hesitant; and 2) I've said this before, transparency does not require you to provide a forum for all comments. I know that you get a lot of really helpful comments and I've read many of them, for example, Dr. Plotkin's comments last week. I know many of the comments have been very valuable, but we also know that the opportunity to comment has been systematically misused by anti-vaccine advocates and activists to create propaganda videos that they use to promote misinformation under the guise of comments to the CDC. Just this week, a comment to your sister committee VRBPAC misrepresenting COVID-19 vaccine as having high risk has been shared as, "the FDA said." We know comments here were used same way. You're not increasing transparency by allowing that. If you want to increase transparency, why not an alternative? You can, for example, set aside half an hour to address the major issues raised in the written comments and potentially also correct major errors like the federal government does in rulemaking. That will not only allow you to address comments, it will show that you've heard the comments and give your members an opportunity to consider the issues. Thank you.

Kevin Kavanagh, MD, MS
Health Watch USA

Thank you very much. Last Friday's meeting to the FDA's Vaccine and Related Biological Products Advisory Committee regarding boosters for the Pfizer-BioNTech vaccine resulted in recommending authorization of boosters for those 65 years of age and older along with those individuals who are at high risk for severe COVID-19. After the formal vote, a poll was taken and the committee unanimously agreed that this recommendation should be extended to HCW and those who are high risk of occupational exposure to SARS-CoV-2. Thus, initially the committee focused on vaccinated individuals who are biologically at high risk of developing severe COVID-19, but finally also recommended boosters for those at high risk of SARS-CoV-2 exposure. However, the degree of exposure is like being pregnant—you either are exposed or you are not. During a raging pandemic, action is needed now. We do not have the luxury of waiting for the

results of randomized controlled trials. I would like to encourage the committee to broaden the FDA's recommendations. The following should be considered. First, at least one FDA committee member indicated that the main goal was to prevent severe disease which is defined as "hospitalizations or death." However, this ignores the lasting and debilitating effects of Long COVID which can afflict 10% to 30% of those with even mild to moderate infections and pose a significant risk to our population. Second, Dr. Alroy-Preis, Israel's Director of Public Health Services, testified that the Pfizer booster created a 10-fold increase in protection in 40 to 60 year olds. With the disease profile of Delta markedly shifting to younger age groups, providing boosters to a wider range of individuals would be good public health policy. Finally, the United States has administered over 386 million doses of vaccines with an extraordinarily good safety record. The FDA committee had concerns regarding myocarditis in the young. However, this is a rare event occurring in approximately 1 in 5,000 young individuals. As stated by Dr. Alroy-Preis, 95% of these cases were not severe. There is a much higher incidence of myocarditis in those who contract COVID-19. In view of the above, I would like to recommend reconsideration of offering Pfizer boosters to all who are 16 years of age or older or at least offering boosters to those who are 30 years of age and older, plus all individuals who are at risk of SARS-CoV-2 exposure. As a side note, we encourage the flu vaccine to be taken by all, not just those at high risk of severe disease or disease acquisition. We need to be consistent with our messaging. Thank you.

Laura Burns
Transplant Vaccine Study Group

Hello, my name is Laura Burns. I'm a double lung transplant recipient and a participant in all four of the Johns Hopkins studies on vaccine efficacy from first dose to fourth. I'm also a member of the Transplant Vaccine Study Committee Group originally formed by study participants, now with over 700 members. On behalf of myself and the group, I want to thank you from the bottom of my heart for authorizing additional doses last August. Indeed, many of us have been blessed with a dramatic response. Sadly, however, many remain with little or no response and all are still wary. Dr. Kotton spoke eloquently to our situation yesterday. If the committee should decide, as was suggested, that the goal of boosters is to prevent hospitalization and death, not infection, please remember that of the fully vaccinated, we are the ones who most likely would be hospitalized and die. Our families are scared to death that they could come home with a mild case and that so-called "mild case" will put us in the hospital. According to the FDA's press release yesterday, those covered under today's EUA are HCW, teachers, day care staff, grocery workers, among others. I'd like to address the term "among others" and hope you will give it wide latitude. Our families, friends, and colleagues are asked to cocoon us—to protect us by being fully vaccinated. With their immunity waning, that means boosters for them not just additional doses for us. One of our members writes, "Our family should get boosters. It's critical to us that they don't bring a breakthrough case into our homes." Another, my husband, is not quite 65 but lives with me, an immunocompromised person. Sadly, his secretary refuses to get vaccinated. Will he be able to access a booster? Yet another, if a person feels that they need a booster to provide more protection for someone vulnerable to their household, then they should be able to do so without them having to go through all kinds of hoops. I agree and I urge you to implement this policy through self-attestation as you did for the immunocompromised. I also hope there will be a speedy way to get a Moderna booster, especially for the elderly. One way would be to simply include the 65 and over among the immunocompromised. The evidence you saw yesterday certainly supports that. Then they could qualify under the current EUAs for both Moderna and Pfizer and get their boosters right away. One last word. Please get some help soon to the immunocompromised who got the J&J. They

have been left stranded. Thank you so much for all you do and for keeping us in mind during your deliberations. Thank you.

Ms. Katherine Falk
Parent and Vaccine Advocate

Hello, once more. I'm having a sense of déjà vu. My name is Katherine Falk and as always, I'm a parent and vaccine advocate from Oakland, California. Thank the committee again for all your hard work. I hope you'll be able to continue independently assessing the data and making decisions free of pressure. In a way, it's a more challenging time than it was before. In the last Administration, we had someone so hostile to public health. But now we have a President who is in some ways a little too enthusiastic. I would happily get a booster if that ends up being the best course of action, but as a layperson member of the public, I really look to the experts to look at what the data show, not just what I wish it would show or fear that it shows. In deciding on who should get boosters, I hope the committee will also keep equity in mind so immunity doesn't become an even greater divide between haves and the have nots. I am glad to see you look specifically at how boosters might impact people in nursing homes. I hope there will also be efforts to look at boosters for other vulnerable segments of the population. Thank you.

Harald Schmidt, PhD
Assistant Professor, Medical Ethics and Health Policy
Perelman School of Medicine, University of Pennsylvania

Next. We'll move on to Harold Schmidt. My name is Harald Schmidt and I'm an Assistant Professor of Medical Ethics and Health Policy at the University of Pennsylvania. I'd like to congratulate the ACIP chairs, members, and especially also staff for once more laying out with such clarity the hard tradeoffs we are facing. I'm also grateful to have the opportunity to share two recommendations that I believe matter for allocating boosters in ways that reduces rather than further increases inequity. Dr. Walensky rightly emphasized the importance of equity earlier. First, we should allocate boosters by universalizing the use of disadvantage indices such as the CDC Social Vulnerability Index. Secondly and directly related, we should recognize that the vast majority of people eligible for boosters are likely trusted vaccine ambassadors and draw on them and the booster rollout to increase initial vaccinations in disadvantaged areas. At ACIP's last meeting, several members rightly recognized that ethically, the case for boosters can be near impossible to justify given the global vaccine access disparities. I emphatically agree with the sentiment and there is a clear moral imperative to keep up the pressure for global access and to learn the lessons for the next pandemic. That said, global allocation is not within the ACIP's agreements. Unfortunately, not recommending boosters in the US does not translate into vaccines where they are needed more. Still, ACIP's recommendations do intersect with global and national equity and here is how. On April 19th when the entire US became vaccine-eligible, the difference between fully vaccinated people in most of these disadvantaged groups using the CDC's Social Vulnerability Index was 4.5%. Currently, it is twice that rate and stands at 9%. Now in the worst case, these inequities are exacerbated if the US's most privileged people quickly snap up boosters as they are made available while the more disadvantaged people fall further behind—whether we are talking about the most disadvantaged among the 65 year olds or among high-risk groups since neither of these groups is homogeneous. The same applies once eligibility is widened to other groups. Alternatively, boosters can be used to reduce inequities and help achieve a less unfortunate scenario in terms of global disparities. We can still close the vaccine equity gap using the very metric that shows the disparity. Colleagues and I showed in *Nature Medicine* earlier this year that in the initial vaccine rollout, the majority of states use disadvantage indices in different ways, including increasing amounts of vaccines for

more disadvantaged areas, planning vaccination site locations, and targeted outreach and partnership. It would be useful for ACIP to recommend that all jurisdictions now adopt disadvantaged indices to promote equity. Plus, we now have tools such as Ariadne Labs' free vaccine equity planner that can identify vaccine deserts and identify facilities in more disadvantaged areas that could potentially serve as vaccination sites. Access is still an issue. Finally, everyone who is eligible for vaccine is a potentially trusted ambassador. My expertise is not in snappy slogans, but a campaign on the title such as, Get your booster and bring an unvaccinated friend or something better should be explored as a priority. Passing up the opportunity to increase first and second doses in rolling out boosters will not help equity. It is important to see the booster opportunity to close the gap in vaccination access across social disadvantage, especially also because it . . . [time expired].

Ms. Lynda Dee, JD
AIDS Action Baltimore

Hi. I've been with AIDS Action for 34 years and have learned the importance of evidence-based medicine the hard way. I've been a community rep on many FDA CDER antiviral advisory committee hearings, provided written comments for both VRBPAC and ACIP COVID-19 meetings, and oral comments for all but one FDA COVID VRBPAC hearing. I've been very impressed with ACIP's deliberations and decision-making process. The committee drills down into many real-world issues and provides answers to extremely important pragmatic questions using a very organized process. That being said, we must acknowledge that the country is trapped in a COVID-19 nightmare. Americans are dazed and confused by vast amounts of data, as well as mis- and dis-information. While it is not ACIP's role to create policy, your decisions definitely promote policy. I'm here to ask you to help prevent severe COVID and death, transmission, vaccine hesitancy, booster confusion, and possible vaccine administration chaos. ACIP can help promote sound public health policies as well as maintain scientific integrity. You can accomplish this by recommending that the CDC's current list of people with certain medical conditions who are more likely to experience COVID be used as the eligibility criteria for third doses of 162b2. This will provide the states with a familiar framework for booster eligibility, as well as more clarity for healthcare providers and a better understanding of complicated information from their communities. We need as much uniformity as possible so as not to further confuse the states and more importantly, the public. I would be remiss if I did not mention that people with HIV would have been entirely excluded, or almost entirely excluded, from COVID-19 vaccine access without the actions of HIV activists. People with HIV were initially excluded from the Pfizer and Moderna Phase 3 trials. They were not included in the CDC's vaccination prioritization category until a few weeks before vaccines were available to the general public. Only a limited portion of people with HIV are included in the current immunocompromised list for third vaccinations. Inclusion of people with HIV and their advocates in ACIP or public comment sessions has also been minimal. I urge you to recommend that people with HIV and the many others listed in the current CDC medical conditions criteria for people who are more likely to experience severe COVID be included as one of your eligibility recommendations for third doses of 162b2. I only have time to address one eligibility recommendation. All of the recommendations based on the FDA EUA are provided in my written comments. I do support broad eligibility criteria for all FDA indications and for people of color based on many of the reasons that have already been discussed here today. I'd like to thank you for your dedication and commitment and for the opportunity to comment.

Mr. Brian Wilkins
Founder, COVID Legal USA
Editor-in-Chief, The COVID Blog
Journalist

I am Brian Wilkins, Founder of COVID Legal USA, Editor-in-Chief of The COVID Blog, and a longtime journalist. Everything I'm about to say can be verified and further researched that thecovidblog.com. Drene Keyes age 58 died 3 hours after her first Pfizer mRNA injection January 30, 2021 Gloucester, Virginia. Sara Stickles age 28 died 5 days after her second Pfizer nRNA injection February 11, 2021 Beloit, Wisconsin. Benjamin Goodman aged 32 died 24 hours after the Johnson & Johnson viral vector DNA injection March 14, 2021 New York, City. Cameron Thomas age 16 developed blood clots and died 11 days after her first Pfizer mRNA injection March 30, 2021 Waunakee, Wisconsin. John Francis Foley age 21 died 24 hours after the Johnson & Johnson viral vector DNA injection April 1, 2021 Cincinnati, Ohio. Griselda Flores age 61 died 48 hours after her second Moderna mRNA injection May 3, 2021 Orange, California. Jacob Clynick age 13 developed myocarditis and died 3 days after his second Pfizer mRNA injection June 16, 2021 Zilwaukee, Wisconsin. James Cooper Sawyer age 77 died 8 days after his third Pfizer mRNA booster August 28, 2021 Cookeville, Tennessee. The list goes on and on and this happens in every country across the globe. The CDC chalks all of these deaths up as pure coincidence. The CDC's own database, the Vaccine Adverse Event Reporting System, has recorded 14,506 post-injection deaths in 2021 alone. But now, the CDC says their own databases are unreliable. The Nobel Prize-winning drug Ivermectin is now dismissed as "horse dewormer" by mainstream doctors and media, but there are more than 66 peer-reviewed studies proving that Ivermectin is a highly effective treatment and prophylaxis against COVID-19. If you truly cared about public health, you would recommend Ivermectin for treatment and prevention protocols and stop the propaganda against this drug. But the CDC receives hundreds of millions of dollars from Pfizer, Baer, Merck, and other pharmaceutical companies so you cannot admit the truth and ruin your partners' Emergency Use Authorizations. Further, the FDA receives 45% of its funding from user fees, meaning that these pharmaceutical companies pay the FDA while seeking approval of their drugs and medical devices. The conflicts of interest are blatant and frankly criminal pursuant to Title 18 of US Code Section 208. It's indisputable fact on statistics from the CDC and Johns Hopkins University that a positive correlation exists between vaccination rates and COVID cases. As the previous rises, the latter rises. In sum, I pray that there's enough humanity and critical thinking left on Earth for all involved in this global genocide to face Nuremberg-type trials. Again, visit thecovidblog.com for more information on everything I just said. Thank you very much for giving me the opportunity to speak.

Ms. Sarah Barry
Pro-Vaccine Activist

My name is Sarah Barry. I am a pro-vaccine activist from Ohio, although some of you might know me better by my online handle, 42believer. Thank you all for continuing to dedicate your time and energy on this critical issue. I'm grateful to share my perspective with like-minded people while simultaneously drawing the ire of the exact same anti-vaccine activists who inspired me to start requesting a spot for public comment in the first place. In my past public comments, I've shared with you all the lengths anti-vax lobbyists went to in an attempt to censor me. Today, I'd like to share with you just how strong a hold anti-vax lobbyists are having on the legislative process in Ohio and update you on what the future holds for anti-vaccine legislation in the Buckeye State. First, HB248. HB248 is a bill that would make it illegal for anybody to require any vaccine—not just a COVID vaccine. A FOIA request revealed that not only would

the language of HB248 created with the help of anti-vaxxers, but the amendments made to the bill were also made because of anti-vaxxers. Further FOIA requests of text messages combined with some Facebook posts proved to me that not only was the language of the bill written by anti-vaxxer lobbyists, but they were significantly involved in the hearing process for HP248. On May 21st, Representative Jennifer Gross texted the Chairman of the Health Committee, Scott Lipps, referencing the anti-vaxxer lobbyists. She claimed that they are, "picking and choosing and promising witnesses without discussing it with me" and also that they "decided the schedule." After reviewing Facebook comments, a member of that same lobbyist group who attended a meeting with Gross and Lipps said that the changes to testimony protocol were discussed in that meeting. Every time I went to submit my own testimony for HB248, I was denied the opportunity to give in-person testimony. Although I don't have direct evidence of them using this new process to censor me yet again, I'm smart enough to read between the lines. Fortunately, HB 248 is dead thanks to Sherri Tenpenny turning Ohio into a national laughingstock with her unhinged testimony and the subsequent infighting amongst the anti-vaccine lobbyists. Unfortunately, anti-vax sentiments are still percolating in the Ohio legislature. Multiple other bills targeting vaccine requirements have been introduced and as I speak, there are plans by the Republican leadership to introduce their own version of such a bill. I have even heard that they plan to bring this new bill to a floor vote "as early as next week," which would certainly not give me or anybody else the requisite time to speak in opposition. Since I feel I have no other option, this is my public plea to Representative Bob Cupp, Representative Tim Ginter, Representative Bill Seitz, Representative Rick Carfagna, Representative Don Jones, and Representatives Cindy Abrams. I was born and raised in Ohio and I've watched with dismay as anti-vax lobbyists plant misinformation in the minds of your colleagues. I urge you to reject anti-vax legislation that goes against public health and that includes any bill that interferes with employers' right to keep the workers and customers safe. I thank ACIP once again and I urge all Americans to pay attention to their state legislatures, lest they become as anti-vaccine as Ohio has.

COVID-19 Vaccine Booster Doses: Benefit-Risk Discussion

Dr. Megan Wallace (CDC/NCIRD) presented on the benefits and risks of the Pfizer-BioNTech vaccine booster doses. To assess the benefit-risk balance of a booster dose, a direct estimation approach was used similar to that presented to ACIP in previous benefit-risk discussions. Benefits were calculated per million doses of Pfizer-BioNTech COVID-19 vaccine booster. The analysis was stratified by 4 age groups: 18-29 years, 30-49 years, 50-64 years, and ≥65 years. A 180 day time horizon was used. Calculations for the benefits of vaccination were based on age-specific case incidence data from CDC[48] and hospitalization data from COVID-NET.[49] For VE for the primary series, age-specific pre-booster EV estimates were averaged from 4 platforms. Given that VE after a booster dose is unknown, post-booster VE was assumed to be 95% for hospitalization and 90% for infection for this analysis. For the point estimates for the current age-specific VE for hospitalization, estimates were averaged from 4 platforms: COVID-NET[50], Scobie et al.[51], VISION[52], and IVY Network[53] for the base case. For harms, the analysis focused on the risk of myocarditis following a booster dose. While it is acknowledged that there may be other risks such as anaphylaxis, they were not considered in this analysis. Like benefits, harms were calculated per 1 million booster doses. Because myocarditis incidence following a

[48] https://covid.cdc.gov/covid-data-tracker/#trends_dailycases
[49] https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html
[50] https://www.medrxiv.org/content/10.1101/2021.08.27.21262356v1
[51] https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm?s_cid=mm7037e1_w
[52] https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e2.htm. Using Pfizer specific estimate.
[53] https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm

third dose is unknown, input was based on VAERS data post-Dose 2. In terms of reporting rates of myocarditis following Pfizer-BioNTech COVID-19 vaccination per million doses administered by age and dose number in the 7-day risk period following vaccination, the incidence of myocarditis was higher among young males following Dose 2.[54] Sensitivity analyses were performed to account for the large amount of uncertainty in the model input. Estimates were varied for how much a booster dose would increase VE and for current VE and modeled increased VE waning by decreasing the current VE estimate by 5% intervals. Finally, variable risk was modeled by considering myocarditis incidence seen after Dose 2 and 2 times that seen after Dose 2.

The framework by which the booster dose benefit-risk analysis was approached was first to evaluate the benefits versus the risks of the COVID-19 booster dose. Then the differential benefits of booster doses were analyzed by age groups. Finally, the differential benefits of booster doses were compared with the primary series. This presentation followed the same sequence. In the base case scenario for benefits and risks after Pfizer-BioNTech COVID-19 booster dose, the VE for hospitalizations averaged from the 4 platforms was used. It was assumed that a boost would bring VE to 95% and that the myocarditis risk would be equivalent to that seen after Dose 2. For all age groups, more COVID-19 hospitalizations would be prevented than myocarditis cases expected. However, this is particularly true for those aged 65 years and older. Building upon the base case, it was next assumed that myocarditis risk was double that seen after the second dose. Assuming this higher incidence of myocarditis, more hospitalizations were still prevented than myocarditis cases expected for each age group. However, it is important to note that myocarditis risk was not evenly distributed by sex after Dose 2. When the risk distribution seen after Dose 2 is applied, 4 cases of myocarditis per million doses would be expected among females aged 18-29 years and 48 per million doses among males.

The scenario to further explore the benefits and risks after Pfizer-BioNTech COVID-19 boosters for persons aged 18-29 years with varying pre-booster VE by sex, hypotheticals were used and pre-booster VE was varied for hospitalization. COVID-19 hospitalization rates were stratified by sex and it was assumed that the booster dose would bring VE to 95%. The myocarditis risk was assumed to be equivalent to the risk seen after Dose 2. To acknowledge the variability of myocarditis risk by age, a range of risks was presented which showed a risk in 25-29 year olds on the low end and an 18-24 year old risk seen on the high end. When taking sex-specific hospitalization rates and myocarditis risk into account, more COVID-19 hospitalizations were expected in cases of myocarditis for all but the highest starting VE. A limitation of this model is that a constant incident was assumed over the 180 day time horizon. To address this, another scenario was run in which incidence rates were 1/3 of the current rate and were similar to the rate seen in June and July of this year. In the scenario of lower incidence, a lower pre-booster VE is needed for the benefits of a booster dose to clearly outweigh the risks in males aged 18 to 29 years.

COVID-19 infection prevented is another potential benefit of COVID-19 boosters. In this analysis, potential cases prevented were included by assuming a current VE for infections of around 78% from Scobie et all.[55] and a boosted VE against infection of 90%. When considering infections as the benefit of interest, giving a million booster doses could prevent between 7,500 to 10,000 infections over the next 6 months, with the most infections prevented among those aged less than 50 years.

[54] Data as of August 18, 2021: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/03-COVID-Su-508.pdf
[55] https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm?s_cid=mm7037e1_w

Looking more explicitly at the differential benefits and risks of booster doses in persons aged 18-29 years compared with those aged 65 years and older, the analyses continued to build on the base case for pre-booster VE against hospitalization. While the benefits outweigh the risks for most potential post-booster VE estimates, the benefits obtained by those aged 65 and older were an order of magnitude larger than benefits obtained by those aged 18 to 29 years. Another way to think about this is the number needed to vaccinate (NNV). The NNV with a booster dose to prevent 1 hospitalization over 6 months in those aged 65 years would be 481 people. Prevention of 1 hospitalization in persons aged 18-29 years would require vaccinating 8,738 people. Prevent 1 hospitalization, 19 times as many 18-29 year olds would need to be vaccinated compared to those aged 65 and older. As mentioned previously, the scenario is based off of current incidents, which is high. As incidents decreases, the NNV will increase. The NNV is substantially lower and more evenly distributed by age for infections compared to hospitalization.

In the scenario looking at the relative benefits of booster doses versus primary series vaccination with Pfizer-BioNTech COVID-19 vaccine, the base case VE for hospitalization was used that was averaged from the 4 platforms and the VE for infections estimated from Scobie et al. It was assumed that a booster dose would bring VE to 95% for hospitalization and 90% for infection. To calculate hospitalizations prevented by a primary series, it was assumed that 1 million doses were used to provide 500,000 primary series and that the primary series provides 95% VE for hospitalization and 90% for infection. The NNV was substantially lower for all age groups for the primary series as compared to the booster dose. For those aged 65 and older, 10 times as many people would need to be vaccinated with a booster dose to prevent 1 hospitalization compared with primary series vaccination. For persons aged 18-29 years of age, the NNV was 22 times as high for booster compared with the primary series vaccinations.

This analysis has several important limitations. The benefit-risk analyses are very sensitive to pre-booster VE estimates and effectiveness estimates for Delta variants are limited. The available age-specific US data are based on month of COVID-19, not on duration since vaccination. The preferred pre-booster data would measure effectiveness by duration since second dose. Post-booster effectiveness and post-booster myocarditis risks are unknown and are based on available evidence from the primary series. Early data have corroborated these estimates. Finally, the model assumes static incidence and VE over a 6-month period.

In summary, this is a direct benefit-risk assessment for Pfizer-BioNTech COVID-19 vaccine booster and myocarditis, which considered individual benefits of vaccination versus individual risks. Using current VE estimates, the benefit-risk balance is most favorable for adults 65 years of age and older and shows smaller benefit for the population less than 65 years of age. The benefits increase in scenarios with lower VE for prevention of hospitalization in cases, which could be seen with those at higher risk of severe disease. The risk of myocarditis after a third dose of mRNA vaccine may vary by age and sex. The highest rates of myocarditis after the second dose were seen in younger males. This presentation focused on the benefits and risks of the Pfizer-BioNTech COVID-19 booster dose by age. For benefits, the focus was on the prevention of COVID-19 hospitalizations in cases, but there may be other additional benefits such as prevention of deaths and possible prevention of transmission. For risks, the focus was on the risk of myocarditis following vaccination. However, there may be other risks such as other rare events after mRNA vaccines and short-term reactogenicity.

Discussion Points

Dr. Maldonado (AAP) noted that in California it is known that among Latinos, 39% of deaths occurred among those under 65 years of age as compared to 15% among White individuals and 31% among Black individuals. In terms of the data on race and ethnicity, there may be a disproportionate number of deaths and potentially hospitalizations for under-represented minority groups under 65 years of age. With that in mind, she wondered whether the modeling team was able to parse the data out to look at race and ethnicity.

Dr. Wallace indicated that while this was not covered in this analysis, it would be covered more explicitly in the upcoming EtR presentation.

Regarding the comment at the end of the presentation that the risk of transmission was not considered in the modeling, Dr. Gluckman (AHIP) recalled that in the approvals pertaining to Prevnar dosing in the elderly, it was eventually concluded that the biggest impact had to do with immunization using that vaccine in younger people. He asked whether there would be a way to think about the extrapolation about the benefits in people at higher risk by reducing the amount of circulating virus and whether that is important.

Dr. Wallace agreed that while this is an important observation, at this point there are no data on transmission or how booster may impact transmission.

EtR Framework: Booster Doses of Pfizer-BioNTech COVID-19 Vaccine

Dr. Sara Oliver (CDC/NCIRD) presented the EtR Framework for Booster Doses of Pfizer-BioNTech COVID-19 Vaccine. She reminded everyone that the EtR Framework is the structure to describe information considered before ACIP makes vaccine recommendations. This provides transparency around the impact of additional factors on deliberations when considering a recommendation. Because questions around the vaccine policy for booster doses are complex, some adaptations were required of the standard EtR recommendation framework. The standard EtR domains include: Public Health Problem, Benefits and Harms, Values, Acceptability, Feasibility, Resource Use, and Equity.

This presentation walked through the through the public health problem to evaluate whether booster doses are needed, the balance of benefits and harms for booster doses by age, values and acceptability in terms of whether people want a booster dose, feasibility in terms of how booster doses would be implemented, resource use with regard to the costs associated with booster doses, and the equity considerations for booster doses. FDA issued a regulatory allowance the previous evening, for which ACIP would now consider recommendations for use. This presentation focused on who should be recommended to receive a Pfizer-BioNTech COVID-19 booster dose under the current EUA based on the balance of benefits and risks.

Turning to the public health problem regarding whether booster doses of COVID-19 vaccines are needed, the US is currently experiencing a large surge second only to the one seen in the past winter. The recent surge may have peaked, especially in some states that experienced their Delta surgery earlier.[56] Over 182 million people in the US are fully vaccinated with a COVID-19 vaccine primary series.[57] Comparing COVID-19-associated hospitalization rates among the vaccinated compared to the unvaccinated population, among adults 65 years of age

[56] https://covid.cdc.gov/covid-data-tracker/#trends_dailycases; Accessed September 22, 2021
[57] https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total; Accessed September 22, 2021

and over, the incidence was 13 times higher in unvaccinated. For those less than 65 years of age, the hospitalization rates are 22 to 23 times higher in unvaccinated individuals.[58] In terms of comparing incidence rates for COVID-19 hospitalizations in the US with severe disease in Israel among vaccinated people, July 2021 was when overall case rates were beginning to increase in both countries. The rates for Israel were approximately 2 to 5 times the rate for the US.[59]

Regarding whether VE rates are waning by age in the US, some decreases have been seen in VE estimates for the last 1 to 2 months. This could be due to both waning immunity due to time since primary series and the impact of the Delta variant. In late May, Delta was around 7% of sequenced isolates. By mid-July, it was 94% a sequenced isolates. To summarize VE by age in the US over time, significant declines have occurred in VE against infection in individuals ≥65 years of age for mRNA products in the Delta period. Smaller declines were observed in VE against hospitalization in individuals ≥65 years of age, but were more substantial than in younger populations. Among adults <65 years of age, vaccines remain effective in preventing hospitalization and severe disease. However, the vaccines may be less effective in preventing infection or symptomatic illness due to waning over time and the Delta variant.[60]

In terms of whether VE is waning for those with underlying medical conditions, there is not a significant difference among VE over time for medical conditions that had enough persons able to provide an estimate.[61] Another study evaluated VE against infections among US veterans with underlying medical conditions in the pre-Delta time period. At that time, VE was high for both those with a low CCI and a higher CCI.[62] To summarize VE by underlying medical condition, there are currently limited data to evaluate VE by a variety of underlying medical conditions. The current data show limited waning in those with at least one underlying medical condition. However, it is important to note that these estimates exclude immunocompromised individuals. In addition, the estimates may not represent effectiveness across all underlying medical conditions. VE studies cannot produce estimates for rare and possibly more severe underlying condition. There is a spectrum of underlying medical conditions with a range of severity, and many have a varying impact in effectiveness and are not fully represented in the estimation here.

[58] Havers et al. https://medrxiv.org/cgi/content/short/2021.08.27.21262356v1. COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years - COVID-NET, 13 states, January 1-July 24, 2021 0 20 40 60 80 100 120 Rate per 100,000 population Week ending 0 20 40 60 80 100 120 140 160 180 200 Rate per 100,000 population Week ending Vaccinated vs. Unvaccinated † 23x higher 22x higher 13x higher 1

[59] Scobie HM, Johnson AG, Suthar AB, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status — 13 U.S. Jurisdictions, April 4–July 17, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1284–1290. Goldberg et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1.full-text

[60] Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021; Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant; National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morbidity and Mortality Weekly Report. 2021 2021;70.; Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021; Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv 2021.08.06.21261707; Keehner J, Horton LE, Binkin NJ et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. NEJM, September 1, 2021. DOI: 10.1056/NEJMc2112981

[61] CDC unpublished, IVY Network

[62] Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 Vaccine Effectiveness in a High-Risk National Population in a Real World Setting. Ann Intern Med. 2021;M21-1577.

Regarding whether VE is waning for those with high-risk occupations, VE against infection has waned in recent months among HCP, first responders, and frontline workers.[63] To summarize VE by high-risk occupation, effectiveness among healthcare and other frontline essential workers is similar to estimates for the general population for the same age where declines have been seen against infection recently. Severe disease among vaccinated essential workers is rare. The previous data demonstrated that VE is waning against infection in this population. It is known that the impact of a lower VE against infection may be different among healthcare and other frontline essential workers. It also is known that many in this group were prioritized for early doses of COVID vaccine and will have had longer duration since their primary series.

With regard to how these data vary by vaccine, data show that VE varies by initial vaccine type. Protection against hospitalization for mRNA vaccines is high, though it is known that this may vary somewhat by age. Protection against infection is lower for all vaccine types.

To summarize for the public health problem, hospitalization rates are 10 to 22 times higher in unvaccinated compared to vaccinated adults. Over 182 million people are fully vaccinated in the US. Although COVID-19 continues to be a public health problem, among persons who have received a primary series, data support continued protection against hospitalization and death. Long-term outcomes among infections after vaccination must continue to be followed.

Turning to the balance of benefits and harms for booster doses by age, the first question regards whether booster doses of the COVID-19 vaccine safe and immunogenic, which is the GRADE aspect of the EtR. In terms of the PICO question for GRADE, the population included persons 18 years of age and over who completed a primary series at least 6 months prior. The intervention was a single dose of the Pfizer vaccine and the comparison was no booster dose. The outcomes included: Symptomatic laboratory-confirmed COVID-19, hospitalization due to COVID-19, death due to COVID-19, transmission of SARS-CoV-2 infection, SAEs, and reactogenicity. In terms of evidence retrieval, 2 WHO records were identified from International Vaccine Access Center (IVAC) systematic review of COVID-19 vaccine literature and 2 were identified through other sources. All 4 were assessed for eligibility and all 4 were included in the evidence synthesis.

There were 2 available observational studies for booster doses, both from Israel.[64] Israel began administering a third dose for immunocompromised individuals on July 12, 2021 and for all residents 60 and over on August 1, 2021. Both studies used large data systems and included individuals who had received their second dose at least 5 months prior to booster administration. For both studies, the control population were individual who had completed a 2-dose series—not the unvaccinated population. Both studies have limited follow-up periods, with a maximum of 21 days for documented infection and 16 days for severe disease. For GRADE purposes, pooled estimates were not generated because the 2 studies had overlapping study populations. The most representative study, Bar-On et al., was used for GRADE assessments. One study was peer-reviewed and one was a preprint. Both studies were conducted in Israel, which required a minimum interval of 5 months following the second dose for booster dose eligibility. The first study by Bar-On et al was used for GRADE because it included nationwide

[63] Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December; 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021; Keehner J, Horton LE, Binkin NJ et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. NEJM, September 1, 2021. DOI: 10.1056/NEJMc2112981

[64] Bar-On et al. BNT162b2 vaccine booster dose protection: A nationwide study from Israel. medRxiv preprint Autust 31, 2021. doi: ttps://doi.org/10.1101/2021.08.27.21262679; and Patalon et al. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. MedRxiv, August 31, 2021

data. The VE comparing booster dose to a 2-dose series was 91%, with a 95% confidence interval of 90.4% to 91.9%.

The GRADE evidence types for the outcome symptomatic lab-confirmed COVID started at 1. Very serious risk of bias was present. The Phase 3 trial among adults 18-55 years had 306 participants and the Phase 1 trial among adults 65-85 years had 12 participants. Although a subset of participants were randomized to a booster dose or other investigational vaccine, none was randomized to placebo. The only data available for GRADE were from a pre/post booster analysis and not according to randomization. Very serious indirectness was also noted because VE was inferred from immunobridging to the same participants after Dose 2 and because the formal immunobridging analysis was only performed on participants ages 18-55 years, which may not be representative of older participants. The ratio of GMTs of neutralizing antibodies at 1 month after booster dose was noninferior to the GMT detected at 1 month after dose 2. The evidence was Type 4, or very low, for this critical outcome.

The observational study for symptomatic laboratory-confirmed COVID-19 started at an evidence level Type 3, or low. Very serious concern for indirectness was noted because the study outcome was any SARS-CoV-2 infection, which was an indirect measure of the PICO outcome of symptomatic COVID. Additionally, the short duration of follow-ups likely limited an accurate assessment of VE. No serious concerns for risk of bias, inconsistency, or imprecision were noted. The relative risk of 0.09 favors a booster dose vaccination. However, the absolute effect was small with an estimated 277 fewer cases per 100,000. The evidence type was 4, or very low, for this observational study data.

One observational study provided data for the outcome of hospitalization for COVID. The initial evidence type of 3 was downgraded for very serious indirectness. The outcome of the study was severe COVID, which is an indirect measure of the PICO outcome for hospitalization for COVID. Additionally, the short duration of follow-up likely limited an accurate assessment of VE. The relative risk of 0.05 favored vaccination. However, the absolute effect was small with an estimated 26 fewer cases of severe COVID per 100,000. The evidence type was 4, or very low, for this critical outcome.

Phase 3 RCT data provided information for SAEs and reactogenicity. For both outcomes, a very serious risk of bias was present because a non-random subset of participants who received the booster dose are compared to the safety population from the 2-dose efficacy trial at the time of the BLA. For SAEs, there also was serious concern for indirectness and very serious concern for imprecision. The relative risk was 0.02 with wide confidence intervals that did not rule out harms. The evidence was Type 4, or very low, for this critical outcome. For reactogenicity, there was serious concern for indirectness and imprecision. The relative risk was 0.06, indicating a lower risk of Grade 3 reactions in the booster compared to the primary series. The evidence type was 4. or very low.

While not specifically included in GRADE, a finding mentioned by Pfizer the previous day was noted. There were 5% percent of individuals in their Phase 3 trial who received the booster doses that reported lymphadenopathy. This was all axillary lymphadenopathy, and only 1 severe event of lymphadenopathy was noted. This was reported more frequently following booster doses at 5.2% compared to 0.4% after the primary series.[65]

[65] Clinical trial data requested by CDC

The experience from Israel can also be used to inform knowledge about the safety of booster doses. Again, the rollout initially began with adults over 60 years of age and was expanded to those over 12 years of age at the end of August. Around 2.8 million third doses have been administered to persons 12 years of age and over, but most of those doses currently have been given to persons over 60 years of age. The rates of reported systemic, local, neurologic, allergic, and other reactions were lower after Dose 3 than after Dose 1 or 2, but there is likely under-reporting. Israel has noted one case of myocarditis to date after a booster dose in an individual 30 years of age and over. Due to limited follow-up time, it was not possible to determine the rates of myocarditis in younger adults from the Israeli data that is available to date.[66]

To summarize the GRADE assessment for the Pfizer-BioNTech COVID-19 vaccine for persons 18 years of age and over who completed a COVID primary series 6 months ago or more, in terms of benefits beginning with the prevention of symptomatic laboratory-confirmed COVID, the available data indicate that the Pfizer-BioNTech booster dose induced an immune response non-inferior to those following Dose 2. Observational data suggest an increased protective effect against any SARS-CoV-2 infection. The evidence type was 4. For hospitalization due to COVID, the observational data suggest a protective effect against severe COVID and the evidence type also was 4. No other data were available on the important outcomes of death due to COVID or transmission of SARS-CoV-2 to infection.

To discuss the benefit/risk assessment by age, the NNV with a booster dose to prevent 1 hospitalization over 6 months varies substantially by age. Over 19 times more individuals 18-29 years of age would need to be vaccinated to prevent 1 hospitalization compared to those 65 years of age and over. The benefit/risk balance among the younger population variers by sex, the VE after the booster dose, rates of myocarditis, and incidence. As incidence declines, there will be more uncertainty around the balance of benefits and risks. To summarize the benefit/risk assessment, the risks of myocarditis after a third dose of mRNA vaccines are unknown. It is known that after the second dose, the risk varies by age and sex, so similar patterns may be seen after a booster dose. The benefit/risk balance is the most favorable for adults 65 years of age and overusing current estimates of VE. The benefit/risk balance among younger populations varies by sex, VE after the booster dose, rates of myocarditis, and incidence. In addition, if COVID incidence increases, the benefits would increase. But as incidence declines, there would be more uncertainty around this balance of benefits and risks.

Moving to the summary of benefits and harms by age and population, the data from the clinical trial are limited in size and age. The booster dose of the Pfizer-BioNTech COVID-19 vaccine increases the immune response in those who have completed a primary series approximately 6 months previously. Again, the individual balance of benefits and risks varies by age. The largest benefit of vaccination is in individuals 65 years of age and over. The benefits to the other ages are incrementally smaller given higher VE currently maintained from the primary series. However, it is known that even within those age categories there is likely variation within the balance of benefits and risks given risk of exposure, medical conditions, and sex. The analysis of the benefits and risks also may be unable to account for other benefits. There may be a possible impact on rates of community transmission as well.

[66] https://www.fda.gov/media/152205/download

Values and acceptability were assessed in terms of whether people want a booster dose. In public surveys completed in August, 76% to 87% of vaccinated adults reported that they would get a booster dose if available. In one survey, this increased to 93% of adults if it was recommended by their primary care provider (PCP).[67] According to detailed data from an unpublished survey in which vaccinated respondents were asked if they would receive a booster dose, around two-thirds said they would get one soon as possible. Others said they would wait to see if it works or if it is safe. Only 2% of vaccinated respondents said that they would definitely not get a booster. When unvaccinated respondents were asked about boosters, around one-third of unvaccinated respondents said that a recommendation for COVID-19 booster doses would make them less likely to get vaccinated at all. In this survey, individuals also were asked who they believe should be prioritized for early receipt of COVID-19 booster doses. Most individuals highlighted HCW, LTCF residents, and those 75 years of age and over. These individuals felt that essential workers, those age 65 to 74, and other countries should be prioritized for vaccines. Adults less than 65 years of age were the least prioritized group.[68] In summary, at least two-thirds of vaccinated adults are willing to receive a booster dose and survey respondents prioritized older adults and HCW for booster doses, while younger adults were less prioritized.

Moving to feasibility and implementation, consideration was given to how booster doses would be implemented. Looking at completed primary vaccination series by week for those who completed the primary series 6 months or more, adults ≥65 years of age were prioritized for early vaccine doses. Overlaying those who would have completed the primary series 6 months and more, those who received their primary series prior to 3/19/21 would be eligible for a booster dose. This table shows the number of people who would be eligible in millions for a booster dose on September 27, 2021:

	≥6 months after primary series			
Age Group	**Pfizer-BioNTech**	**Moderna**	**Janssen/J&J**	**Total**
18-29 years old	2.0	1.5	0.3	**3.9**
30-49 years old	5.5	4.4	0.9	**10.8**
50-64 years old	5.3	4.4	1.2	**11.0**
65+ years old	13.6	12.9	0.8	**27.4**
Total	**26.4**	**23.4**	**3.3**	**53.0**

[67] 1) Axios Ipsos Poll. August 2, 2021; 2) Axios Ipsos Poll. August 30, 2021; 3) Marist Poll. September 3, 2021; https://maristpoll.marist.edu/polls/npr-pbs-newshour-marist-national-poll-covid-september-3-2021/; 4) Morning Consult Poll. August 25, 2021. https://morningconsult.com/2021/08/25/covid-booster-shot-poll/; 5) Reuters/Ipsos Poll. September 1, 2021. https://www.reuters.com/business/healthcare-pharmaceuticals/most-vaccinated-americans-want-covid-19-booster-shots-reutersipsos-poll-2021-09-01/

[68] CDC/University of Iowa unpublished data, August 2021

Of the total of 53 million individuals who would be eligible for a booster as of September 27, 2021, over 27 million are 65 years of age and over. It is known that the jurisdictions have begun preparing for implementation of booster doses. Booster doses will be given in a variety of settings, including: pharmacies, provider offices, health departments, occupational clinics, and federal programs such as the LTCF Program. Over 70% of current COVID vaccine administration is occurring in pharmacies. Many jurisdictions are known to be experiencing a surge in cases of COVID-19, while continuing to engage in outreach for unvaccinated individuals to receive a primary series and beginning the fall and winter influenza campaigns.

There is known to be variation in what has been received as a primary series. There are 3 vaccines currently being administered in the US. For additional doses of mRNA vaccines in immunocompromised persons, the current recommendation states that an additional dose should be the same product as the primary series. If the product given for the first 2 doses is not available, the other products may be administered. However, the evidence reviewed by FDA only evaluated a booster dose of Pfizer-BioNTech vaccine after completion of a Pfizer vaccine. LTCF can arrange for on-site vaccination clinics or can help residents access vaccines in a local community. The federal LTCF program can help implement vaccination in these LTCF settings. It is known that 8.1 million doses were administered during the original LTCF program from December 2020 through March 2021. Of those doses, 6.2 million (76%) were Pfizer-BioNTech and 1.9 million (24%) were Moderna. In addition, those in LTCFs now may not be the same individuals who were there 6 months ago due to substantial turnover over time. Studies have previously demonstrated turnover of 30% per month for residents and 100% per year for staff.

To highlight an issue that could impact implementation, the definition of “fully vaccinated” in the current CDC clinical considerations[69] state, “For public health purposes, immunocompromised persons who have completed a primary vaccine series (i.e., 2-dose mRNA vaccine series or a single dose of the Janssen vaccine) are considered fully vaccinated ≥2 weeks after completion of the primary series.” Based on current data, the definition of “fully vaccinated” would remain the same after recommendations for a booster dose. The “fully vaccinated ≥2 weeks or more after completion of the primary series” can be evaluated as additional information is learned over time.

To summarize feasibility and implementation, 220 million doses of the Pfizer vaccine have been administered in the US to date, demonstrating that the vaccine is feasible to implement. Over 2.25 million individuals already have received an additional dose. Over 27 million adults ≥65 years of age completed their primary series 6 months ago and 50 million adults ≥18 years of age completed their primary series 6 months ago. Pharmacies are delivering the majority of COVID-19 vaccines currently. Recommendations that are clear and simple will facilitate implementation.

In terms of resource use or the cost associated with booster doses, all COVID vaccines, including booster doses, will be provided free of charge to the US population. However, health systems or health departments could incur costs for vaccination program planning and implementation. Fees for administration of COVID-19 vaccines recommended by the ACIP are reimbursable by insurance or other federal programs. The WG has expressed that cost-effectiveness analyses will be important in the future when vaccine is not purchased and distributed by the federal government.

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

With respect to the equity consideration for booster doses, Hispanic or Latino, Black or African American, and AI/AN populations have been disproportionately affected by the COVID-19 pandemic. These populations experience higher rates of infection and mortality compared with the non-Hispanic White population and greater excess mortality, which is the percentage increase in the number of persons who have died relative to the expected number of deaths for a given place and time. In terms of annual excess death incidence rates for persons aged 25-64 years by race and ethnicity in the US during the COVID-19 pandemic in 2020, AI/AN and Black populations had the highest annual excess mortality incidence rates.[70] As of mid-September 2021, AI/AN and Black and Hispanic populations had the highest COVID-19-associated hospitalization rates compared to the overall population; whereas, White and Asian Pacific Islander populations had the lowest.[71]

As of mid-September, AI/AN and Native Hawaiian or other Pacific Islanders and Asians have the highest percentage of those who have received at least 1 dose of vaccine, while the Black population has the lowest at 34%. There has been variation over time for the vaccination rates by race and ethnicity. AI/AN populations have consistently had the highest percentage among those who have received at least 1 dose of the COVID vaccine. Hispanic or Latino populations started at a lower proportion, but has increased faster than other races over recent months.[72]

Among VE platforms able to provide specific evidence for VE by race or ethnicity, no differences were noted. Overall VE against hospitalization among adults ≥50 years of age was 89% (95% CI: 87-91%), for Black individuals was 86% (95% CI: 75-92%), and for Hispanic individuals was 90% (95% CI: 85-93%). VE against hospitalization among VA centers was 86% (95% CI: 77-93%) for Black individuals and 88% (95% CI: 77-94%) for White individuals.[73] To summarize equity, COVID-19 disease and COVID-19 vaccination varies by socioeconomic and sociodemographic groups. However, VE does not vary by race and ethnicity. While the equity gap in vaccines administered by race is closing, disparities were more pronounced this spring, which would be individuals who would be 6 months or more after their second dose.

In terms of the WG's interpretation, the WG continues to emphasize that the top priority should be continued vaccination of unvaccinated individuals. In addition, jurisdictions have a variety of vaccination and disease control priorities such as surges in COVID-19 cases and delivery of primary COVID-19 vaccine and influenza vaccine. The WG discussed that the balance of benefits and risks vary by age. Adults ≥65 years have the clearest benefit/risk. The benefit to other age groups is incrementally smaller, given the high effectiveness maintained from the primary series. The WG discussed the goal of the booster program to be prevention of severe disease. They also recognized that other considerations are important, such as maintaining workforce and healthcare capacity, prevention of transmission, and the individual benefit/risk balance.

[70] Rossen LM, Ahmad FB, Anderson RN, et al. Disparities in Excess Mortality Associated with COVID-19 — United States, 2020. *MMWR Morb Mortal Wkly Rep* 2021;70:1114–1119. DOI: http://dx.doi.org/10.15585/mmwr.mm7033a2

[71] CDC. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed September 21, 2021

[72] CDC. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends as of September 20, 2021, and US Census Bureau National Population Estimates

[73] M Thompson et al. NEJM https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110362?articleTools=tru

Interim Clinical Considerations for Pfizer-BioNTech COVID-19 Vaccine Booster Doses

Dr. Kathleen Dooling (CDC/NCIRD) reviewed the existing interim clinical considerations for the use of Pfizer-BioNTech COVID-19, as well as the proposed groups for whom a booster may be considered. For public health purposes, people who have completed a primary series of a vaccine (i.e., 2-dose mRNA vaccine series or a single dose of the Janssen vaccine) are considered fully vaccinated ≥2 weeks after completion of the primary series. This definition applies to all people, including those who receive an additional dose as recommended for moderate to severely immunocompromised people and those who may receive a booster dose in the future.[74]

Pfizer-BioNTech COVID vaccine (BTN162b2) is administered as a 0.3 ml intramuscular injection. It should be noted that this is the exact same formulation, dose, and route as has been previously authorized and approved for the Pfizer COVID vaccine. With regard to the timing of a booster dose, a single dose should be given at least 6 months or more after completion of the primary series. It is important to note that immunity wanes gradually over time. Therefore, it is not necessary for the booster dose to be given exactly at 6 months. In fact, a booster dose may be given at a period of 6 months or more after the primary series. In terms of co-administration, Pfizer-BioNTech COVID vaccine booster may be given with other vaccines without regard to timing. This includes simultaneous administration of COVID-19 with a Pfizer vaccine and other vaccines on the same day.

To review the groups at risk for severe COVID-19 or SARS-CoV-2 infection even after vaccination with a primary series, increasing age is a strong risk factor for severe COVID. People ≥ 65 years who are fully vaccinated are at an increased risk for severe COVID-19, including hospitalization and death, compared to younger fully vaccinated people. In addition, waning of COVID-19 VE against severe disease has been observed in people ≥ 65 years of age and older. While most residents of LTCFs facilities are over 65 years of age, this is a risk-based group and would include any residents 18 years of age and older. There is likely an increased risk of severe COVID-19 (including hospitalization and death) among fully vaccinated residents compared to fully vaccinated people who are living independently. Waning of COVID-19 vaccine protection against infection and has been observed in LTCF residents. In addition, congregate living settings are associated with increased risk for COVID-19.

The next group is risk-based by occupation or settings. This group includes people 18 years of age and older who are fully vaccinated and may be at increased risk for SARS-CoV-2 infection due to frequent exposure in their occupation or other settings. Moreover, an individual who is absent from their occupations due to SARS-CoV-2 infection may hinder societal functions. Examples include but are certainly not limited to essential frontline and non-frontline workers,[75] paid and unpaid caregivers of frail or immunocompromised persons, paid and unpaid workers who interact within less than 6 feet of others, and people who live in congregate settings (e.g., homeless shelters or correctional facilities).

[74] nocompromised people and those who receive a booster dose https://www.cdc.gov/coronavirus/201 9-ncov/vaccines/fully-vaccinated.html

[75] https://www.cisa.gov/publication/guidance-essential-critical-infrastructure-workforce

The final risk-based group is people 18 years of age and older with underlying medical conditions and fully vaccinated people with underlying medical conditions who may be at risk for severe COVID-19 if they become infected with SARS-CoV-2. Examples of underlying medical conditions associated with severe COVID include, but are not limited to: cancer, cerebrovascular disease, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus type 1 and type 2, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), obesity (BMI ≥30 kg/m2), pregnancy and recent pregnancy, and current/former smoking.[76]

Looking at the factors for considerations for the individual level assessment of benefits and risks of a COVID-19 vaccine booster dose, the potential benefits to an individual are that a booster may confer reduced risk of infection and severe disease. The strongest evidence for the benefit of reduced risk of severe disease is in older adults. The VE of an mRNA primary series remains high in younger age groups. A booster dose of COVID vaccine may confer reduced risk of SARS–CoV-2 infection. Waning of vaccine protection via a combination of factors such as time since vaccination and Delta variant has been observed in most age groups. It is important to note that infections may be symptomatic or asymptomatic. A booster may reduce work absence and preserve the capacity of important sectors. Stated another way, prevention of infection may protect healthcare capacity and other essential services for the COVID-19 response and maintain the overall functioning of society.

To review the potential risks to an individual that should be considered, myocarditis and myopericarditis are very rare but may occur following an mRNA vaccination. It is more common in younger ages, particularly males younger than 30 years old. Most patients with myocarditis have been hospitalized for short periods, the majority of whom achieve resolution of their acute symptoms. The rate of myocarditis following a booster dose is not yet known. Anaphylaxis, although very rare, may occur following a COVID mRNA vaccination. The rate of anaphylaxis following a booster dose is not yet known. Reactogenicity, including transient local and systemic symptoms, are common following mRNA vaccines. The third dose of Pfizer-BioNTech COVID-19 vaccine appears to have similar reactogenicity as the second dose.

When assessing the benefits and risks, individuals should consider their own risk of SARS-CoV-2 exposure. For example, individuals can assess their risk of excessive exposure in occupational, living, and transportation settings. Consideration should be given to their ability, for example, to consistently wear a mask, maintain social distance, and other mitigation measures. In addition, consideration should be given to rates of SAR-CoV-2 infection in the community. Individuals also can consider their risk of developing severe COVID-19 if infected. This may be influenced by underlying medical conditions, particularly if those conditions are not well-controlled. Individuals also can consider their personal circumstances, such as living with or caring for a frail or immunocompromised person or the consequences of the inability to meet personal or occupational obligations due to SARS-CoV-2 infection.

Consideration also must be given to contraindications, precautions, and other AEs following immunization. The contraindications and precautions would be the same for booster doses as for the primary series of a Pfizer COVID-19 vaccine. A contraindication may include severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the Pfizer BioNTech COVID-19 vaccine, or an immediate allergic reaction of any severity to a previous dose or known diagnosed allergy to a component of the vaccine. Polysorbate allergy is a precaution to mRNA COVID-19 vaccinations. If myocarditis or myopericarditis occurs following a

[76] https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

dose of mRNA vaccine, it is recommended to defer a subsequent dose. People who choose to receive a subsequent dose should wait until myocarditis or myopericarditis has completely resolved. It should be noted that the aforementioned conditions, certainly the ones that result in contraindication or precaution, are extremely rare. Many resources can be found on the "Clinical Considerations" section of the CDC website. Those include information about anaphylaxis and its management in the vaccine setting.[77]

Types of Recommendation ACIP Could Make

Dr. Sara Oliver (CDC/NCIRD) reviewed the types of recommendations ACIP can make, as well as what this recommendation would mean for the balance of benefits and risks. The recommendation options are:

- ❑ **ACIP does not recommend the intervention:** This would occur when it is felt that across the population, the risks outweigh the benefits.
- ❑ **ACIP recommends the intervention:** This would be used when the benefits clearly outweigh the risks in the population.
- ❑ **ACIP recommends the intervention for individuals based on assessment of benefits and risks:** This could be used when there is diversity of the benefits and risks within a population. This type of vote could allow for flexibility across the population when there is more variation around the balance of benefits and risks.

The WG proposed two policy options for ACIP's consideration shown in the following tables, with some of the pros and cons identified for each:

Policy Question #1:

Should adults ≥65 years of age and LTCF residents receive a Pfizer-BioNTech COVID-19 vaccine booster dose?

PROS	CONS
• Highest risk of severe disease • Largest impact in waning VE against severe • disease • Prioritized for early doses of COVID-19 vaccines (longer duration since primary series)	• Age cut-off may not represent continuum of risk

[77] https://www.cdc.gov/vaccines/covid-19/downloads/IntermConsid-Anaphylaxis-covid19-vaccine-sites.pdf

Policy Question #2:

Should adults 18–64 years of age at risk for severe COVID-19 due to underlying medical conditions or at risk of SARS-CoV-2 exposure due to occupation/setting receive a Pfizer-BioNTech COVID-19 vaccine booster dose?

Type of Recommendation	PROS	CONS
Standard recommendation	• Simple • Reduces barriers for individuals who may have increased risk of disease • Reduction in infection could reduce work absenteeism	• Not strong evidence of increased risk of hospitalization or death in all individuals • Balance of benefits and risks likely varies • Large number of people initially eligible (>50 million)
Recommended for individuals based on assessment of benefits and risks	• Reduces barriers for individuals who may have increased risk of disease • Reduction in infection could reduce work absenteeism • Reflects uncertainty in current balance of benefits and risks in this population	• Large number of people initially eligible (>50 million) • More complicated to implement

Discussion Points

Dr. Poehling emphasized that ACIP would consider persons who have completed the primary series as being fully vaccinated. This is an important point in that it gives people an opportunity, but not a requirement. She indicated her support for Policy #1 as it was clear from the data that the risk of hospitalization was increasing among those ≥65 years of age and LTCF residents, and that the benefits outweigh the risks. In terms of Policy #2, she thinks a lot about the immunocompromised such as children under 12 years of age for whom there is not yet a vaccine and adults in the full spectrum. It appeared to her that immunocompromised people and their caregivers would be included under this setting. For instance, the caregiver of a child who is medical fragile or immunocompromised would be included. In terms of the two recommendations, it seemed to her that the intent was to allow availability without mandating.

Dr. Oliver confirmed that this would be correct. Settings were drawn to be broad and include settings in which someone is a caregiver for an immunocompromised or frail person.

Dr. Kotton emphasized that for Policy Question #1, making the age cutoff of ≥65 years of age creates an equity issue because this age is not equal across all racial groups. Different outcomes have been observed at different ages across different races with COVID, so this proposed cutoff may not meet the intent for trying to ensure as much equity as possible. She also suggested that perhaps Policy Question #2 should be divided into two separate questions in that it may hard to reach agreement on the two areas of underlying medical conditions and occupation/setting.

Dr. Cohn reminded everyone that these policy questions are based on the language that were in the conditions of use from the FDA authorization from the previous evening. Therefore, they did not have flexibility in terms of Policy Question #1 to shift the age group from ≥65 years of age. Policy Question #2 certainly could be split into a discussion on underlying medical conditions and exposure to occupation/setting. That question did allow for an opportunity to shift some of the ages around. For instance, individuals at a lower age who are at severe risk for disease could have a full recommendation as compared to the more individual level recommendation for other types of groups. Therefore, one way to address the equity issue that could not be addressed in Policy Question #1 would be to shift things around in Policy Question #1.

Dr. Talbot pointed out there are data showing some decline in VE for the Pfizer BioNTech COVID-19 vaccine, and there are reasons for that, including the shorter interval between Doses 1 and 2 compared to the other mRNA vaccine. To her, the most important policy question pertains to the Janssen/J&J vaccine. That vaccine has much lower VE and she worried that they were getting distracted by the question of the Pfizer BioNTech booster when they really need to figure out what to do in the pandemic. Along the lines of fighting the continued pandemic, it is not because people got 2 doses—it is because people are unvaccinated. While giving booster doses to already vaccinated people may move the needle a little bit, the fact is that this is now a pandemic of the unvaccinated and the hospitals are full of people who are not vaccinated. Care is being declined to people who deserve care because hospitals are full of unvaccinated COVID-positive patients. Giving boosters to people is not really the answer to this pandemic.

Dr. Ault noted that as far as knowledge gaps for Policy Question #2, there are pregnant women and those who have underlying medical conditions who are at risk for worsening disease. There also are HCW who are skewed toward younger and female individuals, so this means hundreds of thousands of pregnant and lactating HCW at any one time. There are complicated questions to answer for people who fall within this category, and numerous pregnant women have received zero doses. That also will have to be addressed somehow.

Dr. Sanchez agreed that they must remember that they are talking about booster doses for individuals who already have agreed to receive a vaccine and to be fully vaccinated, so he thought the equity issues were somewhat different. That said, he agreed with Policy Question #1 and had some issues with Policy Question #2 in that it should be further separated out as mentioned by others. He did not think Policy Question #2 helped parents or others who are caring for immunocompromised persons at home if the parents/caregivers are less than 65 years of age and otherwise healthy. While this could be read into the setting, it is not explicitly stated that healthy parents/caregivers less than 65 years of age may need to be vaccinated for the sake of a fragile child. The FDA states that, “Individuals 18 through 64 years of age whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.” Policy Question #2 seemed to be expanding that, which would be fine if allowed. However, he thought that was somewhat different in terms of HCW and younger people who may not be at high risk of severe disease.

Dr. Brooks agreed with Policy Question #1. He emphasized that the evidence for African Americans shows that their increased risk for death and hospitalization increases dramatically at age 50. It is likely that a lot of that is related to underlying medical conditions, so adoption of these policy questions in any fashion would mitigate some of that. He reminded everyone that it was important to remember that these recommendations were only for those who received the full series of the Pfizer vaccine. In addition, a lot of this would be based on the availability of vaccine. About 76% to 93% of people who had two doses expressed a willingness to get a booster, so those who want a booster should be able to get it. Importantly, no major risks were

identified either. One concern was that one-third of the unvaccinated said that a booster would make them less likely to get vaccinated, so a recommendation for a booster might reduce the ability to get the unvaccinated to get vaccinated. On balance, he thought that Policy Question #2 and a flexible recommendation would have a lot of positivity, but if done as a full recommendation it might be perceived as a mandate and that could be somewhat problematic.

Dr. Oliver noted that receipt was broken out by primary series in the presentation. With 6 months or more after the primary series, 26 million received Pfizer and 13 million of those are 65 years of age and over.

Dr. Cohn noted that their FDA colleagues could answer specific questions about the EUA. The issue of people who are living in the home of immunocompromised persons, the language in the FDA EUA states “occupational or institutional risk.” The proposed ACIP language is a little different from the FDA, but is believed to have the same intent. From that perspective, she asked the ACIP members to not worry about how this discussion aligned exactly with the intent of the FDA EUA. CDC will make sure that they are within the conditions of use before issuing any final recommendations. She noted that the questions had now been separated into 3. While they could split the ages of 18–64 years to have different recommendations for different ages, but they certainly want to try to keep the recommendations reasonable from a simplicity perspective.

Ms. Bahta noted that there was nothing in the clinical guidance to address the mixing of vaccine products. She also expressed concern that the policy questions sent a message that the primary series was not enough and people would need more. She also agreed that boosters would not end the pandemic, and pointed out that many of those who did get vaccinated abandoned other mitigation measures. With unvaccinated individuals becoming very ill and vaccinated people were also getting sick, which reduced the confidence people have in the vaccine. With that in mind, she supported Policy Question #1 and thought Policy Question #2 should be adjusted to include a more equitable consideration. They must ensure that they talk about this as only one measure in the midst of a pandemic and explain what everyone needs to do whether they are vaccinated or unvaccinated. In terms of age group, she thought 50-64 years would be suitable because it is known that there is a large group of individuals in that age range who have similar risks. She emphasized that they should not imply that they are not protected, because most people are.

Dr. Long emphasized that it is imperative to protect people from death and hospitalizations. She agreed that people of different races and ethnicities age differently, but there were absolutely no data to suggest that there was a diminution of vaccine protection or antibody responses based on race or ethnicity. Although there may be more severe disease in people under 65 years of age, she had not seen the data in breakthrough disease to suggest that this is the case—at least to any extent. She also assumed that in addition to LTCF as done previously, Policy Question #1 would apply to everyone in congregate living. She wondered whether Policy Question #1 would be a preference for everyone who received Pfizer vaccine, but an allowance for those who received Moderna or Janssen/J&J. She supported Policy Question #1, but thought it would be anathema to preclude people from getting Pfizer if they had a different primary series. For Policy Question #2, there did not seem to be evidence showing that underlying medical conditions reduce protection. There did not appear to be substantial waning in the younger age groups. Risk for severe disease did not seem to extend from caretakers to the people they take care of. Policy Question #3 seemed rather thorny to her.

Dr. Daley expressed strong support for a full standard recommendation for Policy Question #1. His interpretation of Policy Question #2 differed from Dr. Long's and he fully supported a full recommendation for those 50-64 years of age with underlying medical conditions for several reasons. First, that is a group who has underlying medical conditions and some immunosenescence. Second, the risk of myocarditis did not appear to be elevated in this group. Therefore, the benefits for booster in that group are likely to outweigh any risks. Third, that approach may achieve greater equity as mentioned by others. He was contacted by a colleague who reached out with the observation that many in the AI/AN population do not reach the age of 65 years due to underlying medical conditions and the effects of social determinants of health (SDOH). He preferred to hear more about those 18-49 years of age with underlying medical conditions and what type of recommendation would be most appropriate for that group. He tabled his comments for Option #3 for later.

Dr. Fink walked the ACIP through the authorized population and the FDA's rationale for that in order to help answer some of the questions raised. The statutory requirements for EUA would require FDA to find that a booster dose may be effective to prevent a serious disease or condition. FDA also has to evaluate the benefit of a booster dose in relationship to whatever benefit exists from the primary series, because anyone being considered for a booster dose will have received a primary series. They heard evidence during the VRBPAC presentation the previous Friday that FDA thought clearly enough demonstrated a risk of hospitalization and severe COVID (e.g., a serious condition) among individuals 65 years of age and older who had passed some time since their primary series. That was the rationale for including that age group. They did not see evidence presented to support that younger age groups in the general population were at increased risk. In fact, they also did not see evidence to support that specific subgroups within the younger population were being hospitalized at higher rates. However, they did consider that individuals who at baseline were at increased risk of severe outcomes from COVID-19 would reasonably be expected to be at higher risk of severe outcomes and hospitalization even following the primary series with protective immunity. This was the rationale for including in the authorized population individuals 18-64 years of age at high risk of severe COVID, whether that risk is due to underlying medical conditions or some other factor. Regarding the third component of the authorized populations, FDA also considered that frequent and unavoidable exposure to SARS-CoV-2 would increase the risk of symptomatic COVID that would carry increased risk of serious complications of COVID (e.g., severe presentation of COVID; long COVID). It was with this thinking in mind and considering groups that have both frequent and unavoidable exposure to SARS-CoV-2 that the FDA decided to authorize the booster dose in institutional or occupational settings. This construction differentiates those groups who have frequent and unavoidable exposure to the virus in institutional and occupational settings from the general population. The VRBPAC did not find that the totality of evidence supported the use of a booster dose in the general population of younger adults 16-64 years of age.

Dr. Lee thanked Dr. Fink for clarifying FDA's intent and pointed out that ACIP certainly wants to stay within the intent of the regulatory decision that FDA has made, so they would continue to discuss this robustly. She asked him to comment on the question that arose regarding the timing of availability of a booster dose of the Janssen/J&J vaccine and the gap that might emerge, recognizing that there had not been a submission.

Dr. Fink indicated that there were no data available to inform the interchangeability of authorized COVID-19 vaccines, either for completion of a primary series or for use of a booster dose. Consequently, the Pfizer-BioNTech COVID vaccine was authorized for use as a booster dose among certain individuals in the authorized population who completed the primary series of Pfizer-BioNTech COVID vaccine. FDA received Moderna's EUA application for an amendment for a Moderna COVID vaccine booster dose, which is under review and they are working diligently to get that completed. He is also very sensitive to and understands the desire for flexibility regarding use of COVID vaccines, as well was the concern about individuals who received the Janssen/J&J vaccine. Data show that the Janssen/J&J vaccine continues to provide very good protection against severe outcomes, including hospitalization and death. Although notably its protection is not at the same level as the primary series of the mRNA vaccines. As a physician, he is frustrated with the lack of data that would allow for a regulatory allowance and for evidence-based recommendations from the ACIP for evidence-based practice. FDA is working diligently with vaccine manufacturers and its other partners the federal government, including the NIH, to arrive at a solution expediently to address the situation and provide a solution that will comply with legal requirements.

Dr. Marks added that FDA understands the relative urgency of trying to have a solution for anyone who has been vaccinated with any of the authorized or approved vaccines. Unfortunately, they were not able to provide an exact timeline. However, they will proceed with all due urgency to try to get there as rapidly as possible working with the various vaccine sponsors and all of the available data to make a science-based decision so that there is something based on evidence to bring forward.

Dr. Lee emphasized that ACIP appreciates that everyone is working toward the intent of trying to protect the American public, and pointed out that the concerns raised by the committee were really ones of equity and ensuring that the FDA, CDC, all federal colleagues, clinicians on the frontline, and public health colleagues can make sure that they are working to achieve equity in all aspects of vaccine policy.

Dr. Bell observed that there has been some confusion and lack of clarity of about what the FDA, VEBPAC, CDC, and ACIP do. There is now an EUA from the FDA for giving a Pfizer/BioNTech booster to people who received a primary series under the EUA category, which means that this booster is available to people in the US. ACIP needs to consider the totality of evidence and think about what makes the most sense using the tools available, as Dr. Walensky said, to protect as many people as possible. In addition, ACIP must consider how to operationalize this considering other elements, such as feasibility. She stressed that the question before them was very narrow and that there were many moving parts, competing priorities, the issue that this recommendation is only for people who received a Pfizer/BioNTech primary series, potential vaccination authorization upcoming for children, et cetera. She urged committee members not to get stuck on trying to definitively answer a question and come up with policies now in the midst of all of the moving parts and remembering, as Dr. Talbot said, if they really want to move the needle with this pandemic, more people must be vaccinated with the primary series. That should be the focus of the public health infrastructure in her opinion. Given all of that, putting aside Policy Question #1, and since it appeared that there was no evidence of waning VE among people younger than 65 years of age with underlying medical conditions, she was concerned that any inconsistency might cause more problems than anticipated. There was nothing to preclude anyone with an underlying medical condition from getting a booster if they had a primary series with Pfizer/BioNTech. Therefore, she did not have a huge amount of enthusiasm for ACIP making a recommendation with no evidence to boost VE in some populations above that of others. In terms of Policy Question #3, she thought there was ample evidence that

people such as HCWs do not have repeated exposure in their workplace. They are using personal protective equipment (PPE) as they should and are following other policies within the healthcare setting. There is a lot of evidence to suggest that HCW who become infected become infected because of exposures in the community. Therefore, she did not believe the third statement to be scientifically correct and would say the same about teachers. As she mentioned the previous day, she thought a case could be made for vaccinating HCWs to reduce the incidence of infections that they get because of exposures in the community and to reduce absenteeism among vaccinated HCW. Otherwise, she was not ecstatic about voting for a booster dose in a population based on a rationale that she did not think was actually supported by evidence.

Dr. Loehr indicated that he was in favor of Policy Question #1, was against the standard recommendation for Policy Questions #2 and #3, but might consider a judgment call on those two. He felt that the goal was to decrease hospitalizations and that vaccinations would do that, but that they were getting too much ahead of themselves and placing too much hope on the line with boosters. He calculated the numbers and determined that even if boosters were given to all 13 million people over 65 years of age who have had the Pfizer/BioNTech primary series, that might result in 200 fewer hospitalizations a day. While that is a lot, there are 10,000 hospitalizations a day at this point, it is not that much compared to the goals of getting the unvaccinated and children vaccinated. Nevertheless, he emphasized that they should not let the perfect get in the way of the good. If they could do a little bit by giving boosters to those over 65 years of age, he favored that. Regarding Policy Questions #2 and #3, it was clear from public comments and his own anecdotal experience that people want boosters. He agreed that there are no data, so he was hesitant to make a standard recommendation. However, he could see making a recommendation based on clinical judgment.

Dr. Cohn stressed that this was an unusual situation that was not the typical vaccine policy development framework in that there were not public and private vaccines. All of the COVID vaccine had been purchased by the US government (USG). Because of that key difference, the FDA EUA alone is not sufficient to allow for access to population that are also covered by some sort of ACIP recommendation, be it a standard or more individual decision-making focused recommendation. For instance, a vote of “yes” to the first question and “no” to 2 and 3 would mean that only those 65 years of age and above would be eligible to get a booster dose at this time. She was hearing from everyone the very important and clear point that the public health goal right now should be to get people vaccinated who are unvaccinated, and recognized that there were multiple competing priorities at the public health level. In pre-COVID days, the way that ACIP framed a permissive, individual, or shared clinical decision-making recommendation was to think about it as a public health program for a full recommendation. A permissive recommendation for Policy Questions #2 and #3 would not require the same public health focus as a full recommendation. She imagined that individuals in those areas would get their booster doses if they chose to do that in pharmacies and other places that would not have a significant impact on all of the competing priorities of public health. While clearly this would have some impact on public health so she did not want to overstate that, the standard recommendation would be the goals of public health at this time, which is a primary series for all individuals 12 years of age and older, a booster dose for all individuals 65 years and older if they voted “yes” to Policy Question #1, and the additional dose for immunocompromised persons.

Dr. Cineas agreed with others that the top priority was to vaccinate the unvaccinated and that any recommendations should not detract from that priority and goal. For Policy Question #2, she thought that the language should be kept as simple and easy to implement for providers as possible, while allowing for some shared decision-making and discretion and flexibility for providers to provide the additional dose.

Dr. Sanchez agreed with Dr. Bell's comments. He also asked whether pregnancy would be included in underlying medical conditions in Policy Question #2. His expressed concern that Policy Question #3 did not explicitly include vaccinating otherwise healthy individuals who themselves could become infected who are caring from someone at home who could not be vaccinated. While he knew they were addressing just the Pfizer vaccine, they could not continue to ignore the Janssen/J&J product and the individuals who received it. There are data from Europe with heterologous dosing with the adenovirus vector with the AstraZeneca (AZ) vaccine and mRNA vaccine that showed good boosting.

Ms. McNally asked CDC to comment on Policy Questions #2 and #3 in terms of communications and education materials for providers on the needs assessment, particularly as it relates to Question #3.

Dr. Cohn responded that there absolutely would be communications and education materials in the same way that CDC has provided these for individuals to help understand which vaccine may be best for them for the primary series, given the differences between the vaccine. There would be materials for HCP, public health, and the public to support this decision-making. The presentation that Dr. Dooling laid out would form the basis of some of those considerations if ACIP decided to make these recommendations.

In terms of Policy Question #2, Dr. Poehling agreed that VE remained robust when looking at the overall population with high risk conditions. While that is really good news, it is known from clinical experience that there are persons with high risk medical conditions who are very fragile and in whom the most minor cold can cause them to have significant disease that leads to hospitalization. She was struggling about how to make sure that those who are the most medically fragile and younger than 50 to 64 years of age still have access.

It was not clear to Dr. Long how later in the afternoon ACIP was going to tell people 65 years and older that they are at risk for severe disease and death, but that only half of them can protect themselves right now since only those who received the Pfizer primary series would be eligible for the Pfizer booster. It might be the right thing to do, but she might vote against it because it did not sound like a good public health policy. Pregnant women are at an age where they have had robust responses to these vaccines and there is no evidence that they have substantial waning, so she would not include pregnant women in the booster recommendation at this time. She did not like the shared decision-making. Individualized decision-making would mean that people of education, wealth, and ability would go to a pharmacy or provider to get a dose without significant need. The FDA said, "If you were originally at risk for severe disease before you got vaccinated . . ." where she would say, "If you are significantly at risk for X and you are at risk for waning, the data are incomplete but ACIP thinks the benefits now would outweigh the risks."

Dr. Eckert (ACOG) reported that the American College of Obstetricians and Gynecologists (ACOG) had a call on September 20th during which the general consensus was that they feel positive about boosters. At the same time, they recognized that many of the initial pregnant individuals who were vaccinated were HCW and were in the first round. They may have been

delivered by now, so it could be somewhat time sensitive in terms of wondering who should and should not get boosters depending upon whether they are postpartum or lactating. While it is a complicated question, the general feeling was that given the severe disease and the fact that many of the pregnant individuals were in the earliest wave of vaccinees, that ACOG favors consideration of boosters.

Referring to Slide 12 of Dr. Oliver's presentation showing the age-adjusted weekly COVID-19 hospitalization rates, Dr. Lee noted that vaccinated versus unvaccinated for people 50 to 64 years of age was 22 times higher compared to 13 times higher for people 65 years of age and older. However, the baseline rates of hospitalization were higher in the 50 to 64 year olds likely due to additional medical conditions.

Dr. Duchin (NACCHO) highlighted the equity issue illustrated in their own COVID-NET hospitalization rates where hospitalization rates among 50 to 64 year olds non-Hispanic, AI/AN, Black, and Hispanic or Latino people are higher than those among non-Hispanic whites and Asian and Pacific Islanders for 65 years of age and older. In the context of the third dose for immunocompromised persons there is clinical consideration language that set a rather high bar for defining who is immunocompromised. If they were going to consider a recommendation for people with underlying medical conditions, he encouraged ACIP to be clear about what is considered to be an immunocompromising condition. From the local public health perspective, despite the wicked complexity of this problem, simplicity is needed in the guidance for implementation success.

Ms. Howell (AIM) echoed the need for simplicity, including allowing people to self-report underlying conditions, go to large vaccination clinics, and not require proof or a prescription if Policy Question #2 was chosen. While they need to get more unvaccinated people vaccinated, there are many local areas in which a large proportion of the population is unvaccinated and there is a struggle with HCW infrastructure. Policy Question #3 could significantly assist with HCW infrastructure in areas that have large numbers of unvaccinated people and are experiencing outbreaks.

Dr. Goldman (ACP) expressed concern with these policy options because it was not clear to him that there was overwhelming evidence to recommend them compared to the great benefits of the primary series. This is a disease of the unvaccinated. From a boots-on-the ground perspective, he was concerned about the unintended consequences of Policy Questions #2 and #3 in that they may be completely irrelevant and superfluous if implemented. As soon as the Biden Administration advised that boosters would be a guarantee, he had patients who already got a booster dose without anyone asking why. Pharmacies and other vaccinators were giving it to patients without any reason whatsoever. From an equity standpoint, if this is put in place and some type of certification is required from a physician, patients who have diseases who cannot get into physicians because they are already in a health disparity situation to get a form signed to get a vaccine will not get the booster. If no proof is required, people will get vaccines without any reason and may misrepresent underlying conditions just to get a booster. For those reasons, he thought Policy Options #2 and #3 were fraught with peril and would create inequities and problems with implementation.

Dr. Shah (ASTHO) indicated that over the past few weeks, ASTHO has had a chance to speak with state health officials across the country in connection with boosters and the rollout, and two prevailing themes emerged. The first pertained to Policy Question #1 in terms of some permissive allowance for use of a mix and match strategy, particularly in LTCF. Boosters will be peaking around the same time that various states and vaccination forces will be asked and

pressed into service to provide first doses for children 5 to 11 years of age, to say nothing of influenza shots and other healthcare needs. Having to go back to a health facility or LTCF in a few weeks to pick up those who received Moderna will pose a significant operational challenge. He recognized that as Dr. Fink and others pointed out, there are not definitive RCT data on the efficacy of mixing and matching. State health officials requested that as ACIP has done with respect to severely immunocompromised people, making an allowance for a preference for the same vaccine, but if not possible, to allow the mix and match approach. There is good reason to believe that the mix and match strategy would be applicable. The second observation from state health officials was a request for extreme clarity, particularly on Policy Questions #2 and #3. Though he understood it on the screen before them, the language in practice would leave open a lot of questions. For example, the US CDC has 4 tiers for the risk of COVID for underlying medical conditions. It was not clear whether it would be all 4 of those tiers or only certain ones of them. If it would be all 4 tiers, it would include those who are overweight which is about 73% of the population. If the intent is for boosters to be somewhat narrowly construed in only those 18 to 64, if all 4 tiers, soon they would get to the point where overweight + coronary artery disease + hypertension would mean that Policy Question #2 would encompass most of the population. Similarly, clarity around Policy Question #3 with respect to which occupations and which settings would help avoid the patchwork of different states taking different policy approaches as occurred earlier with respect to the primary series.

Dr. Maldonado (AAP) said that in terms of equity, the implication was the risk for underlying medical conditions among under-represented minorities. Frankly, the vast majority of data pertain to frontline workers who are not HCW but who work in settings that put them at risk where they may not be protected by PPE and other practices available in healthcare settings, and who live in communities of high risk would be over-represented in high risk groups. It is known that household density, living conditions, et cetera for these individuals are already a risk. It is clearly not a biological driver for under-represented minorities. It is really about SDOH. This is driving the pandemic overall in addition to unvaccinated people. Vaccinated people in high risk groups who will not have access to boosters is going to further the inequities in those populations. Therefore, she made a case for considering under-represented minority groups who are primarily over-represented in lower socioeconomic groups who may drive the risk of transmission.

Dr. Weiser (IHS) expressed appreciation for the comments regarding booster doses and the impact of severe disease among minority populations, especially those under the age of 65 years. Despite the lack of data on waning of the vaccines in these populations, there is evidence of severe disease occurring in younger ages in these populations. Policy Question #2 would give IHS clinicians the flexibility to provide booster doses to patients who are medically fragile, with multiple medical conditions that put them at high risk for severe disease. Regarding feasibility, the AI/AN population had the highest uptake of COVID vaccination. Many of these vaccines were delivered in IHS Tribal & Urban Indian Health Centers. Those who were going to IHS clinics also have a place they can go where their medical history is known. The ability to understand those who are most at risk and might need a booster dose increases the feasibility in the IHS setting. He suspected that the population who are accessing the Federally Qualified Health Centers (FQHCs) also would receive similar care in a similar setting where their medical history is known and they can receive their booster doses in a place where they know their PCP and have the ability to discuss whether they want to receive a booster dose. He thought booster doses would be very welcomed in the IHS population and they have a proven track record for feasibility in distributing doses.

Speaking as a practicing physician, Dr. Fryhofer (AMA) urged the ACIP members to vote for permissive use. As Dr. Fink said, the statutory requirement is that the booster may be effective to prevent serious disease or condition. There is so much evidence and data coming in every day, physicians like herself who care for patients with multiple medical problems need flexibility in being able to recommend a booster for patients. Policy Question #1 includes over 65 years of age and LTCF residents. Many patients could be in LTCFs who are not 65 years of age or who live at home. Without flexibility, patients in need will be deprived of something that could save their lives. While she understood the need for making public health decisions, but this vaccine has been paid for by the government with tax dollars. There are patients whose VE is decreasing who have multiple medical problems who are very likely going to be some of the ones who die if they get sick. There is so much about this pandemic that is out of control. They cannot make people wear masks or control everything that happens. Making vaccine available to those who want to get a booster is a way of supporting the people who have chosen to be fully vaccinated and appreciating the fact that they want to maintain their protection against this deadly disease.

Dr. Talbot pointed out that in reality, almost every American is at risk due to obesity or medical problems, and/or or live with someone who is high risk, and/or teach children who are not able to get vaccinated yet. While the FDA provided specific caveats, in some way it may make more sense to make it permissive for the US population. That way, patients can have conversations with their providers or pharmacists to think through those risks. She recognized that this would not be the way to stop hospitalizations, but for those who have been vaccinated and done their part it may be okay to say, “If you’re over 18 years of age and you would like a third dose, fine.”

Dr. Daley made a couple of broad and overarching comments before getting to the next stage of this conversation. One question he was asked in the last week or two regarded whether the recommendations made today reflect who they value in society. He wanted to be very clear in stating that they most certainly do not. The goal is to prevent serious illness from COVID-19 for everyone in the country. This is not about who deserves a booster, but instead about who needs a booster. If someone is in a group for whom boosters doses are not universally recommended, it is critically important to understand that the vaccine’s effectiveness against serious outcomes is already very high for those who received the primary series. He reiterated that the decision they would make would be interim decisions that could, would, and should be readdressed as the circumstances and data warrant. He was very concerned about the inability to explicitly address heterologous or mix and match vaccination during this meeting, but hopefully that can be addressed very soon.

Dr. Cohn emphasized that these are referred to as “interim recommendations” and will change in this ever-evolving situation.

Dr. Drees (SHEA) expressed appreciation for the fact that 2 doses were still considered to be fully vaccinated for HCW in particular versus stating that the booster dose is needed as well. That gives employers some flexibility as to whether to also require a third dose or not. She agreed that staffing is stretched and the resources are not available to do the mass vaccination clinics that were done in December and January for healthcare staff. Similar to Dr. Daley’s comments, the data really support lowering of protection for Pfizer and that may change for the others as well. Starting with Pfizer makes sense and is more manageable from a resource standpoint.

Dr. Cohn emphasized that supply for Pfizer vaccine is not an issue right now. There is plenty of Pfizer supply to continue to give the primary series and booster doses. Regarding capacity and whether offering booster vaccine will push out others who still need to get the primary series, the first priority will continue to be focused on getting people their primary series regardless if how the votes turned out during this meeting. One of the important communication messages is that not everybody will need a booster at 6 months. The language in the FDA EUA says that the booster can be given at any time after 6 months. While protection starts to wane, people are still highly protected. Many people may choose to get a booster dose at 7 months, 8 months, 9 months, or 10 months.

Motion/Vote #1

Dr. Oliver (CDC/NCIRD) posted the following proposed recommendation for ACIP Vote #1 Interim Recommendation:

> *A single Pfizer-BioNTech COVID-19 vaccine booster dose is recommended for persons aged **≥65 years**, and **long-term care facility (LTCF)** residents, at least 6 months after the primary series under the FDA's Emergency Use Authorization.*

Motion/Vote #1 Interim Recommendation

Dr. Ault made a motion, which Dr. Poehling seconded, to adopt the language for Vote #1 as presented. No COIs were declared. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Motion/Vote #2

Dr. Oliver (CDC/NCIRD) posted the following proposed recommendation for ACIP Vote #2 Interim Recommendation:

> *A single Pfizer-BioNTech COVID-19 vaccine booster dose is recommended for persons aged **50-64 years** with **underlying medical condition** at least 6 months after the primary series under the FDA's Emergency Use Authorization.*

Motion/Vote #2 Interim Recommendation

Dr. Poehling made a motion, which Dr. Daley seconded, to adopt the language for Vote #2 as presented. No COIs were declared. The motion carried with 13 affirmative votes, 2 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Motion/Vote #3

Dr. Oliver (CDC/NCIRD) posted the following proposed recommendation for ACIP Vote #3 Interim Recommendation:

> *A single Pfizer-BioNTech COVID-19 vaccine booster dose is recommended for persons based on **individual benefit and risk** who are aged **18-49 years** with **underlying medical conditions**, at least 6 months after the primary series under the FDA's Emergency Use Authorization.*

Motion/Vote #3 Interim Recommendation

Dr. Brooks made a motion, which Dr. Ault seconded, to adopt the language for Vote #3 as presented. No COIs were declared. The motion carried with 9 affirmative votes, 6 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Motion/Vote #4

Dr. Oliver (CDC/NCIRD) posted the following proposed recommendation for ACIP Vote #4 Interim Recommendation:

> *A single Pfizer-BioNTech COVID-19 vaccine booster dose is recommended based on **individual benefit and risk** for persons aged **18-64 years** who are in an **occupational or institutional setting** where the burden of COVID-19 infection and risk of transmission are high, at least 6 months after the primary series under the FDA's Emergency Use Authorization.*

Discussion Points

Dr. Long thought this proposed recommendation was very difficult to interpret and too open-ended in the way it was stated. These are properly vaccinated people for whom it is known that the risks of breakthrough and severe disease are very low. Moreover, there is a lack of data for need in any of these groups.

Dr. Sanchez agreed with Dr. Long and thought they might as well just recommend that the booster dose be given to everybody 18 years of age and older. They should not give the impression that the vaccine in not working. The Pfizer-BioNTech COVID-19 vaccine is highly effective and is working, though certainly some higher risk individuals have some waning immunity with time.

Dr. Lee emphasized to clinicians and the public that the benefit/risk balance is individualized. ACIP has previously discussed the risk of myocarditis following vaccination and the many uncertainties around that. She wanted to make sure that if individuals choose to receive an additional dose that they do weigh the benefits and risks to themselves, particularly if they are younger and male receiving an mRNA vaccine. There are many individual patients and scenarios for whom she does believe access would be helpful for them and their families. While

she also was torn about this recommendation, she favored it in part because she felt like in this case access and outstanding patient, public, and provider education are needed. If this all could be done together, it would preserve access for individuals and their families.

Dr. Brooks spoke in favor of the motion. He acknowledged that everything everyone had said thus far was basically true, what was the conundrum. Given that these are difficult decisions, an individual benefit and risk determination must be made. If someone who is 18 and works in a shelter feels that he or she needs a booster, that would be the individual decision. However, he does not believe everyone who is 18 who works in a shelter is going to go get a booster. Some who is 64 years of age working in a shelter might decide to get a booster. He thought the language of the proposed recommendation spoke to everything people were saying and reflected that this is where the pandemic is right now.

Dr. Kotton highlighted that while this is a huge category of people, it may be one of the ways to better protect the estimated 3% of the US population who are immunocompromised and at higher risk and may not be well-protected even after a third dose of vaccine. Better protecting the people around them, often referred to as “cocooning” the patient, may help protect them. While she did not like the language proposed and preferred to delay on this recommendation, but would vote yes if they did take a vote at this time.

Dr. Sanchez pointed out that this proposed recommendation may not take into account the cocooning effect for pediatric patients, given that those parents or caregivers may not be in an occupational or institutional setting. With the vaccines mandates that are being proposed and implemented, including in healthcare settings, he thought it would be important if this recommendation passed, it would be necessary to ensure that a fully vaccinated person has received a booster dose.

Dr. Cohn reminded everyone that vaccine safety is the top priority. As individuals get boosters, vaccine safety data will be presented again to ACIP in the very near future. If there are any concerning signals for increased risk of myocarditis in younger persons who receive a booster, those data will be presented immediately to ACIP for consideration. Just like the original vaccine rollout, vaccine safety will remain a top priority.

Dr. Lee asked whether the word “institution” needed to be included or if they could state “occupation or setting where the burden of COVID infection and risk of transmission are high?”

Dr. Cohn said that they could change the language to state, “Recommended based on individual benefits and risks for persons aged 18-64 who are in an occupation or setting where the burden of COVID-19, acute infection, and risk of transmission are high.” They could vote on that language if ACIP preferred, but they would have to ensure that the language was well-aligned with the FDA language.

It appeared to Dr. Long that ACIP would be expanding on the FDA approval. While they could do this, it is very unusual for ACIP to let light shine between the FDA and the CDC in terms of expansion. This does not at all include the requirement as she understood it for risk of severe COVID disease. It is very unusual for ACIP to let individuals decide on vaccine policy.

Dr. Lee pointed out that they should vote the intent and then seek additional guidance from CDC and FDA colleagues to ensure that the intent was as written.

Dr. Cohn added that to stay within the spirit and intent of the FDA language, she would like to keep “occupational or institutional setting.” She emphasized that these recommendations will continue to evolve.

Ms. McNally found this to be challenging because she thought they were making some assumptions about health literacy that may be problematic, and that implementation of this recommendation would be very challenging.

Dr. Lee agreed and stressed that she was struggling with how much to assume and enable or not enable access versus how much needs to be done to move forward and put out all tools possible, which will never be enough, to ensure that everyone is fully educated on the benefits and risks.

Ms. Stinchfield (NAPNAP) added that in terms of implementation, the proof of one’s risk in a clinical, public health, or pharmacy setting would be next to impossible to ascertain. She has done a lot of mass vaccination clinics for HCW and communities. The burden would be high and cause undue stress on a stressed out healthcare system if people have to go to their clinicians to acquire documentation and then take that to a community vaccine setting.

Dr. Dooling reminded everyone that approximately 70% of COVID vaccines are now given in the setting of a pharmacy. As with the primary series, any booster would require self-attestation and no additional onus for documentation.

Dr. Chen said that he had been very uncomfortable with his own thinking through Vote #3, and he was even more uncomfortable with Vote #4. The focus of this proposed recommendation was not really about direct benefit to the person being vaccinated, but instead focused on indirect benefit to the people surrounding them. It is known that indirect benefit is largely to be gained by getting their primary series. It is not the answer to give them boosters, especially for this age group that does not have underlying medical conditions or predictors that would put them at the highest risk for severe effects of COVID infection. Again, the implementation aspects of this would be fraught with such complexity such that people with great health literacy will get boosters even though they are not really the ones who will get incremental benefit from this or indirect benefit for the people around them.

Dr. Drees (SHEA) noted that from a healthcare workforce perspective, she agreed with Dr. Long that most of these people are not at risk for severe disease, they certainly have been getting infected at increasing rates over the last month or so even though they are fully vaccinated. It is difficult to predict which ones will develop long COVID symptoms. They have been on the frontlines from the beginning and even though they have and use PPE to protect themselves, it is very frustrating and demoralizing to them to get COVID anyway. Therefore, she thought it was reasonable to include them in this vote.

Dr. Long emphasized that the goal should be use the vaccines in hand to immunize everyone in order to protect people from severe morbidity and death and not have to worry about who has coronavirus, who cannot go to school, et cetera. Primary prevention and prevention of the worst cases must be dealt with, which are no doubt going to be the most contagious. She did not think this vaccine would protect against acquisition or transmission for more than a couple of months—even the booster.

Dr. Cohn emphasized that this was not an either/or vote. The primary focus of public health is and will remain on the primary series and there is ample vaccine supply. She appreciated all of the very important concerns raised, but reiterated that this vote would be to allow an individual in one of these settings make a decision to have access to and be vaccinated with a booster dose.

Dr. Shah (ASTHO) commented that from a state health department perspective, this would be exceedingly challenging from an implementation perspective. The analysis required to effectuate this recommendation proceeds along two axes. The first is the pros and cons of the individual benefit determination and then secondarily or in concert with that is the nature of the occupational and institutional risk. Many patients themselves may not know exactly what the components of the individual risk information, let alone their occupational risks. Even if a patient were to know that information, the staff in a pharmacy or a largescale vaccination site on a given day may themselves not have the wherewithal to make that determination and effectuate it in the manner that ACIP may intend. He certainly agreed with the public health spirit underlying the proposed recommendation, but posited that this would result in the inevitable confusion and patchwork that occurred back in January and February.

Dr. Zahn (NACCHO) said that speaking from the local public health standpoint, this recommendation would be extraordinarily difficult to implement. It essentially would convey to individuals to assess their own situation and get vaccinated with a booster if they think it is appropriate. As Dr. Chen noted, people are vaccinated to protect themselves. In most of the high risk situations mentioned, people actually acquire infection at home or in the community. For instance, the primary risk for HCW acquiring COVID-19 is in the community. From a public health standpoint, it is important to convey that a vaccine is being recommended to protect the recipient rather than making them more consistently available as part of a workforce.

Dr. Talbot emphasized that HCW are getting COVID in the community and their children are going back to school and cannot yet be vaccinated. The longer that HCW are symptomatic or have even a mild COVID illness, they cannot go to work and hospitals cannot be sufficiently staffed. Many states are experiencing this issue and having the option to give HCW a third dose will help to maintain staffing. While there are caveats and groups who may not be the best fit for this recommendation, HCW are critical and cannot be forgotten.

Dr. Goldman (ACP) said he thought this was a solution looking for a problem that would not address the issue of the pandemic and that would create more confusion for providers at the implementation level. In addition, he thought it was going far afield of the data and what they are trying to accomplish from a public health perspective.

Dr. Lee made a personal comment that she did not support this as a full recommendation because of all of the concerns raise throughout the day. She has cared for children who have died from COVID, whose family members wished that they had extra protection for their children because they were not symptomatic and no one else was sick at home. Some family members wish to provide this extra level of protection and are willing to take that risk. Although she shared all of the same concerns about safety, health literacy, et cetera, access was very important to her and she worried that by inhibiting access to this, some individuals and families may suffer. If this were a full standard recommendation, she could not personally support it. Because it allowed for an individual risk/benefit decision, she viewed this as different.

Dr. Daley said he was struggling with this as well. Another consideration was that it felt broad enough that it potentially could limit access to other groups such as those over 65 years of age and those 18-64 with high risk conditions. He appreciated the intent of the proposed recommendation and agreed that they needed to think very carefully about the HCW workforce and staffing issues.

Motion/Vote #4 Interim Recommendation

Dr. Ault made a motion, which Dr. Kotton seconded, to adopt the language for Vote #4 as presented. The motion did not carry with 6 affirmative votes, 9 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Points

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

Dr. Talbot requested to make an amendment to the language for a revote on the fourth interim recommendation.

Dr. Cohn responded that given the fact that the meeting had already gone over by 1.5 hours, additional votes would not be entertained and the meeting would be officially closed following any comments from ACIP members regarding their votes. However, consideration would be given to bringing this issue back to the table with potentially different options. There are several ACIP meetings ahead during which this could be done.

Ms. Bahta said she felt like they were being pulled into an emotional decision. The science shows that this is a very effective vaccine. This decision was made for the vaccinated, not the unvaccinated. She did not believe they had the data in the younger age groups to make a decision for a booster dose. To her, it would suggest that the vaccine does not work. While they know this is not true, that is likely how that message will be conveyed to the broader public. That was why she voted “not” for the third and fourth interim recommendations.

Dr. Ault indicated that he voted “yes” on the third recommendation because it would allow clinicians maximum leeway. There were some public comments and written comments in the docket stated the same thing. He voted “yes” on the fourth vote because like Dr. Talbot pointed out, there are areas with tremendous amounts of community spread where all hospitals big and small operating on the thinnest of margins. For HCW to be sick or take time off of work places systems at risk.

Dr. Bell agreed with everything Dr. Bahta said in explaining why she voted “no” and also to emphasize that this represented the beginning of a lot of activity around booster doses and other vaccination efforts that are forthcoming. In this situation, at this moment, and given the lack of evidence about the marginal benefits of booster doses for people in certain groups who received a Pfizer primary series, it was too narrow and too soon. In terms of the potential risks for adverse outcomes of waiting until more is known, there was little marginal benefit to making this booster dose available at this time in her opinion given all of the unknowns.

Dr. Poehling pointed out that during the 30 hours since this meeting started, approximately 2400 Americans died of COVID-19 and most of them were unvaccinated. This COVID-19 vaccine is the most studied vaccine in the US. The development and extensive evaluation and distribution of this vaccine, especially with such extraordinary cold-chain requirements, is an incredible example of what can be accomplished when data are openly shared and everyone collaborates and works together to achieve a goal. What has been learned about COVID-19 provides tremendous hope for the future, and it is possible to get to the other side of this pandemic by truly working together. It will require everyone. This biggest impact on the pandemic, which has been mentioned many times, has come from increasing vaccine coverage with the primary series and using the recommended measures. ACIP has openly shared what is and is not known. They should highlight that there is a lot that is known and that the primary series is highly effective. There is waning for persons over 65 years of age and there is concern about persons in LTCF and those 50 years of age and older with high risk conditions. For those reasons, she voted “yes.” While they do want to provide additional protection for those at increased risk, the most important thing they can do is ensure that they do not take away efforts from the primary series.

Closing Remarks and Adjournment

Dr. Lee (ACIP Chair) thanked the speakers, CDC colleagues, members, *ex officio* members, and liaisons for an incredible 2-day meeting. She expressed appreciation for everyone’s input and respect for diverse opinions, as well as her hope that the discussions would be helpful to their colleagues who need to be able to explain policies and recommendations to their constituents. She anticipated that there would be another meeting soon as the data continued to evolve. As information emerges, ACIP will continue to be updated.

Dr. Cohn (ACIP Executive Secretary, CDC) reminded everyone that there would be a non-COVID meeting on September 20, 2021 that would include a full day of exciting updates and information about everything but COVID. However, the agenda could be adjusted accordingly if new data emerge.

With no further business raised or questions posed, the meeting was officially adjourned.

Certification

Upon reviewing the foregoing version of the September 22-23, 2021 ACIP summary minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate.

ACIP Membership Roster

CHAIR
LEE, Grace M., MD, MPH
Associate Chief Medical Officer for Practice Innovation
Lucile Packard Children's Hospital
Professor of Pediatrics, Stanford University School of Medicine
Stanford, CA
Term: 8/4/2021 – 6/30/2023

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

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

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

BELL, Beth P, MD, MPH
Clinical Professor
Department of Global Health, School of Public Health
University of Washington
Seattle, WA
Term: 7/1/2019 – 6/30/2023

BROOKS, Oliver, MD, FAAP
Chief Medical Officer
Watts HealthCare Corporation
Los Angeles, CA
Past President, National Medical Association
Term: 7/26/2021 – 6/30/2025

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

CINEAS, Sybil, MD, FAAP, FACP
Associate Professor of Medicine, Pediatrics, and Medical Science (Clinical)
The Warren Alpert Medical School of Brown University
Associate Program Director
Brown Combined Residency in Internal Medicine and Pediatrics
Providence, RI
Term: 7/28/2021 – 6/30/2025

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

KOTTON, Camille Nelson, MD, FIDSA, FAST
Clinical Director, Transplant and Immunocompromised Host Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Associate Professor of Medicine, Harvard Medical School
Boston, MA
Term: 12/23/2020 – 6/30/2022

LOEHR, James, MD, FAAFP
Owner, Cayuga Family Medicine
Ithaca, New York
Term: 7/26/2021 – 6/30/2025

LONG, Sarah S, MD
Professor of Pediatrics
Drexel University College of Medicine
Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania
Term: 12/24/2020 – 6/30/2024

MCNALLY, Veronica V, JD
President and CEO Franny
Strong Foundation
West Bloomfield, Michigan
Term: 10/31/2018 – 6/30/2022

POEHLING, Katherine A, MD, MPH
Professor of Pediatrics and Epidemiology and Prevention
Director, Pediatric Population Health
Department of Pediatrics
Wake Forest School of Medicine
Winston-Salem, NC
Term: 7/1/2019 – 6/30/2023

SÁNCHEZ, Pablo J, MD
Professor of Pediatrics
The Ohio State University – Nationwide Children's Hospital
Divisions of Neonatal-Perinatal Medicine and Pediatric Infectious Diseases
Director, Clinical & Translational Research (Neonatology)
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio
Term: 7/1/2019 – 6/30/2023

TALBOT, Helen Keipp, MD
Associate Professor of Medicine
Vanderbilt University
Nashville, TN
Term: 10/29/2018 – 6/30/2022

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification Centers
for Medicare and Medicaid Services
Baltimore, MD

Food and Drug Administration (FDA)
FINK, Doran, MD, PhD
Deputy Director, Clinical, Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Silver Spring, MD

Health Resources and Services Administration (HRSA)
RUBIN, Mary, MD
Chief Medical Officer
Division of Injury Compensation Programs
Rockville, MD

Indian Health Service (IHS)
WEISER, Thomas, MD, MPH
Medical Epidemiologist
Portland Area Indian Health Service
Portland, OR

Office of Infectious Disease and HIV/AIDS Policy (OIDP)
KIM, David, MD, MA
Director, Division of Vaccines, OIDP
Office of the Assistant Secretary for Health
Department of Health and Human Services
Washington, DC

National Institutes of Health (NIH)
BEIGEL, John, MD
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases (NIAID)
Bethesda, MD

LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
ROCKWELL, Pamela G, DO
Associate Professor, Department of Family Medicine, University of Michigan Medical School
Medical Director, Dominos Farms Family Medicine
Ann Arbor, MI

American Academy of Pediatrics (AAP)
MALDONADO, Yvonne, MD
Senior Associate Dean for Faculty Development and Diversity
Professor of Pediatrics and Health Research and Policy
Chief, Division of Pediatric Infectious Diseases
Stanford University School of Medicine
Stanford, CA

American Academy of Pediatrics (AAP)
Red Book Editor
KIMBERLIN, David, MD
Professor of Pediatrics
Division of Pediatric Infectious Diseases
The University of Alabama at Birmingham School of Medicine
Birmingham, AL

American Academy of Physician Assistants (AAPA)
LÉGER, Marie-Michèle, MPH, PA-C
Senior Director, Clinical and Health Affairs
American Academy of Physician Assistants
Alexandria, VA

American College Health Association (ACHA)
CHAI, Thevy S., MD
Director of Medical Services
Campus Health Services
University of North Carolina at Chapel Hill
Chapel Hill, NC

American College Health Association (ACHA) (alternate)
MCMULLEN, Sharon, RN, MPH, FACHA
Assistant Vice President of Student & Campus Life for Health and Wellbeing Cornell Health
Ithaca, NY

American College of Nurse Midwives (ACNM)
HAYES, Carol E., CNM, MN, MPH
Lead Clinician
Clinical Quality Compliance and Management
Planned Parenthood Southeast Atlanta, GA

American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
Midwifery Educator, Human Resources for Health
In partnership with University of Rwanda and University of Illinois, Chicago

American College of Obstetricians and Gynecologists (ACOG)
ECKERT, Linda O, MD, FACOG
Professor, Department of Obstetrics & Gynecology
Adjunct Professor, Department of Global Health
University of Washington
Seattle, WA

American College of Physicians (ACP)
GOLDMAN, Jason M, MD, FACP
Affiliate Assistant Professor of Clinical Biomedical Science, Florida Atlantic University, Boca Raton, Florida
Private Practice
Coral Springs, FL

American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics Geriatrics
Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)
GLUCKMAN, Robert A, MD, MACP
Chief Medical Officer, Providence Health Plans
Beaverton, OR

American Immunization Registry Association (AIRA)
COYLE, Rebecca, MSEd
Executive Director, AIRA Washington, DC

American Medical Association (AMA)
FRYHOFER, Sandra Adamson, MD
Adjunct Associate Professor of Medicine Emory
University School of Medicine
Atlanta, GA

American Nurses Association (ANA)
RITTLE, Charles (Chad), DNP, MPH, RN Assistant
Professor, Nursing Faculty
Chatham University, School of Health Sciences
Pittsburgh, PA

American Osteopathic Association (AOA)
GROGG, Stanley E, DO
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)
FOSTER, Stephan L, PharmD CAPT
(Ret) USPHS
Professor, College of Pharmacy
University of Tennessee Health Sciences Center
Memphis, TN

Association of Immunization Managers (AIM)
HOWELL, Molly, MPH
Immunization Program Manager
North Dakota Department of Health
Bismarck, ND

Association for Prevention Teaching and Research (APTR)
ZIMMERMAN, Richard, MD, MPH
Professor, University of Pittsburgh School of Medicine
Department of Family Medicine and Clinical Epidemiology
Pittsburgh, PA

Association of State and Territorial Health Officials (ASTHO)
SHAH, Nirav D, MD, JD
Director
Maine Center for Disease Control and Prevention
Augusta, ME

Biotechnology Industry Organization (BIO)
ARTHUR, Phyllis A, MBA
Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy
Washington, DC

Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD
State Epidemiologist
Office of Epidemiology, Food Protection and Immunization Idaho
Department of Health and Welfare
Boise, ID

Council of State and Territorial Epidemiologists (CSTE) (alternate)
LETT, Susan, MD, MPH
Medical Director, Immunization Program
Division of Epidemiology and Immunization
Massachusetts Department of Public Health
Boston, MA

Canadian National Advisory Committee on Immunization (NACI)
QUACH, Caroline, MD, MSc
Pediatric Infectious Disease Specialist and Medical Microbiologist
Medical Lead, Infection Prevention and Control Unit
Medical Co-director – Laboratory Medicine, Optilab
Montreal-CHUM
Montreal, Québec, Canada

Infectious Diseases Society of America (IDSA)
BAKER, Carol J., MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

International Society for Travel Medicine (ISTM)
BARNETT, Elizabeth D, MD Professor of
Pediatrics
Boston University School of Medicine
Boston, MA

National Association of County and City Health Officials (NACCHO)
ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of County and City Health Officials (NACCHO) (alternate)
DUCHIN, Jeffrey, MD
Health Officer and Chief, Communicable Disease
Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine
Division of Allergy and Infectious Diseases
University of Washington School of Medicine and School of Public Health
Seattle, WA

National Association of Pediatric Nurse Practitioners (NAPNAP)
STINCHFIELD, Patricia A, RN, MS, CPNP
Director
Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)
SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Foundation for Infectious Diseases (NFID) (alternate)
DALTON, Marla, PE, CAE
Executive Director & CEO
National Foundation for Infectious Diseases (NFID)
Bethesda, MD

National Medical Association (NMA)
WHITLEY-WILLIAMS, Patricia, MD Professor and Chair
University of Medicine and Dentistry of New Jersey Robert Wood
Johnson Medical School
New Brunswick, NJ

Pediatric Infectious Diseases Society (PIDS)
O'LEARY, Sean, MD, MPH
Associate Professor of Pediatrics
Pediatric Infectious Diseases
General Academic Pediatrics
Children's Hospital Colorado
University of Colorado School of Medicine

Pediatric Infectious Diseases Society (PIDS) (alternate)
SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pharmaceutical Research and Manufacturers of America (PhRMA)
ROBERTSON, Corey, MD, MPH
Senior Director, US Medical, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B, MD, MSEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)
DREES, Marci, MD, MS
Chief Infection Prevention Officer & Hospital Epidemiologist
ChristianaCare
Wilmington, DE
Associate Professor of Medicine
Sidney Kimmel Medical College at Thomas Jefferson University Philadelphia, PA

Acronyms Used in the Document

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
AMA	American Medical Association
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APRN	Advanced Practice Registered Nurse
ASTHO	Association of State and Territorial Health Officers
BLA	Biologics License Application
Caltech	California Institute of Technology
CBER	Center for Biologics Evaluation and Research
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CICP	Countermeasures Injury Compensation Program
CID	*Clinical Infectious Disease*
CISA	Clinical Immunization Safety Assessment
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CLI	COVID-Like Illness
CMI	Cell-Mediated Immunity
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
COVID-NET	COVID-19-Associated Hospitalization Surveillance Network
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DFO	Designated Federal Official
DNA	Deoxyribonucleic Acid
DNR/DNI	Do Not Resuscitate/Do Not Intubate
DoD	Department of Defense
DPA	Dynamic Pregnancy Algorithm
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EDD	Estimated Data of Delivery
EHR	Electronic Health Record
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EU	European Union

EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FQHC	Federally Qualified Health Center
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GEE	Generalized Estimating Equation
GMC	Geometric Mean Concentration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HCO	Health Care Organization
HCP	Healthcare Personnel / Providers
HCW	Health Care Workers
HEROES-RECOVER	Healthcare, Emergency Response, and Other Essential Workers Surveillance Study-Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel
HHS	(Department of) Health and Human Services
HRSA	Health Resources and Services Administration
ICATT Partnership	Increasing Community Access to Testing Partnership
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IIS	Immunization Information Systems
IM	Intramuscular
ISD	Immunization Services Division
ISO	Immunization Safety Office
IVAC	International Vaccine Access Center
IVY Network	Influenza and Other Viruses in the Acutely Ill Network
KPSC	Kaiser Permanente Southern California
LSR	Living Systematic Review
LTCF	Long-Term Care Facilities
MMWR	*Morbidity and Mortality Weekly Report*
MI	Myocardial Infarction
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
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHSN	National Healthcare Safety Network
NIAID	National Institute of Allergy and Infectious Diseases
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
PBMC	Peripheral Blood Mononuclear Cell
PCP	Primary Care Provider/Practitioner
PCR	Polymerase Chain Reaction

PEA	Pregnancy Episode Algorithm
PHAC	Public Health Agency Canada
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PPE	Personal Protective Equipment
PREP Act	Public Readiness and Emergency Preparedness Act
RA	Rheumatoid Arthritis
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RN	Registered Nurse
RNA	Ribonucleic Acid
ROA	Route of Administration
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
SDOH	Social Determinants of Health
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SNF	Skilled Nursing Facility
SUPERNOVA Network	SUrveillance Platform for Enteric and Respiratory iNfectious Organisms at the VA Network
SVI	Social Vulnerability Index
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
URI	Upper Respiratory Infection
US	United States
USG	United States Government
VA	(US Department of) Veteran’s Affairs
VAERS	Vaccine Adverse Event Reporting System
VaST WG	Vaccine Safety Technical Work Group
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
VYF	Vaccinate Your Family
WG	Work Group
WHO	World Health Organization