MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JULY 19, 2022
EXECUTIVE SUMMARY

CONTENTS

MEETING PURPOSE

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on July 19, 2022. The meeting took place remotely via Zoom, teleconference, and live webcast. This document provides a summary of the meeting, which focused on the epidemiology of COVID-19; COVID-19 vaccine coverage; updates on vaccine-associated myocarditis; Novavax COVID-19 vaccine safety, immunogenicity, and efficacy in adults ages 18 years and older; Evidence to Recommendations (EtR) Framework: Novavax COVID-19 vaccine for adults ≥18 years of age; Clinical Considerations update; and a vote on Novavax COVID-19 vaccine in adults ages 18 years and older.

TUESDAY: JULY 19, 2022

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Grace Lee (ACIP Chair) called to order and presided over the July 19, 2022 ACIP meeting. She conducted a roll call, which established that a quorum was present. No conflicts of interest (COIs) were declared. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document.

CDC Announcements

Dr. Melinda Wharton (ACIP Executive Secretary, CDC) noted that copies of the slides for the day were available on the ACIP website and were made available through a ShareLink™ file for voting ACIP Voting Members, *Ex Officios*, and Liaisons. She indicated that the ACIP is at its heart a public body. Engagement with the public and transparency in the ACIP processes is vital to the committee's work. She indicated that there would be an oral public comment session prior to the vote at approximately 12:20 PM Eastern Time (ET). To create a fair and more efficient process for requesting to make an oral comment, people interested in making an oral comment are requested to submit a request online in advance of the meeting. Priority is given to these advanced requests, and if more people request to speak than can be accommodated, a blind lottery is conducted to determine who the speakers will be. Speakers selected in the lottery for this meeting were notified in advance of the meeting. Members of the public also can submit public comments through https://www.regulations.gov using Docket Number CDC-2022-0085. Information on the written public comment process, as well as information on how to make a comment, can be found on the ACIP meeting website.

As noted in the ACIP Policies and Procedures manual, ACIP members agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, CDC has issued limited COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those vaccines, but these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions with the provision that he or she abstains from all votes related to the vaccines of

that company. ACIP members state any COIs at the beginning of each meeting. Applications and nominations are currently being accepted for candidates to fill upcoming vacancies on the ACIP practices. Detailed instructions for submission of names for potential candidates to serve as ACIP members are now available on the ACIP website. The deadline for applications for ACIP membership has been extended to August 15, 2022 for the 4-year year term beginning in July 2023 at which time 6 positions will be filled, including a Consumer Representative position.

CORONAVIRUS DISEASE 2019 (COVID-19) VACCINES

Session Introduction

Dr. Matthew Daley (ACIP, WG Chair) provided the session introduction on behalf of the ACIP COVID-19 Vaccines Work Group (WG). He reported that in terms of trends in daily number of COVID-19 cases in the US from the start of the pandemic and July 14, 2022, there have been more than 89 million cases reported in the US.[1] In total, there have been more than 1 million deaths due to COVID-19 reported in the US since the beginning of the pandemic.[2] Depending upon the data source, between 10.3% and 13.9%[3] of all adults in the US have not received any vaccines. That translates to approximately 26 to 37 million US adults who have not yet received a COVID-19 vaccine. Among those who have received at least 1 dose, there are many individuals who need to complete the primary series and their booster, so they are not fully protected. Since ACIP last met, the COVID-19 Vaccines WG has reviewed data on the epidemiology of COVID-19 in adults; COVID-19 vaccine coverage in adults; the benefits of COVID-19 vaccination in adults; rare events of myocarditis following COVID-19 vaccination; and safety and the efficacy of the Novavax COVID-19 vaccine 2-dose primary series in adults ≥18 years of age. In addition, the COVID-19 Vaccines WG developed its interpretation of the safety and efficacy of the Novavax COVID-19 vaccine primary vaccine series.

Epidemiology of COVID-19 & COVID-19 Vaccine Coverage

Katherine E. Fleming-Dutra, MD (COVID-19 Epidemiology Task Force, CDC) reiterated that from the beginning of the pandemic through July 14, 2022, there have been more than 89 million total recorded cases of COVID-19 in the US, and that the 7-day moving average was more than 120,000 cases per day at that time. The COVID-19 pandemic has disproportionately affected certain racial and ethnic communities. Hispanic/Latino persons, American Indian/ Alaska Native (AI/AN) persons, and persons of multiple/other races who are non-Hispanic have been disproportionately affected by COVID-19 infections.[4] The Omicron variant is currently predominant in the US. Through the week ending July 9th, Omicron has been over 99% predominant for many months. The BA.5 sub-lineage has comprised 65% of specimens and BA.4 has compromised 16.3%.[5]

[1] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed July 14, 2022
[2] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths Accessed July 13, 2022; Per National Center for Health Statistics Death Certificate Data: Total number of COVID-19 total deaths as of July 13, 2022, were 1,015,431. https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#AgeAndSex
[3] COVIDVaxView. Estimates produced by NORC at the University of Chicago using CDC's National Immunization Survey-Adult COVID-19 Module (NIS-ACM). https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html. Accessed July 14, 2022 COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-additional-dose-totalpop. Accessed on July 13, 2022.
[4] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed July 11, 2022.
[5] https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed July 13, 2022

During the pandemic, there have been more than 4.9 million total hospital admissions for COVID-19. Focusing on the most recent time period, there has been an uptick in hospitalizations since April 2022. The vast majority (97.2%) of these admissions are occurring among adults 18 years of age and older. Higher hospitalization rates occur in the older age groups. Patients ≥70 years of age, 60-69 years of age, and 50-59 years of age have the highest admission rates, followed by other adult age groups. Importantly, recent increases in hospitalization rates have been driven by older age groups, especially among patients ≥70 years of age.[6] Looking at COVID-19-associated hospitalization rates by race and ethnicity, COVID-NET provides more granular information on COVID-19-associated hospitalizations. Cumulative population-based rates of COVID-19-associated hospitalizations through June 25th among persons of all ages by race and ethnicity show that AI/AN persons, Black persons, and Hispanic/Latino persons have been disproportionately affected by COVID-19-associated hospitalizations.[7]

In terms of mortality due to COVID-19 reported in the US since the beginning of the pandemic, tragically, there have been 1,018,578 deaths due to COVID-19 reported to CDC cumulatively in the US as of July 14, 2022.[8] In terms of weekly trends in COVID-19-associated mortality rates by age group, data show that higher mortality rates are consistently observed in older age groups and more than 99% of deaths occur in adults. The highest mortality rates occur among those ≥75 years of age, 65-74 years of age, and 50-64 years of age.[9] Similar to hospitalization rates, there has been a recent increase in COVID-19 death rates among older age groups, especially among those ≥75 years of age. Looking at weekly COVID-19 mortality rates by race and ethnicity over the course of the pandemic, there has been a changing and complex relationship between race and ethnicity and mortality rates. Early in the pandemic, Black persons had the highest rate of death compared to persons of other race and ethnicities. AI/AN persons have been disproportionately affected throughout much of the pandemic. During the Omicron surge, Hispanic persons have had the highest rate of COVID-19 mortality.[10] Race and ethnicity are risk markers for other underlying conditions that affect health, including socioeconomic status (SES), access to healthcare, and exposure to the virus related to occupation (e.g., frontline, essential, and critical infrastructure workers).

Regarding COVID-19 disease trends by vaccination status as of June 2022, unvaccinated people ≥5 years of age had a 2.8 times higher risk of testing positive for COVID-19 compared to people vaccinated with at least a primary series.[11] Looking at age adjusted rates of COVID-19-associated hospitalizations by vaccination status in adults ≥18 years of age, hospitalizations for COVID-19 were higher among unvaccinated persons than among vaccinated persons. In May 2022, unvaccinated adults ≥18 years of age had a 3.5 times higher risk of COVID-19-associated hospitalization compared to people who completed a primary vaccine series and received at least one booster or additional dose.[12] In terms of the age-adjusted rates of COVID-19-associated deaths by vaccination status, unvaccinated people ≥12 years of age had higher mortality rates than people who received a primary series or a primary series and a booster dose. In May 2022, unvaccinated people ≥12 years of age had a 9 times higher risk of dying

[6] Unified Hospital Dataset: https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions. Accessed July 13, 2022
[7] COVID-NET: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed July 8, 2022
[8] Source: CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths. Accessed July 18, 2022; Per National Center for Health Statistics Death Certificate Data: Total number of COVID-19 total deaths as of July 13, 2022, were 1,015,431; https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#AgeAndSex. Accessed July 18, 2022
[9] https://covid.cdc.gov/covid-data-tracker/#demographicsovertime and https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed July 11, 2022.
[10] https://covid.cdc.gov/covid-data-tracker/#demographicsovertime. Accessed July 11, 2022.
[11] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status. Accessed July 15, 2022
[12] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination. Accessed July 11, 2022

from COVID-19 compared to people vaccinated with a primary series and a booster dose.[13] The benefits of vaccination are more pronounced when the disease burden is high. With future COVID-19 surges, the unvaccinated will continue to bear the burden of disease.

It is important to note that monitoring rates of cases, hospitalizations, and deaths by vaccination status has limitations. These are not vaccine effectiveness (VE) studies. VE studies offer a more robust analyses as compared with surveillance and a better understanding of how well vaccines are working in periods of high and low disease incidence.

In terms of opportunities to increase COVID-19 vaccination rates among US adults who have yet to receive a COVID-19 vaccine and thus would be eligible for a primary series with Novavax vaccine should ACIP recommend this vaccine, trends over time by age group and the percent of people who have received at least one dose of COVID-19 vaccine show that vaccination coverage is higher in older age groups. As of July 6, 2022, just over 20% of US adults 18 through 24 years of age, just under 20% of adults 25 through 39 years of age, and 13% of adults 40 through 49 years of age have yet to receive a COVID-19 vaccine.[14] Data from CDC's National Immunization Survey Adult COVID-19 Module (NIS-ACM) and vaccine administration data from COVID Data Tracker show the percent of US adults ≥ages 18 years of age who have not yet received a COVID-19 vaccine. The NIS-ACM conducted in May 2022 showed that 13.9% of surveyed adults reported not yet receiving a COVID-19 vaccine versus 10.3% of the vaccine administration data in COVID Data Tracker. Using these data and Census data, it can be estimated that there are about 26 to 37 million US adults who have not yet received a COVID-19 vaccine.[15]

Data by race and ethnicity from May 2022 in the NIS-ACM show that 22% of persons of Other/ Multiple races, 20% of AI/AN persons, 14% of Hispanic persons, and 14% of White persons have yet to receive a COVID-19 vaccine. Looking at the same data stratified by age group and race/ethnicity, higher proportions of younger adults 18 through 49 years of age remain unvaccinated than among older age groups. Among adults ages 18 through 49 years, people of Other/Multiple races who are non-Hispanic have the highest percentages remaining unvaccinated, while Hispanic persons have the lowest percentages remaining unvaccinated. Among adults 50 through 64 years of age, people of Other/Multiple races who are non-Hispanic have the highest percentages remaining unvaccinated and Black persons in this age group have the lowest proportion remaining unvaccinated. Very few adults ≥65 years of age remain unvaccinated. Looking at the same data by Metropolitan Statistical Area (MSA), a higher percentage of US adults living in rural areas remain unvaccinated as compared to those living in suburban or urban areas. Looking at the same data by income and poverty status, a higher percentage of US adults with incomes less than $75,000, particularly those living below poverty, remain unvaccinated compared to adults are higher incomes. Looking at these data by markers of access to healthcare, a higher percentage of US adults who do not have a regular primary care provider (PCP) remain unvaccinated compared to those who do and a higher

[13] adults ages ≥50 years and immunocompromised individuals. CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status. Accessed July 15, 2022

[14] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends. Accessed July 11, 2022.

[15] COVIDVaxView. Estimates produced by NORC at the University of Chicago using CDC's National Immunization Survey-Adult COVID-19 Module (NIS-ACM). https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html. Accessed July 14, 2022 COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-additional-dose-totalpop. Accessed on July 13, 2022.

percentage of those who do not have health insurance remain unvaccinated compared to those who have health insurance.[16]

In conclusion, as of July 14, 2022, more than 89 million COVID-19 cases and more than 1 million COVID-19 deaths have occurred in the US. COVID-19 continues to cause new cases, hospitalizations, and deaths. COVID-19 has contributed to health inequities. AI/AN, Black, and Hispanic/Latino persons have been disproportionately affected by COVID-19-associated hospitalizations and deaths. Vaccination is known to prevent COVID-19 cases, hospitalization, and deaths. However, about 26 to 37 million US adults have not yet received a COVID-19 vaccine. These adults will benefit from starting a COVID-19 vaccine primary series.

Discussion Summary

Dr. Poehling emphasized the importance of the focus on unvaccinated persons, particularly in the context of the new vaccine being discussed. She asked whether there is any information about how many people have been boosted once and twice, given that Omicron is circulating and having a boost offers additional coverage.

Dr. Oliver indicated that these data had not been presented because the primary focus if this meeting was on Novavax, which is a primary series. The information on boosters doses is posted on the COVID Data Tracker. Among the population ≥65 years of age, 70% have received the first booster dose and 35% have received a second booster dose. There is definitely room for improvement, especially with the second booster dose in adults ≥50 years of age.

Dr. Daley ask Dr. Fleming-Dutra to expand on the extent to which the disparities in terms of COVID-19 hospitalizations and deaths by race are a reflection of disparities in vaccination coverage versus other social determinants of health (SDOH), recognizing that there are surveillance data and that there are limitations to what can be concluded from them.

Dr. Fleming-Dutra emphasized that this is a very important question. As noted, these data are based on surveillance. The cases are based on data reported to CDC on total cases, hospitalizations are based on COVID-NET data, and deaths come from the National Vital Statistics System (NVSS). While these sources reflect vaccination coverage, other SDOH and vaccine coverage are not included in this particular analysis.

Dr. Taylor from COVID-NET added one caveat for the hospitalization data is that the analysis by age adjusted rate ratios is cumulative, so it takes into account all hospitalizations that occurred from March 2020 through the period ending June 11, 2022. That includes a large portion of time when there was no effect of vaccination on hospitalization rates. This would make it difficult to dig much into the effect of vaccination on hospital rates.

Dr. Daley said if felt like perhaps qualitatively some of the disparities in vaccination coverage by race have lessened, but there are disparities by other important characteristics (e.g., SES, poverty, rurality, healthcare access, not having health insurance). These data made it seem like there had been at least some progress in disparities and coverage by race.

[16] Source: COVIDVaxView. Estimates produced by NORC at the University of Chicago using CDC's National Immunization Survey-Adult COVID-19 Module (NISACM). https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html. Accessed July 14, 2022

Dr. King (NMA) pointed out that just because this is cumulative does not necessarily determine the latest trends based on race, deaths, and hospitalizations in terms of what is occurring from a demographic standpoint among racial and ethnic populations.

Dr. Fleming-Dutra indicated that they would take this back to the various teams to conduct this analysis for the last year.

Dr. Lee emphasized that both the cumulative numbers and more recent numbers are helpful. While the cumulative data are incredibly helpful, in terms of supporting real-time decision making, having more recent real-time vaccination data would help support clinical and public health responses by increasing awareness of gaps and opportunities.

Updates on Vaccine-Associated Myocarditis

Tom Shimabukuro, MD, MPH, MBA (CDC/NCEZID) provided an update vaccine-associated myocarditis, with a focus on classic myocarditis and myocarditis associated with mRNA COVID-19 vaccination and an update on myocarditis following mRNA COVID-19 vaccination with a focus on people ≥18 years of age in the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

Classic myocarditis usually has an infectious cause, typically viral or presumed to be viral. Although infection with a pathogen is frequently not identified. A pathogen is identified only about 40% of the time.[17] It can be due to direct microbial infection of myocardial cells and/or ongoing inflammatory response, with or without clearance of the pathogen.[18] Rarer causes include autoimmune, hypersensitivity, and giant cell myocarditis. The incidence in males is greater than females, starting after 5 years of age.[19] It is common not to identify a pathogen or possible infectious etiology for myocarditis. Based on case series, where autopsy tissues were examined and tissue-based infectious disease testing was performed, a specific infectious cause was only identified in 13% to 36% of cases across age groups.[20] For a case series where endomyocardial biopsy tissues were tested, viral nucleic acids were detected in heart tissues in approximately 38% of adults and children combined.[21]

In terms of the epidemiology of myocarditis in children and adults, after early childhood when genetic or congenital conditions are suspected to contribute to myocarditis, incidence is low and then begins to increase starting in adolescence. Incidence peaks in adolescence and gradually decreases with age. There is a striking male-to-female predominance, but that attenuates around middle age.[22] The following table compares the characteristics of myocarditis associated with mRNA COVID-19 vaccination and viral myocarditis:

[17] Bowles et al. J Am Coll Cardiol. 2003;42:466-72; Simpson et al. J Am Coll Cardiol; 2013;61:(10_Supplement) E1264; and Park et al. J Korean Med Sci. 2021;36:e232.
[18] Caforio et al. Eur Heart J. 2013;34:2636-48, 2648a-2648d; Feldman et al. N Engl J Med. 2000;343:1388-98; and Guarner et al. Hum Pathol. 2007;38:1412-9
[19] Arola et al. J Am Heart Assoc. 2017;6:e005306.
[20] Guarner et al. Hum Pathol. 2007;38:1412-9; Arola et al. J Am Heart Assoc. 2017;6:e005306; Weber et al. Arch Dis Child. 2008;93:594-8; and Ilina et al. Pediatrics. 2011;128:e513-20.
[21] Bowles et al. J Am Coll Cardiol. 2003;42:466-72
[22] Vasudeva et al. *American J. Cardiology*, 2021 (children); and Kyto et al. *Heart*. 2013 (adults)

Characteristic	Myocarditis associated with mRNA COVID-19 vaccination*,†	Viral myocarditis‡
Inciting exposure	mRNA COVID-19 vaccination • Dose 2 > Dose 1	Viral illness • 30–60% with asymptomatic viral course
Demographics	Most cases in adolescents and young adults, males > females	Males > females, male incidence peaks in adolescence and gradually declines
Symptom onset	A few days after vaccination, most within a week	1–4 weeks after viral illness
Fulminant course	Rare¶	23%
ICU level support	~2%	~50%
Mortality/transplant	Rare¶	11–22%
Cardiac dysfunction	12%	60%
Recovery of cardiac function	Nearly all	~75%
Time to recovery of cardiac function (ejection fraction on cardiac echo), if initially poor	Hours to days	Days to weeks to months

† Oster et al. JAMA. 2022;327:331-340.
‡ Law et al. Circulation. 2021;144:e123-e135. Ghelani et al. Circ Cardiovasc Qual Outcomes. 2012;5:622-7. Kim et al. Korean Circ J. 2020;50:1013-1022. Messroghli et al. Am Heart J. 2017;187:133-144. Patel et al. J Am Heart Assoc. 2022;11:e024393.
¶ There are rare reports in the literature, especially from other countries, but it is unclear to what extent such cases were investigated

For vaccine-associated myocarditis, the inciting exposure is mRNA COVID-19 vaccination. Incidence is greater, following Dose 2 compared to Dose 1. For viral myocarditis, with 30% to 60% having an asymptomatic viral course. For a vaccine-associated myocarditis, most cases are in adolescence and young adults, with more cases in males compared to females. For viral myocarditis, incidence is higher in males compared to females. Male incidence peaks in adolescence, and then gradually declines with age. For vaccine-associated myocarditis, symptom onset clusters within a few days after vaccination. Most of the vaccine-associated cases appear to occur within the week of vaccination. For viral myocarditis, onset is typically 1 to 4 weeks after viral illness. In general, myocarditis associated with mRNA COVID-19 vaccination has been relatively clinically mild compared to viral myocarditis. There are VAERS and VSD data to support these observations.

As a reminder, VAERS is the national spontaneous reporting system that is co-managed by CDC and FDA. As a passive surveillance system, VAERS accepts reports from anyone regardless of the plausibility of the vaccine-causing the event or the clinical seriousness of the event. The key strengths of VAERS are that it can rapidly detect potential safety problems and can detect rare adverse events (AEs). The key limitation is that generally, cause and effect cannot generally be determined from VAERS data alone.

In terms of US reports to VAERS of myocarditis after mRNA COVID-19 vaccination among people ≥18 years of age following a primary vaccine series and the first booster dose through the end of May 2022, there were 1,836 preliminary reports of myocarditis. Of these, 11 remain under review and 504 did not meet the CDC case definition.[23] That leaves 1,321 reports of myocarditis that were verified to meet the case definition. To put that number in perspective, there were approximately 491.9 million primary series and first booster mRNA COVID-19 vaccine doses administered in the US among people ≥ages 18 years of age at that time comprised of 213.3 million first doses, 185.1 million second doses, and 93.4 million first booster doses.

[23] CDC myocarditis case definition available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

In terms of the time to onset for these case reports to VAERS among persons ≥18 years of age, reported cases tended to cluster within a few days of vaccination. The overwhelming majority occurring within 1 week of vaccination. Among the 1,321 reports of verified myocarditis according to the CDC case definition among people ≥18 years of age, the median age where available was about 28 years (IQR: ages 21–42 years). Median time to symptom onset where available was 3 days (IQR: 2–5 days). A minority (19%) of reports had symptom onset 7 days after vaccination. Most of these reports occurred after Dose 2 (n=962) and most of these reports occurred in males (n=960). In terms of VAERS reporting rates of myocarditis per 1 million doses administered, after mRNA COVID-19 vaccination in Days 0-7 and Days 8-21 post-vaccination, the risk both in males and females was concentrated in the Days 0-7 after vaccination. Elevated reporting rates were not seen with respect to background rates in the 8-21 days following vaccination. Reporting rates were substantially higher in males compared to females and the highest reporting rates were observed following Dose 2, with reporting rates for boosters tending to fall in between the values for Dose 1 and Dose 2. The older age groups for males were after 49 years of age, which was younger for females. Elevated reporting rates are not seen with respect to background rates. The differences in sex appear to attenuate.

CDC's enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in various case reports among people 12 through 29 years assesses functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination. It is a 2-component survey conducted at least 90 days after the onset of myocarditis symptoms that includes a patient survey and an HCP survey. Focusing on the main findings of the cardiologists or healthcare provider survey among those providing aftercare for these case patients, most patients (81.7%) were judged by their providers to have fully (66.6%) or probably fully (15.1%) recovered from their myocarditis. In terms of the key findings from the patient surveys at least 90 days after myocarditis diagnosis, most patients who were reached reported no impact on their quality of life and most did not report missing school or work. Of note, there was substantial heterogeneity in initial follow-up treatment and testing and there did not appear to be a single test that was indicative of recovery. The next steps are additional follow-up with patients who are not yet recovered at the time of the 90+ day survey and their HCP to further assess recovery status at 12 months.[24] Follow-up and evaluation of myocarditis cases in children 5 through 11 years of age is ongoing.

Now moving to the findings from the VSD. As a reminder, the VSD is CDC's electronic health record (EHR)-based system that is used for surveillance and research and is a collaborative project between CDC and 9 integrated healthcare organizations around the US. VSD conducts Rapid Cycle Analysis (RCA), the aims of which are to: 1) monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes; and 2) describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity. This table delineates the VSD COVID-19 vaccine RCA pre-specified surveillance outcomes and the settings in which they are monitored:

[24] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis – **First in 7 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient
Cerebral venous sinus thrombosis	Emergency dept, Inpatient
Disseminated intravascular coagulation	Emergency dept, Inpatient
Encephalitis / myelitis / encephalomyelitis	Emergency dept, Inpatient
Guillain-Barré syndrome	Emergency dept, Inpatient
Immune thrombocytopenia	Emergency dept, Inpatient, Outpatient
Kawasaki disease	Emergency dept, Inpatient
Multisystem inflammatory syndrome in children/adults (MIS-C/MIS-A)	Emergency dept, Inpatient
Myocarditis / pericarditis – **First in 60 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Seizures	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient

The primary VSD RCA analytic strategy is a vaccinated concurrent comparator analysis. This involves analyzing the number of outcomes observed in the risk interval after COVID-19 vaccination compared to the number expected. The expected was derived from "vaccinated concurrent comparators" who were in a comparison interval after COVID-19 vaccination. That is simply looking at rates in a risk interval in vaccinated individuals compared to rates in a comparison interval in vaccinated individuals. The prespecified outcome of myocarditis/ pericarditis cases were verified using the CDC case definition. Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, and calendar date.

In terms of mRNA COVID-19 vaccine doses administered in the VSD among people 18 through 39 years of age by week, there was statistically significant clustering in the several days after vaccination. The overwhelming majority of these occurred within a week of vaccination, which is consistent with the data observed for VAERS reports. There were statistically significantly elevated rate ratios after Dose 2 and after a booster dose. Looking at product-specific findings, there were elevated adjusted rate ratios after Dose 2 and the booster dose of Pfizer-BioNTech and after Dose 2 for Moderna. The event counts were substantially lower among females than for males, and the number of statistically significantly elevated adjusted rate ratios also were less for females. Females had a statistically significantly elevated adjusted rate ratio after Dose 2 for the Moderna or Pfizer-BioNTech products. The adjusted rate ratios for males and females were statistically significant, but the excess cases in the risk period were substantially greater for males. That is because the condition is much more common in males than in females. In the 0 to 7 days following mRNA COVID-19 vaccination, the general findings in the VSD are that the incidence rates are substantially greater in males compared to females and in general, the incidence rates are highest after Dose 2. While there are some exceptions, the numbers are fairly small and point estimates may be unstable for those exceptions.

Regarding verified myocarditis and pericarditis within 0 to 7 days of any primary series dose of mRNA COVID-19 vaccine by level of care and age group/product, most cases observed in the VSD were hospitalized and had short lengths of stay. The median stay for either product was 1 day, and all verified case patients were discharged home. Booster doses were very similar to the primary series in that most cases were admitted to the hospital, their length of stay was short at a median of 1 day, and they were discharged home.

In summary, the current evidence supports a causal association between mRNA COVID-19 vaccinations and myocarditis and pericarditis. Myocarditis is a rare event following vaccination. CDC verified 1,321 cases in people ≥18 years of age after 491.9 million doses administered in this age group in the US. Cases tend to cluster within the first week of vaccination. The risk is greatest in adolescents and young adults and is higher after Dose 2 compared to Dose 1 of the primary series. There is a higher in males compared to females. Some risk estimates for females in the VSD are comparable to males, but case counts are small and excess risk in females is substantially lower than for males. The risk appears to decrease with age and the male-to-female predominance of cases attenuates with age. Reporting rates in VAERS are highest following Dose 2. Reporting rates following Dose 1 and the first booster dose tend to be lower. Incidence rates in the VSD of verified myocarditis and pericarditis 0 to 7 days following vaccination are generally highest following Dose 2. The available information suggests that most persons with myocarditis after mRNA COVID-19 vaccination recover from myocarditis by 3 to 8 months after diagnosis.

Discussion Summary

Dr. King (NMA) inquired as to whether males who are athletes who engage in prolonged vigorous exercise after their vaccination could trigger the higher rate of myocarditis for males compared to females since there are more male athletes than female athletes. Perhaps there should be a recommendation for teens and young adults not to undergo strenuous physical activity for perhaps a week after receiving vaccination.

Dr. Shimabukuro indicated that this level of detail is not available from the surveillance regarding association with physical activity.

Dr. Oster added that this information has not been collected systematically, but having reviewed most of these charts and having taken care of some of these patients, the classic story is that it seems to appear out of nowhere (e.g., resting, sleeping, watching TV, attending church, attending school, et cetera). While some cases have occurred with activity, onset in the vast majority has been at rest. Once diagnosed with evidence of cardiac inflammation, current guidelines are to restrain from competitive sports for about 3 months even though this cohort of young adults tends to recover sooner than in classic myocarditis. Males historically are more likely than females to get myocarditis, and there are a lot of different theories as to exactly why that could be. One of the most predominant theories is that testosterone levels are higher in males, and that can affect the receptors on the cardiac tissue that are at play here. At this time, there are no data to suggest that a recommendation should be made to limit activity following vaccination.

Dr. Sanchez inquired as to whether timing of doses could have an impact and if there are or would be data regarding the timing of booster doses and the occurrence of myocarditis.

Dr. Shimabukuro indicated that there is good information that in the US during the period of this analysis, adherence to the primary series schedule was quite good. The timing of the booster dose may need further assessment. CDC has done a direct head-to-head comparison between the Pfizer and Moderna products and other groups have done comparisons as well. The findings from the recent VSD analysis, which was recently published in *Vaccine*, showed some evidence of an increased risk of myocarditis for Moderna compared to Pfizer. This did reach statistical significance in one of the sub-analysis CDC did. FDA did a similar analysis in their Biologics Effectiveness and Safety System (BEST) that did not detect an increased risk. There are data from other countries that have looked at this as well. The general trend is that a modest increased risk has been observed for Moderna compared to Pfizer, but this has not been consistent across all systems and analyses.

Dr. Poehling observed that because most adults adhered to the timing for the primary series, there would not be an opportunity to look at spreading the dose. He expressed her hope that for children, it would be possible to assess whether spreading the primary series 8 weeks apart would be feasible. She asked for clarification regarding whether this analysis was any booster dose or just the first booster and if it was just the first booster dose, whether there would be an opportunity to assess a second booster dose.

Dr. Shimabukuro said his understanding was that this analysis was limited to what they believe to be the first booster dose and looking at additional booster doses would be assessed in an additional analysis.

Dr. Klein added that these analyses were adjusted for time since the primary series and the booster doses.

Dr. Loehr reminded everyone that even though it is clear that there is a causal association with vaccination, it is important to remember that there is a higher risk of getting myocarditis and pericarditis from having COVID-19 disease.

Dr. Oster further elaborated on the risk of adverse cardiac outcomes with disease compared to vaccination, noting that data were presented previous and published in the *Morbidity and Mortality Weekly Report (MMWR)* showing that across all groups, the risk of the cardiac manifestations of myocarditis and pericarditis is certainly higher after getting SARS-CoV-2 versus having vaccines. Even in the highest risk group of adolescent and young adult males, the risk was 2 to 6 times greater of having significant heart involvement after getting COVID-19 than after getting COVID-19 vaccine. COVID-19 is a serious disease that can have significant cardiac manifestations in a small but higher subset.

Dr. Daley pointed out that while they all would argue that it is very important to understand what is occurring, in the context of the day's discussion, consideration needed to be given to how these data should help them think about myocarditis related to a new vaccine that is focused on spike protein but uses different technology. He asked Dr. Shimabukuro to remind them what the surveillance plans would be should ACIP vote to recommend the Novavax vaccine later in the day. He also requested that data from additional studies, if any, assessing the underlying pathophysiology of vaccine-associated myocarditis be brought to the ACIP.

Dr. Shimabukuro said he would reach out to those doing the work and would be happy to return to describe any work assessing the underlying pathophysiology of vaccine-associated myocarditis. Regarding surveillance, myocarditis/pericarditis is an AE of special interest (AESI) for VAERS, so they will be specifically looking for reports suspicious of myocarditis and pericarditis and will review and follow-up on every report, including obtaining medical records and contacting healthcare providers to obtain sufficient information to apply the CDC case definition to verify reports. Enhanced surveillance for myocarditis and pericarditis after a Novavax will be conducted similar to what has been done for the mRNA vaccines. Surveillance for Novavax will be incorporated into the VSD RCA. How the RCA is done may depend on how much uptake there is and how much meaningful data are reported to VSD. There also is the Clinical Immunization Safety Assessment (CISA) that is available as a consult service for US healthcare providers to receive a consultation on patients with complex AEs for Novavax or any other vaccines.

Safety, Immunogenicity, and Efficacy of Novavax 2-Dose Primary Series in Adults ≥18 Years of Age

Filip Dubovsky, MD, MPH (Novavax, Inc.) Dr. Dubovsky presented on the safety, immunogenicity, and efficacy of Novavax COVID-19 vaccine, NVX-CoV2373, in adults ≥18 years of age. He noted that their team provides an important new approach in the fight against COVID-19 and believes that supportive policy recommendations will improve vaccine availability and accessibility, with the ultimate goal of increasing vaccination rates in the US. NVX-CoV2373 is based on Novavax's platform technology with its recombinant protein antigen formulated as a particle and Matrix-M™ adjuvant, which is a saponin-based adjuvant (SBA). SBAs are used in other approved vaccines. Adjuvant is important in helping the Novavax vaccine generate broad immune responses, including against variants.

This vaccine has key attributes that support increased access and ease of use. It is dispensed in a 10-dose vial and is a preservative-free, ready to use liquid suspension. It can be transported and stored at refrigerator temperatures, making it easy to ship, store, and administer. Each dose contains 5µg of antigen and 50µg of Matrix-M™ adjuvant. This vaccine is a 2-dose series administered 3 weeks apart with a 0.5 mL intramuscular (IM) injection using standard needles and syringes. The authorized indication in the US is for individuals ≥18 years of age. Currently, vaccination in the US is incomplete. Based on data from CDC from July 7, 2022, 1 in 10 Americans have yet to receive a single dose of COVID-19 vaccines. The rates are even lower for a primary 2-dose series and boosters. Novavax believes a protein-based alternative may help increase vaccine uptake in individuals who prefer a well-understood vaccine platform.

The NVX-CoV2373 clinical development program included 4 studies, which constitute the body of data used for global regulatory approval. This presentation focused on the Phase 3 studies, Study 301 (US/MX) and Study 302 (UK). Safety and efficacy were initially evaluated in Study 302 in the UK (N = 15,187),[25] which was followed by an even larger study in the US and Mexico to enable licensure from the US. As part of the US/Mexico Phase 3 study, effectiveness and clinical efficacy was studied in adolescents 12 through 17 years of age (N = 2,247),[26] and these data are currently under review by the FDA.

[25] Heath et al., NEJM, 2021; Toback et al., The Lancet Res Med, 2021
[26] Dunkle et al., NEJM, 2021

To briefly summarize the Phase 3 results, VE against mild, moderate, or severe disease in both Phase 3 trials was 90%. Importantly, there was 100% protection against severe disease. These trials were conducted when the virus had started to evolve rapidly. In fact, the majority of cases in both of these studies were attributed to variants of concern (VOC) or variants of interest (VOI). High levels of efficacy were observed against these variants, which is a hallmark of the Novavax vaccine technology.

The US/Mexico Phase 3 study, Study 301, was conducted in the US population and the data from the study was the basis of authorization by the FDA. In Study 301, participants were randomized 2:1 to receive vaccine or a placebo. This was done in order to gather additional safety data on the vaccine from a larger number of participants. About 4 months after the initial vaccination period, the study remained blinded and crossed over to the opposite treatment arm. This was done so that all participants in the study could receive active vaccine. Participants are being followed 2 years following primary vaccination.

Demographics and baseline characteristics were well-balanced between the 2 arms. In both the NVX-CoV2373 and placebo arms, 13% of participants were ≥64 years of age. It is important to note that enrollment in older adults was somewhat limited. This is because COVID-19 vaccines became authorized and recommended for those ≥64 years of age while Novavax was enrolling. Black or African American participants made up 12% of the study population, 7% were American Indian, and 22% were Hispanic or Latino, which is representative of the overall US population. In line with one of the study goals, 95% of participants were considered at increased risk for COVID-19 either due to underlying medical conditions or their occupations.

The primary efficacy endpoint of the study was achieved with 90% protection from mild, moderate, and severe disease. The lower bound was 84%. In fact, there were only 17 (0.1%) mild cases in the 17,272 vaccine recipients compared to 79 (0.9%) cases in the 8,385 placebo recipients. As mentioned earlier, 100% protection was achieved against moderate or severe illness, an important secondary endpoint. This means that all the cases in the vaccine group were mild. The vaccine showed 93% (95% CI: 86, 97) efficacy against VOCs or VOI. The most commonly identified variants were Alpha, Iota, Epsilon, and Gamma with fewer cases being attributed to Beta, Delta, Kappa, and Eta. Again, all of the variant cases that did occur in vaccine arm were mild in severity. Efficacy was 97% (95% CI: 74, 100) for isolates that would be considered more closely matched to the original vaccine strain. Efficacy against these strains was pre-specified as a key secondary endpoint of the study. The vaccine provided consistently high levels of protection across all subgroups. Though the confidence intervals widened in the subgroups, the point estimates continued to support VE.

In conclusion of Study 301 efficacy, NVX-CoV2373 vaccine was highly efficacious in preventing COVID-19. Its efficacy was demonstrated against all the variants circulating during the study. The vaccine also provided complete protection for moderate or severe disease in adults. This vaccine demonstrated consistently high efficacy in adults across subgroups, including race, gender, and in individuals with medical comorbidities.

Now turning to safety. The total safety database includes approximately 50,000 people enrolled across 4 studies. This is a large database that provides confidence that this vaccine has a well-characterized safety profile that supports a positive benefit-risk and favorable reactogenicity profile across a diverse population.

Beginning with a summary of solicited AEs collected through electronic diary entries for 7 days following each vaccination, there were fewer local events overall among those ≥65 years of age compared to younger adults 16 through 64 years of age. Pain and tenderness were the most commonly reported events. While many participants did not report reactogenicity events at all, those who did mostly reported events that were Grade 1 (mild) or Grade 2 (moderate) in severity. Grade 3 or higher events occurred at low rates. Overall, these events resolved quickly with the median duration of 1 to 2 days. As expected, events occurred more frequently following the second dose and more participants in the vaccine group experienced these symptoms. Most events were mild or moderate in severity with low numbers of Grade 3 or higher events. The median duration was 1 to 2 days.

In terms of systemic reactogenicity, malaise, fatigue, muscle pain, and headache were most commonly reported. Once again, lower frequencies were reported in those ≥65 years of age. The vast majority of events reported were mild or moderate and resolved quickly with a median of duration of 1 to 2 days. Notably, the rates of fever are quite low in less than 1% of vaccinees. Following the second does, while higher overall, most systemic events remain mild to moderate in severity. Grade 3 or higher events were uncommon with the median duration of 1 to 2 days. Even after the second dose, a low proportion of participants reported fever. Overall, the frequency of unsolicited AE was comparable between vaccine and placebo groups, and severe adverse events (SAEs) were recorded in only 2 participants. Medically attended adverse events (MAAEs) and potential immune-mediated medical conditions (PIMMC) were similar between groups. SAEs also were balanced between the vaccine and placebo groups. Death occurred at similar or low rates between treatment arms.

Given the importance of the topic of myocarditis/pericarditis, Dr. Dubovsky presented the myocarditis/pericarditis data from the Novavax pooled safety database. As they learned through the investigations described earlier, natural events of myocarditis will occur in any sufficiently large database. In addition, young males are at higher risk for both vaccine-induced myocarditis and other forms of myocarditis, which most often is caused by non-specific infections. COVID-19 infections also can cause myocarditis. It is important to note that the Novavax studies were conducted largely during the time of heightened awareness for myocarditis. Overall in the placebo-controlled phase of the NVX-CoV2373 clinical development program, the rates of myocarditis were balanced between the vaccine and placebo arms at 0.007% (2 cases) for the vaccine arm and 0.005% (1 case) for the placebo arm. No pericarditis was reported. In Study 301 (UK Phase 3 study), 1 case occurred in the active arm and 1 case occurred in the placebo arm. Of the 2 cases in vaccine recipients, one 67-year-old male also had concurrent severe COVID-19 infection after Dose 1. The other case from Study 302 occurred in a 19-year-old male 3 days after the second dose of vaccine and occurred without a definitive alternative cause.

In the post-crossover portion of Study 301 and Study 302 during which all participants were exposed to the vaccine, events of myocarditis or pericarditis occurred within expected background rates as determined by the European Medicines Agency (EMA) ‘vACcine Covid-19 monitoring readinESS’ (ACCESS) study. This study was specifically designed to determine background rates of interest for COVID-19 vaccines. There were 3 reports of myocarditis or pericarditis, all of which had alternate possible infectious etiologies. A notable case occurred in a 16-year-old male 2 days after the second crossover dose of vaccine who had a viral illness diagnosed by a healthcare provider. A 20-year-old male had strep throat preceding the events of pericarditis. This was diagnosed by electrocardiogram (EKG) findings with a normal troponin level. A 28-year-old male had features of myocarditis and was diagnosed by an attending cardiologist with non-ST elevation myocardial infarction (NSTEMI).

Novavax's latest monthly Summary Safety Report (SSR) with post-authorization data includes more than 1 million doses administered and was submitted in July with the date of cutoff of June 30, 2022. For a spontaneous report using a broad Standardised MedDRA Queries (SMQ) search strategy, 68 potential reports were identified. As is typical for spontaneous reports, many have limited information. Out of the potential reports from this broad search, 17 met the Brighton Collaboration definition of "definite" or "probable" myocarditis or pericarditis (1 definitive, 6 probable myocarditis, 10 probable periocarditis). As a result of discussions with the FDA, the US label includes a warning that states that clinical trial data provide evidence for increased risk of myocarditis and pericarditis. Novavax is carefully monitoring its post-authorization data to understand the nature and magnitude of this risk. Additionally, they intend to follow-up each case with targeted questionnaires. These data are being communicated to all regulatory agencies in Novavax's monthly SSRs. This close monitoring also will include post-authorization safety studies that cover large populations in administrative client databases and electronic health records (EHRs).

For the other events of interest, there were no reports of anaphylactic reactions or thrombosis with thrombocytopenia (TTS) in the Novavax integrated safety database. However, based on 2 post-authorization reports of anaphylaxis, this labeling has been included in the NVX-CoV2373 label. There was also 1 case of neuropathy from UK Study 302 for which follow-up information was received that meets the Brighton Collaboration definition of Guillain- Barré Syndrome (GBS). Novavax will continue to monitor these carefully in all of its post-authorization surveillance activities.

Because pregnant women were excluded from all studies, there is limited information on pregnancy. For all women of childbearing potential, a negative urine pregnancy test was required during screening and prior to vaccinations. However, as in all Novavax studies with one follow-up, there were some reports of pregnancies. As of the 15th of March, a total of 147 pregnancies were reported across the entire clinical program. Of these pregnancies, 56 are ongoing, 41 resulted in live births, 23 experienced miscarriages, 13 women elected to have voluntary terminations, and one had an ectopic pregnancy. No fetal deaths or stillbirths have been reported. Overall, these data do not indicate a potential risk for mother or fetus and are generally consistent with background rates. There are no specific restrictions for pregnant women in Novavax's US or global labels. Novavax also has plans to conduct multiple post-authorization studies to assess additional safety and effectiveness data. They will be conducting 2 effectiveness studies and 2 safety studies using administrative claims and health record databases. To characterize the safety profile in the post-marketing study, Study 405 is a global registry that will provide important data in pregnant women who receive Novavax COVID-19 vaccine.

In terms of the Novavax COVID-19 vaccine's immune response against the Omicron variant, a multidimensional presentation of the immune responses for the US/Mexico Phase 3 study, called antigenic cartography, explains the ability of the vaccine-induced antibody to recognize variant spike proteins. Antigenic cartography showed 100%seroconversion to all Omicron subvariants after 2 doses. The antigenic difference between the matched prototype strain and the Omicron subvariants is 7.9- to 11.8-fold different. After a single boost, the antigenic distance decreases for all of the Omicron variants, with BA.5 decreasing to just a 2.9-fold difference, which can be considered a masked response. This phenomenon is believed to be driven by broader recognition of new variants, which is further enhanced by the Matrix-M™ adjuvant. This analysis leads Novavax to believe that as people are immunized with additional doses of the NVX-CoV2373 recombinant spike protein vaccine, antigenic distance will be minimized, and a more universal response will be observed against variants. While it is unclear what variant will

emerge after BA.5, boosting with the Novavax technology may be an attractive option as it provides high levels of antibody recognizing variants and a durable immune response.

Although it is not certain that variant-specific vaccine will provide significant clinical benefit, Novavax is evaluating a number of constructs in clinical studies. Novavax began a study in May 2022 among adults 18 through 64 years of age who were previously vaccinated with mRNA vaccine. This ongoing study will compare antibody responses between 5 arms: NVX-CoV2373, Monovalent Omicron BA.1, Bivalent Prototype + Omicron BA.1, Monovalent Omicron BA.5, and Bivalent Prototype + Omicron BA.5. This study will compare the variant-specific immune responses among the trial arms to support a data-driven decision by the utility of variant vaccines as it applies to the Novavax adjuvant recombinant protein technology. If it continues to be deemed desirable, the goal is to have variant vaccines available in the 4th quarter.

In summary, Novavax COVID-19 vaccine achieved high levels of efficacy in 2 large randomized controlled Phase 3 studies, including high efficacy against variants of concern and variants of interest. This vaccine is based on a platform that is well-understood. Recombinant vaccines have been used globally for decades. This can be important, especially for those who are vaccine-hesitant. The Matrix-M™ adjuvant is a natural SBA product. SBAs are used throughout the world. The data show that combining the Novavax SARS-CoV-2 spike protein with an immune enhancing adjuvant simulates a broad and robust immune response and provides a high level of clinical efficacy. Importantly, this vaccine is not highly reactogenic. This may be important for vaccine compliance, as boosting continues to be recommended. Novavax COVID-19 vaccine presentation and storage support ease of use and wide access. Dr. Dubovsky expressed gratitude to the tens of thousands of people who volunteered for the Novavax clinical trial in the US and abroad, the healthcare providers, investigators, study personnel, and partners. He stressed that their involvement is making a difference in the lives of people around the world.

Discussion Summary

Dr. Poehling asked what placebo formulation was used in the study and requested additional information about the case of neuropathy that met the GBS definition.

Dr. Dubovsky indicated that the placebo formulation was normal saline. In terms of the GBS case, he noted that they have seen other cases of GBS in the post-authorization period.

Dr. Kim, Chief Safety Office at Novavax, added that the case of GBS occurred in the UK in Study 302 in a 65-year-old female. Over the course of a year, she experienced progressive motor and sensory deficits and had confirmatory laboratory testing. The case definition was met only recently when Novavax received follow-up information. There was some delay in reporting by the patient participant as the initial presentation was mild. She was being followed-up through the year, received additional testing, and the progressive nature of the motor and sensory deficits were confirmed. The initial symptoms presented as tingling and occurred within about 9 days after the post-crossover Dose 1 and progressed over the next 9 months into sensorimotor polyneuropathy that was confirmed by electromyographic (EMG) studies. The symptoms did improve after steroid treatment.

In response to a question about whether Novavax has data related to effectiveness against the Omicron variant, Dr. Dubovsky indicated that both efficacy studies were conducted before Omicron emerged. Therefore, they do not have any efficacy data that speaks to Omicron specifically. The data he showed with the antigenic cartography does have some information

about the Omicron variant, which showed that there was 100% seroconversion to all variants after a 2-dose priming series—including BA.5. The antigen distance narrowed with a subsequent dose.

Dr. Kotton noted that she is especially interested in protecting immunocompromised patients, but there does not appear to be a lot of data available with Novavax among persons who are immunocompromised. Australia recommended that it could be used as part of the 3-dose primary series in immunocompromised patients. She wondered whether he had data in that population and/or if it would be included in the study that began in May 2022 looking at Novavax after mRNA vaccine.

Dr. Dubovsky indicated that there is limited information about how the vaccine, especially multiple doses of vaccine, performs in people of various levels of immunocompromise. The US Phase 3 study includes some participants who are living with HIV. For the immune response in those who were HIV-negative versus those who were living with HIV, there was a small diminishing in the overall titers in those living with HIV. This is the smallest dataset with only 9 participants. For those who previously were exposed to COVID-19 and then were vaccinated, the priming with the 2-dose series provided very high titers well above that which is associated by protection in Phase 3 study. Novavax is conducting a study in South Africa that is evaluating people without HIV as well as more immunocompromised people living with HIV. This study is comparing a 3-dose versus a 2-dose series with various intervals to try to understand how better to use the Novavax vaccine in this population. In terms of CD4 counts, the participants in the data shown are very well-controlled. In the South Africa study, the population is heterogenous and includes people who are well-controlled and people who are less well-controlled.

Dr. Kotton emphasized that it is estimated that about 3% of the US population is immunocompromised, are much more vulnerable to severe life-threatening infection, and are less responsive to vaccination. She asked whether Novavax has work underway with non-HIV immunocompromised populations.

Dr. Dubovsky said their post-marketing studies are going to be able to address this quite well as very large studies are planned.

Dr. Sanchez expressed excitement with having another COVID-19 vaccine, particularly one that has a more traditional format. He requested definitions for *mild*, *moderate*, and *severe*; where hospitalization fit into the criteria for *severe*; whether there was routine testing for asymptomatic infection; and given vaccine hesitancy, whether aborted fetal cells were used in the development of the Novavax COVID-19 vaccine.

Dr. Dubovsky indicated that they do have information on asymptomatic disease from following people who were anti-seroconverters or who were PCR-positive. No aborted fetal cells were used in the development of the Novavax COVID-19 vaccine. He called upon Dr. Dunkle who ran the study to speak to severity.

Dr. Dunkle, the physician who ran the study, confirmed that they did not use hospitalization as a criterion for severity. Most of the participants who were hospitalized for COVID-19 did not have their PCRs confirmed at the University of Washington and therefore were counted as SAEs due to the hospitalization. One succumbed to his disease but was not counted as an endpoint. In terms of asymptomatic infection, the best data come from the UK in Study 302 in which people were followed for up to 6 months. That is when their cases were collected. The median follow-

up was 101 days in that study. Among people who either seroconverted or were PCR-positive, efficacy against any infection (symptomatic or asymptomatic) was 83% with a lower bound of 75%.

Ms. Hayes (ACNM) requested further information about how women were discovered to be pregnant and when during their vaccine investigation trial experiences that they were pregnant.

Dr. Dubvosky noted that the data he presented were from the totality of data from the studies Novavax started almost 2 years ago. These women are still under surveillance at this time. The vast majority of the pregnancies occurred at a distant time period after well after vaccines were administered. In these studies, they rely on women to them when they become pregnant and they try to estimate when their last menstrual periods occurred. Without a systemic way to capture that, these data are incomplete. Recollection of last menses is incredibly unreliable in most women.

In regard to a comment that the rate of miscarriages seemed very high, Dr. Dubovsky indicated that these rates are difficult to compare with the denominator. From their analysis, this seems to be within the reported norms. The problem is that people are much more likely to report when they have a poor outcome versus that they are just pregnant. Therefore, the denominator is probably incomplete.

Dr. Kim confirmed this to be correct. Pregnancies were not systematically collected, which makes it difficult to interpret this kind of data and compare it to background rates. With the data they do have and a background rate of spontaneous abortions that is around 20% in the general population of spontaneous abortions, this finding is generally consistent with the background rates.

Dr. Drees (SHEA) noted that it seems the best way to reach people who still do not have their primary series would be through individual practices when they are seeing their physician or provider for something else. These individuals may be less likely to seek out a vaccine at a pharmacy or a dedicated vaccination event. She worries that a provider may see only 1 or 2 of these individuals in a given day. Despite the fact that CDC and others have said that it is okay for providers to waste the remaining doses in a vial if they have the opportunity to vaccinate 1 person, they are still somewhat reluctant to do that. While she was aware that Novavax was asked to provide this vaccine in multidose vials, she wondered whether there might be an opportunity in the US to provide single dose vials or if they would have to go back through the FDA regulatory process.

Dr. Dubovsky indicated that the format licensed in the US is a 10-dose vial. They have other formats that are licensed in other territories and by their partners. Novavax is working feverishly to get a lower format presentation that can be submitted to the regulators for approval in due course. They have some experience with this vaccine being made available alongside other vaccines in other countries. In certain countries, they have decent visibility into how the vaccine is being used. In Australia, they know that about 60% of vaccines being used are used as a primary series. That is in a country where people have a choice from among multiple vaccines and are selecting the Novavax product specifically. The proportion is even higher in Korea. It is important to offer this as a choice for people as it gives them some control. It allows vaccinees, physicians, healthcare, and the public health community to weigh the benefits and risks of which vaccine to take.

Dr. Eckert (ACOG) pointed out that the expected rate of miscarriages is 17% and that the study is well within what is expected. She asked whether any data are available on the Matrix-M™ adjuvant being used in other vaccines given to pregnant individual and data on gestational age at birth and live births outcomes among women who were vaccinated.

Dr. Dubovsky replied that this vaccine has not been used in women who are pregnant deliberately. Other saponin-based vaccines that are authorized globally are either used against shingles, which would be in an elderly population, or in children for malaria vaccines. A toxicology study showed no adverse impacts to either the infant or the new mothers. The amount of adjuvant is fairly low.

Dr. Kim added that in terms of gestational age at birth among women who have live births after receiving the vaccine, the reports were spontaneous and often have limited information. While they do their best to follow-up to get as much complete information as possible, a vast majority of these cases do not have gestational age. Study 301 collected pregnancy information and pregnancies are being followed. The cases that have resulted in live births have not been reported to have had been pre-term deliveries.

Dr. Duchin (IDSA) asked the potential for waning protection over time and the likely need for a booster dose of the Novavax COVID-19 vaccine.

Dr. Dubovsky indicated that data from the US/Australia Phase 1/Phase 2 study in terms of the immune responses against the prototype and against the BA.2 variant showed that at Day 35 after the primary series, high titers were achieved that decayed over 6 months. This is the normal decay pattern associated with IgG. After a single boost at 6 months, higher titers were achieved that once again decayed over the following 6 months. Intervals between 6 months and 12 months in the Phase 3 study were associated with protection. Consistent with the antigenic cartography, subsequent doses increase the immune response against even the quite distant strains. In terms of median duration in the context of efficacy, in the primary data there was a median of approximately 60 days of observation. In that range, they had to institute crossover. That terminated the ability to have continued placebo control follow-up. In countries where the vaccine has been used longer, they are just now at the 6-month timepoint. Where authorized, some countries have policy recommendations supporting boosting. To data, Novavax has not received information on waning efficacy because those data are still being collected.

Dr. Poehling asked about the median duration of follow-up for safety and for more discussion about Grade 3 responses and if lymphadenopathy is a common finding. She clarified that she was trying to understand how long it took the Grade 3 symptoms to resolve and if they differed by local reactogenicity.

Dr. Dubovsky indicated that for the Novavax COVID-19 vaccine, safety follow-up was comparable between the vaccine and placebo groups, with a median duration of 92 days after Dose 1. Grade 3 or 4 symptoms did not necessarily last any longer. A relatively small proportion of people had solicited AEs that lasted longer than 7 days. Lymphadenopathy was not a common finding, but lymphadenopathy was not collected as a specified solicited AE.

Dr. Sanchez requested to hear more about SAEs in terms of the symptoms involved and whether these affected people’s normal daily lives and their ability to work.

Dr. Kim indicated that SAEs were broken down into system organ class (SOC). They were balanced between the active and placebo arms. No patterns of concern were raised. Deaths infrequent at <0.1%, which is the range that would be expected in the general population. There were some cardiovascular deaths that occurred at about the same incidence between the placebo and treatment arms, as well as a scattering of causes of death (CODs) from events such as accidents, gunshot wounds, accidental overdose, et cetera. Novavax has an ongoing study that is trying to understand the impact of the vaccine on daily activities, such as work.

Dr. Daly requested more details about what is known about the safety of saponin as an adjuvant in other vaccines as well as what is known about VE against hospitalization and death either from Phase 3 trials or from post-authorization trials elsewhere in the world.

Dr. Dubovsky responded that other versions of SBAs have been used extensively. Novavax has used it extensively in other kinds of development programs, including influenza for which they had a very nice Phase 3 study that ended a couple of years ago. It is being used in the malaria vaccine Novavax is associated with in Western Africa. In that study, the same dosage levels were taken down to children as young as 5 months of age, and it was thought to be tolerable. As far as the Novavax COVID-19 vaccine, their partners in India have taken the adult dose down into children as young as 2 years of age among whom it is thought to be tolerable with no safety signals detected to date. These are relatively small studies of just several hundred to several thousand individuals. The saponin story is that it has a 2-fold activity. It has a very short local reactivity where it induces cytokine and chemokine production and recruits antigen-presenting cells to the injection site. All of that resolves by 72 hours. There is slightly prolonged activity in the draining lymph nodes where there is increased antigen uptake presentation. It induces a polyfunctional CD4 immune response and high levels of neutralizing antibodies. This short duration is thought to be associated with the short duration of reactogenicity events displayed. In terms of VE against hospitalization and death, in the placebo-controlled portion of the study, protection from hospitalization and death was 100%. The total count in the US-Mexico Phase 3 study was 6 hospitalizations including 1 death in the placebo group versus zero in the vaccine group. Post-authorization from elsewhere in the world are not yet available. However, prevention of severe disease has held up in all of Novavax's studies in South Africa, the United Kingdom (UK), and the US.

Dr. Lee noted that it would be helpful to ACIP, particularly in the context of Omicron, to have an update on the post-authorization data when they become available.

Public Comment

The floor was opened for public comment during the July 19, 2022 ACIP meeting at 12:35 PM ET. All speakers submitted a request in advance of the meeting and the final list of public commenters was determined via a lottery. Everyone was reminded that the ACIP appreciates diverse viewpoints that are respectful in nature and issue-focused. The comments made during the meeting are included in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket No. CDC-2022-0085. Visit http://www.regulations.gov for access to the docket or to submit comments or read background documents and comments received.

Dr. Brian Dressen
Self

My name is Dr. Brian Dressen. I have extensive career experience thoroughly researching and assessing the degree of safety and efficacy of new products. I have no conflicts of interest and my words are my own. The clinical trials for Novavax reveal incidences of myo and pericarditis, as well as neurological complications like GBS. Most marketing reports reveal that these adverse reactions continue in the general population. Novavax, like Pfizer, Moderna, Johnson & Johnson, and AstraZeneca has been temporarily associated with a long COVID-like disabilities, cardiovascular issues, POTS, neurological disorders, neuropathies, and autoimmunity. A simple look at Australia and vaccine injury reports show Novavax is no different. The CDC and FDA are charged with ensuring the American public is provided with safe and effective vaccines—safe and effective. A publication in *JAMA Internal Medicine* last month examined the safety of mRNA vaccines in more than 433,000 people: 3.1% had Bell's palsy, paralysis, paresthesia, seizure, syncope, or vertigo; 2.7% experienced arrythmia; 3.4% had thrombocytopenia, anemia, lymphopenia or neutropenia; 0.75% had a stroke; 0.6% had myocardial infarction; and over 8% of the dataset were diagnosed with at least one of the serious adverse events. Compared against previous vaccines, the COVID vaccines are far more dangerous. We are repeatedly assured that serious complications are rare. The World Health Organization defines adverse events happening to 1 out of 100 persons or 1% taking a drug as common. This report shows that these reactions are common, not rare. You have failed at managing the pandemic. You have failed at ensuring safe and effective vaccines are available to the American people. We have learned that the CDC is not performing the required analysis of the pharmacovigilance systems. This is the reason no safety signals are identified. The CDC is not looking for them. The COVID vaccines do not prevent infection or transmission and cause serious harms to some of those who take them. The continuation of the pandemic is evidence that the COVID products are not effective. Data have been presented today showing low expectation of protection for current variants. My wife was severely injured by a single COVID vaccine dose in the clinical trial. Rather than report her reaction, the drug company dropped her from the trial and left her out of the report. We must do better. Those injured in a trial are a critical piece of vaccine safety data. They are being hidden, ignored, tossed aside, and forgotten. My wife’s family has changed forever. The clinical trial is also not appropriately evaluating the data. The FDA and CDC and the drug companies continue to deflect the persistent and repeated cries for help and acknowledgement, leaving the injured as collateral damage. You have a very clear responsibility to appropriately assess the safety and risks of these vaccines. It is obvious that this is not happening. Serious questions regarding pregnancy, heart problems, Phase 3 reactions, missing work, and others have been raised today without answers. I ask, does this show that we can say they’re safe? Thank you.

Mrs. Aubrey Fick
Individual

Okay, 15 months ago I received 1 dose of the Pfizer vaccine, and my life has not been the same since. Within hours of receiving the vaccine, I developed neck spasms and a heavy feeling in my head. Two weeks later, symptoms rapidly progressed. I developed internal vibrations in my brain, paresthesia, electrical shock sensations, tremors, neuropathy, vertigo, blurred vision, heart palpitations, chest pains, tachycardia, and joint pain. It became difficult to walk, and sometimes my legs would suddenly stop working. Sleep was next to impossible. When I finally would fall asleep, my body would continue to jolt wide awake as though I had an electric shock, and I would be gasping for air. Each night I went to sleep, I feared my heart would stop, and I would not make it through the night. I went to the emergency room and was quickly dismissed

by the ER doctor who suggested that I had anxiety or acid reflux. I was advised to take Tums and sent on my way. I was utterly shocked. I knew then that I would be facing this battle alone with no support from the medical community. To this day, I continue to suffer from a variety of neurological issues, particularly neuropathy and POTS symptoms. As a formerly healthy 35-year-old woman, this experience has been traumatizing, and to watch the aftermath has been appalling. I experienced significant challenges in reporting to VAERS and Pfizer that have left me deeply concerned about the tracking and adverse events. I fervently scoured the internet and found social media groups with thousands of others suffering neurologically whose lives have been drastically altered. We are routinely silenced, labeled as misinformation, and met with incredulous eyes. We are simply citizens of the United States of America that trusted that our government would provide aid and research in the event of adverse events. We need full acknowledgement and disclosure of neurological reactions from our federal agencies so that the medical communities can be made aware. We need robust large-scale research funding so that healthcare providers can be equipped with the necessary knowledge and possible treatment. How is progress to be made if we simply have small research studies with 3 or 4 cases? Why were we affected? What about our bodies caused it to attack itself and our autonomic nervous system to stop functioning properly? Doctors should not have to fear repercussions from the Medical Board in the event they come across a patient adversely impacted, and patients should not have to be gaslit in their nightmare. I urge you to assist in creating a dialogue where vaccine injury can be openly discussed. If this happened to your wife or your child, I trust that you would desire transparency with investigation and research funding. I trust that you would not want their stories censored. We must be compassionate and take urgent actions on all those suffering in the pandemic, irrespective of modality. We must be cognizant of using sweeping generalizations that the vaccines are safe and effective when clearly, for my body and thousands of others, it was toxic. Thank you for your time.

Ms. Ashley Scott
Policy and Outreach Coordinator
Blue Star Families (BSF)

My name is Ashley Scott. I am the Policy and Outreach Coordinator with Blue Star Family, a 501(c)(3) organization that conducts IRB approved studies of the experience, perception, opinions, and beliefs of military and veteran expectant families with our partners at Syracuse University. Respondents to our April 2021 COVID Collaborative Pulse Check Poll indicated that having a choice in which vaccines to receive would increase their likelihood of receiving it. And this phenomenon is particularly prominent among Active Duty service members. When we conducted the poll again in April of 2021, 66% of Active Duty respondents who were unvaccinated and had no appointment scheduled reported that the opportunity to choose their vaccine would increase their likelihood of receiving a vaccine. The same was true for 43% of Active Duty spouses, 41% of veterans, and 48% of veteran spouses. And again, those are just of the respondents to our COVID Collaborative Pulse Check Poll. Based on these results, we believe it is possible that expanding vaccine choices could increase the likelihood of receiving the vaccine in military-connected populations. Thank you all for your time.

Ms. Elizabeth ("Liz") Ditz
Vaccinate California

Thank you. Good morning committee members and those listening to today's meeting. My name Liz Ditz. While I'm a member of Vaccinate California, today I'm speaking for myself. My date book tells me that I first expressed concern about this new pneumonia in the Far East 888 days ago. This committee has worked tirelessly over those days, and I appreciate the efforts

you have made to make the decision factors public and transparent. I'm also an active member of a Facebook group, Vaccine Talk, an evidence-based discussion forum that has almost 79,000 members worldwide. Some of the Vaccine Talk members are physicians who are all internists or other professions involved in vaccine safety. These experts have volunteered their time to educate other members. Today, I especially want to recognize 2 of them, Vincent Iannelli, MD who has developed a web resource, Vaxopedia, which addresses vaccine questions in a timely manner, and Nathan Boonstra, MD, who cohosts the podcast Vax Talk sponsored by Voices for Vaccine. At Vaccine Talk, one theme in the conversation about vaccine refusal, and vaccine hesitancy, and vaccine anxiety has been largely expressed for the newness and to them the strangeness of the mRNA vaccine technology. Some of those folks previously said, “I’m not taking a COVID-19 vaccine yet” have also indicated that the vaccine discussed today, Novavax, would be acceptable. If Novavax is approved for use in the US, I am hoping the data will be gathered on the number of recipients who have previously refused vaccines as opposed to those who had found the access difficulty to see if the hypothesis that having a choice makes a difference. Going forward in public health planning, planning on more robust and effective information platform, in my view, would reduce vaccine hesitancy. As you all know, there’s a large literature on how to address vaccine hesitancy, and I hope the government can recruit and train community-level experts. Thank you again committee members for your work.

Lindsay Burmeister
COVID Vaccine-Injured Individual
Founding Member of CVI/WA

I want to start by acknowledging to the committee that I attest I have no financial conflicts of interest. My name is Lindsay Burmeister, and I am COVID vaccine-injured. I have multiple neurological issues, including brain inflammation due to the Moderna vaccine that I received in March of 2021. In my quest for healing, I’ve come across communities of individuals with debilitating neurological adverse reactions like mine. I am one of the founding members of an independent non-partisan group of COVID Vaccine Injured in Washington State called CVI/WA. We have met with the offices of several members of Congress in our state and have done multiple media interviews in respected publications and medical journals. Due to the intentional suppression of our reaction by the CDC, FDA, and social media outlets, the injured are unable to find support and access essential medical care. There is no funding for research, and there is no recovery plan or financial support available for us. As of July 2022, the CICP (Countermeasures Injury Compensation Program) has received almost 6,000 injury or death claims from the COVID vaccine products and has yet to pay out a dime. Both Britain and Canada have started paying out COVID vaccine injury claims. Even Thailand has compensated over 14,000 people around $50 million to settle COVID vaccine injury claims. Again, by contrast, the US has paid out nothing. We were asked to protect others by getting this vaccine only to find out there is no support or protection for us in return. The total COVID vaccine injury is filed in the VAERS database as of June 2022 with 878,425 claims. And we know that only 1% to 10% of injuries are actually reported to that system. The claims are grossly underreported. And yet, this number continues to climb. More and more people know someone whose health has been negatively impacted by the COVID vaccine products. And yet, you stay silent. This lack of transparency is eroding the public’s trust in your agency. CDC, we need you to acknowledge us. Hear me when I say we need help. Without an acknowledgement from the CDC of our injuries, proof of causation cannot be met. And in many cases, doctors refuse to believe us or treat us. The injured are losing their homes, their jobs, their insurance. They are going into massive debt, and in some cases, they’re losing their lives. We did our part. You assured us this was safe, and

we are suffering. It is time the government stepped up and put money and resources to this effort. We are pleading for help. Thank you.

Martha Nolan
HealthyWomen

Good afternoon. My name is Martha Noland, and I am speaking on behalf of HealthyWomen, the nation's leading non-profit health information organization for women providing consumers and healthcare providers accurate evidence-based information about diseases and conditions, innovations in biomedical research, and changes in policy that impact the treatment and care women receive. We requested to speak today to encourage the committee to recommend usage of a protein-based vaccine against COVID-19 that was recently approved by FDA that would be administered as a 2-dose primary series given 3 weeks apart. Providers need more options to reach those who remain unvaccinated in our country while the pandemic continues. COVID has been particularly devastating to Black and Latinx populations. While the disease is expected to reduce overall life expectancy by 2021 by just over a year, estimated reductions for Black and Latinx populations are 3 to 4 times more at risk than Whites. There are many reasons for vaccine hesitancy. As some have concerns or believe the massive misinformation efforts around using the mRNA technology and design and do not understand how they work. For those, perhaps the use of a more traditional protein-based vaccine designed similarly to the more well-known flu vaccine might overcome hesitancy. There are also millions of vulnerable Americans who have limited options for protection against COVID-19 and remain isolated and frustrated that they could be left on the sidelines while society continues to disregard safety protocol. I'm referring to the estimated 7 million immunocompromised individuals in the US for whom the stakes may be even higher than they were 2 years ago. We know that current vaccines don't work for everyone, and some are unable to take any of the options now offered. And the risks to those who remain vulnerable to the severe disease, including COVID-19, is compounded today by the removal of mask requirements—the push to return to normal and ever-diminishing social distancing as caution by individuals. Organ transplant patients and those who rely on medications that suppress their immune systems do not feel protected. People living with conditions that compromise the strengths of their immune systems such as HIV, cancer, and many autoimmune diseases feel exposed. And many older American who manage their chronic conditions to multiple medications are now severe limited in their options for treatment given the fear of drug interactions. We believe having a more traditional protein-based COVID-19 vaccine option available would help overcome any of these issues. Additionally, having a simpler storage method that could make the vaccine more widely distributed to rural and inner cities as well as healthcare practitioners who do not have ability to store refrigerated vaccines will create greater vaccine access to the US and around the world, particularly in areas that typically do not have equitable access to vaccines. We thank this committee for this tireless work and for diligently remaining at the forefront of dissolving threat to our health and wellbeing. Your work is critical in the fight against COVID-19, and we hope you will provide a recommendation in favor of more vaccine options. Thank you.

EtR Framework: Novavax COVID-19 Vaccine in Adults

Evelyn Twentyman, MD, MPH (CDC/NCIRD) provided updates to the EtR Framework on as it pertains to the Novavax COVID-19 vaccine, adjuvanted as a primary series in adults ≥18 years of age. Beginning with the mechanism of action of the Novavax COVID-19 vaccine, this is the first protein subunit COVID-19 vaccine authorized in the US. Pfizer-BioNTech and Moderna mRNA vaccines and the viral vector Janssen/J&J COVID-19 vaccine use genetic material

to encode a SARS-CoV-2 viral antigen and induce an immune response to that antigen. In contrast, adjuvanted protein subunit vaccines like the Novavax COVID-19 vaccine use the viral antigen without any genetic material and with an adjuvant added to help induce a strong immune response. The Novavax COVID-19 vaccine includes a purified, full-length, and stable recombinant spike protein as the viral antigen and uses Matrix-M™ adjuvant to enhance the magnitude of the immune response to the spike protein. T-cells then recognize the spike protein as a viral antigen and stimulate B-cells to produce neutralizing antibodies to this viral antigen and help protect the vaccine recipient against COVID-19.

The policy question for this EtR Framework assessment was, "Should the Novavax COVID-19 vaccine (2 doses, 5μg antigen + 50μg Matrix-M™ adjuvant, IM, 21 days apart) be recommended for persons ages 18 years and older under an Emergency Use Authorization?" The PICO (population, intervention, comparison, outcomes) question considered the population to be people ages 18 years and older. The intervention was a 2-dose primary series vaccination with Novavax COVID-19 vaccine with the doses given 21 days apart. The comparison was no vaccine. The outcomes of interest included symptomatic laboratory-confirmed COVID-19, hospitalization due to COVID-19, death due to COVID-19, asymptomatic infection, SAEs, and reactogenicity. The WG was guided by the EtR Framework domains of the public health problem, benefits and harms of the intervention, values, acceptability of the intervention to key stakeholders, feasibility of implementation, and the impact of the intervention on health equity.

In terms of the public health domain, the WG considered the magnitude of the COVID-19 public health problem and how COVID-19 vaccines in general are protecting people from this problem in terms of reducing the risk of cases, hospitalizations, and death due to COVID-19. COVID-19 continues to pose a significant threat to public health in the US. As of July 14, 2022, there have been over 83 million cases of COVID-19 in the US.[27] COVID-19 vaccines continue to mitigate the burden of COVID-19 cases. In June 2022, unvaccinated people ≥5 years of age had a 2.8 times higher risk of testing positive for COVID-19 compared to people vaccinated with at least the primary series.[28] COVID-19-associated hospitalizations also continue and have been on the rise recently. The burden of COVID-19-associated hospitalization is significantly higher among adults ≥18 years of age compared to children ≤17 years of age.[29] COVID-19 vaccines continue to reduce the risk of COVID-19-associated hospitalization for vaccine recipients. In May 2022, unvaccinated adults ≥18 years of age had a 3.5 times higher risk of COVID-19-associated hospitalizations compared with people who had completed their primary series and at least 1 booster dose.[30]

Tragically, COVID-19 continues to kill. As of July 14, 2022, a total of 1,018,578 people had lost their lives to COVID-19 in the US.[31] That is 1,018,578 too many. More than 99% of these people were ≥18 years of age—the population under consideration during this meeting. Fortunately, COVID-19 vaccines continue to mitigate the risks of COVID-19 mortality for those who get vaccinated. In May 2022, unvaccinated people ≥5 years of age had a 6 times higher risk of dying from COVID-19 compared to people who had received a primary series. Unvaccinated people ≥12 years of age had a 9 times higher risk of dying from COVID-19 compared to those with a primary series completed and a booster dose.[32]

[27] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed July 14, 2022
[28] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed July 15, 2022
[29] Unified Hospital Dataset: https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions Accessed July 13, 2022
[30] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed July 11, 2022
[31] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths Accessed July 13, 2022; Per National Center for Health Statistics Death Certificate Data: Total number of COVID-19 total deaths as of July 13, 2022, were 1,015,431; https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#AgeAndSex
[32] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed July 15, 2022

In terms of daily trends in doses of vaccine administered there fortunately has been outstanding success in getting hundreds of millions of COVID-19 vaccine doses administered across the US overall.[33] There are still important opportunities to improve vaccination rates, particularly among people 18 through 49 years of age. In this group, less than 70% are fully vaccinated with a primary series, and less than 30% are up-to-date (UTD) with a COVID-19 booster vaccination. Coverage does appear to improve with increasing age.[34] This helps speak to the question raised earlier about who has received booster doses among those eligible. Certainly, being UTD is the most effective protection against COVID-19. The first step toward that is completing a primary series vaccination. Looking at these data by the percent of people with at least 1 dose of COVID-19 vaccine since these vaccines first became available, there is a struggle to complete vaccine coverage among the adult populations in particular.[35] This illustrates opportunities to improve vaccine coverage.

To summarize the public health problem, COVID-19 continues to pose a significant health problem. COVID-19 vaccines continue to mitigate cases, hospitalizations, and deaths. However, not all people in the US have received the benefits that COVID-19 vaccines provide. In fact, about 26 to 37 million US adults have not yet received a single dose of a COVID-19 vaccine and would benefit from starting a primary series. In this context, the ACIP COVID-19 Vaccines WG unanimously considered COVID-19 disease among adults ≥18 years of age to be of public health importance.

Moving now to the domain of benefits and harms, ACIP and CDC develop vaccine recommendations using an explicit evidence-based method based on the GRADE approach (Grading of Recommendations, Assessments, Development, and Evaluation). One study provided the data used as GRADE evidence. This was the Novavax Phase 3 randomized controlled trial (RCT) otherwise known as Study 301. The data were obtained directly from the sponsor for the purposes of this analysis. These data did not include the 6 hospitalizations and 1 death occurring in the placebo group. The data cutoff date was September 27, 2021, with a median placebo-control follow-up at 2.5 months. Study enrollment and efficacy follow-up occurred during December 27, 2020 to September 27, 2021 and mainly when the Alpha variant of SARS-CoV-2 was predominant. A total of 29,925 adults were randomized 2:1 to receive either the vaccine or placebo. The numbers of persons available for the analysis in the full analysis set that was used to assess SAEs included 19,963 vaccine recipients and 9,982 placebo recipients. The per-protocol set included 17,272 vaccine recipients and 8,385 placebo recipients. There was no immunologic or virologic evidence of prior SARS-CoV-2 infection and there were no major protocol deviations.

Using the per-protocol population for all persons ≥18 years of age, there were 17 cases among the 17,272 persons in the vaccine arm and 79 among the 8,385 persons in the placebo arm, which resulted in a VE estimate of 89.6% (82.4%, 93.8%). This is the outcome that was used for GRADE. VE was at least 76% in those ≥65 years of age and those at risk due to the presence of a comorbidity. To provide support with data for effectiveness in persons ≥65 years of age in there were few events. An immunogenicity comparison between participants 50 through 64 years of age demonstrated a VE of 90.7% (72.9%, 96.8%) in a post-hoc efficacy analysis to those ≥65 years of age. The Day 35 neutralizing antibody GMT was slightly lower for persons ≥65 years of age compared with those 15 through 64 years of age, with a GMT ratio of 0.91 (0.68, 1.2). The lower bound of the associated 95% confidence interval would have met FDA's

[33] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-trends Accessed July 18, 2022
[34] CDC COVID Data Tracker. COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-count-total Accessed July 18, 2022
[35] CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed July 18, 2022

usual success criterion for immunobridging non-inferiority of >0.67. VE of approximately 90% or higher was observed across racial and ethnic groups with the exception of Hispanic or Latino participants in whom VE was 75.7% with a confidence interval from 46% to 89.1% was observed.

In terms of the GRADE assessment for the outcome of symptomatic laboratory-confirmed COVID-19, the relative risk was 0.10 (0.06 to 0.18). The absolute risk demonstrated in the trial was 848 fewer cases per 100,000. In the past, there has been a heavier reliance on the relative effects because risk varied substantially from trial-to-trial. However, moving toward a longer-term vaccination strategy, absolute risks will be discussed more. For this outcome, there were no serious concerns in the certainty assessment, so the WG determined the certainty to be Type 1 (high certainty).

The second outcome for consideration was hospitalization for COVID-19. In addition to hospitalization due to COVID-19, the protocol included a definition of severe illness due to COVID-19 per FDA guidance of aCOVID-19 case with ≥1 of following: clinical signs at rest indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. This did not require hospitalization. For the outcome of severe COVID-19, there were no cases in the vaccine group and there were 4 in the placebo group for a VE of 100%. There were no hospitalizations for COVID-19 in either the vaccine or placebo groups of which the WG was aware, so the WG used a surrogate measure of severe COVID-19. Using this method, the relative risk was 0.05 (0.00 to 1.00) and absolute risk was 45 fewer cases per 100,000 with a 95% confidence interval from 48 fewer to 0 fewer. There was a serious concern for indirectness because severe COVID-19 is a surrogate outcome for hospitalization due to COVID-19. There was also serious concern for imprecision due to the small number of events. The final evidence certainty was Type 3 (low certainty).

For the outcome of SAEs, there were 199 events among 19,735 participants in the vaccine group and 105 events in 9,847 events in the placebo group for a comparison of 1% experiencing SAEs in the vaccine group compared to 1.1% in the placebo group. In the vaccine arm, 5 participants experienced SAEs that were considered potentially related to vaccination. Among these, FDA considered 1 event of angioedema as potentially related to vaccination. There was 1 event of myocarditis in a 67-year-old male with concomitant COVID-19 infection 28 days after Dose 1, which was not considered related to vaccination but rather to COVID-19. Initial cases of myocarditis were observed after placebo crossover. For the GRADE assessment of the outcome of SAEs, the WG observed a relative risk of 0.92 (0.73 to 1.16). The absolute risk was 88 fewer SAEs per 100,000 with a confidence interval from 296 fewer to 175 more. There were no serious concerns in the certainty assessment, so the final evidence certainty was Type 1 (high certainty).

For the outcome of severe reactogenicity, 16.3% of vaccine recipients experienced Grade 3 or 4 local or systemic reactions after either dose compared to 4% in the placebo group. For the GRADE assessment of this outcome, the relative risk of reactogenicity was 4.11 (3.70 to 4.57). The absolute risk was 12,323 more per 100,000 (10,698 to 14,146). There were no serious concerns in the certainty assessment, and the evidence was determined to be Type 1 (high certainty).

In summary of the GRADE analysis, Novavax COVID-19 vaccine is effective in preventing symptomatic COVID-19 during a period of Alpha variant predominance with an evidence certainty of Type 1 (high certainty). Severe COVID-19 was used as a surrogate for the outcome of hospitalization due to COVID-19. Novavax COVID-19 vaccine demonstrated efficacy in preventing severe COVID-19, but the evidence certainty was Type 3 (low certainty). SAEs were balanced between the vaccine and placebo arms with an evidence certainty of Type 1 (high certainty). Severe reactions were more common among the vaccinated, with any Grade 3 or higher reactogenicity reported in 16.3% of vaccinated versus 4% of placebo recipients. The evidence certainty for reactogenicity was Type 1 (high certainty).

To consider additional information to assess VE and safety, the WG moved beyond the data considered through the GRADE to look at some additional evidence to inform their EtR Framework. With respect to efficacy, they included observations regarding circulating variants across the duration of a pandemic and observations of efficacy in the context of other variants. Toward the strongest possible evaluation of safety, they looked at data pertaining to pre- and post-crossover vaccine recipients in Study 301 plus adolescent and booster expansions of Study 301 and all vaccine recipients across Novavax clinical trials globally including Studies 301, 302, 501, and 101. To better understand myocarditis and/or pericarditis after Novavax, the WG considered a broader safety set and publicly available post-authorization data globally to allow for the experience of other countries with Novavax.

Some of the remaining questions about VE include VE in certain populations, VE against asymptomatic infection, and VE in the context of Omicron. Novavax VE in Study 301 was assessed in the period of predominance of the Alpha variant of SARS-CoV-2. Of 96 cases accrued in the primary efficacy analysis, pre-crossover from December 20, 2020 through September 27, 2021, there were 75 cases with sequence data as follows: 53% Alpha, 11% Iota, 7% Epsilon, 4% Gamma, 3% Beta, 1% Delta, 1% Kappa, and 1% Zeta. It is important to explore why variant circulation might matter in the assessment of the benefits of a COVID-19 vaccine. First, in neutralizing antibody studies assessing the immune response of people who received mRNA vaccines, study participants who completed their second dose of the mRNA vaccine earlier mounted a weaker neutralizing antibody response against new variants as compared with Alpha. For Omicron, neutralizing titers were much lower compared with Alpha and ancestral strains.

Moving out of the laboratory and into real-world VE studies, VE from CDC's VISION Network against hospitalizations for 2 doses of mRNA vaccines during the period of Alpha predominance was approximately 90% for both Pfizer-BioNTech and Moderna vaccines. Estimates during the Delta predominance period indicated combined 2-dose mRNA VE. However, there was a large drop in the period of Omicron BA.1 predominance down to just under 70%. There was another drop in the era of Omicron BA.2 and BA.2.12.1 to less than 60%.[36] Returning to Novavax COVID-19 vaccine, 1 study investigated the efficacy of Novavax COVID-19 vaccine against the Beta (B.1.351) variant of SARS-CoV-2 in South Africa from 2020—2021. Among 2684 participants seronegative at baseline, VE against symptomatic COVID-19 disease was 49.4% (6.1%, 72.8%). Among HIV negative participants who were seronegative at baseline, VE was 60.1% (19.9%, 80.1%). Of 41 sequenced isolates, 38 (92.7%) were Beta variant. Post-hoc VE

[36] Alpha estimates for Pfizer-BioNTech and Moderna separately from: Thompson et al. NEJM https://www.nejm.org/doi/full/10.1056/nejmoa2110362; Delta estimates for mRNA vaccines combined from: Thompson et al. MMWR https://www.cdc.gov/mmwr/volumes/71/wr/mm7104e3.htm; and Omicron estimates for mRNA vaccines combined from: Link-Gelles et al. *MMWR* https://www.cdc.gov/mmwr/volumes/71/wr/mm7129e1.htm

against the Beta variant was 51.0% (-0.6%, 76.2%).[37] All this to say that the exact VE of the Novavax COVID-19 in the context of Omicron or future variants is unknown.

Transitioning now to the broader safety dataset, there were several events of myocarditis and/or pericarditis with a possible relationship to vaccine detected over the expanded safety dataset of approximately 41,546 recipients ≥16 years of age. In addition, 1 event angioedema was identified in Study 301 and 1 event of GBS was identified in Study 302. To contextualize the events of myocarditis and/or pericarditis, intensive post-authorization COVID-19 vaccine surveillance has identified a small risk of myocarditis associated with mRNA vaccination, particularly after a second dose in adolescent males and young men.[38] COVID-19 disease itself is associated with risk of multiple serious cardiac outcomes, including myocarditis, pericarditis, stroke, acute coronary syndrome, myocardial infarction, heart failure, arrhythmia, and cardiac death.[39]

In this context, it is very clear that benefits of COVID-19 vaccine outweigh risks. The risk of cardiac complications is higher after COVID-19 than after mRNA COVID-19 vaccinations among males and females of all ages. Teen boys 12 through 17 years of age have a 2 to 6 times higher risk of cardiac complications after infection compared to after vaccination, and young men 18 through 29 years of age have a 7 to 8 times higher risk of cardiac complications after infection compared to after vaccination. COVID-19 vaccine is the best way to protect against COVID-19 and rare cardiac complications.[40]

To briefly review what is known about myocarditis and/or pericarditis after mRNA vaccination from 2 of the platforms that make up the most intensive vaccine safety surveillance in US history, VAERS reporting rates of myocarditis and/or pericarditis following mRNA vaccination by age group and sex show the highest reporting rate of 38.9 among males 18 through 24 years of age following Dose 2 within Days 0 to 7 after vaccination. VSD also demonstrated excess risk among young people following Dose 2. Now turning to what was observed in the Novavax clinical trials.[41] In the total clinical safety database of over 40,000 vaccine recipients, 4 cases myocarditis and/or pericarditis were identified as having a temporal relationship to vaccination and concern for a causal relationship to the vaccine. All 4 patients were hospitalized and all 4 experienced complete clinical resolution. There were 3 additional cases identified across clinical trials, 2 in vaccine recipients and 1 in a placebo recipient, all of which had an alternative explanation for the etiology.

Myocarditis and pericarditis also have been identified in international post-marketing safety data. To date, over 744,000 doses[42] of Novavax COVID-19 vaccine have been administered post-authorization and/or approved in Australia, Canada, European Union, New Zealand, and South Korea. These data were submitted by responses to FDA in advance of their consideration at the Vaccine and Related Blood Products Advisory Committee (VRBPAC) meeting on June 7, 2022. Internationally, 35 unique reports including 36 unique myocarditis and/or pericarditis events have been identified. There were 29 cases of pericarditis and notably 5 of the individuals

[37] Shinde et al. Efficacy of NVX-CoV2372 COVID-19 vaccine against the B.1.351 variant. NEJM 2021; 384:1899-1909
[38] Oster et al. JAMA. 2022;327(4):331-340. doi:10.1001/jama.2021.24110;
[39] 2 Basu-Ray I, Almaddah Nk, Adeboye A, et al. Cardiac Manifestations Of Coronavirus (COVID-19) StatPearls Publishing; 2022 Jan. https://www.ncbi.nlm.nih.gov/books/NBK556152/
[40] Block JP, Boehmer TK, Forrest CB, et al. Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination — PCORnet, United States, January 2021–January 2022. *MMWR* Morb Mortal Wkly Rep 2022;71:517-523. DOI: http://dx.doi.org/10.15585/mmwr.mm7114e1
[41] FDA VRBPAC Briefing Document. June 7, 2022. https://www.fda.gov/media/158912/download
[42] Lee L. FDA review of effectiveness and safety of Novavax COVID-19 vaccine in adults ≥18 years of age. June 7, 2022. https://www.fda.gov/media/159004/download

with pericarditis had a history of pericarditis following mRNA vaccination. There also were 4 cases of myocarditis, 2 cases of myopericarditis, and 1 case of carditis not otherwise specified. The median known age of patients was 35 years, with 20 males and 15 females identified. This table summarizes what is known about myocarditis and pericarditis following Novavax COVID-19 vaccine in clinical trials and post-vaccine data so far:

Summary of cases of myocarditis and/or pericarditis following Novavax vaccination, doses administered & reporting rates

Setting	Cases	Doses administered	Reporting rate** (cases/million doses administered)
Novavax COVID-19 Vaccine clinical trials[1]	4–6*	41,546	**96–144**
Sponsor submission of post-marketing reports in Australia, Canada, EU, New Zealand & South Korea[2]	36	744,235	**48**
Australia post-marketing reports[3]	15	160,000	**94**

[1] Total expanded safety population approximated from FDA EUA Novavax Letter of Authorization July 13, 2022: Study 1 = 26,151; Study 2 ≈ 10,800; Study 3 + 4 ≈ 5500. Precise denominators requested of the sponsor.
[2] Lee L. FDA review of effectiveness and safety of Novavax COVID-19 vaccine in adults ≥18 years of age. June 7, 2022. https://www.fda.gov/media/159004/download.
[3] https://www.tga.gov.au/periodic/covid-19-vaccine-safety-report-30-06-2022#section-1865. Of these 15 cases reported in Australia, 3 were likely to represent myocarditis; 12 were likely to represent pericarditis.

*Includes a 16-year-old vaccine recipient from the adolescent safety data set; 4 = cases in temporal relationship without alternative etiology, 5 = cases in temporal relationship, with or without alternative etiology, 6 = all cases in vaccine recipients in clinical trials, regardless of temporal relationship or alternative etiology
**Reporting rate calculated as: (# cases)/(# doses administered*1,000,000)

An FDA EUA Fact Sheet for providers warning about myo/pericarditis reads, "Clinical trials data provide evidence for increased risks of myocarditis and pericarditis following administration of Novavax COVID-19 Vaccine, Adjuvanted."[43] The EUA Fact Sheet for recipients cautions recipients to tell vaccine providers about a history of myocarditis or pericarditis and also counsels what symptoms to watch for.[44]

To summarize the benefits and harms domain, Novavax COVID-19 vaccine had high efficacy in the setting of the Alpha variant (B.1.1.7) consistent with other authorized COVID-19 vaccines at that time. The efficacy with recent SARS-CoV-2 variants and future variants is unknown. Reactogenicity reported after Novavax vaccine was similar to what has been reported for other COVID-19 vaccine primary series. There were reports of myocarditis and/or pericarditis after Novavax COVID-19 vaccine during clinical trials, and several cases are evident in early post-authorization data. Based on the available data, it is important to point out that VE or myocarditis rates for Novavax and mRNA COVID-19 vaccines cannot be directly compared. Post-authorization monitoring for both VE and safety will be important moving forward. Based on these data, the WG felt that the desirable anticipated effects of the Novavax COVID-19 vaccine are large, the undesirable anticipated effects are small, and that the desirable effects outweigh the undesirable effects—favoring the intervention of Novavax COVID-19 vaccine.

[43] FDA. EUA Novavax HCP Fact Sheet. July 13, 2022. https://www.fda.gov/media/159897/download
[44] FDA. EUA Novavax Fact Sheet for Recipients and Caregivers. https://www.fda.gov/media/159898/download

Now to discuss the domain of values, a survey was designed by the CDC, University of Iowa, and RAND Corporation to assess vaccination intentions for protein-based COVID-19 vaccine with or without adjuvant among unvaccinated Americans. Data were collected from January 27-February 2, 2022 with a sample size of 541 respondents. This presentation focused on the vaccination intention of protein-based COVID-19 vaccine with adjuvants, such as Novavax COVID-19 vaccine among unvaccinated adults. Among the unvaccinated respondents, 16% said that they probably or definitely would get an adjuvanted protein-based COVID-19 vaccine. However, 52% of these unvaccinated respondents said that they probably or definitely would not get an adjuvanted protein-based COVID-19 vaccine. These results varied somewhat by several demographic characteristics, but not by others. Vaccine intentions were significantly higher among men than among women, and vaccine intentions were significantly lower among non-Hispanic White adults than among non-Hispanic Black adults or among Hispanic adults. Vaccine intentions did not vary by US region, metropolitan status, age, or education.

In another survey conducted June 18-23, 2022 among a representative sample of 1,788 unvaccinated US adults, some unvaccinated adults were less adamantly against traditional vaccines than others. In other words, more long-standing platforms than others. Those in urban areas, adults under 35, and Black and Hispanic adults all were less likely than the average unvaccinated American to say that they would skip a traditional protein-based vaccine. Given that few unvaccinated adults are interested in traditional protein-based COVID-19 vaccines, unvaccinated adults were asked if they would get a traditional protein-based COVID-19 vaccine if one were authorized for use in the US. The top concerns among unvaccinated adults who do not want a protein-based COVID-19 vaccine include side effects, followed by worries that the vaccine moved through clinical trials too fast, and/or a belief that the vaccine will not be effective. The survey also detected a very interesting difference in beliefs about safety in protein-based vaccines versus mRNA vaccines. Among all adults, these assessments of safety were similar but interestingly, vaccinated adults seemed to more commonly express the belief that mRNA vaccines were safer while unvaccinated adults seemed to more commonly believe that protein subunit vaccines were safer.

To summarize values, when asked in early 2022, 16% of unvaccinated respondents probably or definitely would get an adjuvanted protein-based COVID-19 vaccine like Novavax. However, 52% of these unvaccinated respondents said that they probably or definitely would not. There were no significant differences by US region, metropolitan status, age group, or education, but vaccination intentions were lower for females than males and lower for non-Hispanic White adults. Among unvaccinated adults, 77% said they would not get a traditional protein-based COVID-19 vaccine if one were authorized. Among unvaccinated adults, 28% said they view these traditional or more longstanding protein-based vaccines as safe compared with 17% who said mRNA shots or vaccines were safe. The WG felt that the desirable effects in terms of their view within the target population were varied, that patient and caregiver views would vary, and that the valuation of this intervention varied. Additionally, the WG felt that there is probably important uncertainty or variability in this valuation.

Moving to domain of acceptability, the most significant apparent influences upon an individual's assessment of vaccine acceptability were assessed by a Kaiser Family Foundation (KFF) survey.[45] Personal doctors were identified as the most trusted for COVID-19 vaccine information, with survey respondents' own doctor most frequently ascribed a great deal or a fair amount of trust and pediatricians following next. CDC is investing in a variety of diverse partnerships to work to enhance the acceptability of vaccines across the nation, including investing in jurisdictions to launch new programs to enhance access, acceptance, and updates; in communities hard-hit by COVID-19; in health departments to address COVID-19 disparities; in community health organizations; and in partnership with the Federal Retail Pharmacy Program to ensure vaccine access.[46] Impressions from a jurisdictional partner listening session with 26 jurisdictions present on July 7, 2022, most of the partners stated that they would order Novavax vaccine if it became available, expressed a high interest in support related to Novavax COVID-19 vaccine, and described highly varied intent of use including in private provider offices, pharmacies, local health departments, and all of the above.

To summarize the acceptability domain, the great majority of adults (85%) trust their own doctors to provide reliable information about COVID-19 vaccines. The CDC will continue to do everything the agency can to enhance vaccine acceptable, access, and uptake in communities disproportionately impacted by COVID-19 and elsewhere. As with other COVID-19 vaccines, Novavax COVID-19 vaccine is likely to be acceptable to implementing partners. Overall, the WG felt that the Novavax COVID-19 vaccine is probably acceptable to key stakeholders.

Turning now to feasibility, the WG considered standard known barriers to vaccine implementation, including complexity of recommendations and communication thereof, vaccine storage and handling requirements, financial barriers, and supply barriers. The complexity of recommendations does not pertain to Novavax COVID-19 per se but instead applies to the complexity of the many vaccine recommendations it comes alongside as potentially the fourth approved COVID-19 vaccine in the US. The Novavax COVID-19 vaccine is supplied in a carton containing 10 multiple-dose vials with each vial containing 10 doses. This is stored in a refrigerator and does not need to be frozen. It has a beyond-use date of 6 hours after the first puncture and must be discarded shortly thereafter. This vaccine is preservative-free and does not require reconstitution or dilution. There is an interesting factor that pertains to the expiration date in that they are not on the labels. To find the expirations dates, partners must navigate to www.Novavaxcovidvaccine.com. In the realm of financial barriers, COVID-19 vaccines continue to be provided to US populations free of charge. Health systems and/or health departments do incur some costs for vaccine implementation, clinics, outreach, and education. In addition, financial hardship can arise if vaccine recipients have to take time off to receive the vaccine or afterwards if they experience post-vaccination reactogenicity that prevents them from working.

In terms of supply barriers, the US has demonstrated that distribution of vaccine per se is feasible to implement broadly. The purchase of Novavax COVID-19 vaccine thus far includes 3.2 million doses with the intent to distribute following an ACIP recommendation, if indeed recommended. Some relative logistic advantages of Novavax vaccine include easy storage, familiar schedule, and easy preparation. The disadvantages in terms of feasibility might include that short seal beyond use date time and the need to discard after puncture. Additionally, there are no recommendations for unrefrigerated storage prior to puncture. The 10-dose packaging is

[45] KFF COVID-19 Vaccine Monitor (April 13-26, 2022). https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-april-2022/ Accessed July 7, 2022

[46] CDC. COVID-19 Vaccine Equity for Racial and Ethnic Minority Groups. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/vaccine-equity.html Accessed July 7, 2022

currently only authorized for use as a primary series, which could lead to increased wastage. In addition, this is a new product for providers.

In summary of the feasibility domain, the Novavax COVID-19 vaccine would be the fourth COVID-19 vaccine with an EUA. All vaccines will continue to be provided free of charge. The US has demonstrated success in distributing about 600 million doses of COVID-19 vaccine across the country, which is excellent. There are some relative logistical advantages and a few disadvantages of Novavax vaccine as well. Overall, the WG felt that Novavax COVID-19 vaccine would indeed be feasible to implement among adults ≥18 years of age as a primary series.

Turning now to the equity domain, the most severe COVID-19 outcomes have weighed more heavily on some populations than on others. These inequities are seen as a manifestation of long-standing inequities and/or also contributors to continued and future inequities. Everyone needs to do everything possible to reduce health inequities. This is fundamental for those working in public health and in clinical medicine. No single vaccine has the ability to overcome all disparities—not the vaccine under discussion during this meeting or any other single vaccine. There are several issues related to vaccine equity and health equity. It is critical to continue to investigate these persistent health inequities and do everything possible to resolve them, and it is important to underscore that any inequity in COVID-19 vaccine access or use has the potential to further exacerbate disparities in COVID-19's impact. This table is a reminder of the powerful cumulative inequities and the higher risk of hospitalizations and deaths due to COVID-19 among AI/AN persons, non-Hispanic persons, Black or African American non-Hispanic persons, and Hispanic or Latino persons as compared to White non-Hispanic persons:

Risk for COVID-19 infection, hospitalization, and death by race/ethnicity, age-adjusted

Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
Cases[1]	1.5x	0.8x	1.1x	1.5x
Hospitalization[2]	3.0x	0.8x	2.3x	2.2x
Death[3, 4]	2.1x	0.8x	1.7x	1.8x

Race and ethnicity are risk markers for other underlying conditions that affect health, including socioeconomic status, access to health care, and exposure to the virus related to occupation, e.g., frontline, essential, and critical infrastructure workers.

[1] Data source: Data reported by state and territorial jurisdictions (accessed June 22, 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate. Calculations use only the 66% of case reports that have race and ethnicity; this can result in inaccurate estimates of the relative risk among groups.

[2] Data source: COVID-NET (March 1, 2020 through June 11, 2022). Numbers are ratios of age-adjusted rates standardized to the 2020 US standard COVID-NET catchment population. Starting the week ending 12/4/2021, Maryland temporarily halted data transmission of COVID-19 associated hospitalizations, impacting COVID-NET age-adjusted and cumulative rate calculations. Hospitalization rates are likely underestimated (link). As of June 11, 2022, this situation remains unchanged.

[3] Data source: National Center for Health Statistics provisional death counts (https://data.cdc.gov/NCHS/Provisional-Death-Counts-for-Coronavirus-Disease-C/pj7m-y5uh, data through May 29, 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate.

[4] Data on COVID-19 deaths comes from the National Vital Statistics System (NVSS). The NVSS COVID-19 surveillance webpages and data file updates are paused between June 6, 2022 through June 21, 2022. COVID-19 data updates are expected to resume on June 22, 2022.

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Updated June 24, 2022 and accessed July 14, 2022.

Given the power of COVID-19 vaccines to reduce the risk of these severe outcomes, COVID-19 vaccines represent a potential way to decrease these disparities over time. If distribution, access, acceptance, and uptake of COVID-19 vaccines is not inevitable, the intended effect of vaccines on these disparities may not be achieved. Thus far, inequities do persist and receipt of COVID-19 vaccine data from the NIS-ACM demonstrate that 22% of persons of Other/Multiple Races, 20% of persons who are AI/AN, 14% of the persons who are Hispanic, and 14% of persons who are White have yet to receive the COVID-19 vaccine. Data pertaining to other disparities also highlight that there is room to improve COVID-19 vaccination. Significantly more

adults residing in a rural area have not received a COVID-19 vaccine compared to those residing in suburban or urban areas. Additionally, a higher percentage of adults with incomes less than $75,000 per year or living in poverty have not yet received a COVID-19 vaccine compared to adults with higher incomes. Other markers such as access to healthcare are still significant. A higher percentage of US adults who do not have a regular primary care provider or health insurance have not received a COVID-19 vaccine compared to those with a regular provider and those who are insured. These disparities are important to note, particularly in the context of COVID-19 vaccines having been made available free of charge and without the need for either primary care physicians or health insurance.

There may be more to learn about the barriers to COVID-19 vaccination in this space. The US Census Bureau Household Pulse Survey (HPS)[47] shows that adults who had not received a single dose of the COVID vaccine tend to be younger, have lower levels of education attainment, are more likely to be non-white, are less likely to be married, are more likely to be economically disadvantaged, and are more likely to report a disability or a different ability than those who received at least 1 dose of COVID-19 vaccine. In an effort to make advancements toward vaccine equity for all, CDC launched the *Partnering for Vaccine Equity* program that is focused on increasing equity in adult immunization. Anyone who is interested in learning about these important efforts is invited to visit the *Partnering for Vaccine Equity Vaccine Resource Hub* to learn more and join CDC in these efforts.[48]

In summary of the equity domain, there are notable disparities in COVID-19 cases, hospitalizations, and mortality rates by race and ethnicity. Vaccine status differs by age, level of education, race, and ethnicity. An additional COVID-19 vaccine utilizing traditional or longstanding vaccine technology will provide an additional option for unvaccinated individuals. Improving vaccine equity requires continued efforts. National-, state-, local-, and community-level partners are focused on diverse endeavors to improve equity in adult immunizations among disproportionately affected populations. Overall, the WG felt that the impact of the Novavax COVID-19 vaccine alone probably would have no impact on health equity.

To summarize the EtR Framework evaluation overall, the WG workgroup felt that COVID-19 is of public health importance and that anticipated desirable effects of the vaccine are large while anticipated undesirable effects are small. The WG felt that the balance of desirable and undesirable effects favors the intervention. The certainty of evidence for critical outcomes ranged from high for prevention of symptomatic COVID-19 SAEs to low for prevention of hospitalization. The WG felt that the target population valuation of the Novavax COVID-19 vaccine varies, with probably important uncertainty or variability. It was thought that the Novavax COVID-19 vaccine is probably acceptable to key stakeholders and it is feasible to implement, but that the Novavax COVID-19 vaccine alone probably would have no impact on health equity.

The WG interpretation of the data presented thus far is as follows. The WG understands that the vaccine had high efficacy against symptomatic COVID-19 disease in the setting of Alpha predominance. Reports of myocarditis and/or pericarditis after Novavax COVID-19 vaccine are none during both clinical trial and early post-authorization data. Based on available data, the WG cannot directly compare VE or myocarditis rates for Novavax and mRNA vaccines, and that post-authorization monitoring for both VE and safety will be important. Vaccination remains the

[47] US Census Bureau Household Pulse Survey (HPS) United States Census Bureau. Who Are the Adults Not Vaccinated Against COVID? https://www.census.gov/library/stories/2021/12/who-are-the-adults-not-vaccinated-against-covid.html Accessed February 24, 2022

[48] https://vaccineresourcehub.org/

best way to protect against SARS-CoV-2 and the rare cardiac risks of COVID-19 disease. As always, the top priority remains vaccination of unvaccinated individuals. An additional COVID-19 vaccine utilizing traditional or more longstanding vaccine technology will provide an additional option for unvaccinated individuals. Overall, the WG felt that the benefits of Novavax COVID-19 vaccine outweigh risks. In the balance of consequences evaluated, the WG felt that the desirable consequences probably or clearly outweigh the undesirable consequences in most settings and recommended the intervention.

Interim Clinical Considerations: Novavax COVID-19 Vaccine

Dr. Elisha Hall (CDC/NCIRD) presented Interim Clinical Considerations for Novavax COVID-19 vaccine. Novavax is authorized for people ≥18 years of age. People who are not moderately or severely immunocompromised should receive 2 primary doses separated by 3 to 8 weeks. People who are moderately or severely immunocompromised should receive 2 primary doses separated by 3 weeks. A third primary dose for people who are immunocompromised is not currently authorized. At this time, only the 2-dose primary series is authorized for both populations. If and when a third dose is authorized, CDC could then add guidance to that effect. Additionally, just like when other COVID-19 vaccines were first authorized for a primary series, only primary doses are authorized at this time. Neither a homologous or heterologous booster is authorized. It is expected that at some point in the future, people who choose this primary series would be able to get a booster when they need it. CDC provides clinical guidance for what FDA authorizes. Once authorized, these doses can be added to the COVID-19 vaccination schedule.

In terms of a mixed primary series, COVID-19 vaccines are not interchangeable, including Novavax. The same vaccine product should be used for all doses in the primary series. If a mixed primary series is inadvertently administered, the series is considered completed and doses do not need to be repeated. This is considered to be an error and should be reported. As an exception to this rule, if a person starts but is unable to complete the primary series with the same COVID-19 vaccine due to a contraindication, any other non-contraindicated age-appropriate COVID-19 vaccine may be administered to complete the series at a minimum of 28 days from the last dose. This would not need to be reported to VAERS because it is included in CDC's guidance.

Existing co-administration guidance that applies to other COVID-19 vaccines also applies to Novavax vaccine. In general, COVID-19 vaccines may be administered without regard to timing of other vaccines and may be given on the same day or any time before or after. Routine administration of all age-appropriate doses of vaccines simultaneously is recommended for people for whom no specific contraindications exist at the time of the healthcare visit. The only exception is that there are additional considerations for orthopoxvirus vaccines. When deciding whether to co-administer another vaccine with Novavax vaccine, providers may consider whether a person is behind or at risk of becoming behind on recommended vaccines, the likelihood of the person returning for another vaccination, the person's risk of becoming infected with a vaccine-preventable disease, the person's risk for severe disease if infected, and the reactogenicity profile of the vaccines. In terms of the exception to the co-administration guidance related to orthopoxvirus vaccination, there are 2 different scenarios because of the observed risk for myocarditis after receipt of ACAM2000, Moderna, Novavax, and Pfizer vaccines and the unknown risk for myocarditis after JYNNEOS vaccine. If a person receives an orthopoxvirus vaccine first, they might consider waiting 4 weeks before receiving Moderna, Novavax, or Pfizer COVID-19 vaccine. If a person instead receives Moderna, Novavax, or Pfizer first and are then recommended to receive an orthopoxvirus vaccine for prophylaxis in the setting of an outbreak, administration of the orthopoxvirus vaccine should not be delayed

because of the recent receipt of one of the COVID-19 vaccines. This is because the benefit of administering an orthopoxvirus vaccine as soon as possible when indicated for prophylaxis outweighs the possible risk of myocarditis by administering them too close together.

Regarding preparation and administration of Novavax COVID-19 vaccine indicated for persons ≥18 years of age, 1 dose contains 5μg of SARS-CoV-2 recombinant spike protein antigen + 50μg Matrix-M™ adjuvant. The injection volume of 1 dose is 0.5 mL. The vaccine should not be diluted and contains 10 doses per volume. As with the other COVID-19 vaccines, it should be injected intramuscularly in the deltoid muscle for adults. The Novavax COVID-19 vaccine should be stored refrigerated between 2° to 8°C (36°to 46°F). It should be removed from refrigerated storage only when ready to use. An unpunctured vial should not be stored at room temperature. Although some other COVID vaccines can be frozen, this one should not be frozen. Once punctured, the vial must be used within 6 hours. As Dr. Twentyman mentioned, the expiration date is not printed on either the vial or the carton. Therefore, it is very important to use the Novavax expiry date checker tool to avoid administering expired vaccines.[49]

In terms of contraindications and precautions, the currently authorized or approved COVID-19 vaccines are classified into 3 types: 1) mRNA vaccines, including Moderna and Pfizer-BioNTech vaccines; 2) adenovirus vector, which includes only Janssen vaccine; and 3) protein subunit, which includes only Novavax. Contraindications include a history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component Novavax COVID-19 vaccine, or a history of a known diagnosed allergy to a component of Novavax COVID-19 vaccine. The Clinical Considerations currently state that an allergy-related contraindication to one type of vaccine is a precaution to another. For Novavax COVID-19 vaccine, that language has been slightly modified to state that, “People with an allergy-related contraindication to one type of COVID-19 vaccine have either a contraindication or precaution to the other types of COVID-19 vaccines.” The only contraindication is for people with a known allergy to polysorbate. This means they have a contraindication to both Novavax and Janssen vaccines, which contain polysorbate. In all other cases, an allergy-related contraindication to one type of COVID-19 vaccine is a precaution to both of the other types.

The other changes to contraindications and precautions in the existing guidance apply only to Novavax COVID-19 vaccine and include the following:

- ❑ History of an immediate allergic reaction to any vaccine other than COVID-19 vaccine or to any injectable therapy
- ❑ History of a non-severe, immediate (onset less than 4 hours) allergic reaction after a dose of Novavax COVID-19 vaccine
- ❑ Moderate or severe acute illness, with or without fever
- ❑ History of MIS-C or MIS-A
- ❑ History of myocarditis or pericarditis after a dose of an mRNA or Novavax COVID-19 vaccine

[49] https://www.novavaxcovidvaccine.com/

Myocarditis or pericarditis after a dose of an mRNA or Novavax vaccine is a precaution to a subsequent dose of any COVID-19 vaccine. Considerations for subsequent vaccination include whether the myocarditis or pericarditis was considered unrelated to mRNA or Novavax vaccination, personal risk of severe acute COVID-19, and timing of immunomodulatory therapies. For people ≥18 years of age who choose to receive a subsequent COVID-19 vaccine, some experts advise using Janssen. People who choose Janssen should be informed of the risk of TTS. The highest risk is in females 30 through 49 years of age. Additionally, a history of myocarditis or pericarditis prior to COVID-19 vaccination is not a precaution. People with this history may receive any currently authorized or approved COVID-19 vaccine after the episode of myocarditis or pericarditis has resolved. Again, much of this guidance already has been in place for mRNA COVID-19 vaccines and is simply being extended to Novavax COVID-19 vaccine.

There are no specific data on an extended interval between Dose 1 and Dose 2 of Novavax COVID-19 vaccine. However, there is evidence of benefits of an extended interval in mRNA recipients. Some studies in adolescents and adults have shown that a small risk of myocarditis or pericarditis associated with mRNA COVID-19 vaccines might be reduced and peak antibody responses and VE might be increased. Therefore, an 8-week interval may be used between Doses 1 and Dose 2 to potentially reduce the risk of myocarditis or pericarditis. The 3-week interval is more appropriate for people who are moderately or severely immunocompromised, for people ≥65 years of age, and when protection needs to be achieved soonest, such as having another high-risk reason for severe disease or living, working, or traveling to an area with high COVID-19 community levels. The 8-week interval could be considered for the potential to reduce myocarditis risk, especially in young adult males and for optimized VE.

Discussion Summary (Twentyman & Hall)

Dr. Twentyman briefly recapped what the “big picture” of the COVID-19 vaccine recommendations would look like if the ACIP recommended the Novavax COVID-19 vaccine. For the primary series vaccinations, ACIP would recommend mRNA COVID-19 vaccines, Modern and Pfizer-BioNTech, and Novavax COVID-19 vaccine. For booster vaccination, mRNA vaccines would be recommended. Novavax COVID-19 vaccines are not currently authorized for booster doses and no COVID-19 vaccines are currently authorized for booster dose use in Novavax COVID-19 vaccine primary series recipients. Just like when other COVID-19 vaccines were first authorized for a primary series, only primary doses are authorized at this time for the Novavax COVID-19 vaccine. Neither homologous nor heterologous boosters are authorized. It is expected that at some point in the future, people who choose this primary series would be able to get a booster when they need it. The Janssen COVID-19 vaccine should be used only in limited situations, which are described at length in the Interim Clinical Considerations.

Dr. Poehling said she was surprised that there is no expiration date on the vials and that providers would have to go to a website to check each and every vial to find out the expiration dates. She worries about the feasibility of doing that and the potential for error. She was not familiar with this approach for other vaccines.

Dr. Hall said that she does not think this is typical. This has come up with a QR code rather than having the date with one of the COVID-19 vaccines. CDC has a COVID-19 vaccine expiration date tracker to help aid with It is not as ideal as having the expiration on the vial, but it is available with CDC’s clinical education materials so that providers can look up the expiration and lots and write that down and note it on the carton immediately to help prevent vaccine administration errors. There is certainly a higher risk for administering expired vaccine. She

asked whether Novavax would like to comment about the label in terms of the reason for not including expiration dates.

Dr. Dubovsky indicted that the reason was strictly a logistical one. They are working toward providing labeling that is more complete.

Dr. Lee asked FDA colleagues to comment on whether this type of labeling is reviewed in advance of approval of a Biologics License Application (BLA), and if there are requirements for labeling and consistency across vaccines being used under an EUA. The last few vaccine approvals have gotten overly complex, so she wondered whether this might be an opportunity for improvement or if this is already in the works at FDA.

Dr. Rebecca Reindel from FDA acknowledged the concern and indicated that she would doublecheck the specifics of each vaccine label or Fact Sheet to try to determine why information was or was not included. There may be specific considerations that inform that on a case-by-case basis. Working on the labeling to make it more consistent still would fall within the bounds of the regulations and what each specific fact sheet or label requires.

Dr. Kotton expressed appreciation that immunocompromised patients were included in the Clinical Considerations. However, based on all other vaccine data in immunocompromised patients, it would be anticipated that these patients would need more than 2 doses of vaccine to engender significant protection. For now, the company did not include immunocompromised patients other than a very small subset of people living with HIV in their clinical trials. It is likely that these data will not be available for a while. It is disappointing that this estimated 3% of the US population who are vulnerable to severe life-threatening disease now have an option for a vaccine, but it is likely to be less than fully protective. She expressed disappointment that this leaves providers in a situation where for the near foreseeable future, there will not be data to guide the ability to make a better decision for that population with this new vaccine.

Dr. Sanchez noted that he did not hear much about allergic reactions from Novavax in terms of adverse reactions, and he heard about the angioedema that possibly was related. In terms of the Clinical considerations, he did not hear anything about having to monitor individuals who have received Novavax for 15 minutes or so after its receipt.

Dr. Kim indicated that Novavax looked broadly at possible allergic reactions, particularly hypersensitivity reactions. There was a standard MedDRA query that was utilized for broad search that found a 0.77% incidence in Novavax COVID-19 vaccine recipients and a 0.57% incidence in the placebo arm. They were not serious and the most frequent were rash, urticaria, and contact dermatitis. There were no events of anaphylaxis reported in the clinical program. For the single case of angioedema, there were some multiple confounding factors that were reported for that particular case. There were no other similar events observed in the clinical program or across the adjuvant program. This event occurred about 5 days after the first dose and resolved on the same day. There was no respiratory distress, and it was confounded by concomitant antibiotic use, concurrent infection, and a history of penicillin allergy.

Dr. Hall indicated that CDC’s guidance for the observation period has not changed. There are some minor edits to the language, but the meaning has not changed. Those with a history of anaphylaxis due to any cause should be observed for 30 minutes. Those with a history of an immediate allergic reaction of any severity to non-COVID-19 vaccines or injectable therapies, a history of non-severe immediate allergic reaction after a previous dose of the COVID-19

vaccine, and people with a contraindication to a different type of COVID-19 vaccine that have a precaution to this one, and for all other people 15 minutes is the observation period.

In terms of product mixing and matching, Dr. Sanchez pointed out that some places give only one type of vaccine. If someone receives Novavax and then only one of the mRNA vaccines is available for their second dose but the Novavax vaccine is not approved for booster dosing, what booster dose should that person receive?

Dr. Twentyman responded that the fundamental principle is that homologous primary series vaccines are recommended. If a mixed primary series is inadvertently administered, the primary series is considered completed and those doses do not have to be repeated. It is considered an error though. If someone did not intend to receive an mRNA vaccine at any point and that was why they were getting a Novavax series, they probably would not want to proceed with another mRNA dose.

Dr. Romero added that CDC will issue a statement on this and recommendations in upcoming Clinical Guidance.

Dr. Sanchez expressed disappointment in the myocarditis data. A lot has been said about this in terms of mRNA vaccines. Though the rates are not as large for the Novavax COVID-19 vaccine, they are still substantial. It seemed to occur equally between males and females, and he wondered whether there was any more information on this.

Dr. Twentyman responded that they take any and every event extremely seriously, including this one. The numbers that have been seen of myocarditis and/or pericarditis in clinical trials and in post-marketing data globally are small. It was not clear that anything could be said about the balance between males and females yet, or that this risk is very well-characterized at this point. The data are not yet sufficient to feel confident about comparing the risk between mRNA and Novavax COVID-19 vaccines. However, this further underscores the importance of the intensive vaccine safety surveillance efforts that are ongoing through VAERS and VSD and the work that supports those and other safety platforms. Much has been learned about the risk that COVID-19 disease itself poses to the human heart, and that these vaccines are protective against those cardiac risks—even among those who are known to be at higher risk for these rare cardiac complications after mRNA vaccines. There is a lot more to learn and this will be evaluated closely. In the meantime, she encouraged everyone to complete the primary series.

Dr. Sanchez asked whether, if the Novavax COVID-19 vaccine was approved during this meeting, it would be added to v-safe[SM].

Dr. Shimabukuro indicated that any COVID-19 vaccines available can be included in v-safe[SM] and a similar survey will be used as has been used with the other products.

Vote: Novavax COVID-19 Vaccine in Adults ≥18 Years of Age

Evelyn Twentyman, MD, MPH (CDC/NCIRD) presented the proposed recommendations for a Novavax COVID-19 vaccine in adults ≥18 years of age as follows:

> "A two-dose Novavax COVID-19 vaccine, adjuvanted is recommended as a COVID-19 vaccine primary series for persons ages 18 years and older under the EUA issued by FDA."

Discussion Summary

Dr. Long requested a clarification that did not need any word change in terms of the recommendation and vote, which looked straightforward. Instead, she offered a plea to hold the manufacturer to the fire to have an expiration date on the label. While she thought she heard Dubovsky from Novavax say that this will happen, she received a lot of feedback that the 2 previous immunizations ACIP recommended had the wrong volume and wrong age. Having to understand the border—whether it is maroon, or brown, or whatever color—is not acceptable. This is cutting off a step, and in this case, with the probability that maybe 12% to 15% at most of the 10% of the population who are not immunized might choose this vaccine. There is no rush to have it without proper labeling to minimize risk. She expressed surprise that the FDA would authorize a vaccine without an expiration date, and she did not think ACIP should recommend it without an expiration date right on the vial. It is not acceptable to ask the poor, overworked, under-resourced administrators to go find a website and look it up for the particular vial in their hand. They are taught to look at the vial to confirm that they have the right age, the volume to administer, and the expiration date before drawing and administering the shot. ACIP is losing credibility with the people who have to administer these vaccines, so she would like that caveat to be understood before this vaccine is provided for the US population.

Sandra Fryhofer (AMA) said that speaking as a practicing physician, she greatly understood Dr. Long's comments. She explained that when her office had Moderna vaccine to administer, the expiration dates were changing and increasing at unscheduled times. Her office received vaccine late on what they thought was the last day it could be administered, but it turned that Moderna had extended the expiration date. A moving expiration date is not new, but it is very confusing. It is even more confusing when the concentration of the vaccine is not on the vial.

Dr. Lee added that from an implementation standpoint, having a standard approach for how ACIP does this consistently across vaccine products would greatly ease implementation and barriers. Because everyone is worried about making errors, ACIP should make sure they are making it easier for people to do the right thing.

Motion/Vote: Novavax COVID-19 Vaccine in Adults ≥18 Years of Age

Dr. Loehr made a motion for ACIP to adopt the verbiage of the recommendation stating that, "A two-dose Novavax COVID-19 vaccine, adjuvanted is recommended as a COVID-19 vaccine primary series for persons ages 18 years and older under the EUA issued by FDA." Dr. Poehling seconded the motion. No conflicts of interest (COIs) were declared. The motion carried with 12 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Summary

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 emphasized that they have been moving at warp speed as the Operation Warp Speed (OWS) name has said to make sure that vaccines are available for everyone, but ACIP will continue to look back and to determine what can be done better, such as labeling. Hopefully by the time they are talking about booster doses and immunocompromised doses for this vaccine, the labels will be updated.

Dr. Kotton expressed her hope that there would be an anticipated timeline for booster doses for the late Summer and Fall. Some people have been asking whether they should be getting booster doses now when they are due or if they should wait. She is worried about that approach with BA.5 and thinks that a rough timeline that could be used for clinical decision-making would be useful for clinicians and vaccine recipients. She also encouraged further discussion during ACIP meetings about the monkeypox vaccine. There is a very active vaccine rollout, and as much information as possible would be very helpful. The presentations during the last meeting were useful and very welcomed by her colleagues. She also reiterated the importance of additional methods of prevention. While there is a lot of discussion about immunization for people who are immunocompromised, monoclonal antibodies can be used for prevention as well. A minority of immunocompromised patients who would qualify for EVUSHELD™ have received even a first dose. There is now a recommendation for a second dose 6 months after the first dose. It seems key for the CDC to mention all methods of prevention, whether infection control vaccines or monoclonal antibodies. For clinicians listening for patients who are immunocompromised and their family members, she strongly requested consideration of EVUSHELD™. It is effective in the setting of BA.5 and she has seen it be a significant game changer in combination with a full vaccine series for immunocompromised patients.

Dr. Brooks noted that the primary target population for Novavax will be the 10% to 13% of those who are unvaccinated. Given that this is more or less the only indication right now, he understood the need to focus on that population, with the hope that perhaps this protein subunit vaccine will change them from being unvaccinated to vaccinated.

Dr. Lee emphasized that she is very positive about the Novavax COVID-19 vaccine and having a fourth option.

Dr. Sanchez said he was very positive about this vaccine, especially for those who are hesitant. A large population has voiced concern that this vaccine is made from aborted fetal tissue, which is not accurate and should eliminate some of that pushback. Physicians need some guidance about waiting for boosters until the Fall, given that there may be a bivalent COVID-19 vaccine available in the future. They cannot keep boosting every 3 months, but it seems there will be some urgency in FDA commenting on booster for those who are due a booster and those who receive the Novavax vaccine.

Dr. Kotton agreed, noting that people feel that they may be penalized if they get a booster now in the setting of raging BA.5 subvariant disease in that they think that their next booster may need to be significantly delayed. Increased transparency would help in terms of sharing more information about people receiving boosters now versus later.

Dr. Poehling highlighted that a lot has been learned throughout the pandemic and knowledge has evolved. At this point, the knowledge is that 3 doses of vaccine are really important.

Dr. Long emphasized that people will be thinking about boosters in August and September. Millions of Americans are now at 6 months or more beyond their second boosters and they do not know what to tell people about whether to get the same vaccines that have been given previously, or to wait for an optimized booster that will be available.

In terms of equity, it is important to keep in mind that people of color, people who are living in poverty, homeless populations, et cetera often experience major access issues and cannot or will not go get another booster dose every 3 to 4 months. It is critical to know more about the bivalent booster as soon as possible in order to inform these individual.

Dr. Wharton expressed appreciation for the community's engagement on the day's issues. This has been an extraordinary couple of years, and unprecedented demands have been made on ACIP to repeatedly engage as recommendations have incrementally expanded for a number of vaccines that have been initially authorized by the FDA under EUA. The demands have been extraordinary, and CDC is very grateful for the ACIP's support in advising the agency on appropriate use of these products. The timeframe for additional boosters is not completely clear yet, but additional information will be shared with the COVID-19 Vaccine WG, full ACIP, and the public as it becomes available.

CERTIFICATION

Upon reviewing the foregoing version of the July 19, 2022 ACIP meeting minutes, Dr. Grace Lee, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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
WHARTON, Melinda, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

MEMBERS

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 – 6/30/2024

LOEHR, Jamie, 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)
GRIMES, Reed, MD, MPH
Chief Medical Officer
Division of Injury Compensation Programs
Rockville, MD

Indian Health Service (IHS)
CLARK, Matthew, MD, FAAP, FACP
Physician
Chair, IHS National Pharmacy & Therapeutics Committee
Durango, CO

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)
HOGUE, Michael D., PharmD, FAPhA, FNAP
Dean and Professor of Loma Linda University School of Pharmacy
Director, Center for Interprofessional Education & Practice
Loma Linda, CA

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)
DEEKS, Shelley, MD, MHSc, FRCPC, FAFPHM
Deputy Chief Medical Officer of Health, Department of Health and Wellness, Nova Scotia
Associate Professor, Dalla Lana School of Public Health, University of Toronto
Chair, National Advisory Committee on Immunization
Halifax, Nova Scotia

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 THIS DOCUMENT

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Event
AESI	Adverse Event of Special Interest
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
AR	Adverse Reaction
ASTHO	Association of State and Territorial Health Officers
BEST	Biologics Effectiveness and Safety System
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CMS	Center for Medicare and Medicaid Services
COD	Cause of Death
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DFO	Designated Federal Official
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DVA	Department of Veterans Affairs
ECG/EKG	Electrocardiogram
EHR	Electronic Health Records
EMA	European Medicines Agency
EMR	Electronic Medical Record
ET	Eastern Time
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GBS	Guillain- Barré Syndrome
GMT	Geometric Mean Titers
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HHS	(Department of) Health and Human Services
HIV	Human Immunodeficiency Virus

HRSA	Health Resources and Services Administration
IDSA	Infectious Disease Society of America
IHS	Indian Health Service
IM	Intramuscular
J&J	Johnson & Johnson
KFF	Kaiser Family Foundation
LTCF	Long-Term Care Facilities
MAAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MMWR	*Morbidity and Mortality Weekly Report*
MSA	Metropolitan Statistical Area
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAPNAP	National Association of Pediatric Nurse Practitioners
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NIH	National Institutes of Health
NIS-ACM	National Immunization Survey Adult COVID-19 Module
NMA	National Medical Association
NSTEMI	Non-ST Elevation Myocardial Infarction
NVSS	National Vital Statistics System
OWS	Operation Warp Speed
PCP	Primary Care Provider/Practitioner
PEP	Post-Exposure Prophylaxis
PHAC	Public Health Agency Canada
PIDS	Pediatric Infectious Disease Society
PIMMC	Potential Immune-Mediated Medical Condition
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SAHM	Society for Adolescent Health and Medicine
SBAs	Saponin-Based Adjuvant
SDOH	Social Determinants of Health
SES	Socioeconomic Status
SHEA	Society for Healthcare Epidemiology of America
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SSR	Summary Safety Report
TTS	Thrombotic Thrombocytopenia Syndrome
UK	United Kingdom
US	United States
USG	United States Government
UTD	Up-To-Date
VA	(US Department of) Veteran’s Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness
VOC	Variants of Concern

VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
WG	Work Group