MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

JANUARY 27, 2021

SUMMARY MINUTES

The Centers for Disease Control and Prevention (CDC) convened an emergency meeting of its Advisory Committee on Immunization Practices (ACIP) on January 27, 2021. These summary minutes provide an overview of the meeting which was devoted solely to the topic of coronavirus disease 2019 (COVID-19) vaccines. **Dr. José R. Romero** (ACIP Chair) opened the COVID-19 vaccines session.

Dr. Beth Bell (ACIP WG Chair) gave an introduction, highlighted 3 MMWRs on the interim recommendations for use of Pfizer-BioNTech and Moderna vaccines and updated interim recommendation for allocation of COVID-19 vaccines, and reviewed work group activities since the last meeting.

JANUARY 27, 2021

ASTRAZENECA COVID-19 VACCINE (AZD1222)

Dr. Tonya Villafana (AstraZeneca) provided a detailed review of the clinical development program and early clinical trial data for the AstraZeneca COVID-19 vaccine (AZD1222).

- Phase I/II study showed induction of binding and neutralizing antibodies as well as T-cell responses, with a favorable safety and reactogenicity profile, supporting advance to Phase III trials.
  - AZD1222 was well tolerated in phase I/II studies. Local and systemic reactions were 20% less frequent after the second dose. Adverse events were similar in nature to those reported with mRNA vaccines. Less reactogenicity was observed in adults over 70 years (30% fewer mild/moderate local reactions compared to adults <55 years and 20% fewer systemic reactions compared to adults <55 years).
- Phase III trials started in August 2020 and include subjects 18+, with a goal of 25% over 65 years of age. 32,459 participants have been enrolled, with 26,327 receiving the second dose by January 21, 2021. Of this total population enrolled, about 3,600 were in Peru/Chile, and the rest of the participants were enrolled in the US. In the US population enrolled, the racial and ethnic breakdown is as follows: 11.2% Hispanic, 9.8% Black, 5.3% Asian, 1.8% American Indian, 0.4% Hawaiian/Pacific Islander, 71.5% White. Of the US population enrolled 23.6% were 65+ years old and 57.8% had a comorbidity.
- AstraZeneca paused the study on September 6th, 2020 in response to an event of transverse myelitis in the phase II/III study in the UK. The study restarted October 28th, 2020. AstraZeneca made changes to the protocol, established an independent expert neurology panel, and accelerated/increased safety reporting.
- Results from the non-IND Phase II/III Program were presented as a pooled analysis across 4 ongoing studies with 23,745 participants enrolled across studies, and 11,636 participants met inclusion for primary efficacy analysis. Results of interim efficacy analysis from Non-IND trials conducted outside

the US showed 62.1% (95.8% CI: 41.0% to 75.7%) efficacy at preventing symptomatic COVID-19 with the dose/intervals being studied in the US.

- No hospitalizations or severe COVID-19 were reported in vaccinated participants. Serious adverse events were reported in 168 participants (79 received AZD1222, 89 received control MenACWY or saline). Four were considered possibly related (pyrexia and transverse myelitis in AZD1222 group, and autoimmune hemolytic anemia and transverse myelitis in control group). Solicited adverse events were similar to those described above for Phase I/II studies.

SUMMARY OF DISCUSSION

AstraZeneca Team Members responded to questions from Committee members.

- AZD1222 effect on Sars-CoV-2 variants
  - AstraZeneca is continuing to work to understand activity of vaccine against circulating variants. Analysis is underway currently for the UK variant looking at neutralizing activity data. This variant has been dominant in UK, so AstraZeneca will also put together analysis on efficacy within a week or two. AstraZeneca is also currently looking at neutralizing activity against South African variant, and it will also be possible to potentially look at efficacy. Trial sites in Brazil are not around the epicenter for the Brazil variant, so AstraZeneca may not be able to make direct comments on efficacy in Brazil, but they will look at neutralizing antibody against virus.
- Question on trial participants dropping out in US as they become eligible for vaccine – about 3000 participants have dropped out so far.
- Prophylactic use of paracetamol did not have any impact on immunogenicity in AstraZeneca studies
- A pregnancy registry is being set up. About 21 pregnant women (women who became pregnant after vaccination) were included in the dataset analyzed, and they are being followed through birth of child. Data is not yet available.
- Bell's palsy: Three cases in the vaccine group and three cases in control group
- Does baseline population have preexisting immunity to chimp adenovirus? Generally no, preexisting immunity is low in all populations, but there is variability. Have not seen any significant differences in immune response to spike protein in different countries.
- Are any subgroup analyses being done stratified by age, co-morbidities, or racial/ethnic composition? From Oxford studies, efficacy in co-morbidities population was 74.3%. In terms of older adults, they did not have large number of older adults for interim analysis, but will report results in subsequent analyses.
- Question regarding potential for development of adaptive immunity to adenovirus platform and likelihood it could impact booster responses
  - So far, do not see a relationship between anti-vector immunity and spike protein response with second dose. In the UK trial there is a small subgroup who were previously in trials with same viral vector and have now received two doses of coronavirus vaccine so will be able to answer this question soon.
- Differences in efficacy between low dose/standard and standard/standard groups

- Responses look very much the same between the two groups, so AstraZeneca thinks the interval differences is what is associated with the increased efficacy in low dose/standard group because many of them were in the longer interval group

COVID-19 EPIDEMIOLOGY AMONG CHILDREN

Dr. Angela Campbell (CDC/NCIRD) provided a brief overview of COVID-19 epidemiology, epidemiology in children and teens, and multisystem inflammatory syndrome in children (MIS-C).

COVID-19 reported incidence is lowest for children <18 years of age; multiple factors have contributed to under detection of COVID-19 in children.

A study conducted in Mississippi from May through September 2020 showed seroprevalence among children <18 was 10.9% overall. Seroprevalence was higher in non-white children. A case-ascertained household transmission study was conducted in TN and WI to understand susceptibility and transmissibility in children. Interim analysis of this study showed younger children <12 years were less likely to be symptomatic, symptomatic children seem to transmit less than adults, and children exposed in the household had a similar risk of secondary infection as adults. A similar study in UT and WI from March to May 2020 showed children were as susceptible to SARS-CoV-2 infection as adults.

Children <18 have lowest cumulative rate of COVID-19 associated hospitalizations, but children with certain underlying conditions may be more likely to have severe illness. 52% of children <18 hospitalized with COVID-19 had underlying medical condition, and the most common underlying condition was obesity. Children <18 are similarly likely to be admitted to the ICU but are less likely than adults to experience mechanical ventilation and death. COVID-19 mortality rates are lowest among children <18.

As of most recent January update, 1,659 MIS-C cases were reported, including 26 deaths. The estimated MIS-C incidence from April-June 2020 based on population-based incidence estimates was 1to 8.5 MIS-C cases per million person months. Incidence was also estimated using the denominator of estimated SARS-CoV-2 infections, which showed a higher incidence in non-white children.

SUMMARY OF DISCUSSION

Dr. Campbell responded to Committee members' questions.

- Data is not currently available on impact of SARS-CoV-2 variants on MIS-C, but we do plan to look at this question
- Understanding disproportionate burden of MIS-C in Black and Hispanic children
  - Dr. Campbell explained that for overall COVID-19 cases race data is missing for a large portion of cases, there are multiple factors contributing to this burden, and that some could be testing bias.
- Are type 1 diabetics at the same risk as type 2 diabetics?
  - COVIDNET data does not differentiates between type 1 and type 2 diabetes
  - Suggestion from a committee member to potentially update the CDC website risk factor list to not specifically mention type 2
- Data available on myocarditis in children not associated with MIS-C like has been seen in adults?

  - Paper currently under review comparing MIS-C and severe COVID-19 in children that will include this data
- There is research being devoted to long term COVID-19 outcomes

PEDIATRIC COVID-19 CLINICAL TRIALS

Dr. Emily Erbelding (NIH) presented an overview of the plans for SARS-CoV-2 vaccine trials in children, including the rationale for pediatric SARS-CoV-2 vaccine trials. Pediatric burden of disease is significant and there is a disproportionate burden among children in minority communities. Shell protocols were developed by pediatric and maternal working groups, IDCRC, and shared with manufacturers.

- Pfizer-BioNTech has fully enrolled down to age 12 and hope to be licensed down to age 12 in the first half of 2021. They are also currently planning studies in children less than 12 in early 2021.
- Moderna has launched a standalone protocol (TeenCOVE) for adolescents and are planning for younger groups in early 2021. Enrollment in TeenCOVE opened in December, and they are currently enrolling, with a target enrollment of 3000.
- Janssen has announced that they plan to start trials in 12-17 year olds 4-6 weeks after results from their adult trial. Of note, this platform has already been widely used in teens, infants, and children
- AstraZeneca will begin trials in adolescents in early 2021
- Novavax is currently enrolling for adults, but no details are available on plans for adolescents
- Protocols are in development for dose-ranging studies

SUMMARY OF DISCUSSION

Dr. Erbelding responded to Committee members' questions.

- For adult trials, there was an emphasis on having a racially and ethnically diverse population. Is there the same effort for trials in children?
  - Trials funded by USG will help fund recruitment to focus on this
- Request for future presentation on protocol for enrolling pregnant women
- What placebos would be considered in these trials? These are still in development, so may be a true placebo or another active vaccine

COVID-19 VACCINE SAFETY UPDATE

Dr. Grace Lee (ACIP, VaST Co-chair) reviewed the purpose of VaST and preauthorization activities. Currently VaST is reviewing data from v-safe, VAERS, and CISA, and they are beginning to see data from two systems with population based data available.

Dr. Tom Shimabukuro (CDC/NCEZID) presented a COVID-19 vaccine safety update.

- V-safe: smart phone based text to web survey with daily check ins for the first week
  - V-safe has 2,080,216 registrants across Pfizer-BioNTech and Moderna vaccines of almost 22,000,000 vaccinated. Local and systemic reactions are very similar between the first dose of the two vaccines. The second dose of Pfizer-BioNTech is substantially more reactogenic than the first dose. There are 227 pregnancies enrolled in registry as of January 22nd, 2021.
- VAERS: passive surveillance system

    - There are 9096 reports in VAERS. There are 372 reports per million doses administered for non-serious adverse events and 45 reports per million doses administered for serious adverse events, which is comparable to what is seen for other vaccines given to adults.
- CISA responded to 143 clinical inquiries/consultation requests about COVID-19 vaccine safety
- VSD has data available on 162,575 vaccinees for dose 1, and 34,182 vaccinees for dose 2. No signals have been reported as of January 16th for 21 outcomes being monitored.
- Update on anaphylaxis following COVID-19 vaccine
    - Suspected anaphylaxis reports to VAERS through January 18th, 2021 were reviewed. There were 50 confirmed anaphylaxis cases for Pfizer-BioNTech and 21 for Moderna. Cases tended to occur quickly after vaccinated, with a median of 10 minutes for both vaccines. A high percentage of these confirmed anaphylaxis cases had a documented history of allergies and 24% reported a documented history of prior anaphylaxis. The updated reporting rate of anaphylaxis is 5.0 per million doses administered for Pfizer-BioNTech and 2.8 per million per doses administered for Moderna.
- Reports of death and mortality following COVID-19 vaccine
    - VAERS has received reports of 196 deaths due to any cause following COVID-19 vaccination. The median age is 79 years; 66% were long term care residents. 113 received Pfizer-BioNTech and 83 received Moderna. These deaths should not be assumed to be causally related. The overall impression is that mortality in LTCF residents is high due to underlying health status of this population and does not suggest a safety problem with respect to deaths in older adults in LTCF. Deaths in LTCF are consistent with expected all cause mortality in this population. VAERS has received 28 reports of death following COVID-19 in community dwelling adults aged <65 years. Cardiac issues account for the majority of these where a death certificate or autopsy is available.
- Overall, the safety profiles are reassuring and consistent with that observed from the pre-authorization clinical trials.

Dr. Grace Lee (ACIP, VaST Co-chair) summarized VaST's assessment of the safety data. Consistent with clinical trial data, local and systemic reactions are commonly reporting following vaccination in v-safe and VAERS. Limitations are that this is numerator only data, is descriptive, and is subject to reporting bias. During the later phase of the US vaccination program, VaST will start to rely more on data from population-based surveillance system.

In summary, anaphylaxis is being closely monitored and in response to reported events, CDC has recommended mitigation strategies. Serious adverse events following COVID-19 vaccination are being closely monitored. Data in the US and Europe suggest case reports are consistent with all-cause mortality rates. VaST will continue to update ACIP on a regular basis.

SUMMARY OF DISCUSSION

Dr. Lee and Dr. Shimabukuro responded to Committee members' questions.

- VaST is currently reviewing pregnancy data as it comes in and would be happy to present at a later date when they have sufficient data.
- Encouragement from committee member to make sure patients are aware of potential reactions
- Question regarding reactions in patients who previously had COVID-19
  - Not currently collected in v-safe, but exploring some options for further assessing this issue
- V-safe pregnancy registry is enrolling women through the duration of their pregnancy and following the infants for 3 months, so will have information on infant outcomes
- Emphasis from committee member on how timely and comprehensive this safety monitoring is, and how critical these data are for public confidence

UPDATE ON COVID-19 VACCINE ADMINISTRATION

Dr. Amanda Cohn (CDC/NCIRD) presented a high level update of COVID-19 vaccine administration. ACIP prioritization recommendations are intended as a framework to support equitable and efficient administration of COVID-19 and jurisdictional flexibility. CDC is committed to transparency on vaccine administration data.

As of January 25th, 11 states are in Phase 1a, 38 states are in phase 1b, and 2 states are in phase 1c. Vaccines have been shipped to over 18,000 providers. Over 44 million doses have been distributed, with over 23 million administered. Almost 20 million people have received 1 or more doses, and nearly 3.5 million have received 2 doses. Both products are being used broadly.

There is a need to improve efficiency of vaccination at administration sites. We are working to improve throughput at the site, improve schedule, better match supply and throughput capabilities, improve vaccine supply and demand mismatch, and share best practices from states that are doing this well.

In summary, supply continues to be a rate-limiting factor. As vaccination expands and vaccine uptake increases, we need to focus on rapidly administering doses and reducing bottlenecks in the system. Emphasis on equitable access, reducing barriers, and increasing engagement to build trust in communities.

SUMMARY OF DISCUSSION

Dr. Cohn responded to Committee members' questions.

- Question regarding supply – this is one of the more challenging barriers, not being able to predict. Additional discussions are being had, and we are trying to better understand and work with companies for forecasting.
- Strong emphasis from the committee that we need to ensure we are prioritizing equity
  - Dr. Cohn expressed that we are engaging with additional partners to address this and supporting the jurisdictions however we can to focus on equity

COVID-19 VACCINE EFFECTIVENESS STUDIES

Dr. Katherine Fleming-Dutra (CDC/NCIRD) presented plans for COVID-19 Vaccine Effectiveness studies. There is a need for post-authorization or post-licensure vaccine effectiveness estimates. Real world protection may differ from efficacy under trial conditions. Dr. Fleming-Dutra also summarized challenges associated with observational COVID-19 VE studies including that the decision to be vaccinated may correlate with risk of disease, prior infection may bias estimate, imperfect laboratory testing poses a risk of misclassification, COVID-19 epidemiology is highly dynamic, and multiple products are being used simultaneously.

The immediate priority is assessing if the vaccine works as expected to prevent symptomatic disease. Plans for vaccine effectiveness studies were outlined including assessing VE among healthcare personnel, assessing VE among adults 65 years of age and older, assessing VE among residents of LTCF, assessing VE against infection and transmission, assessing VE for disease severity and key populations, assessing VE for regiment related questions, assessing if viral genome changes threaten VE, and assessing VE among children and pregnant women.

In summary there is an urgent need for VE data to guide vaccine policy. The VE portfolio leverages multiple platforms, data sources, and methods.

WORK GROUP INTERPRETATION AND NEXT STEPS

Dr. Sara Oliver (CDC/NCIRD) summarized the data which the Work Group (WG) reviewed.

- **Clinical Trial Data from AstraZeneca:**
  - WG reviewed immunogenicity information, safety, and efficacy information
  - Overall, the WG felt that the Phase I/II data shows induction of binding and neutralizing antibodies as well as T-cell responses, favorable for moving forward with Phase III
  - Safety pauses are expected with large clinical trials, but transparency is critical
  - We await Phase III data
- **COVID-19 and children**
  - Given the disparities noted among COVID-19 cases in children and in MIS-C cases it will be crucial for clinical trials in children to enroll a diverse population
- **Vaccine Effectiveness**
  - Real world VE studies are needed for a variety of population, ages, and conditions
  - Diverse trial designs will be important to address a variety of questions
  - Isolates obtained through VE platforms can help address concern around SARS-CoV-2 variants
- **SARS-CoV-2 Variants**
  - In the fall of 2020, several variants emerged that can confer increased transmissibility
  - Several preprint studies reviewed the implications of these variants for vaccination, and overall, there was minimal to moderate reduction in neutralization activity for vaccine-immune sera in some persons. The clinical relevance of this is unclear, and these are limited studies with small numbers, so it will be important to continue to review the data.
  - There are several ongoing projects to conduct stain surveillance in the US
- **COVID-19 vaccine dosing and schedule**
  - Summarized the recent updates to clinical considerations around dosing and schedule

SUMMARY OF DISCUSSION

- Question regarding co-administration when we begin vaccinating children – Is there any opportunity between now and then to gather data on this so we can be better prepared?
    - Discussions around addition studies on this population related to this issue are ongoing. Additionally, the current clinical considerations are limited to mRNA vaccines in the adult population, and these are being updated regularly and will be updated to include considerations for children when appropriate.