Motion/Vote #1: Chikungunya Vaccines for Travelers

Dr. Daley made a motion to approve the proposed Vote #1 recommendation for chikungunya vaccines stating, "Chikungunya vaccine is recommended for persons aged ≥18 years traveling to a country or territory where there is a chikungunya outbreak. In addition, chikungunya vaccine may be considered for the following persons traveling to a country or territory without an outbreak but with evidence of chikungunya virus transmission among humans within the last 5 years: Persons aged >65 years, particularly those with underlying medical conditions, who are likely to have at least moderate exposure to mosquitoes, OR Persons staying for a cumulative period of 6 months or more." Dr. Long seconded the motion. No COIs were declared. The motion carried with 12 favoring, 0 opposing, and 1 abstaining. The disposition of the vote was as follows:

12 Favored: Brooks, Beigel, Chen, Cineas, Clark, Daley, Grimes, Hance, Kotton, Loehr, Long, Marshall
0 Opposed: N/A
1 Abstained: Kaslow

Vote #2: Chikungunya Vaccines for Laboratory Workers

Dr. Hills read the following proposed ACIP voting language into the record for chikungunya vaccines pertaining to laboratory workers:

> *Chikungunya vaccination is recommended for laboratory workers with potential for exposure to chikungunya virus.*

Motion/Vote #2: Chikungunya Vaccines for Travelers

Dr. Loehr made a motion to approve the proposed Vote #2 recommendation for chikungunya vaccines stating, "Chikungunya vaccination is recommended for laboratory workers with potential for exposure to chikungunya virus." Dr. Cineas seconded the motion. No COIs were declared. The motion carried with 13 favoring, 0 opposing, and 0 abstaining. The disposition of the vote was as follows:

13 Favored: Brooks, Beigel, Chen, Cineas, Clark, Daley, Grimes, Hance, Kaslow, Kotton, Loehr, Long, Marshall
0 Opposed: N/A
0 Abstained: N/A

Members and *Ex Officios* were invited to make comments following the votes. Dr. Chen noted that while the chikungunya vaccine was first licensed in the US, the burden of disease is global. He expressed his hope that the discussions they had throughout the day would not negatively affect the consequences of implementation of the vaccine globally. He would like to continue to see additional vaccines for other mosquito-borne agents in the US and around the world.

DIPHTHERIA AND TETANUS TOXOID (DT) VACCINE

Dr. Michele Hughes (CDC/NCIRD) provided an update on CDC's guidance for Td vaccines for young children. As part of the routine vaccination schedule, CDC recommends a primary series of the pediatric diphtheria-, tetanus-, and pertussis-containing vaccines (DTaP) vaccines for children <7 years of age. For children<7 years of age who developed a contraindication to pertussis-containing vaccines, CDC previously recommended the pediatric diphtheria and tetanus toxoid vaccine (DT) instead of DTaP. Recently, the sole DT vaccine manufacturer in the US discontinued DT production. The last available lot expired in April 2023. There is no longer DT vaccine available in the US.

The only contraindication specific to the pertussis component in DTaP is encephalopathy within 7 days of vaccination that is not attributed to another cause. While the exact numbers are not known, the occurrence of this AE is extremely rare. In light of DT no longer being an available option, CDC issued the following updated vaccination guidance for the use of Td in young children with a contraindication to pertussis-containing vaccines:

- ❑ CDC recommends young children receive DTaP as the first dose in the diphtheria, tetanus, and pertussis childhood vaccination series.

- ❑ CDC recommends continued use of DTaP unless a contraindication to pertussis-containing vaccines develops.

- ❑ For young children who develop a contraindication to pertussis-containing vaccines, vaccine providers may administer Td for all recommended remaining doses in place of DTaP.

The impact on diphtheria protection is uncertain. Td is a tetanus- and diphtheria toxoid-only formulation licensed only for ages ≥7 and older. The use of Td in this situation would be an off-label use. Td contains a lower dose of diphtheria toxoid compared to DT and the impact of this lower dose on the protection provided against diphtheria in young children is uncertain. There are no available data evaluating the effectiveness of Td against diphtheria when used as part of the primary series in young children. Children may have less protection against diphtheria and no additional protection against pertussis if they receive Td instead of DTaP. CDC has posted this guidance on its website at www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/td-offlabel.html. In order to be covered by VFC for children <7 years of age, a minor update is needed.

Dr. Jeanne Santoli (CDC/NCIRD) gave an update on the current Td supply and the proposed VFC updates. As noted, MassBiologics has discontinued production of their Td vaccine, TdVax™. Grifols, who is the exclusive distributor for TdVax™, expects to have product available through approximately June 2024. Sanofi, who manufacturers Tenivac®, the only other US-licensed Td vaccine, is taking steps to augment their available supply of Td for the US. However, it is anticipated that the supply of Td vaccine in the US market will be constrained during 2024. Temporary ordering controls have been put into place in the public and private sectors to help manage the gap in supply. Adult formulation tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap) is available from both US-licensed manufacturers without supply constraints at this time. Based on the rarity of developing a contraindication to pertussis-containing vaccines, the temporarily constrained supply of Td vaccine is not anticipated to prevent providers from utilizing Td vaccine for these children in the VFC program.

Dr. Santoli indicated that the purpose of this resolution was to: 1) add Td vaccine for use in children <7 years of age for whom receipt of the pertussis component is contraindicated; and 2) update the language regarding the Tdap booster to align with ACIP recommendations. Eligible groups include children and adolescents aged 6 weeks through 18 years, which was unchanged.

Because Td is not currently included in the VFC program, the proposed language to add it to the VFC resolution is as follows:

> *Approve the Vaccines for Children (VFC) resolution for diphtheria, tetanus, and pertussis vaccines.*

Dr. Long noted that with anticipation that Td is frequently not stocked in places like emergency departments anymore, there already is language in the Red Book stating that Tdap can be used if there is no Td.

Dr. Santoli indicated that in terms of the VFC Resolution, Tdap is absolutely covered for persons >7 years of age. It is not covered for the persons <7 years of age.

In terms of the recommendation, Dr. Hughes added that ACIP's previous recommendation that Tdap can be used in lieu of Td would remain.

Dr. Long made a motion to accept the proposed wording for a vote, which Dr. Kotton seconded.

Vote: VFC Resolution for Diphtheria, Tetanus, and Pertussis Vaccines
While public comment was presented prior to the votes, the votes were combined in this summary with their respective sessions for the purpose of continuity.

> *Approve the Vaccines for Children (VFC) Resolution for diphtheria, tetanus, and pertussis vaccines.*

Motion/Vote: VFC Resolution for Diphtheria, Tetanus, and Pertussis Vaccines

Dr. Long made a motion to approve the proposed recommendation for the VFC Resolution stating, “Approve the Vaccines for Children (VFC) Resolution for diphtheria, tetanus, and pertussis vaccines.” Dr. Kotton seconded the motion. Dr. Chen declared a COI due to his active collaboration with MassBiologics, the maker of a DT vaccine. The motion carried with 12 favoring, 0 opposing, 0 abstaining, and 1 recusing. The disposition of the vote was as follows:

12 Favored:	Brooks, Beigel, Cineas, Clark, Daley, Grimes, Hance, Kaslow, Kotton, Loehr, Long, Marshall
0 Opposed:	N/A
0 Abstained:	N/A
1 Recused:	Chen

INFLUENZA VACCINES

The influenza session was opened by Dr. Jamie Loehr, ACIP Influenza Vaccine Work Group Chair.

Dr. Aaron Frutos (CDC/NCIRD/ID) presented CDC's interim estimates of 2023/2024 seasonal influenza VE. This year, 4 networks contributed to the interim estimates of VE against laboratory-confirmed influenza for children, adolescents, and adults in the out-patient and in-patient settings.

The methods used by each network to estimate influenza VE are very similar. All enrollees across all networks sought medical care for acute respiratory illness (ARI). Patients are included from fall 2023 to early 2024. Each network uses a test-negative design, which compares the vaccination odds among case patients with influenza confirmed by molecular assay versus control patients testing negative for influenza and SARS-CoV-2. Vaccination status was determined as the receipt of any of the 2023-2024 seasonal influenza vaccines according to medical records, immunization registries, claims data, and/or self-report. VE estimates were calculated for influenza A subtypes A(H1N1)pdm09 and A(H3N2) when possible. VE was not estimated for some age groups and settings when the sample size was small or when models did not converge.

Pediatric VE against any influenza ranged from 59% to 67% in out-patient settings and 52% to 61% in the in-patient setting. VE estimates were consistent across networks. Pediatric VE against influenza A ranged from 46% to 59% in out-patient settings and 46% to 56% in the in-patient setting. Pediatric VE against influenza A(H1N1)pdm09 ranged from 54% to 61% in out-patient settings and was 60% in the in-patient setting. Pediatric VE against influenza A(H3N2) was 55% in out-patient settings and was not estimated in the in-patient setting. Pediatric VE against influenza B ranged from 64% to 89% in out-patient settings and was not estimated in the in-patient setting.

For adults ≥18 years and older, vaccination prevalence ranged from 39% to 52% among test-negative controls across settings. Adult VE against any influenza ranged from 33% to 49% in the out-patient settings and 41% to 44% in the in-patient setting. Adult VE against influenza A ranged from 27% to 46% in out-patient settings and 40% to 42% in the in-patient setting. Adult VE against influenza A(H1N1)pdm09 was 25% in out-patient settings and 50% in the in-patient setting. Adult VE against influenza A(H3N2) was 54% in the out-patient setting and was not estimated in the in-patient setting. Adult VE against influenza B was 78% in out-patient settings in 2 networks and 60% in the in-patient setting. Again, consistent results were observed across networks.

Among adults ≥65 years of age, the prevalence of vaccination among test-negative controls ranged from 48% to 68% across settings. VE against any influenza ranged from 41% to 51% in out-patient settings and was 42% in 2 networks in the in-patient setting. Among adults ≥65 years of age, VE against influenza A ranged from 40% to 52% in out-patient settings and 42% to 47% in the in-patient setting. VE against influenza B for adults ≥65 years of age was 69% in out-patient settings and was not estimated in the in-patient setting.

These estimates showed that vaccination with the 2023-2024 influenza vaccine reduced the risk for medically-attended influenza out-patient visits and hospitalizations among children, adolescents, and adults across 22 US states. Vaccination was effective against both influenza A, mostly subtype A(H1N1)pdm09, and B Victoria viruses that have circulated this season.

Dr. Sophie Zhu (California Department of Public Health and CDC/PHIC/DWD) presented interim influenza VE against laboratory-confirmed influenza in California for October 2023—January 2024. New public health data reporting requirements in California offer an opportunity to calculate VE against laboratory-confirmed influenza, resulting in estimates that are available ahead of traditional platforms. As of January 1, 2023, all influenza vaccination records became reportable to the California Immunization Registry (CAIR). Positive influenza results have been reportable in California since October 2019. Negative influenza results became reportable as of June 15, 2023 to the California Reportable Disease Information Exchange (CalREDIE), the state electronic communicable disease reporting system.

For this analysis, influenza laboratory results were matched to immunization registry data to calculate early VE estimates against laboratory-confirmed influenza in California during the 2023-2024 influenza season. The estimates from this analysis reflect VE against laboratory-confirmed influenza using nucleic acid amplification tests and include persons tested for influenza from diverse care settings and symptom severity levels. VE is calculated using a case-control design in which persons testing positive for influenza are case patients and persons testing negative for influenza are control patients.

Persons included in the analysis were all California residents ≥6 months of age with molecular tests for influenza A or B captured by the state electronic laboratory reporting system. Most influenza testing performed at clinical and commercial laboratories that report influenza A and B test results do not perform subtyping. The dates of this analysis were October 1, 2023, through January 31, 2024. Participants were considered vaccinated if there was at least 1 dose of seasonal influenza vaccine documented in CAIR ≥14 days before testing. Adjusted VE was calculated as VE = (1 – adjusted odds ratio) x 100%. A mixed-effects logistic regression model was used that was adjusted for age, ethnicity, testing week (random effect), and county (random effect).

In California, overall influenza virus positivity the week of February 19, 2024, was 6.5% and had declined from prior weeks. Based on subtyping at public health laboratories in California, this is a predominantly H1 season so far. Of the samples, 82% have been influenza A and 75% have been H1. A total of 678,422 individuals were included in this analysis. This included 77,501 influenza-positive cases, which is about 11% positivity, and 600,921 influenza-negative control patients. The median age was 31 years for case patients and 44 years for control patients. There was a similar breakdown of race and ethnicity for the case and control patients. Overall, 28% of individuals were vaccinated and 18% of case patients were vaccinated overall versus 29% of controls. Vaccination increased month-by-month from 13% during October to 34% during April. A similar lower vaccination rate was seen in case versus control patients throughout all time periods.

Adjusted VE against laboratory-confirmed influenza overall was 45%. VE declined with increasing age and was highest at 56% in children ≤18 years of age, 48% in adults 18–49 years of age, 36% in adults 50–64 years of age, and lowest at 30% in adults ≥65 years of age. VE against influenza A was lower than overall influenza VE, but was still protective at 42%. Over 90% of cases in this analysis were influenza A, which is consistent with both California and national trends.

Age-specific VE declined with increasing age and was lowest for adults ≥65 years of age at 29%. VE for influenza B was high at 76%. Estimates were generally comparable across younger age groups, ranging from 75% to 79% for persons 6 months–49 years of age. Similar to influenza A, estimates were lower among adults ≥50 years of age. Less than 10% of cases were influenza B.

Mandatory public health data can be leveraged to calculate timely in-season influenza VE as an additional estimate supporting existing public health influenza prevention efforts. Earlier estimates can inform public health action and messaging for additional prevention measures prior to the peak of influenza infections and could be especially informative for healthcare settings that may need to reallocate resources to prepare for increased hospital capacity.

C. Buddy Creech, MD, MPH (Vanderbilt University Medical Center) presented on the safety of quadrivalent live attenuated influenza vaccine (LAIV4) in children with asthma. In this study, 151 children and adolescents 5–17 years of age with persistent asthma were randomized to LAIV (n = 79) or quadrivalent inactivated influenza vaccine (IIV4) (n = 72). The primary objective was to compare the proportion of participants who experienced asthma exacerbation during the 6 weeks after LAIV4 versus IIV4. Persistent asthma was defined as provider diagnosis of asthma plus prescription of a long-acting controller medication and an asthma exacerbation was defined as an acute episode of progressively worsening shortness of breath, cough, wheezing, chest tightness, or respiratory distress for which the patient sought medical attention or received a new prescription for systemic corticosteroids.

LAIV4 was not associated with increased asthma symptoms or asthma exacerbations in the 14- or 42-day windows following immunization. Rates of reactogenicity were similar between the 2 groups, although myalgia and sore throat were more common in the IIV4 arm. LAIV4 may be a suitable option for children ≥5 years of age who have asthma, including those with moderate to severe asthma.

Dr. Lisa Grohskopf (CDC/NCIRD/ID) provided an update on influenza B/Yamagata surveillance. Up until the late 1970s, the number of viruses in influenza vaccines varied from year-to-year. There was variability in the formulation from year-to-year, starting around the 1978-1979 season. Consistent seasonal vaccination has been available with trivalent vaccines with an A/H1, A/H3, and 1 B virus. During the 1980s, there was an appreciation that there were 2 lineages of influenza B viruses for which research evidence suggested that there was not optimal cross-immunity. There was only one B lineage in the vaccine, so one of the two had to be selected for inclusion in the vaccine. Quadrivalent influenza vaccines became available in the market in 2013-2014 and contained 2 B viruses, 1 from each lineage. After the 2013-2014 season, there was a gradual phase-in of the quadrivalent influenza vaccines. Some manufacturers went from one season to the next from trivalent to quadrivalent. Some phased them in within their brand over time. The transitioned to quadrivalent influenza vaccines was largely complete before the 2021-2022 season, with only 1 lot of trivalent released that season. There have now been a couple of seasons with only quadrivalent vaccines.

As Dr. Kondor presented during the October 2023 meeting, there have been no confirmed naturally occurring influenza B/Yamagata viruses in global surveillance since March 2020. The LAIV contains B/Yamagata, so it is conceivable that this might be seen in surveillance. However, there have been no wild-type detections of naturally occurring B/Yamagata viruses. During the Fall 2023 discussions for Southern Hemisphere influenza vaccine composition, WHO and FDA concluded that coverage of influenza B/Yamagata was no longer warranted and should be removed from vaccines as soon as feasible.

Since then, WHO met and made recommendations for the Northern Hemisphere for the 2024-2025 season that include a second B virus for those countries that elect to use/market a quadrivalent vaccine. Decisions regarding the composition are made by individual national regulatory authorities. For the US, that is the FDA. The FDA is set to discuss composition of 2024-2025 US influenza vaccines on March 5, 2024.

Ms. Rebecca Coyle (AIRA) pointed out that the codes for trivalent vaccine have been inactivated because they have not been used in the last several seasons. For any upcoming decisions, particularly by manufacturers that will be moving to trivalent influenza vaccine as soon as this year, it will be to be important to have conversations as soon as possible about reactivating the old codes versus trying to create new codes. There is a relatively short period of time between now and the next influenza season, so the time is now to make sure the codes are correct for billing to make this as seamless as possible.

POLIO VACCINE

Dr. Oliver Brooks, chair of the ACIP Polio Vaccine Work Group, introduced the polio vaccine session.

Dr. Sarah Kidd (CDC/NCIRD) reminded the committee that paralytic disease occurs in <1% of poliovirus infections and approximately 75% of infections are asymptomatic. There are 3 poliovirus serotypes with different epidemiological and clinical characteristics and immunity to one serotype does not result in significant immunity to other serotypes. The ratio of paralytic cases to infections varies by serotype, ranging from approximately 1 in 190 infections for Type 1 to approximately 1 in 1,900 infections for Type 2. Poliovirus is considered highly infectious and is spread through the fecal-oral or oral-oral routes. Fecal-oral transmission is considered the most important pathway, particularly in settings with suboptimal hygiene and sanitation. Virus may be present in the stool of infected persons for up to 6 weeks and sometimes longer. Individuals who are asymptomatic can still shed virus and transmit it to others.

Inactivated polio vaccine (IPV) is the only polio vaccine that has been used in the US since 2000. It contains inactivated poliovirus Types 1, 2, and 3. It cannot replicate, infect, or cause disease. It induces effective humoral immunity and prevents paralysis. It also induces some nasopharyngeal mucosal immunity but does not provide substantial intestinal immunity or prevent gastrointestinal shedding.

Oral polio vaccine (OPV) is no longer used in the US. It is a live-attenuated vaccine that can come in different formulations. Trivalent vaccine (tOPV) contains poliovirus Types 1, 2, and 3. Bivalent vaccine (bOPV) contains Types 1 and 3 poliovirus. Monovalent OPV (mOPV) contains just a single serotype. OPV replicates in the gut and is shed in the stool. It induces both humoral and mucosal immunity, so that it prevents paralysis and transmission of poliovirus. For this reason, it has been considered the historical vaccine of choice for countries experiencing polio outbreaks. However, the attenuated vaccine virus can revert to a neurovirulent form that causes paralysis. nOPV2 is a next-generation version of the Sabin Type 2 mOPV that was designed to be more genetically stable and less likely to revert to a neurovirulent form. Between March 2021 and December 2023, almost a billion doses were administered as part of outbreak responses in 35 countries under a WHO Emergency Use Listing (EUL) approval. As of December 2023, it earned WHO prequalification status.

In the US, the incidence of paralytic polio decreased rapidly after the introduction of the Salk IPV in 1955. The Sabin OPV was used for routine childhood immunization for decades, but an enhanced potency IPV was introduced in 1997 as part of a sequential schedule with OPV. In 2000, the US moved to an IPV-only schedule. IPV has been the only polio vaccine recommended in the US since that time. Wild poliovirus type 1 (WPV1) and vaccine-derived polioviruses are still circulating in certain parts of the world. Approximately 450 paralytic polio cases caused by WPV1 and circulating vaccine-derived polioviruses (cVDPV) that have been identified in the last 12 months.

A case of paralytic polio caused by VDPV Type 2 (VDPV2) was confirmed in an unvaccinated young adult from Rockland County, New York on July 21, 2022. Genetic sequencing has indicated a linkage between this case to polioviruses collected in wastewater in Israel, the UK, and Canada. Of note, Rockland County has reported overall low vaccine coverage for over 20 years. When this case was identified in summer 2022, only 60% of children under 2 years of age had received 3 doses of IPV. ZIP Code level coverage in the area was as low as 37% in some areas. Fortunately, no additional paralytic cases were identified.

Poliovirus related to the case was detected in wastewater in several New York State (NYS) counties and in New York City (NYC). Retrospective testing detected poliovirus in the area as early as April 2022, indicating circulation and asymptomatic infections in the area since at least that time. Related virus continued to be consistently detected in wastewater until the beginning of November 2022. The most recent detection was February 22, 2023, in Rockland County. Samples collected in the last year have all been negative.

The primary vaccination response to the 2022 outbreak was focused on identifying under-vaccinated and unvaccinated persons and providing catch-up vaccination with IPV. However, in fall 2022 when there were still wastewater detections of poliovirus, it was unclear whether the strategy was going to be sufficient to interrupt circulation. WHO recommendations for polio outbreaks in countries like the US with exclusive IPV vaccination and high sanitation and hygiene are to conduct a timely outbreak response with IPV only if poliovirus transmission is confined in a well-defined population group or geographic area. However, if transmission persists, WHO recommends considering an OPV response. Therefore, the work group was asked to discuss considerations for the potential use of nOPV2 as an outbreak response measure in the US.

Given that the New York outbreak had already waned at the time of the work group discussions, the question the work group took up was a theoretical one, “Should nOPV2 be used in combination with a catch-up IPV campaign during a future Type 2 poliovirus outbreak in the US?” The population under consideration would be persons living in an area with circulating poliovirus. The intervention would be nOPV2 vaccination for the general population in addition to catch-up IPV vaccination for un- or under-vaccinated persons. That would be compared to the intervention of catch-up IPV vaccination only. The outcomes of interest were prevention of paralytic poliomyelitis; the extent and duration of poliovirus circulation in the community; serious adverse events, including vaccine-associated paralytic polio; and possible introduction of a new VDPV2.

The work group used the ACIP EtR Framework and domains to frame their discussions. Based on the information presented, the work group had previously agreed that polio is a problem of public health importance. For potential benefits and harms, the work group noted that there are high rates of seroconversion following 1 and 2 doses of nOPV2 when administered to infants.

Given that vaccination with IPV is already recommended in this country, the main benefit of nOPV2 would be to confer gastrointestinal immunity.

Sabin OPV2 reduces the odds of fecal shedding following a subsequent oral challenge dose by more than 90% compared to no vaccination. There are no direct data for nOPV2, but it has performed as expected in the field in terms of slowing or stopping outbreaks. A small Phase 1 study among adults showed evidence of gastrointestinal immune response following nOPV2 administration. It is known that nOPV2 is a live virus and it is shed in stool by nOPV2 recipients following vaccination. When measured by PCR, 85% had detectable vaccine virus in stool at 7 days. This decreased to 40% to 57% by 28 days. When measured by culture, which is probably a better measure of infectious virus, 40% were shedding at 7 days. This decreased to 1% to 14% by 28 days.

nOPV2 was developed to be more genetically stable than Sabin OPV2 and less likely to regain neurovirulence in the laboratory. However, there is still a risk of vaccine-associated paralytic polio (VAPP) in recipients. The estimated risk of VAPP for nOPV2 is estimated to be 0.07 cases per million recipients or 1 case per 14.3 million recipients. This is compared to Sabin OPV with an estimated case rate of 0.25 to 4 cases per million recipients or 1 per 0.25 million to 4 million recipients. The risk of VAPP is known to be highest in previously unimmunized children who are receiving their first dose of OPV or in immunocompromised patients. And the risk of VAPP could be mitigated by limiting nOPV2 administration to persons who had previously received at least 1 dose of IPV. It also is known that there is a risk of ongoing transmission of the nOPV2 virus with reversion to a VDPV.

The risk is difficult to quantify, but so far, there have been at least 7 separate emergences of new cVDPV2 linked to nOPV2 (cVPDV2-n) and at least 61 associated paralytic cases worldwide from these emergences. These are the numbers that have been published in the literature so far, but the actual numbers are likely higher as nOPV2 use increases globally. However, nOPV2 is estimated to be 80% less likely than Sabin OPV to seed a new cVDPV2. The risk of a new cVDPV is highest when campaign coverage is low in a population with low immunity against polioviruses.

When thinking about the balances of risks and harms for the individual recipient, most recipients will have already been vaccinated with IPV during childhood immunization and are already protected against paralytic disease. The anticipated benefits of nOPV2 to the individual recipient would be a higher anti-polio Type 2 antibody titer and increased odds of mucosal immunity to poliovirus Type 2. For an under-vaccinated person, this would mean additional protection against paralytic disease. However, for a previously vaccinated person, there is unlikely to be a clinically significant benefit of vaccination. For potential harms, there is an extremely low but non-zero risk of VAPP. There also is a risk of chronic infection if nOPV2 is given to a child with unrecognized immunocompromise.

At the population level, decreased transmission among nOPV2 recipients potentially could result in the outbreak ending earlier and fewer paralytic cases. Given that the vaccine virus can be shed in stool and transmitted to others, there likely would be some degree of passive vaccination of unvaccinated persons, which also would lead to decreased transmission and fewer paralytic cases. Potential harms at the population level include passive vaccination of the unvaccinated and a risk of VAPP among the unvaccinated, possible ongoing transmission of the nOPV2 virus leading to a new cVDPV2 virus, and possible chronic infection in immunocompromised persons.

The magnitude of these benefits and harms will depend on nOPV2 coverage and the extent of mixing between nOPV2 recipients, unvaccinated persons, and immunocompromised persons.

Dr. Kim Thompson and her colleagues at Kid Risk modelled the expected number of paralytic cases under different mixing scenarios for a cVDPV2 outbreak similar to the 2022 New York outbreak. They compared the number of cases expected with an IPV-only response to responses that used a Sabin OPV2 or an nOPV2. In their model, they assumed that the number of vaccine doses administered was the same as the number of IPV doses that were actually administered during the 2022 New York outbreak. They concluded that use of any type of OPV2 likely would have ended transmission slightly earlier than with IPV alone. However, less than 1 additional paralytic case was predicted in all IPV or OPV2 vaccine scenarios. They also ran a similar model for an aVDPV1 outbreak instead of aVDPV2 outbreak. Recall that Type 1 poliovirus infection is associated with a higher rate of paralytic disease than Type 2. The results of this model suggested that use of an OPV1 would likely end VDPV1 transmission faster and result in fewer paralytic cases than use of IPV alone.

When assessing how substantial the desirable anticipated effects of nOPV2 would be on both the individual and population levels, approximately half of the work group felt the desirable effects of using nOPV2 in addition to IPV were small. Some members felt that the desirable effects would be minimal, while some felt they would be moderate. When asked about the undesirable anticipated effects, the work group was evenly divided between minimal, small, and moderate. When asked whether the desirable effects of nOPV2 would outweigh the undesirable effects, half of the work group felt that the desirable effects would not outweigh the undesirable effects, and that the information favored the use of IPV only. However, about 1/3 of the group felt that it varies depending on the situation.

Moving to resource use and feasibility, nOPV2 is not yet approved for use in the US. If the US wanted to use nOPV2, the mechanism for doing so would be the Expanded Access Investigational New Drug Application (EA-IND), formally known as “Compassionate Use.” This requires application to the FDA and FDA authorization. If implemented, the nOPV2 EA-IND program must include signed informed consent by vaccinees and/or their guardians, an enhanced system for monitoring vaccine safety, enhanced surveillance for possible VAPP cases and environmental surveillance for new VDPVs, and a system for tracking and accounting for every dose for containment purposes. This includes every dose given, every dose wasted, and doses returned.

The work group had a variety of opinions on whether this would be a reasonable and efficient use of resources. Half of the work group responded that it was probably not a reasonable use of resources, but about 1/4 responded that it would vary depending on the specifics of the situation. The work group also was divided about whether an nOPV2 campaign would be feasible to implement. Half of the work group responded that it probably would be feasible, but about a third responded that it probably would not be feasible.

For values and acceptability considerations, tOPV was removed from the US vaccination schedule in 2000 and was replaced with IPV because any risk of VAPP was deemed unacceptable at that time. This removal might be a barrier to acceptance of a new OPV vaccine in the future. In addition, the need for a signed informed consent likely will be a deterrent, especially for those who are concerned about vaccine safety and new vaccines. It is unclear whether the general public will accept an OPV vaccine if they are already protected from paralytic infection by IPV. It is unclear whether the general public will accept a vaccine to reduce community transmission and risk to others if they would not benefit from it individually.

Similarly, it is unclear whether the populations most at risk (e.g., those with low childhood vaccination coverage and those with high rates of vaccine skepticism) would accept an OPV vaccine.

The work group noted that perceptions of risk and vaccine acceptance might shift in an outbreak setting, particularly if there is more than 1 paralytic case in a community. A clear majority of the work group agreed that the target population probably does not feel that the desirable effects of nOPV2 are large relative to the undesirable effects. However, they were divided about whether there was important uncertainty or variability in how much people would value the main outcomes. The work group was similarly divided about whether nOPV2 would be acceptable to key stakeholders. Some felt that it probably would not be acceptable to stakeholders, some felt that it probably would be, and some felt that it would vary.

In terms of equity considerations, there is only 1 manufacturer of nOPV2, BioFarma in Indonesia, which is managed via a global stockpile. Supply shortages have occurred in the past. In the US, IPV is readily available and provides protection against paralysis from cVDPV2. In many countries with cVDPV2 outbreaks, there is limited protection against cVDPV2, unless there are nOPV2 or Sabin OPV2 campaigns. In terms of equity within the US, the work group noted that preventing transmission of the outbreak virus does protect unvaccinated, under-vaccinated, immunocompromised persons. Again, there was a spread of opinions among the work group members. The plurality of the work group felt that using nOPV2 probably would not have a significant impact on health equity.

Putting it all together, most of the work group felt that the undesirable consequences of using nOPV2 during an outbreak in the US probably outweigh or are closely balanced with the desirable consequences.

In summary, the work group believes at this time that the undesirable consequences of using nOPV2 probably outweigh or are closely balanced with the desirable consequences. The main considerations for the work group's interpretation was that IPV is readily available in the US and protects against paralytic disease, and that the primary benefit of adding nOPV2 to an outbreak response would be to reduce transmission of outbreak virus and reduce risk of paralytic disease in under-vaccinated and immunocompromised persons. There were differences of opinion regarding the value of reducing asymptomatic transmission or ending asymptomatic transmission earlier during an outbreak. The work group was concerned about the extremely low but non-zero risk of VAPP or new cVDPV2. There was uncertainty about public and stakeholder acceptance of a nOPV2 vaccine. However, the work group did acknowledge that the balance of undesirable consequences compared to desirable consequences might shift in the future depending on size and scope of the outbreak. As modeling showed, the calculus might be different for a Type 1 outbreak where more paralytic cases would be expected, and public perception of risk might be higher.

Dr. Kidd then introduced the topic of fractional doses of IPV. Wild poliovirus Type 2 was eradicated in 2015, prompting a global switch in April 2016 during which all the Sabin Type 2 virus was withdrawn from routine immunization. Countries that were still using OPV as part of routine immunization replaced tOPV with bOPV that contains only Types 1 and 3. At the same time, it was recommended that countries that still used OPV include at least 1 dose of IPV as part of their routine immunization schedule. Subsequently, based on clinical trial data and limited IPV availability in some countries, WHO has supported the use of 2 fractional doses of IPV (1/5 full dose IPV) given intradermally in place of a single full dose.

Clinical trials have shown that 1 fractional dose of IPV (fIPV) is less immunogenic than 1 full dose of IPV; clinical trial data also have suggested that 2 fractional doses are more immunogenic than 1 full dose of IPV.

Currently, 6 countries representing about 20% of the global birth cohort use fIPV in their routine immunization schedules (Bangladesh, Cuba, Ecuador, India, Nepal, Sri Lanka). They all use 2 fractional doses in combination with at least 3 bOPV doses. One example would be India's polio vaccination schedule in which a child would receive 5 doses of bOPV and 2 doses of fIPV. The current US guidance recommends a total of either 3 or 4 doses of IPV, depending on the age of the last vaccination. When assessing vaccine records for vaccines administered outside the US, the guidance is that only tOPV doses or IPV doses are considered valid for the US vaccination schedule. If a child who was vaccinated under the India vaccination schedule immigrated to the US and wanted to attend school in the US, current guidance is that none of their bOPV or fIPV doses would be considered full doses. The child would need either 3 or 4 full IPV doses to be considered fully vaccinated against polio in the US.

Therefore, the question for the work group was, "Should 2 fIPV doses administered outside the US be counted as either 1 or 2 doses toward the US vaccination schedule?" A meta-analysis was conducted to update to the meta-analysis that was previously published in 2021.

Overall, 2 fractional doses were associated with higher rates of seroconversion compared to 1 full dose of IPV. Infants receiving 2 doses of fIPV were 1.5 times as likely to seroconvert compared to infants who received 1 full dose of IPV. Moving to comparisons between 2 fractional doses and 2 full doses, 2 fractional doses were associated with slightly lower rates of seroconversion than 2 full doses of IPV. This especially is the case when administered at younger ages. Peak antibody titers are also lower after 2 fractional doses compared to 2 full doses. Based on this information, the work group group agreed with the following proposed language to be included in CDC Clinical Considerations for persons receiving polio vaccines outside of the US:

- ❑ For persons who received fractional (1/5 full dose) IPV administered intradermally outside of the United States, 2 fractional doses of IPV (fIPV) should be considered valid and counted as 1 full intramuscular dose of IPV toward the US vaccination schedule.
- ❑ If a person received only 1 dose of fIPV, this dose should not be considered valid or counted toward the US vaccination schedule.

Following discussion, several ACIP members expressed that they thought it was reasonable to accept 2 fractionated doses as 1 IPV dose and agreed with the work group's recommendation.

PUBLIC COMMENTS

The floor was opened for public comment on February 28, 2024, at 1:40 PM EST. The comments made during the meeting are summarized in this document. Members of the public also were invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2024-0001. Visit regulations.gov for access to read comments received.

Diana Olson
National Foundation for Infectious Diseases

Diana Olson from the National Foundation for Infectious Diseases thanked the committee for its work. She highlighted the public health and economic benefits of COVID-19 vaccines but pointed out that coverage with an updated 2023-2024 COVID-19 vaccine remains low. Immunization rates for other recommended vaccines also remained below public health goals. Only about half of US children and adults have received an influenza vaccine during the current season and only about 22% of eligible adults aged 60 years and older and about 16% of eligible pregnant women have received an RSV vaccine. Clearly, there is more work to be done to build vaccine confidence, address health disparities, and increase overall immunization rates. NFID supports implementation of a Vaccines For Adults program to build upon the Vaccines for Children and Bridge Access Program and further expand access to these lifesaving tools; continued support for US vaccine safety systems; and strong public health infrastructure to help ensure that ACIP, CDC, and state and local public health agencies have the resources to do their important work.

Mr. Robert Blancato
Executive Director
National Association of Nutrition and Aging Services Programs

Mr. Blancato spoke as Executive Director of the National Association of Nutrition and Aging Service Programs (NANASP) and on behalf of 18 other national aging and patient advocacy associations, calling on ACIP to reverse your June 20 recommendation requiring shared decision-making for the use of the new RSV vaccines for adults 60 and over. CDC has reported that only 21.9% of adults and reported receiving the RSV vaccine; Mr. Blancato stated that this low coverage was a consequence of ACIP's recommendation with shared clinical decision-making, which he stated was difficult for health care providers to implement. He stated that these organizations also oppose shared decision-making due to its negative impact on vulnerable adults who are part of already underserved communities. He stated support for co-administration of these vaccines and that he was encouraged by the morning's discussion on the recommendation for an additional COVID vaccine shot and the resulting amendment in favor of "should" instead of "may." If the goal is preventing serious health outcomes in older Americans from respiratory illness, clear, broad, and easy to communicate guidance should be the standard for adult vaccines.

Martha Nolan, JD
Senior Policy Advisor
HealthyWomen

Martha Nolan, Senior Policy Advisor for HealthyWomen, asked for clarification of recommendations in several areas. She expressed concern around how the seasonal recommendations for maternal RSV vaccine translate to reimbursement and coverage. Specifically, many are confused about whether there is cost-sharing on the part of the patient if they receive the vaccine after January 31, 2024, because the CDC guidance notes that in certain US jurisdictions where RSV seasonality differs, providers may consider RSV vaccination after January 31, but it is not clear if insurance will cover the cost. She asked that ACIP consider ways to ensure there are no coverage barriers for patients, particularly when considering future seasonal recommendations. Lack of coverage for a vaccine is a barrier that often leaves patients to forego that care option. She expressed discouragement over the low uptake of RSV and COVID vaccines in older adults during the '23-'24 respiratory season.

Despite there being many tools to protect ourselves against respiratory illnesses than ever before, there is also increasing confusion about who should receive what vaccine and when. She asked ACIP to evaluate existing guidance and provide necessary changes to ensure clarity around who should receive them and when and ensure coverage for all populations.

Hannah Berk
Unaffiliated Community Member

Hannah Burke asked the committee to support the proposed recommendation on a booster dose of the COVID-19 vaccine in this meeting and to develop action steps to go further after this meeting. She stated that people of all ages and health statuses need updated COVID vaccines covered by insurance and/or public funds at least every 6 months. Twice annual vaccination allows healthy people to safely share space with high-risk family and friends so long as they take precautions, which include vaccinating after immunity wanes significantly after 4 to 6 months and multiple COVID-19 infections compound systemic damage to the body that makes any person more vulnerable to illness and disability, even if they are otherwise healthy. She expressed her hope that the committee will approve the proposal to announce COVID vaccine recommendations on an earlier timeline this year, which can help ensure appropriate time to increase the accessibility of these vaccines. Ms. Burke shared that many of her friends and relatives have asked their doctors about booster availability and have been told they don't need the vaccine, and uninsured friends received their boosters months later than they could have because they hadn't heard about the Bridge Program. She expressed her support for a “should” recommendation on boosters for older adults and for an expedited vaccine decision-making timeline. She urged the committee to make updated vaccines accessible twice annually for people of all ages and at no cost and to recommend continued vaccination in the clearest, strongest terms.

Maria Shreve, RN
Parents, Nurses, Herself

Ms. Shreve is a Registered Nurse and said that her family is so grateful to have access to children's COVID vaccines and now the new RSV vaccine, but it wasn't easy. She asked the committee to make children's vaccines available before school starts this year, which would help decrease transmission and infection. She said that children's uptake would be higher if supply was available and urged support for more accessible locations for kids of all ages, and mass vaccination clinics where parents can take kids of all ages for vaccines together instead of taking one to a pharmacy, one to the pediatrician, and one to the Minute Clinic. She said a better plan is quickly needed for the development and implementation of more RSV and COVID treatments. Unvaccinated children's hospitalization rates last year with COVID were as high as the elderly, which could have been prevented by increased access to vaccines. She also expressed support for options that allow access to vaccines every 6 months instead of yearly.

AGENCY UPDATES

Centers for Disease Control and Prevention

Dr. Demetre Daskalakis highlighted CDC's work during the winter respiratory season. Influenza, COVID-19, and RSV are still elevated in some parts of the country. As of February 10th, 22% of adults ≥18 years of age and 12% of children 6 months to 17 years of age have received COVID-19 vaccination. Pharmacies have administered over 750,000 doses of COVID-19 vaccines and over half a million doses were ordered by public health providers through the Bridge Access Program. In the US, influenza vaccine coverage rates have decreased; about 6.5 million doses of influenza vaccine have not been given this season compared to last.

The ACIP was a very important part of RSV vaccine launches for pregnant people and immunization launches for newborns. Despite an initial supply and demand mismatch with nirsevimab, 30% of infants <8 months of age received nirsevimab and about 16% of eligible pregnant persons received an RSV vaccine between 32 and 36 weeks gestation. In the context of new vaccine products, this is remarkable uptake.

As of February 22, 2024, a total of 35 cases of measles have been reported this year in 15 jurisdictions compared to 58 cases of measles last year in 20 jurisdictions in the US. This is not a good slope of the curve, particularly given that measles is preventable with safe and effective vaccines. As measles continues to increase in other parts of the world, importations continue to happen. When importations occur in places where coverage is low, there is risk for ongoing larger outbreaks.

Centers for Medicare and Medicaid Services

Mary Beth Hance began by announcing the passing earlier in the month of Dr. Jeffrey Kelman following an illness. Dr. Kelman was a Centers for Medicare and Medicaid Services (CMS) colleague who was the Chief Medical Officer for CMS's Center for Medicare. He was involved with the ACIP for many years, representing CMS on many work groups. Dr. Kelman was a pulmonologist by training, which fit perfectly into much of the work he did supporting CMS on the influenza, pneumococcal, COVID, and many other ACIP work groups. He also worked closely with FDA on using data and was absolutely committed to the idea that valuable data within agencies could be used across agencies. Dr. Wharton and other colleagues in attendance mourned the loss of Dr. Kelman and acknowledged his many important contributions.

In terms of updates, on February 12, 2024, CMS issued an updated Medicaid and CHIP vaccine toolkit that reflects the change in commercialization of COVID vaccines and the Inflation Reduction Act provisions that impacted mandatory coverage of vaccines for adults in Medicaid.

Food and Drug Administration

Dr. David Kaslow reported that since the last FDA agency report during the October 2023 ACIP meeting and apropos of discussions earlier in the day on chikungunya, FDA approved IXCHIQ®, a vaccine indicated for the prevention of disease caused by chikungunya virus in individuals ≥18 years of age who are at increased risk of exposure to chikungunya virus (CHIKV). This indication was approved under accelerated approval based on anti-CHIKV neutralizing antibody titers.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies. The highlights of the US prescribing information include warnings and precautions that IXCHIQ® may cause severe or prolonged chikungunya-like adverse reactions. Other regulatory actions include scores of supplemental Biological License Applications (sBLAs), some pertaining to manufacturing changes and some regarding labeling changes.

Given the ACIP agenda for the next day, Dr. Kaslow highlighted the work FDA continues to do to monitor the safety and effectiveness of vaccines for respiratory illnesses using the Biologics Effectiveness and Safety System (BEST) and the CMS System. Ongoing projects include safety and effectiveness of RSV vaccines, influenza vaccines, and COVID-19 2023-2024 formula vaccines. Although the Vaccines and Related Biological Product Advisory Committee (VRBPAC) has not met since the October 2023 ACIP meeting, FDA anticipates convening VRBPAC twice before the June 2024 ACIP meeting. The VRBPAC is scheduled to meet on March 5, 2024, in open session to discuss and make recommendations on the selection of strains to be included in the influenza vaccine for the 2024-2025 influenza season. As mentioned earlier in the day, VRBPAC is scheduled to meet in open session on May 16, 2024, to discuss and make recommendations on the selection of strains to be included in the 2024-2025 formula for COVID-19 vaccines. Other convenings of VRBPAC may occur as needed. As in the past, Dr. Kaslow took the opportunity to personally thank the review teams, their supervisors, and management at Center for Biologics Evaluation and Research (CBER) who worked and continue diligently to conduct research and review to protect and enhance public health. In addition, he thanked CDC staff for their many contributions and their collegial support of collective efforts to protect and enhance public health for immunization.

Health Resources and Services Administration

CDR Reed Grimes, MD, MPH provided the Health Resources and Services Administration (HRSA) update the National Vaccine Injury Compensation Program (VICP) continues to actively process claims. In Fiscal Year 2024, as of January 1, petitioners have filed 314 VICP claims. Over $41 million was awarded to petitioners and over $13 million was awarded to pay attorney's fees and costs. In addition, the VICP had approximately 600 claims alleging vaccine injury awaiting activation for review. Previously, there was nearly a 12-month wait period between when a petition was found to have adequate medical records to review by a HRSA provider and when a review was completed. As of January 1, 2024, the wait period has been reduced to less than 1 month. More data about the VICP can be found on its website at www.hrsa.gov/vaccine-compensation/data/index.html.

In the decade prior to COVID-19, fewer than 500 claims had been filed with the Countermeasures Injury Compensation Program (CICP). CICP received a direct appropriation for the first time in Fiscal Year 2022, and the program has used those funds to increase its capacity to conduct medical reviews by hiring and training new review staff and contractors as well as to pay compensable claims and improve IT and other communications with requesters. As of January 1, 2024, 12,854 claims alleging injuries or death from COVID-19 countermeasures had been filed with the CICP, including 9,682 claims alleging injuries or death from COVID-19 vaccine. CICP has rendered decisions on 2,214 COVID-19 claims as of January 1, 2024, representing more than 4 times in the prior decade. More information about the CICP can be found at its website at www.hrsa.gov/cicp.

These same findings extend to preterm infants. In a separate study, it was shown that preterm infants born to people who are vaccinated for COVID-19 have roughly the same antibody titers as those of term infants. Moreover, in all infants, antibodies to the spike protein were higher among those born to individuals who received 3 or more vaccines before delivery compared to those who only had 2. These findings may help allay concerns that fewer antibodies might pass from preterm infants compared to term infants.

In a study regarding the ancillary benefits of COVID-19 vaccines versus a prospective cohort study of adults, researchers identified SARS-CoV-2 infections and followed them for the presence of post-acute sequelae. COVID vaccination not only prevented disease, but also was associated with lower prevalence and severity of long COVID symptoms. There also was an interesting study about looking at the spike in preterm birth rates that started at the beginning of the pandemic. That analysis showed that by late 2022, widespread COVID-19 vaccination in pregnant people likely halted the spike in preterm infants, and those rates have come down toward normal. This underscores the need for pregnant people to keep current on COVID-19 vaccination.

In October 2023, the Nobel Prize for Physiology or Medicine was awarded to Drew Weissman, MD, PhD and Katalin Karikó, PhD for their work on messenger ribonucleic acid (mRNA) that enabled the development of mRNA vaccines. Dr. Weissman and Dr. Karikó had decades long work on mRNA with incremental steps in the science. Ultimately, those steps and those scientific advancements were critical to enable the unprecedented development of the mRNA vaccines that stemmed the pandemic.

For influenza, Dr. Beigel highlighted a study that evaluated 2 doses of high-dose trivalent influenza vaccine (HD-TIV) compared to standard dose quadrivalent influenza vaccine in a pediatric hematopoietic stem cell transplantation (HSCT) population. The high-dose vaccine resulted in higher antibody responses, especially for influenza A. Because influenza causes substantial morbidity and mortality in that population, optimization of vaccine strategies is critical. The use of high-dose inactivated vaccines may be a practical strategy to overcome the poor immunogenicity in that population.

Office of Infectious Disease and HIV/AIDS Policy

CDR Valerie Marshall reported that the Interagency Vaccine Working Group (IVWG) of the HHS is scheduled to convene in March 2024 to deliberate on an interagency progress report which addresses the achievements and strides made from 2021 to 2023 toward achieving the goals outlined in the Vaccines National Strategic Plan (VNST). This collaborative effort underscores the commitment of multiple federal agencies toward transparent communication and the pursuit of vaccination goals. The National Vaccine Advisory Committee (NVAC) held a meeting on February 22-23, 2024, to discuss critical policy matters related to vaccination. The committee's deliberations included a discussion on the resurgence of measles cases, which underscored the pressing need for proactive public health measures to improve vaccine confidence and counter misinformation about vaccines.

With no additional business posed for the day, the ACIP meeting stood in recess until 8:00 AM on February 29, 2024.

THURSDAY: FEBRUARY 29, 2024

WELCOME AND INTRODUCTIONS

Call to Order/Roll Call

Dr. Melinda Wharton (ACIP Executive Secretary & Acting Chair, CDC) called to order and presided over the February 28-29, 2024 ACIP meeting because the process for the new ACIP Chair to join the committee had not yet been completed. As allowed under the ACIP charter, the ACIP's six *Ex Officio* members were temporarily designated as voting members. She then conducted a roll call, which established that a quorum was present. A list of Members, *Ex Officios*, and Liaison Representatives is included in the appendixes at the end of this summary document. No COIs were identified for the second day of this meeting.

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINES ADULTS

Dr. Camille Kotton, Chair, ACIP Adult RSV Work Group, introduced the RSV session, reminding everyone that in June 2023 ACIP recommended that adults ≥60 years of age may receive RSV vaccination using shared clinical decision-making. There are currently 2 licensed and recommended products for adults ≥60 years of age:

- ❑ GSK RSV vaccine (AREXVY), which is a 1-dose adjuvanted (AS01E) recombinant prefusion F (preF) protein vaccine.
- ❑ Pfizer RSV vaccine (ABRYSVO®), which is a 1-dose recombinant preF vaccine.

In October, GSK presented data to the ACIP demonstrating that the humoral immune response to a single dose of GSK RSV vaccine in adults 50–59 years of age was non-inferior to that in adults >60 years of age. The ACIP Adult RSV Work Group shared their early interpretations of this data and the potential role of RSV vaccination in adults younger than 60 years of age, including subpopulations who would benefit most from vaccine and equity implications. At that time, ACIP members expressed the importance of reviewing safety surveillance data to inform future preferred policy recommendations.

The work group has been simultaneously reviewing additional data to prepare for the upcoming policy decisions, especially focusing on the risk of severe RSV disease in adults 50–59 years of age, especially those with chronic medical conditions; RSV vaccine uptake among different demographic groups; and potential policy options that would transition away from shared clinical decision-making. The work group also has begun reviewing data from Moderna on their investigational RSV vaccine (mRNA-1345) in adults ≥60 years of age.

Dr. Rituparna Das (Moderna) presented clinical data on Moderna's investigational RSV candidate vaccine, mRNA-1345, among adults ≥60 years of age. The data package on adults ≥60 years of age was submitted to the FDA for review in September 2023. The investigational RSV vaccine, mRNA-1345, is a lipid encapsulated mRNA-based vaccine that encodes the RSV fusion (F) glycoprotein stabilized in the prefusion conformation. The prefusion F protein contains epitopes that elicit antibodies that are potently neutralizing and cross-reactive between RSV-A and RSV-B. Following administration of a single 50 microgram (µg) dose, robust immunogenicity was observed in Phase 1 that was persistent through 12 months post-vaccination.

The pivotal Phase 2/3 safety and efficacy trial, Study 301, enrolled adults ≥60 years of age. Participants were randomized 1:1 to receive mRNA-1345 or saline placebo and 24 months of planned follow-up. Randomization was stratified by age (60─74 years and ≥75 years) and presence or absence of congestive heart failure (CHF) or COPD. The study started in November 2021 and weekly surveillance was conducted via electronic diary to look for RSV symptoms. Given the importance of risk factors on morbidity and mortality with RSV in older adults, participants also were included with a number of high-risk medical conditions. Frailty status was assessed of all participants at entry using the Edmonton Frail Scale (EFS). Participants were characterized on a 0- to 17-point scale as being fit (0-3), vulnerable (4-5), or frail (6-17).

A total of 36,550 participants were enrolled as of the April 30, 2023 data cutoff, approximately 50% of whom came from the US. Vaccinations in Study 301 began in late November 2021 and continued through December 2022. The primary analysis was driven by the accumulation of a target number of cases, and study success was declared at that time. The study continued in a blinded fashion. When nearly all study participants reached 6 months of follow-up, an additional analysis was conducted as agreed with the FDA. The median follow-up for this additional analysis was almost 9 months, with a range up to 17.7 months.

The demographics of Study 301 were well-matched between the vaccine and placebo recipients. The median age was 67 years, 30% of the study participants were 70─79 years of age, just under 3,000 participants were ≥80 years of age, 12% were Black or African American, and 33% identified as Hispanic or Latino. Race/ethnicity in the study was representative of the US population. Approximately 2,600 participants had CHF or COPD, almost 1/3 of trial participants had 1 or more of the comorbidities that put them at higher risk for RSV-related morbidity or mortality, 16% percent of the population was considered vulnerable, and 6% were considered to be frail.

The median safety follow-up was 8.6 months and almost all participants had been followed for more than 6 months. In general, mRNA-1345 was well-tolerated. Injection site pain was the most common local reaction, followed by axillary swelling or tenderness. Most events were mild, with onset within 1 to 2 days post-injection and lasting 1 to 2 days. Solicited systemic reactions of fatigue, myalgia, and headache were the most common. Fever was rare and most reactions were mild, with onset within 1 to 2 days post-injection and lasting 1 to 2 days. Severe events also were rare. Unsolicited events were well-balanced overall between vaccine and placebo recipients. The occurrence of SAEs, AEs leading to discontinuation, and AESIs also were balanced between vaccine and placebo recipients. There was 1 event in the vaccine group, which was aspiration following intoxication. There were 6 fatal events in the placebo group.

There were no cases of Guillain-Barré syndrome (GBS) or acute disseminated encephalomyelitis (ADEM). There was no imbalance in neurological disorders such as Bell's palsy or facial paralysis. For cardiac events, there was no imbalance in cardiac arrhythmias, including atrial fibrillation. No myocarditis was identified in vaccine recipients and there were no cases of pericarditis with onset within 6 weeks of vaccination.

Co-primary endpoints were protection against RSV-lower respiratory tract disease (RSV-LRTD) with ≥2 or ≥3 signs and symptoms. Protection against RSV-associated acute respiratory disease (ARD) and RSV-related hospitalizations were key secondary endpoints. RSV-LRTD was defined as new or worsening of ≥2 or ≥3 of signs/symptoms for ≥24 hours and RSV-ARD was defined as new or worsening of ≥1 signs/symptoms for ≥24 hours. Identification of a symptom prompted a visit to the site and a nasopharyngeal swab.

All cases had to be confirmed for RSV by reverse transcription polymerase chain reaction (RT-PCR). Continuous year-round weekly surveillance was conducted throughout the study.

The target number of cases for the first analysis was met in November 2022 which became the primary analysis. Follow-up was a median of 3.7 months, with a range from 0.5 to 12.6 months. The efficacy against RSV-LRTD with ≥2 symptoms was 83.7% (66.0%, 92.2%) and efficacy against RSV-LRTD with ≥3 symptoms was 82.4% (34.8%, 95.3%). Efficacy against RSV-ARD, the secondary objective, was 68.4% (50.9%, 79.7%). The observed RSV cases were subtyped for RSV-A and RSV-B, with efficacy observed for both RSV-A and RSV-B.

Efficacy was maintained in older ages and was similar for those with or without co-morbidities and in those who were considered vulnerable or frail. There were no hospitalizations in the primary analysis. For LRTD with shortness of breath as a marker of severity, efficacy was 86.7%. For RSV cases that were medically attended in the emergency department or urgent care, there were 5 cases in placebo recipients and no cases among vaccine recipients.

An additional analysis of efficacy was conducted at the end of April 2023; the median follow-up was 8.6 months, with the upper bound of the range being 17.7 months. The efficacy of mRNA-1345 against RSV-associated LRTD and ARD remained high, with overlapping confidence intervals to the primary analysis estimates over this longer follow-up time. VE against LRTD with ≥2 symptoms and ≥3 symptoms was 63% (48.7%, 73.7%) and for ARD was 54% (40.5%, 64.3%). Protection was seen for both RSV-A and RSV-B.

Efficacy was consistent for adults 60─69 years of age and 70─79 years of age. Among adults ≥80 and older, there were only 11 cases of LRTD with ≥2 symptoms, precluding the conclusions. The group of adults ≥80 years of age had the lowest incidence of RSV in the placebo recipients compared to adults 60─69 years of age and 70─79 years of age, perhaps as a carryover of pandemic measures in these trial participants. Efficacy in participants with co-morbidities and participants who were vulnerable or frail also were very consistent in this analysis. Assessing the impact of mRNA-1345 on preventing severe RSV as indicated by the shortness of breath measure, efficacy was 74.6% (50.7%, 86.9%). More participants in the placebo groups sought a higher level of care in an ED or UC, with efficacy of 61.8% (-7.35, 86.45). A total of 2 participants were hospitalized, a 73-year-old and an 84-year-old, both of whom had asthma and were from the placebo group. There were no hospitalizations in the vaccine group.

The vaccine was immunogenic, resulting in an 8-fold rise in the RSV-A neutralizing titers and a 5-fold rise in the RSV-B neutralizing titers. Responses were consistent across the age spectrum and there was no evidence of decreasing response as age increased. Cellular immune responses were evaluated for CD4 and CD8 in a separate study of adults 50─75 years of age. The vaccine was found to elicit strong and persistent T-cell responses as well. In the Phase 1 study, antibody remained detectable at 12 months, with GMTs 2- to 3-fold over baseline for both RSV-A and RSV-B. In that study, re-vaccination at 12 months was evaluated. Administration of a second dose of mRNA-1345 increased both RSV-A and RSV-B neutralizing titers 5- to 7-fold. The question of re-vaccination is important since protection from RSV by natural infection is not lifelong, but additional durability data will be needed to determine the timing. Moderna is studying re-vaccination at 1 and 2 years in Phase 3 studies.

Co-administration was explored with standard-dose quadrivalent influenza vacCcine (Afluria) and the Moderna bivalent COVID-19 vaccine in adults ≥50. Concomitant administration of the RSV and influenza vaccines was immunogenic for RSV-A, RSV-B, and all 4 influenza types and was well-tolerated in terms of local and systemic reactions. The same trend was observed with concomitant administration of mRNA-1345 and COVID-19 vaccine.

To summarize, the mRNA-1345 vaccine was well-tolerated in over 19,000 adults ≥60 years of age. No cases of GBS, ADEM, or other safety concerns were identified. The vaccine was shown to be efficacious, met all pre-specified criteria for licensure, and continued to be efficacious through a median of 8.6 months with a range up to 17.7 months. The vaccine prevented severe RSV disease as evaluated by the prevention of shortness of breath and medically-attended AEs. Strong antibody and cellular immune responses were seen through 12 months, and boosting was evident at 1 year. The antibody responses were similar across age groups, including those ≥80 years of age. Pre-specified immunogenic criteria were met, and no new safety signals were seen with concomitant administration.

Dr. Daley observed that VE was lower in the later data than the earlier data and asked Dr. Das to expand on how the results were interpreted for the durability of a single dose.

Dr. Das indicated that durability of a single dose was assessed in several ways. The confidence intervals at both time points overlapped. A detailed time-to-event (TTE) analysis was performed, which was reassuring in that the cases that were occurring in the longer follow-up were not in people who were vaccinated earlier. Efficacy also was consistent in a before 6 months and after 6 months analysis. Perhaps there is some waning, but there also is an effect from underlying force of infection. Immune responses lasting out to 12 months are also reassuring.

Dr. Long said that regarding the immunogenicity of the second dose at 1 year, “boost” is a word that could be used. “Reinforcing might be another word. However, no data were shown to suggest that there was an anamnestic response. Since the GMTs after the second dose did not quite equal the titers after an initial dose in the mRNA vaccines against COVID and influenza, she wondered whether a similar lack of robustness was observed after a second dose or if this specific to RSV and if there were any ideas about why this is different.

Dr. Das responded that for RSV, there is still a highly seropositive population. While a good response was observed in these small studies, both 1 and 2 years are being examined to determine whether there is any benefit to a 2-year gap. In terms of COVID-19 vaccines, the boosts have gone higher than the initial vaccination, but the immunologic experience with COVID at the point that those studies were conducted was quite different and it may not be completely fair to put those vaccines side-by-side. To reiterate, persistent immune responses are observed through 12 months. While boosting is observed with a second dose, it does not recapitulate the original dose, but it is quite close. Again, Moderna will be bringing the larger studies forward for both 1-year and 2-year revaccination later in 2024.

Dr. Beigel (NIH) asked whether Moderna had thought about or started work on correlates of protection to help understand what titers are actually needed.

Dr. Das responded that Moderna is very well-positioned to perform a correlates of protection analysis since samples were collected from every person in this study at baseline and Day 29. Initial analyses have been performed of the correlates, which show that RSV neutralizing titers are very well-correlated with protection. These data are being investigated in more detail to look for whether a threshold can be determined.

Rebecca C. Woodruff, PhD, MPH (CDC/NCCDPHP) presented preliminary results exploring chronic conditions as risk factors for RSV-associated hospitalizations. Using methods developed for a previous study, 3 data sources were leveraged to calculate RSV hospitalization rates during the 2017-2018 RSV season stratified by chronic condition and age group. The data source for the numerator was RSV-NET and the data sources for the denominator were the BRFSS and Census county-level population estimates.

RSV-NET is a population-based hospitalization surveillance platform. Currently, RSV-NET conducts active population-based surveillance of laboratory-confirmed RSV-associated hospitalizations for more than 300 acute care hospitals in 58 counties across 12 states (Oregon, California, Utah, Colorado, New Mexico, Minnesota, Michigan, New York, Connecticut, Maryland, Tennessee, Georgia). This area includes about 8.6% of the US population. In the 2017-2018 surveillance season, the catchment area was slightly smaller. It included about 38 counties across 8 states. Hospitalizations reported to RSV-NET include all of those where a positive RSV test was reported within 14 days prior to or during hospitalization. Testing for RSV is driven by clinical judgment and facility policies.

The BRFSS is an annual CDC-funded telephone-based health survey that operates in 50 US states, DC, and 3 US territories. BRFSS uses both landlines and cell phone numbers for sampling and collects about 400,000 interviews of adults each year. The questionnaire assesses a variety of health-related characteristics, including self-reported history of select chronic conditions. The BRFSS sample is designed to represent the civilian community-dwelling adult population ≥18 years of age in each jurisdiction. Adults who are not community-dwelling, including those living in nursing homes or other LTCFs, are not eligible to participate.

The study evaluated 9 chronic medical conditions as potential risk factors for RSV-associated hospitalization, including asthma; chronic kidney disease (CKD); chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), current smoking, diabetes mellitus, obesity (body mass index 30-39 kg/m^2), severe obesity (body mass index ≥40 kg/m^2), and stroke. This list was determined based on chronic conditions that were abstracted by RSV-NET and included in the BRFSS questionnaire.

RSV hospitalization rates were calculated using RSV-NET data to obtain counts of RSV hospitalizations among community-dwelling adults ≥50 years of age with and without chronic medical conditions of interest. These counts served as the numerator data in the rate calculation. To align with the BRFSS data, RSV-NET cases were excluded among adults living in nursing homes or other LTCFs. Next, a combination of BRFSS and the Census data were used to obtain estimated counts of community-dwelling adults ≥50 years of age with and without chronic medical conditions for the 38-county RSV-NET catchment area, which served as the denominator data for the rates. These data were used to calculate RSV hospitalization rates per 100,000 population among adults with and without each chronic medical condition, which was summarized by 3 age groups: 50─64 years of age, 65─74 years of age, and ≥75 years of age. Finally, rates were multiplied by burden multipliers to account for the under-detection of RSV among hospitalized adults and sensitivity of diagnostic tests. To calculate the rate ratios, the RSV-associated hospitalization rates in adults were divided with versus without chronic medical condition overall and within each age group. Monte Carlo simulation and generalized Poisson models were used to estimate rate ratios and 95% Monte Carlo intervals after adjusting for sex and race or ethnicity group.

For adults 50–64 years of age, the RSV hospitalization rate was about 7.9 times higher for adults with versus without CKD, 5.8 times higher for adults with COPD, about 4 times higher for adults with severe obesity or CAD, and about 2 to 3 times higher for adults with asthma, diabetes, and current smokers. The RSV hospitalization rates were similar for adults regardless of obesity or history of stroke. To put these rates into the context, adults ≥75 years of age have substantially higher hospitalization rates compared with adults 50–60 years of age.

For adults 65–74 years of age, the rates were higher across the board than for adults 50–64 years. There also was a generally similar pattern with RSV hospitalization rates at about 6 times higher for adults with CKD, 4.5 times higher for adults with severe obesity, 4.2 times higher for adults with COPD, and 2 to 3 times higher for adults with asthma, current smokers, CAD, or diabetes. For context, the RSV hospitalization rate was about 6.1 times higher for adults ≥75 years of age with versus without CKD, 4.2 times higher for adults with COPD, and about 2 to 3 times higher for adults with severe obesity, asthma, or CAD.

RSV hospitalization rates were lowest among adults in the youngest age group of 50–64 years of age and were highest among adults in the oldest age group of ≥75 years of age. Although the absolute rates clearly increased with age group, the adjusted rate ratios did not. Among adults ≥50 years of age, RSV hospitalization rates were about 6.5 times higher for adults with CKD, about 4.6 times higher for adults with COPD, around 3 times higher for adults with asthma or severe obesity, and about 2 times higher for adults with CAD, diabetes, and current smokers. The adjusted rate ratio for stroke and obesity were not statistically significant.

Adults with 2 or more chronic conditions had the highest RSV hospitalization rates compared to those with no chronic conditions. The adjusted rate ratios comparing the RSV hospitalization rate among those with 2 or more conditions to those with no conditions ranged from about 6.4 to 12.4 depending on the age group. The adjusted rate ratios comparing RSV hospitalization rate among those with 1 condition to those with no conditions ranged from about 2.6 to 2.9 depending on the age group.

Based on these preliminary results, the conclusion was that select chronic medical conditions were associated with greater rates of RSV-associated hospitalization among community-dwelling adults ≥50 years of age and varied by condition and age group. This information could help identify populations that might benefit most from RSV vaccines available to adults.

Dr. Carla Black (CDC/NCIRD) presented data on implementation of older adult RSV vaccines during the 2023-2024 season. Based on information from immunization information systems (IISs) submitted by jurisdictions to CDC through December 2023, coverage among adults ≥60 years of age who had received ≥1 dose RSV vaccine varied by state and ranged from about 5% to about 18% among the 37 states reporting at that time. Data are not available from all states, so these data are likely incomplete and probably are an underestimation of coverage.

According to the National Immunization Survey, as of February 3, 2024, coverage among adults ≥60 years of age was about 22.4%. Notably, the number who said they probably would get vaccinated or were unsure has remained consistent over time. Looking at coverage by demographics based on monthly data using a Kaplan-Meier estimation procedure using all data collected since September and including coverage as of the end of December 2023, coverage was slightly lower. By age group, coverage was lowest in adults 60–64 years of age and highest in all age groups ≥65 years of age. Coverage was highest among White adults at 22.5%. Asian adults had similar coverage to White adults at 16.7%, but every other racial ethnic group had lower coverage compared to White adults.

For example, Black adults had about 10 percentage points lower coverage at 12.9%. Some groups like NH/OPI had quite low coverage, which was 3.2%.

Adults ≥60 years with 1 or more chronic conditions had significantly higher RSV vaccination coverage of about 25% than those with no chronic conditions at about 18%. Each individual chronic condition was elevated compared to people with no conditions, with the exception of people with neurological conditions who had lower coverage compared to people with no conditions. Coverage decreased as the Social Vulnerability Index (SVI) of the county of residence increased. Coverage was higher among people who received an influenza vaccine for the season or an updated COVID vaccine. Among people who received an influenza vaccine, RSV coverage was about 30.5% and among those who had an updated COVID vaccine, RSV coverage was 38.5%. Coverage also varied by region. Coverage was lower among people residing in rural areas compared to those in urban and suburban areas. Coverage increased with increasing income and with increasing education.

Regarding co-administration among adults ≥60 years of age, among those who received an RSV vaccine, 57.1% received RSV alone, about 20% received RSV and influenza together, about 15% received 3 vaccines together (RSV, Influenza, COVID), and 8.5% received RSV and COVID vaccines together. The most recent data show that 84.4% of people were vaccinated in a pharmacy compared to about 14% who were vaccinated in medical settings (e.g., physician offices, hospitals, health departments, mass vaccination sites, and other medical settings).

IQVIA data are based on medical claims from pharmacies and physicians practicing in medical offices. IQVIA uses a sample of claims from medical offices to project vaccinations given in all medical offices in the US, which is based on a fairly small number of physicians. There is a lag with the medical office data, which do not completely mature until about 2 months. The national retail pharmacy data are a projection based on a much larger percentage of all pharmacies in the US. Claims from pharmacies come in much faster, so there is higher confidence in the completeness of the pharmacy data. None of the IQVIA data include vaccinations given in other medical settings such as public health clinics and hospitals, nor do they include vaccinations given in non-medical settings. Therefore, it is known that this is not a complete assessment of all RSV vaccines given in all settings in the US.

In terms of cumulative projected vaccines given to date in pharmacies and physician offices, a combined total of 9.65 million RSV vaccinations were administered in retail pharmacies (9.36 million) and physician medical offices (291,599) as of February 3, 2024. An additional 164,254 RSV vaccinations were administered in long-term care pharmacies. Each week, the majority of vaccines were the GSK product at about 69% compared to 31% of the Pfizer product. In pharmacies, vaccinations peaked in about late October to early November and have been declining since. Co-administration data from IQVIA showed similar patterns as in the NIS data among all people who received RSV vaccine and other vaccines that were given on the same day. About 52% received RSV only, about 22% received RSV and influenza vaccine, about 12% received RSV and COVID vaccine, and approximately 13.5% received RSV, influenza, and COVID vaccines together.
Using data from both NIS and IQVIA, the estimated range of persons vaccinated was approximately 11–18 million and estimated percent of persons vaccinated was 14%–22%.