Immunization Update and ACIP Highlights – February 2023

March 7, 2023

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) met virtually on **February 22, 2023**, for its regular triennial vaccine meeting with an additional meeting **February 24** to discuss bivalent COVID-19 vaccines. For archives of minutes and slides, go to the ACIP meeting website and click on "Meeting Materials." COVID vaccine recommendations are available on the CDC's Clinical Considerations website. Below are the key highlights:

- **Mpox Vaccine Vote —** Human monkeypox virus has been renamed "mpox." ACIP voted to recommend the use of JYNNEOS orthopoxvirus vaccine in persons ages 18 and older at risk of mpox during outbreaks.
- **Influenza —** Preliminary vaccine effectiveness results for the 2022–2023 season and U.S. influenza activity showed high effectiveness during this season in which the vaccine was well matched to the circulating virus strains.
- **Pneumococcal Vaccines —** Evidence to Recommendation (EtR) pneumococcal conjugate vaccine 20-valent (PCV20:Prevnar20) for the standard pneumococcal series in children age <2 years and for children ages 2–18 years with chronic medical conditions was presented for a recommendation vote in **June 2023**, pending FDA approval.
- **Meningococcal Vaccine —** Pfizer pentavalent (subtypes A, B, C, W, Y) meningococcal vaccine clinical trial data was presented in anticipation of a potential recommendation in **October 2023**. Recommendation for the GSK candidate A, B, C, W, Y meningococcal vaccine will potentially follow in 2024. A dosing schedule for a combined Men B vaccine with Men A, C, W, Y vaccine has not yet been determined.
- **RSV Vaccines**
  - **Infant:** Cost-effectiveness analyses and EtR were presented for Nirsevimab Respiratory Syncytial Virus (RSV) monoclonal antibody pre-exposure prophylaxis to be administered to all infants during their first year of life and to high-risk infants in their second year.
  - **Maternal:** Pfizer presented the safety and efficacy data from the randomized control trial of their RSV bivalent prefusion F (RSVpreF) vaccine for use in pregnant women given as a single dose at 24–36 weeks gestation to prevent lower respiratory tract infections in infants due to passive maternal antibody transfer in utero.
  - **Adult:** Cost-effectiveness and EtR for GSK's candidate adjuvanted RSV vaccine and Pfizer's candidate non-adjuvanted RSV vaccine for adults aged 60 and older were reviewed.
- **COVID-19 Vaccines**
  - ACIP continues to recommend Pfizer mRNA COVID-19 vaccine after reviewing a safety monitoring signal for ischemic stroke in persons ages 65 and older after receiving a bivalent booster dose and discussing its benefits and risks.
  - ACIP discussed and supported transitioning from monovalent to bivalent COVID-19 vaccines for the primary series once FDA provides authorization and transitioning to an annual bivalent COVID-19 booster, but members wished to allow flexibility for more frequent

administration to highest risk patients, such as the immunocompromised, at provider discretion.

- **Other Topics — Polio** vaccine for adults, **Dengue** vaccine**,** and **Chikungunya** vaccine, **Varicella** vaccine impact and CDC respiratory season **dashboards** were also discussed.

Mpox Vaccine

Human infection with the Monkeypox orthopoxvirus has been renamed "mpox." The mpox virus consists of two clades, I and II, which initially infected humans from zoonotic sources and are transmissible human to human.

Bavarian Nordic:JYNNEOS orthopoxvirus vaccine is FDA approved and CDC recommended for use as a subcutaneously administered vaccine to persons ages 18 and older, given in a 2-dose series with a 1-month interval. Previously, the ACIP only recommended JYNNEOS for prophylactic use in those at occupational risk for mpox. During this meeting, the ACIP voted to recommend the use of JYNNEOS in persons ages 18 and older at risk of mpox during mpox outbreaks.

Additional experience with the JYNNEOS vaccine during the recent 2022 mpox outbreak in the U.S. has provided more data for consideration. The first case was identified in **May 2022**, associated with international travel resulting in over 30,000 cases reported with 7.7% of cases hospitalized and 32 deaths. The majority of cases have occurred in gay, bisexual, and men having sex with men (MSM). Other persons, including children and teens, have been infected with mpox. Transmission to adolescents ages 13–17 years were associated with sexual contact in 97% of cases, while 100% of those cases in ages 5–12 years were due to household contact and 93% of those in ages 0-4 years were from household contact with 7% attributed to other sources of contact, such as perinatal. In the U.S., 53% of cases were in HIV-positive persons. There is no evidence that people who are infected but asymptomatic can spread mpox, but mpox has been contracted from some symptomatic people as early as 1 to 4 days prior to their symptom onset.

JYNNEOS was administered to almost 1.2 million persons during the 2022 outbreak. Mpox incidence among unvaccinated individuals was 7.4 times higher than in persons receiving one dose of JYNNEOS and 9.6 times higher than in persons receiving two doses of JYNNEOS vaccine with no difference in effectiveness between subcutaneous and intradermal administration. In multiple studies, vaccine effectiveness (VE) ranged from 66%–83% in those with two doses and from 36%–86% in those with one dose. Safety monitoring of the vaccine has not identified any new or unexpected safety concerns. Rates of myocarditis and pericarditis following vaccine administration were no greater than historical background rates in unvaccinated persons although a small increased risk cannot be ruled out. JYNNEOS was administered to 1,245 persons age <18 years with no serious adverse events.

Influenza Vaccines

The 2022–2023 influenza season virus started early and peaked from **late November to early December 2022**. Subtype A(H3N3) predominated with some A(H1N1) activity and 111 pediatric deaths.

Preliminary vaccine effectiveness (VE) rates for the 2022–2023 influenza season using test-negative, case-control study design in persons with respiratory illness include:

- VE was 54% in outpatient medically attended ages 6 months through 64 years for influenza A and 60% for subtype A(H3N2).
- VE for symptomatic influenza in children was 71% in a pediatric prospective cohort study.
- VE for emergency department (ED) visits in children was 42%.
- VE for hospitalization in children was 68%.
- VE for ED/urgent care visits in adults was 44% with VE of 30% in the subset of immunocompromised adults.
- VE for hospitalization in adults was 39–43% with VE of 31–44% in the subset of immunocompromised adults.

Pneumococcal Vaccine

Pneumococcal conjugate vaccine 20-valent (PCV20), Pfizer:Prevnar20 is anticipated to be FDA approved for use in children prior to the June 2023 ACIP meeting. The workgroup proposed that the ACIP vote in their next meeting to recommend PCV20 as an option for pneumococcal conjugate vaccination according to currently recommended pneumococcal vaccine dosing and schedules for U.S. children ages <2 years, and for children ages 2 through 18 years with underlying medical conditions, which increase the risk of pneumococcal disease. Pneumococcal Polysaccharide Vaccine 23-valent (PPSV23) would not be recommended for those at-risk children. Use of Prevnar 13 (PCV13) would be replaced by Prevnar 20.

Evidence to recommendation was presented for the use of PCV20 in children. The proportion of invasive pneumococcal disease caused by vaccine serotypes was 15% for those types in PCV15 but not in PCV13 and was 30% for those types in PCV20 but not in PCV13. The estimated incidence of pediatric outpatient visits and antibiotic prescriptions due to acute otitis media, pneumonia, and sinusitis attributable to PCV20 (non PCV13) serotypes is four to five times the incidence attributable to PCV15 (non PCV13) serotypes with volumes up to 830,000 outpatient visits and 730,000 antibiotic prescriptions in U.S. children annually. Cost-effectiveness analyses will be presented at the next meeting.

Meningococcal Vaccines

Pfizer presented data on their immunobridging trial of pentavalent meningococcal vaccine containing serogroups A, C, W, Y, and B (MenABCWY) given in 2 doses at either a 6- or 12-month interval to persons ages 10 through 25 years. The vaccine was not studied in immunocompromised persons who are a key group requiring meningococcal protection. A data gap also exists for adults ages older than 25 years. The MenACWY component of the vaccine, conjugated to a tetanus toxoid, confers seroprotection persistence up to 4 years in ACWY-naïve participants. Waning of immunity for serogroup B, when part of the pentavalent vaccine, is very similar to waning observed with meningococcal B vaccine (MenB), dropping substantially by 12 months post-dose 2. Booster response was observed following a dose of MenABCWY 4 years after a 2-dose primary series for all five serogroups.

Seroresponse rates of 98.3–100% were higher with a 12-month interval between the two doses than with a 6-month interval. Pfizer's MenABCWY vaccine appears to be noninferior to MenACWY plus MenB based

on the clinical trial data presented. A vote to recommend the Pfizer vaccine is planned for the October 2023 ACIP meeting, pending FDA approval. A recommendation for the GSK pentavalent vaccine is anticipated in 2024. A dosing schedule for a combined Men B vaccine with Men A, C, W, Y vaccine has not yet been determined.

Historically, antimicrobial resistance in N. meningitis was rare. New strains have recently emerged in the U.S. predominantly effecting racial and ethnic minority groups. A novel ciprofloxacin- and penicillin-resistant serogroup Y virus was detected in 2020 with 78% of cases occurring among Hispanic or Latino persons. No cases were in vaccinated individuals. An unusually lethal strain of serogroup Y has recently caused 11 cases and 3 deaths predominantly in Black or African American persons.

Respiratory Syncytial Virus (RSV) Vaccine

Infant: Nirsevimab is a novel RSV monocolonal antibody potentially used as pre-exposure prophylaxis against respiratory syncytial virus. It is given as a single, annual dose by intramuscular injection as opposed to monthly injections of Palivizumab. Although Nirsevimab is not a vaccine, it is being evaluated by the ACIP's RSV workgroup for recommendation even though many of the implementation, funding, and monitoring systems around it would not lie in the purview of those systems set up for vaccines. Since this is a therapeutic rather than a vaccine, it would not be included in the Vaccines for Children program, which could cause inequities for uninsured children. Adverse event reporting would be through the FAERS database rather than the VAERS database.

ACIP reviewed cost/effectiveness studies, EtR, and clinical considerations for its use in preventing lower respiratory tract infections when administered to all infants <8 months of age entering their first RSV season and all infants born during the RSV season and children <24 months of age who remain at increased risk of severe disease entering their second RSV season using the same criteria for risk as with Palivizumab per American Academy of Pediatrics recommendation.

Nirsevimab would be cost effective if priced in the lower end of the $200–$300/dose range according to CDC analyses. Sanofi used a price of $500/dose in its cost analysis, which would potentially lead to an overall cost of $1 billion per birth cohort, which amounts to one-fourth to one-fifth of the entire U.S. vaccine program budget. Committee members are hesitant to recommend without knowledge of the actual cost and its implications.

Clinical considerations proposed by the workgroup to accompany a future recommendation include:

- One dose of nirsevimab administered at birth to infants born during October to March and to infants ages <8 months born April to September when entering their first RSV season, most likely during a 2-, 4-, or 6-month well-child check. Local jurisdictions could determine whether an earlier start date or later end date might be needed depending on local RSV epidemiology.
- One dose of nirsevimab administered in October to November for children ages <20 months entering their second RSV season who are eligible for palivizumab.

Maternal: Pfizer presented the safety and efficacy data from the randomized control trial of their RSV bivalent prefusion F vaccine (RSVpreF) for use in pregnant women given as a single dose at 24–36 weeks gestation to prevent lower respiratory tract infections in infants due to passive maternal antibody transfer in utero. Geometric mean neutralizing titers are maintained in infants for several months after birth. Currently there are no data available on the efficacy of the first lifetime dose during subsequent pregnancies or the safety of additional doses given in subsequent pregnancies. The committee is requesting data on maternal coadministration of influenza and Tdap vaccines.

Vaccine efficacy (VE) against medically attended lower respiratory tract infection was 57.1% during the first 90 days of life and 51.3% at 6 months. For medically attended severe lower respiratory tract infection, the VE was 81.8% during the first 90 days of life and 69.4% at 6 months.

A vote to recommend is anticipated in **October 2023** if the product is licensed by that time. With the simultaneous recommendation of a novel maternal vaccine and novel infant prophylactic monocolonal antibody therapy, the impact of these two protective strategies on each other needs to be evaluated.

Adult: Two efficacious respiratory syncytial virus (RSV) vaccines covering RSV A and RSV B are being considered for approval for adults aged 60 years and older:

1. GSK's adjuvanted F protein candidate vaccine (RSVpreF3 vaccine), containing 120mcg antigen and an ASO1 adjuvant
2. Pfizer's non-adjuvanted F protein vaccine (bivalent RSVpreF vaccine), containing 120mcg antigen and no adjuvant

Licensure is anticipated in **fall 2023**. Cost effectiveness analyses and EtR were presented to the committee, which was asked to consider whether these vaccines should be recommended for use in persons ages 60 years and older or in persons ages 65 years and older.

The number needed to vaccinate with the **GSK vaccine** would be:

- 84 adults age 65+ years or 90 adults ages 60+ years to prevent one outpatient visit
- 1,097 adults ages 65+ years or 1,348 adults ages 60+ years to prevent one hospitalization
- 21,442 adults ages 65+ years or 27,284 adults ages 60+ years to prevent one death

The number needed to vaccinate with the **Pfizer vaccine** would be:

- 95 adults age 65+ years or 103 adults ages 60+ years to prevent one outpatient visit
- 1,275 adults ages 65+ years or 1,567 adults ages 60+ years to prevent one hospitalization
- 24,927 adults ages 65+ years or 31,717 adults ages 60+ years to prevent one death

The CDC's cost-effectiveness model used a price per dose of $100. GSK's model used $148 per dose, and the Pfizer model used $200 per dose, giving some indication of what pricing might be. RSV vaccination for older adults could be cost effective if priced low enough. Vaccination of older age groups would be more cost effective than vaccination of younger age groups. Uncertainty remains concerning the duration of protection and protection against hospitalization with use of these RSV vaccines. Groups at highest risk of

severe disease, such as immunocompromised, were under represented in clinical trials. Safety and efficacy data are not available for those ages 75 and older. At least one case of inflammatory neuropathy has been observed among recipients of each investigational vaccine. At this time, one dose would potentially be recommended with one season of impact. The work group was leaning toward a recommendation starting at age 65 years with a minority of the opinion not to recommend the vaccine. ACIP members discussed the pros and cons of the potential ages to initiate vaccination and seemed divided in opinions.

COVID-19 Vaccines

The COVID-19 vaccination program is anticipated to remain essentially the same after the discontinuation of the Public Health Emergency on **May 11, 2023**. The move to commercialization of COVID-19 vaccine is not anticipated until the **fall of 2023** to coincide with the next iteration of the bivalent vaccine.

Safety: As of **February 8, 2023**, 52.5 million COVID-19 mRNA bivalent booster doses have been administered to people ages 5 years and older in the U.S., including 22.3 million doses in people ages 65 years and older. Multiple complementary safety monitoring systems concurrently evaluate the safety of bivalent booster vaccines, and their data continue to support the CDC recommendation that everyone eligible for a COVID-19 mRNA bivalent booster gets vaccinated.

The Vaccine Safety Datalink (VSD) examines electronic health records of 12.5 million individuals and looks for prespecified safety outcomes using vaccinated concurrent comparators. The risk of prespecified outcomes in the period of 1 to 21 days following a bivalent vaccination are compared with bivalent vaccinated individuals who are concurrently 22 to 42 days following their bivalent dose. Safety signals are followed with subsequent analyses. The CDC reported a safety signal in the VSD system for ischemic stroke/TIA in persons ages 65 and older who had received a Pfizer bivalent booster dose. The rate ratio has attenuated since that time and has only intermittently met signaling criteria. Supplemental analyses have suggested those in the comparator group of 22 to 42 days have a lower rate of ischemic stroke than expected, leading to a higher rate ratio in the 1 to 21-day group. When comparing boosted to un-boosted concurrent comparators, the rate ratio (RR) for ischemic stroke is 1.07, while simultaneous administration of high-dose or adjuvanted influenza vaccine resulted in a RR of 1.65. RR is not elevated for stroke in persons receiving only influenza vaccine. No other safety monitoring system in the U.S. or internationally has detected a safety signal for stroke. No signals have been detected for stroke for primary series or monovalent boosters for Pfizer or Moderna COVID-19 vaccines. Approximately 4.25 million doses of the Pfizer bivalent booster have been administered in the CMS database to persons 65 years and older, and 38% of Medicare recipients have had concomitant influenza vaccine administration with no signal for stroke. Incidence of acute ischemic stroke is 10 times higher during the 3 days following a COVID diagnosis, and COVID-19 vaccination is associated with a reduced risk of stroke after COVID-19 with an adjusted hazard ratio of 0.41 for ages 65 years and older.

Investigations will continue into possible confounders and will examine the possibility of reduced risk in those past 22 days from vaccination and coadministration with influenza vaccine. The ACIP continues to be confident in recommending bivalent booster vaccines to persons ages 65 years and older.

With 556,000 doses of bivalent mRNA vaccine administered to persons ages 12–39 years, there has only been one case of myocarditis in a male between ages 18–29 years.

Bivalent booster effectiveness: Compared to adults who received a bivalent booster dose, the monthly rate of hospitalizations is 16.0 times higher among unvaccinated and 2.6 times higher in vaccinated adults without an updated booster dose. In **November 2022**, persons ages 5 years and older receiving a bivalent booster had 12.7 times lower risk of dying from COVID-19 compared to unvaccinated people and 2.4 times lower risk of dying from COVID-19 than people vaccinated without having received a bivalent booster. Nearly 1,500 children and adolescents have died from COVID-19 and half of hospitalized children and adolescents had no underlying medical conditions, while 96% of adults hospitalized for COVID-19 had at least one underlying medical condition. Relative VE for symptomatic infection (comparing those boosted with the bivalent vaccine to those persons who have received 2 to 3 monovalent doses and no bivalent doses) is as follows (with effectiveness decreasing over time from vaccination):

- 65% for those ages 5 to 11 years
- 68% for those ages 12 to 17 years
- 51% for those ages 18 to 49 years
- 46% for those ages 50 to 64 years
- 38% for those ages 65 years and older

Relative VE for hospitalizations in all adults ages 18 years and older and for only those ages 65 years and older is 52% for both groups. Note that with calculations of bivalent vaccine relative VE, residual protection from previous doses may lower the relative effectiveness of the bivalent booster dose. Uptake of the bivalent booster has been best in the older population with 41% of those ages 65 and older having received a bivalent booster.

Bivalent primary series: Although the FDA's VRBPAC voted earlier in the month to move toward using the bivalent vaccine for the primary series, no change in the Emergency Use Authorization has been made by the FDA at this point. There was no vote or recommendation by the ACIP on the use of bivalent vaccine for the primary series and no new clinical considerations provided by the CDC. This meeting was pre-decisional, providing more data to inform discussion regarding potential changes. FDA regulatory allowance will need to occur prior to CDC/ACIP recommendations for use.

During the discussion, ACIP members mostly concluded that a primary series was probably still be needed in children, especially the youngest children who may not have been exposed to COVID-19 virus. A study of a bivalent vaccine containing the BA.1 variant administered to children ages 6 months to 5 years produced neutralizing antibody titers against BA.1 that were 25 times higher than the geometric mean titers of antibodies produced when the original monovalent vaccine was administered. There was no consensus on whether other persons will need a primary series or whether documentation of infection would be sufficient to skip a primary series and receive just an annual dose of COVID-19 vaccine. More data is needed about the effectiveness and duration of a single bivalent dose.

Committee members felt an annual fall bivalent booster seemed reasonable for most persons. A simplified, annual recommendation could help reduce vaccine and message fatigue and implementation.

Simplification of the schedule would reduce errors and increase safety. It is becoming difficult for some to obtain a monovalent vaccine dose. Data were insufficient to determine whether older adults or immunocompromised persons should receive more than one dose annually, although the committee would like providers to have the flexibility to make that decision. Data will be needed to determine whether pregnant women should be vaccinated during each pregnancy to provide transplacental passive immunity to their newborn infants. Bivalent vaccine primary series trials are still ongoing in young children, although the low uptake of the vaccine has impacted study enrollment. A single dose formulation rather than multi-dose vial will increase the number of potential immunizers.

For the latest CDC COVID vaccine recommendations, visit the CDC's Clinical Considerations website.

Other Topics

Polio: Due to the recent vaccine-derived poliovirus, type 2 (VDPV2) outbreak in New York State, the polio work group is planning to submit a revised recommendation for adult polio vaccination for vote at the **June 2023** ACIP meeting. Currently, the year-2000 recommendation for inactivated polio vaccine (IPV) for adults is that those who are unvaccinated and at increased risk should receive a primary series with IPV, and those who have had a primary series of oral polio vaccine (OPV) or IPV who are at increased risk can receive another dose of IPV. Rather than waiting until there is an outbreak of polio that puts adults at increased risk, the majority of the work group proposed that all adults who are unvaccinated or incompletely vaccinated in the U.S. complete their primary polio vaccination series with IPV. The clinical consideration accompanying that recommendation is in general, unless there are specific reasons to believe they were not vaccinated, adults who were born and raised in the U.S. can assume they were vaccinated against polio as children. The work group recommends keeping the current permissive single lifetime booster recommendation for adults who are at increased risk for poliovirus exposure.

Dengue: Dengue is the most common mosquito-borne virus globally. There are four serotypes of dengue virus. Disease with one serotype gives life-long protection against that serotype but only provides short-term cross protection against the other types. A second dengue infection is the most important risk factor for severe disease.

Pfizer:Dengvaxia vaccine is FDA licensed and CDC recommended for prevention of dengue in individuals ages 9 to 16 years with laboratory confirmation of previous dengue virus infection living in endemic areas. It is a live-attenuated quadrivalent vaccine using a yellow fever backbone given as a 3-dose series (0, 6, 12 months). It has an efficacy of ~80% among seropositive children. Puerto Rico is now administering Dengvaxia.

The dengue vaccine workgroup reviewed data on Takeda TAK-003 dengue vaccine, a live-attenuated quadrivalent vaccine with a dengue virus serotype 2 backbone given in a two-dose series separated by 3 months. TAK-003 is immunogenic against each of DENV-1, -2, -3, and -4 serotypes. It has long-term efficacy against all four serotypes in baseline seropositive participants with a VE of 64.2% for disease, 85.9% for hospitalization and efficacy against DENV-1 and DENV-2 in baseline seronegative participants with a VE of 53.5% for disease, and 79.3% for hospitalization. Data suggest TAK-003 lacks efficacy against

DENV-3 in baseline seronegative participants, and data were insufficient to rule out an increased risk among recipients. The trial was not able to assess efficacy against DENV-4 due to low incidence.

Chikungunya – Four chikungunya vaccines are in clinical trials. Valneva's chikungunya vaccine could potentially be FDA approved as soon as **August 2023**. Data were presented about global epidemiology, disease in U.S. travelers and chronic arthralgia after infection in anticipation of a vote to recommend in adult travelers and lab workers in **2024**. As many as 50% of persons continue to have arthralgia three months after infection, and one-third of cases can still have symptoms 12 months later.

Impact of 25 years of Varicella Vaccine celebrated

In the past 25 years of U.S. administration of varicella vaccine, 91 million cases, 238,000 hospitalizations, 1,934–2,446 deaths have been averted at a societal savings of $23.4 billion. Each year, more than 10,500 hospitalizations are averted due to varicella vaccination.

New respiratory season dashboards

The CDC is providing new dashboards to help with surveillance of respiratory viruses during the respiratory season. RESP-NET provides data on hospitalizations caused by respiratory viruses, and emergency room visits for COVID-19, Influenza, and RSV are tracked in the National Emergency Department respiratory virus dashboard.

If you have any questions regarding immunization, feel free to contact Tamara Sheffield, MD, MPA, MPH, Senior Medical Director, Preventive Medicine, Intermountain Healthcare, at **801-442-3946**.