Immunization Update and ACIP Highlights – June 2020

July 1, 2020

The Advisory Committee on Immunization Practices (ACIP) of the CDC met on June 24 in a shortened 1-day virtual meeting to provide guidance on vaccines. For archives of minutes and slides, go to the ACIP meeting website and click on Meeting Materials. Below are the key highlights:

- Only two recommendations were voted on and approved:
  - Adding the newly approved Meningococcal quadrivalent vaccine conjugated to tetanus toxoid protein, MenACWY-TT (MenQuadfi™/Sanofi Pasteur) to the Vaccines for Children (VFC) program, and
  - Influenza vaccine recommendations for the 2020-2021 season
- A preliminary report on the 2019-2020 influenza season was provided
- A presentation by the newly formed COVID19 work group concerning COVID-19 and its epidemiology, the immunology of SARS CoV-2, the development of a vaccine to protect against SARS CoV-2 and principles regarding its distribution

The following includes details of vaccine evidence presented, committee discussion and votes.

Meningococcal

MenQuadfi provides protection against four serogroups of meningococcus, A, C, W, and Y antigens that are individually conjugated to tetanus toxoid protein. MenQuadfi is supplied in a single dose vial and will be distributed starting in 2021. It has been approved by the FDA for individuals ages 2 years and older. Sanofi is pursuing an age indication down to age 6 weeks, and should that approval be given, the plan is to phase out their Menactra® MenACWY-D and replace it with MenQuadfi.

MenQuadfi has been shown to be non-inferior in terms of immunogenicity for healthy individuals compared to other MenACWY vaccines with a good safety profile. Its impact on potential future localized reactions to tetanus containing vaccines has not been studied. It has not been studied in individuals at high-risk for meningococcal disease. In persistence studies out to 3 years, it is non-inferior to other meningococcal vaccines for serogroups C, W and Y but had a lower GMT and did not show non-inferiority for serogroup A. Since there is little circulation of serogroup A in the US, that is not a problem for individuals domestically, but it is of concern for those who plan to travel outside the US.

Menactra is not recommended to be given until the pneumococcal series has been completed in persons at high-risk for pneumococcal disease such as those with asplenia or AI/AN populations due to interference with the efficacy of PCV13. It has also been shown to have interference with the response to certain pertussis antigens in pertussis containing vaccines.

In one study, interference was not seen between MenQuadfi and PCV13. No interference was seen with HPV, tetanus or diphtheria in coadministration studies. In coadministration studies with Tdap, non-

inferiority for pertussis toxoid antigen was observed, but noninferiority was not met for pertussis FHA, pertactin and FIM antigens.

The ACIP members unanimously voted to approve the use of MenQuadfi within the VFC program

Influenza

Preliminary influenza vaccine efficacy for the 2019-2020 season was 39% overall: 44% for influenza B (Victoria lineage) which predominated the first half of the season, and 31% for influenza A H1N1pmd09 which predominated the last half of the season. The Influenza B protection was critical for children given the severity of disease in that group during the 2019-2020 season. CDC estimates the burden of disease due to influenza in the 2019-2020 season to be 39-56 million illnesses, 18-26 million medical visits, 410K-740K hospitalizations and 24K-62K deaths.

The CDC continues to recommend yearly influenza vaccine in all persons ages 6 months and older, and this will be of particular importance in the 2020-2021 season as a COVID-19 mitigation strategy to reduce healthcare resource use and to prevent coinfection, with its higher mortality. A 30.4% death rate has been seen in patients with COVID-19 and influenza B coinfection compared to a 7.6% death rate in those solely infected with COVID-19.

Changes to the 2020-2021 recommendations include three updated vaccine components (A/H1N1, A/H3N2, B/Victoria), this being the first time that the variations in the reference strains for non-egg based products (RIV and ccIV) are being listed. Note that even if the recommended strains names for egg and non-egg vaccines are different, they belong to the same antigenic group (for each subtype/lineage).

Egg based influenza vaccines will contain hemagglutinin derived from:

- an A/Guangdong-Maonan/SWL2536/2019 (H1N1)pmd09-like virus;
- an A/Hong Kong/26712019 (H3N2)-like virus;
- a B/Washington/02/3019 (Victoria lineage)-like virus; and
- for quadrivalent vaccines, a B/Phuket/3073/2013 (Yamagata lineage)-like virus

Non-egg based influenza vaccines will contain hemagglutinin derived from:

- an A/Hawaii/70/2019 (H1N1)pmd09-like virus;
- an A/Hong Kong/45712019 (H3N2)-like virus;
- a B/Washington/02/2019 (Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (Yamagata lineage)-like virus

Other changes include the listing of two new products, Fluzone® high-dose quadrivalent (with a volume of 0.7mL/dose) and Fluad® adjuvanted quadrivalent for ages 65 years and older. Contraindications for live attenuated influenza vaccine (LAIV) FluMist® including functional or anatomic asplenia, cochlear implant, and active CSF leak are now added to the contraindications table. Non-egg containing vaccines FLUCELVAX® (ccIIV4) and Flublok® (RIV) do not need to be given to egg allergic patients in a supervised medical setting as is recommended for egg-containing vaccines. Because antivirals may interfere with the effectiveness of a live vaccine, their use is limited before and after the administration of FluMist.

Newer antivirals have longer half-lives, and recommendations based on the half-life have been determined. Intervals when antivirals should be avoided:

- Oseltamivir and Zanamivir – 2 days before to 14 days after LAIV
- Peramivir – 5 days before to 14 days after LAIV
- Baloxavir – 17 days before to 14 days after LAIV

The ACIP members unanimously voted to approve the 2020-2021 Influenza vaccine recommendations.

Coronavirus Disease 2019 (COVID-19)

Coronaviruses are RNA viruses. There are 7 known coronaviruses: 4 which cause mild illness in humans, 3 which causes severe disease (SARS-CoV-1, MERS, SARS-CoV-2). SARS-CoV-2 averages a 5-day incubation period. Peak infectiousness is 4 days before symptom onset (pre-symptomatic) to shortly after the patient becomes ill. Longer periods of transmissibility can occur in the most severely ill and immunocompromised, with shedding of culturable virus up to 20 days. For healthy persons with mild to moderate illness, after 8-10 days, replication-competent virus cannot be recovered from respiratory swabs. PCR tests can remain positive for weeks after recovery after persons are no longer infectious leaving individuals in "PCR purgatory" or unnecessary isolation. A substantial fraction of infections (an estimated 30-35%) are asymptomatic. Respiratory droplets within the droplet "zone" (~6 feet) appear to be the key mode of transmission, and although virus may be present more generally airborne in an aerosolized state for a long time, transmission is less likely by that route.

Of adults with COVID-19 illness, 13.8% have severe disease, and 4.7% have critical illness. About half of the adults with critical illness die. The frequency of critical illness in children is very low, only 0.4% with 2.5% of children having severe disease. Emerging data concerning the immunocompromised appears reassuring. For people with HIV, the risk is likely greatest at low CD4 cell counts or for those not virally suppressed. There is no definitive evidence that cancer therapy worsens outcomes in COVID-19 patients (including immunosuppressive therapy). Unique complications of COVID-19 include diffuse endotheliitis, hypercoagulability (local and embolic) and peri- and post-infectious hyperimmune reactions.

Immunology: The coronaviruses that cause mild disease produce only transient protection from future infection, with a decrease in neutralizing antibodies over time. SARS-CoV-2 infection produces IgG, IgM, and IgA antibodies. Most people with COVID-19 develop antibodies, usually within 2 weeks, and many mount a neutralizing antibody response (although a study of healthy sailors showed 41% didn't have neutralizing titers). We don't know the duration of immunity following infection or what the immunologic correlates of protection are. The magnitude of antibody response correlates to the severity of infection. Persons with more severe COVID-19 disease have more robust and faster antibody responses. Older patients develop higher neutralizing antibodies titers than younger patients.

Epidemiology in the US: Multiple populations are high risk for disease or severity. Occupational risks include healthcare and agriculture. Individuals at risk are older adults and those with underlying medical conditions. Those with social determinant risks include American Indian, Black or Hispanic race/ethnic groups, those in long-term care, in correctional facilities or experiencing homelessness. Those with underlying medical conditions were 6 times as likely to be hospitalized and 12 times more likely to die.

We don't know the proportion of viral transmission contributed by children, the incidence of multisystem inflammatory syndrome in children, the risk of disease and severity in pregnant women or current levels of population immunity.

Development of COVID-19 vaccines: Multiple steps are involved in making COVID-19 vaccines available in the U.S. Clinical preparation includes vaccine testing and manufacturing. The FDA will need to approve emergency use authorization (EUA), investigational new drug use (IND) and licensure. ACIP will need to review the scientific evidence and make recommendations. CDC will need to adopt ACIP recommendations and help in vaccine distribution and monitoring.

Multiple platforms for development are being used such as DNA, mRNA, replicating viral vector, nonreplicating viral vector (such as adenovirus), protein-based (subunit, virus-like particles), inactivated, and live attenuated. CDC believes that multiple approaches increase the chances of developing safe and effective vaccines to meet national and global needs. Vaccines must meet stringent safety standards in clinical trials, otherwise, the vaccine will not be used in the population. We don't know the number of vaccine doses that will be needed per individual. DNA and mRNA vaccines will need more than one dose, while one dose may be sufficient for a viral vector vaccine. We don't know if administration will be SC or IM or if electroporation will be needed (which is used to get a DNA vaccine into the cell nucleus). We don't know the storage temperature. We don't know immunogenicity and efficacy by age and risk group, the interval from vaccination to protection, the effect on acquisition of infection and transmission, the adverse event profile by age and risk groups, or which populations will be included in FDA approval.

Provision of COVID-19 Vaccines: The goals for the COVID-19 vaccine program are to find safe and effective vaccines that reduce transmission, morbidity, and mortality, to minimize disruption to society and the economy, and to maintain healthcare capacity while maintaining equity in allocation and distribution. Guiding principles will be: first, vaccine safety, inclusiveness in clinical trials, efficient and equitable distribution, and flexibility at the state and local levels. The ACIP has been asked to assist the CDC in refining plans for prioritization and staged vaccine distribution as it becomes available.

Substantial disruptions to routine childhood vaccination services have occurred during the COVID pandemic. We need to encourage parents to bring their children now to get recommended vaccines in order to have capacity for back-to-school and influenza vaccines in the fall, and we need to provide information on the measures we are taking to provide those vaccines in a safe environment. We need to provide VFC information to parents. Before the economic disruption of COVID-19, 50% of children were eligible for free VFC vaccine, and now even more children should be eligible. The CDC has published an informational handout for parents, "Did you know your child can get free vaccines?"

ACIP is planning to meet again virtually prior to the regularly scheduled October meeting, possibly for one-day meetings in August and September in order to consider COVID-19 vaccine issues.

If you have any questions regarding immunization, feel free to contact Tamara Sheffield, MD, MPA, MPH, Medical Director, Community Health and Prevention, Intermountain Healthcare, at (801) 442-3946.