Advisory Commission on Childhood Vaccines (ACCV)

Teleconference

March 2, 2023

Members Present

Albert Holloway, Jr. MD (2024)
Dana DeShon, DNP, APRN, CPNP-PC (2024)
Daniel Boyle (2024)
Timothy Thelen, JD (2024)

Division of Injury Compensation Programs (DICP), Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (HHS)

CDR Reed Grimes, MD, Director, DICP, Chair, ACCV
Pita Gomez, Principal Staff Liaison, ACCV
Andrea Herzog, Program Analyst

Welcome and Chair Report, CDR Reed Grimes, MD, Director, DICP and Chair, ACCV

Dr. Grimes called the meeting to order and welcomed everyone. Dr. Grimes announced that all current commissioners and ex officio members were present which constituted a quorum.

Public Comment on Agenda Items, CDR Reed Grimes, MD, Director, DICP and Chair, ACCV

Dr. Grimes invited public comment on the meeting agenda and there were none.

Epidemiology of Dengue Virus (DENV), Gabriela Paz-Bailey, MD, PhD, MSc, Chief Medical Officer, Centers for Disease Prevention and Control (CDC)

Dr. Paz-Bailey explained that dengue virus (DENV) is transmitted by mosquitos, which are endemic in six U.S. territories and freely associated states. Dengvaxia is an FDA-approved vaccine for children aged 9 to 16 years of age, who had dengue before. A second dengue vaccine (TAK-003) is currently under review by the Food and Drug Administration (FDA) and the Advisory Committee on Immunization Practices (ACIP), and a third dengue vaccine (TV-003) is in Phase III trials. There are four serotype DENVs that cause infection and results in lifelong immunity to the specific serotype causing the infection and short-tern immunity to the other three, usually 1-2 years. DENV is predominantly transmitted to humans via a mosquito bite, but can also be spread through exposure to the saliva of an infected individual.

Only about one in four DENV infections are symptomatic. The majority of infections presents as asymptomatic or mild, undifferentiated febrile illness with nausea, vomiting, headache, muscle pain, body pain, joint pain, or a rash. DENV is often undiagnosed, and mortality is rare, less than one percent if treated, about 15% when untreated. The risk factors for severe dengue fever include increased risk for infants with seropositive mothers, elderly population, repeat infections with the second infection usually being the most severe, and the

potential for comorbidities. Data from a Nicaraguan cohort study showed that antibody levels after a primary infection typically peak within four months and recede by the eight months and remain stable thereafter.

Dr. Paz-Bailey provided a map to show the global disease burden of dengue, which is highest in tropical areas in South America and Southeast Asia. Dengue incidence is likely to increase as the climate warms.

In the U.S., the CDC has developed the Yellow Book Criteria to assess dengue risk levels. Dengue is endemic in six territories, which is considered to be frequent when 10 cases occur in three or more years over a 10-year period. Puerto Rico reports the most dengue fever cases in the U.S. (95%) mainly in the 10-19 age groups, and all serotypes are represented. There is a higher incidence of fatal dengue cases among the adult populations. Dengue is not endemic in the 50 U.S. states, but the mosquito that transmits the virus is present in several states, including Hawaii, Florida, and Texas. Most cases reported in the U.S. originate in travelers.

Dr. Paz-Bailey discussed challenges with the development of DENV vaccines. The only currently approved vaccine, Dengvaxia, a tetravalent live attenuated vaccine given in three doses, separated by six months which takes a year to complete. In 2015, the first trial showed increased risk of severe disease in younger children (2–5-year-olds). In 2016, the World Health Organization (WHO) recommended initiating the series in children nine years and older in endemic areas. However, in 2017, WHO revised the recommendation to vaccinate only children 9 to 16 with lab confirmed evidence of prior infection. The only approved vaccine, Dengvaxia, protects against all four serotypes of dengue fever, and against hospitalization and severe disease. Dengue is endemic in six U.S. territories. Puerto Rico has the highest level of dengue cases, accounting for 95% of cases from endemic areas of the U.S.

Concerning harms from Dengvaxia vaccination, children with previous infection were protected from hospitalization and severe dengue fever, while children without previous infection had a higher risk of hospitalization and severe disease three years after vaccination. The vaccine was licensed by FDA in 2019 and recommended by ACIP in 2021 for individuals ages 9 to 16 after lab confirmation of previous infection and living in endemic areas. There are nearly 300,000 children in Puerto Rico who might be eligible for Dengvaxia, which is the first vaccine that requires a pre-vaccination lab test. This requires multiple visits to a health care provider or a lab for testing and administration of the three-shot series. Despite the complex logistics, the first DENV in Puerto Rico was administered on September 7, 2022.

Dr. Paz-Bailey briefly discussed the newest vaccines, TAK-003 and TV003. TAK-003 is a two-dose series that has been approved for prevention of DENV in other countries, but has recently been submitted to FDA for approval. TV003 is only one dose, was developed by the National Institutes of Health (NIH) and licensed to Merck and currently in Phase 3 trials. With regard to vaccine safety, the rate of serious adverse events was similar among those who received the vaccine versus the placebo as was the incidence of death.

Dr. Paz-Bailey's presentation concluded, and they invited questions. Dana DeShon expressed interest in whether dengue is present in other states and whether the approved vaccine (Dengvaxia) should be made available more broadly. Dr. Paz-Bailey explained that the recommendation for the vaccine is only applicable to residents of the endemic areas, and the lab screening is only recommended for the same endemic areas. Dr. Paz-Bailey stated that it had been shown that giving the vaccine to individuals who had not been infected previously (seronegative individuals) actually increased the risk of serious disease if they then became infected.

There is evidence that high seroprevalence is found on the Mexico side of the border, and low seroprevalence is found on the U.S. side of the border. Therefore, it is not cost effective to screen children in the U.S. Dr. Paz-Bailey reiterated that the risk of adverse events usually occurs three years after vaccination, and because there is risk of serious infection in those who have not been infected before, those who are seronegative, the process to identify and track infection is very important and complex and involves multiple visits to labs and physicians to identify the infection and to treat it. This highlights the complexity of the process. Dr. Grimes asked if the other territories where dengue might occur have healthcare systems as robust as Puerto Rico. Dr. Paz-Bailey responded that areas like the U.S. Virgin Islands are watching the efforts of Puerto Rico and their best practices to be able to respond when circumstances permit. Dana DeShon commented on looking at the benefit versus the harm of the vaccine. Dr. Paz-Bailey shared that in 100,000 vaccines that completed the series, there were 4,000 averted symptomatic cases, nearly 3,000 averted hospitalizations and 51 vaccine-induced hospitalizations. Daniel Boyle commented that the system that includes monitoring and surveillance must also include care and rehabilitation if an adverse event occurs, since this isn't something that exists for most routine vaccinations.

Epidemiology of Respiratory Syncytial Virus (RSV) in Children, CDR Jefferson Jones, MD, MPH, CDC

Dr. Jones stated CDC maintains National Respiratory and Enteric Virus Surveillance System (NREVSS) to monitor Respiratory Syncytial Virus (RSV) seasonality in children and adults. NREVSS is a passive, laboratory-based surveillance system that has about 300 laboratories report their RSV results. All test types are reported on a weekly basis, while most tests are usually polymerase chain reaction (PCR) tests. During 2011-2020, RSV circulation was seasonal with peak activity during December through February annually. Additionally, Dr. Jones identified geographic differences in RSV seasonality. RSV followed a consistent seasonal pattern, but the COVID-19 pandemic interrupted the seasonal circulation for many respiratory illnesses. After a year of limited RSV circulation, RSV experienced its peak early in August 2021.

RSV is the leading cause of hospitalization in U.S. infants. Most infants (68%) are infected in the first year of life and nearly all (97%) by age two. Premature infants had hospitalization rates three times higher than term infants. Preterm infants have three times higher rates of intensive care unit (ICU) admission and the need for mechanical ventilation, and the cost of hospitalization in these cases is four times higher. Most children (79%) hospitalized with RSV had no underlying medical conditions.

It is estimated that each year, in children less than five years of age, RSV results in up to 300 deaths, up to 80,000 hospitalizations, about 520,000 emergency room (ER) visits, and 1.5 million outpatient visits. RSV-associated hospitalization rates vary by year, study design and statistical assumptions. An industry-sponsored systematic review estimated median annual hospitalization rate of 25.6 per 1,000 in infants aged 0-5 months. For cost-effective analyses, CDC uses estimates from active surveillance in primary analyses and others will inform sensitivity analyses. CDC generates RSV-associated disease burden estimates from the New Vaccine Surveillance Network (NVSN). The NVSN has conducted year-round acute respiratory illness (ARI) surveillance at three sites between 2000 to 2009, expanded to seven sites thereafter, and included PCR testing for multiple respiratory viruses, including RSV.

NVSN estimated emergency and outpatient visits for two periods, 2002-2004 and 2004-2009. In the first period, the highest rates of ER visits were among infants between 5 and 11 months of age (about 56 per 1,000), and infants 0 to 5 months in the second period, 75 per 1,000. For outpatient pediatric clinic visits, in infants 6-9 months for the two periods, there were 177 and 246 visits per thousand, respectively. RSV-associated hospitalization rates in children aged 0 to 11 months are highest in the first and second months of life and declined significantly thereafter.

Palivizumab (Synagis®) is the only licensed product for the prevention of RSV in the U.S. It is a humanized monoclonal immunoglobulin G (IgG) against F glycoprotein requiring monthly administration because it has a very short half-life. Clinical trials demonstrated 55% efficacy against RSV-associated hospitalization in preterm infants and infants with chronic lung disease, and 45% efficacy for infants with congenital heart disease. The American Academy of Pediatrics (AAP) recommends its use, but there is no ACIP recommendation for its use at this time.

In summary, pre-pandemic RSV seasonality is well defined with limited geographic variability in most of the U.S. It is the most common cause of hospitalization in U.S. infants, with the highest rates in the first months of life. Risk declines with increasing age in early childhood. Prematurity and other chronic diseases increase risk of RSV-associated hospitalization, but most hospitalizations are in healthy, term infants. The currently licensed prevention product, Palivizumab, targets only 2%-3% of U.S. infants.

Dr. Jones' presentation concluded, and they invited questions. Dana DeShon commented that it will be really interesting to see the data from the end of 2022, since RSV was found in three and four-year olds. Dr. Jones commented that they are still working on 2022 data, but also would like to see how RSV incidence rates compare to previous seasons.

Epidemiology of RSV in Adults, Michael Melgar, MD, CDC

Dr. Melgar commented that RSV is a frequent cause of severe respiratory illness in older adults, although there is a lower level of awareness in that age group because the focus of RSV is on children. RSV testing is often not performed in adults, frequently resulting in under-detection. Additionally, there is no recommended vaccine or treatment regimen for RSV in adults. Despite the challenges in RSV detection, adults older than 65 years of age reveals about 6,000 – 10,000 deaths annually, about 60,000 – 160,000 hospitalizations, and about 1 – 1.5 million medical encounters each year. These are wide ranges, but we know RSV causes substantial morbidity and mortality in older adults. Dr. Jones shared an analogous pyramid of disease burden of influenza. Generally speaking, the number of RSV in adults is of a similar magnitude, which is usually lower than influenza. However, there is an influenza vaccine that is widely used among older adults and that probably attenuates the annual influenza burden.

The RSV-NET is a CDC population-based hospitalization surveillance system that tracks RSV infections in 12 states. It reveals that RSV hospitalizations in adults rise with increasing age, while hospitalization rates were especially high among adults in their 70s or 80+ years of age. The RSV-NET also showed that the median age for hospitalizations involving American Indian, Black and Hispanic patients was lower than White or Asian/Pacific Islander. RSV also causes a substantial burden of medically attended outpatient visits in older adults. Underlying cardiopulmonary disease, increase the burden by a factor of two. Dr. Melgar discussed that pre-pandemic, RSV hospitalizations in adults peaked in January. However, the COVID-19

pandemic affected incidence, as there were no RSV hospitalizations in the first year and an atypical surge in the summer into the fall of 2022. It appears that RSV seasonality may be gradually returning to pre-COVID-19 pandemic patterns.

Major underlying conditions affect 94% of hospitalized adults; over half of adults have serious conditions like cardiovascular disease, chronic lung disease and diabetes, and a significant number of patients have renal disease, immune compromise, and neurologic disorders. RSV hospitalization rates are much higher in individuals with congestive heart failure, and 14 times higher for those 50-64 years of age with congestive heart failure.

Long-term care facility (LTCF) residents are vulnerable to outbreaks and serious illness. RSV is a frequent cause of symptomatic illness in LCTF residents, including a negative effect on functional status. One study showed that over 13% of all residents at a single facility had symptomatic PCR confirmed RSV in a single month of this outbreak.

In summary, RSV causes severe illness in older adults, adults with co-morbidities, immunocompromised adults, and LTCF residents. RSV hospitalization rates increase with increasing age. Additionally, RSV can cause severe illness in hospitalized adults of any age.

Dr. Melgar concluded their remarks and invited questions. Daniel Boyle commented that he appreciated the comparison between RSV and influenza disease burden in adults. Dr. Melgar commented that influenza, by contrast, is well understood as cause of severe illness in adults, but RSV doesn't get as much attention.

Overview of RSV Vaccine, Sonnie Kim, MS, NIAID

Sonnie Kim described the physical structure of the RSV virion and how the current vaccines developed target specific proteins. Sonnie Kim explained that RSV is the leading cause of acute lower respiratory infection (ALRI) in young infants, but it also impacts elderly and immunocompromised individuals. Globally, there are 34 million RSV-associated ALRI cases, where 10% of these cases would lead to hospitalizations annually, up to 200,000 deaths, and 99% of these cases are in developing countries. In the U.S., 80,000 hospitalizations occur among children less than 5 years of age and 120,000 hospitalizations occur among adults over 65 years of age. There is no approved vaccine and treatment options are limited.

Sonnie Kim reviewed the history of RSV. The virus was originally identified and isolated in 1963, and an early RSV vaccine was tested in the late 1960s. Unfortunately, this unexpectedly resulted in enhanced disease for infants, where infants who were vaccinated and exposed to natural RSV infection developed lower respiratory tract infections resulting in hospitalizations and two deaths. After these infant deaths, research was interrupted until the 1980's when Ribavirin was tested. Unfortunately, it failed to achieve positive results. In 1996, RespiGam was FDA approved, which was a polyclonal antibody. Finally, Palivizumab, a monoclonal antibody, was approved in 1998 by FDA for those at high risk for severe disease.

Sonnie Kim commented on the challenges to vaccine development, including the fact that the mechanism of enhanced disease is unknown; there are multiple target populations (infants, elderly and immunocompromised) that are impacted by the disease; and recurrent infections often occur. Therefore, there are different approaches to vaccine development. Infants at birth and to about three months of age rely on the mother's antibodies; infants from four to six months can be introduced to monoclonal antibodies; and infants six months or older can develop their own immune systems and can get vaccinated, if an RSV vaccine was available.

There were significant advancements in vaccine design by 2010, including research on live attenuated vaccines. Two manufacturers developed promising RSV vaccines, GSK and Pfizer. Pfizer's RSV vaccine for adults over 60 years of age was safe and well tolerated with 85.7% vaccine efficacy. GSK's RSV vaccine in adults older than 60 years, was safe and well tolerated with 82.6% vaccine efficacy. There continues to be a need for more vaccines for the pediatric populations.

Sonnie Kim provided a snapshot slide (updated in January 2023) that shows current RSV vaccine development, their target population, and their current research phase. There are two promising candidates for FDA approval – AstraZeneca's Nirsevimab and Pfizer's RSV maternal vaccine. The latter has shown an 82% efficacy against severe RSV in infants for the first 90 days of life, and a 70% efficacy for the first six months. Sonnie Kim believed that vaccine hesitancy needs to be considered to ensure successful implementation of RSV vaccines. Additionally, RSV needs to be tested more often, similar to flu or COVID-19 tests, so physicians can better consider treatment options. Sonnie Kim's presentation was concluded and invited questions.

Tim Thelen commented that the progression of information about RSV vaccines was helpful to see. Daniel Boyle also found this presentation helpful to better understand challenges in vaccine development. Dana DeShon is excited that RSV prevention is being considered for both children and older populations. Dr. Grimes asked about the Pfizer protein-based F protein formulation noted on one of the slides. He asked if there was a timeline for when that formulation would be close to FDA review. Sonnie Kim responded that although the RSV vaccines point to good vaccine efficacy, more studies are needed to monitor safety. At a recent Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, there was some discussion of vaccine safety and a possible relationship to Guillain Barré Syndrome, the need to establish a history of effectiveness over multiple years, and assess the circumstances that might exist when the RSV vaccine and the flu vaccine are co-administered.

Overview of Dengue Vaccine, Kaitlyn Morabito, PhD, NIH/NIAID

Dr. Morabito explained that DENV is a flavivirus transmitted by mosquitos or ticks. Most of the DENV infections in the U.S. are travel-related, but there has been locally acquired disease in Florida and in U.S. territories. We expect this to increase with climate change. The DENV infection is febrile, and symptoms include headache, eye pain, nausea and vomiting, rash, and joint, bone or muscle pain. It is usually mild, not requiring hospitalization, but it can progress to more severe forms. There is no specific treatment for dengue fever. Care is usually supportive care, including oral or intravenous (IV) hydration, and can often reduce the risk of a fatal outcome from 20% to 1-2%. Severe disease occurs in up to approximately 10% of patients, febrile disease occurs in approximately 20% of patients, and approximately 80% of cases are asymptomatic.

There are many factors that influence the clinical severity of DENV infection – the magnitude of the viremia load, how clinical care is managed, underlying comorbidities, and particularly the patient's immune response. The patient's immunity is a big factor when considering vaccine development, since it could vary if they had a previous DENV infection, the timing between DENV infections, the sequence of DENV infections, and the anti-DENV IgG antibody titer. The complexity of the DENV virus structure makes it very difficult for the antibodies to recognize the real infection threat.

Despite the complexity, pursuing development of a DENV vaccine is worthwhile because of the need to prevent significant illness and morbidity. The most advanced DENV vaccine candidates are quadrivalent, live-attenuated vaccines. There are three vaccine developers (Sanofi, Takeda and NIH/Merck/Butantan/Serum Institute of India) that use different vaccine structures. The Sanofi – Dengvaxia has a Biologics License Application and an ACIP recommendation for use in 9–16-year-old seropositive individuals. The Takeda – QDENGA vaccine is still under FDA and ACIP review. The NIH/Merck/Butantan/Serum Institute of India vaccine is still under Phase III analysis. Research is ongoing to assess immune response to better understand protection.

In summary, severe DENV infection is rare but serious; DENV vaccines prevent significant morbidity; the current live-attenuated vaccines are safe and efficacious in seropositives, and finally, safety and efficacy are less clear for seronegative, and will need to be evaluated for each vaccine. Dr. Morabito's presentation was concluded and invited questions.

During discussion, Dana DeShon asked if the antibody lab test delivered a quantitative result rather than a simple positive/negative result. Dr. Morabito responded that there is no specific value that is known to be protective, although research is ongoing in this area. It is complicated by the fact that infected persons could recover with different levels of antibodies and different serotypes.

Future Agenda Items/New Business

Dr. Grimes invited discussion of future agenda items/new business. Dr. Grimes addressed the question raised by Daniel Boyle at the previous meeting, regarding the process to petition the Secretary and propose regulations to amend the Vaccine Injury Table (Table). Dr. Grimes shared that the ACCV must vote in favor of the plan to send to the Secretary a petition proposing to modify the Table regarding specific injuries, onset periods, or vaccines. The ACCV then must draft the petition and vote in favor of sending it to the Secretary. The final draft of the petition will need to be signed by all voting members of the ACCV and then sent to the Secretary. The Secretary will consider the petition and decide whether to propose regulations to amend the Table. If the Secretary determined that the Table should be modified, the Secretary will initiate the Federal Rulemaking process, which historically has taken over two years because it includes the development of a Notice of Proposed Rulemaking, a 6-month public comment period and a public hearing, and a Final Rule addressing public comments. If the Secretary determines that the Table should not be modified, then a notice must be published in the Federal Register stating the reasons for not conducting the Federal rulemaking.

Dr. Grimes affirmed that if additional information was deemed appropriate, an agenda item would be the proper next step. Daniel Boyle indicated an interest in proceeding with that next step. Dr. Grimes explained that the motion could be to simply discuss the issue at the next meeting, or the motion could be to obtain more information prepared by staff or schedule a presentation on the matter. A separate motion would be required to act on the information/presentation. The ACCV made a motion and took a vote to discuss brachial neuritis (also known as Parsonage Turner Syndrome or neuralgic amyotrophy) being added to the Table for influenza vaccines at one of the September 2023 meetings. Daniel Boyle specifically requested for data and research on the influenza vaccine and the prevalence of incidents of

developing brachial neuritis. The ACCV made a motion and took a vote for more information to be presented at the September meeting. Research presentations and discussion will be added as agenda items.

Public Comment

Dr. Grimes invited public comment. One comment was made by Theresa Wrangham, the Executive Director for the National Vaccine Information Center (NVIC). Theresa expressed concern that a current ACCV member is not chairing the meeting and that there continues to be many vacancies on the ACCV. Theresa Wrangham thanked all guest presenters but brought concern around the dengue vaccine. The CDC previously presented that vaccine-induced hospitalization from dengue vaccines would be delayed. This was raised as a concern since the timeframe of vaccine-induced hospitalizations would possibly conflict with the statute of limitations on filing a VICP claim. Additionally, Theresa Wrangham shared that NVIC encourages the ACCV to look at the research gaps highlighted by the Institute of Medicine vaccine safety reports that previously were shared to the ACCV. The Government Accountability Office has also issued more than one report on the lack of expansion of the Table as contributing to the backlog. The NVIC encourages the ACCV to look at recommendations from the Institute of Medicine in 2005 relating to data sharing program with the CDC's Vaccine Safety Data Link to see if these barriers have been resolved. There were no additional comments requested by the public.

Dr. Grimes invited a motion to adjourn. On motion duly made and seconded, the meeting was adjourned.