MAYO CLINIC

Routine Childhood Vaccines Given From 1 through 18 Years of Age

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Abstract

In addition to the vaccines due in the first year of life, the US Advisory Committee on Immunization Practices recommends that children continue to receive vaccines regularly against a variety of infectious diseases. Starting at 12 to 15 months of life, these include the two-dose measles-mumps-rubella vaccine series and the two-dose varicella vaccine series. Also in the second year of life, infants should begin the two-dose hepatitis A vaccine series and complete the *Haemophilus influenzae* type B vaccine series as well as the pneumococcal conjugate vaccine series. Before 19 months of life, infants should receive the third dose of the poliovirus vaccine and the fourth dose of diphtheria-tetanus-acellular pertussis (DTaP) vaccine. The final doses of poliovirus and tetanus-diphtheria-acellular pertussis vaccines are both due at 4 to 6 years of life. Before each influenza season, every child should receive the influenza vaccine. Those less than 9 years of age who previously received less than two doses need two doses a month apart. At 11 to 12 years of life, all should get two doses of the human papillomavirus vaccine, the adolescent/adult version of the tetanus-diphtheria-acellular pertussis vaccine, and begin a two-dose series of meningococcal ACWY vaccine. Each of these vaccines is due when the vaccine works to protect against both an immediate risk as well as to provide long-term protection. Each vaccine-preventable disease varies in terms of the nature of exposure, the form of the morbidity, the risk of mortality, and potential to prevent or ameliorate its harm.

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As noted in the thematic review entitled "Routine Childhood Vaccines Given in the First Eleven Months of Life,"[1] US public health officials identified routine childhood immunizations as one of the most important public health achievements of the 20th century and again in the first decade of the 21st century.[2-4] Throughout that time and even since, the routine childhood immunization schedule has evolved with new additions of vaccines to that schedule as well as important revisions to the timing and dosing of well-established routine childhood immunizations.[5] This thematic review surveys those routine child immunizations given starting at 12 months of life and continuing through age 18 years (Table 1).[6] While the World Health Organization (WHO) has adopted international standards for routine childhood immunization,[7] the framework presented here will reflect the routine childhood immunization as recommended by the US Advisory Committee on Immunization Practices (ACIP),[5] and the data regarding those immunizations will reflect US epidemiology[8,9] and US uptake.[10] For each routine immunization recommended, the review will examine what the ACIP recommends, why the ACIP recommends what it recommends, what that immunization has accomplished, where the recent developments have occurred, and what still needs to be done.

MEASLES

Measles or rubeola infection causes a severe acute illness characterized by a prodrome of fever, cough, coryza, and conjunctivitis.[8] This prodrome is followed by a high fever and a generalized rash that spreads centripetally from face to trunk to limbs along with malaise, lethargy, and the appearance of pathognomonic Koplik spots on the buccal surfaces of the oral mucosa. In 2019, the United States suffered the largest number

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of measles cases since 1992 with 1249 cases of measles reported in 22 separate outbreaks in 31 states.[11] Ten percent were hospitalized and 20% of these were infants less than 12 months of age. Five percent had pneumonia. One had encephalitis. No deaths were reported although the overall death rate is 0.2%.[8,11] Sequelae include commonly persisting mild to moderate immunosuppression[12] and rarely subacute, sclerosing panencephalitis.[8] The infection is highly contagious and is the most contagious disease known. Ninety percent of susceptible individuals exposed to an individual sick with measles will contract the infection.

The virus is spread by airborne droplet nuclei, the dried residua of exhaled respiratory droplets, that can remain suspended in the air, and, the case of measles, infectious for up to 2 hours after the infected person has left the area.[8] Susceptible individuals exposed become contagious from the time they develop a prodrome of fever followed by cough, coryza, and conjunctivitis preceding the rash for 2 to 4 days and remain contagious for 3 to 4 days after the rash appears.[8] Before universal vaccination, all children eventually developed measles as preschoolers or as young school-aged children. Maternal immunity from the wild form of the virus provided passive immunity that protected most infants until their second year of life. Universal vaccination begun in the 1960s combined with public health efforts to identify and manage cases and their contacts resulted in the elimination of endemic measles from the United States in 2000. Since then, outbreaks have occurred sporadically across the United States and chains of infection from person to person have not been sustained over a year. All cases occurring are believed to have been either directly imported from international travel or the result of contagion from those imported cases.[8,11] In 2019, 89% of the 1249 cases were either unvaccinated or had an unknown vaccine status.[11] Among the 81 internationally imported cases that led to the 22 outbreaks, only 10% were known to be vaccinated against measles.

Current recommendations call for all infants to undergo immunization against measles, starting the two-dose series at 12 to 15 months of life, when passively received immunity from the mother via the placenta has waned to the point that it does not interfere with the vaccine's immune response.[13] The child should receive the second dose at 4 to 6 years of age before beginning elementary school. The vaccine series is 98% effective and studies show that waning is rare and that the immunity persists apparently for life.

The vaccine is a live, attenuated viral vaccine generated from the Edmonston-B strain of measles.[14] One manufacturer is licensed in the United States to make the measles-containing vaccines—Merck & Co (Kenilworth, NJ). Measles-containing vaccines include both a measles-mumps-rubella (MMR) vaccine and a measles-mumps-rubella-varicella (MMRV) vaccine.[15] Whereas combinations in general are preferred over individual components because of the increased risk of fever and thus febrile convulsions in children in the first few years of life, experts recommend either using the MMR vaccine at 12 to 15 months for the first dose or counseling the parents regarding the increased risk of fever and thus febrile convulsions if using the MMRV formulation as the first dose at that age.[13]

Universal vaccination against measles in children began in 1963. Along with the live form of vaccine, an inactivated form of measles vaccine was available for use in the United States from 1963 to 1967 but was removed from the market with the rise of concerns for failure to protect against measles and for an apparent atypical measles syndrome that would result following exposure to the measles virus.[16] It remained in use in other countries in the early 1970s. For the live viral vaccine, initially one dose was recommended starting at 9 months but it was recognized maternal immunity from past measles infections interfered and the timing was moved to 12 months and then 15 months of age.[17] Later when most women bearing children had measles immunity from vaccine rather than disease, that age was moved to 12 to 15 months.[16] Furthermore, outbreaks beginning in the late 1980s and

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

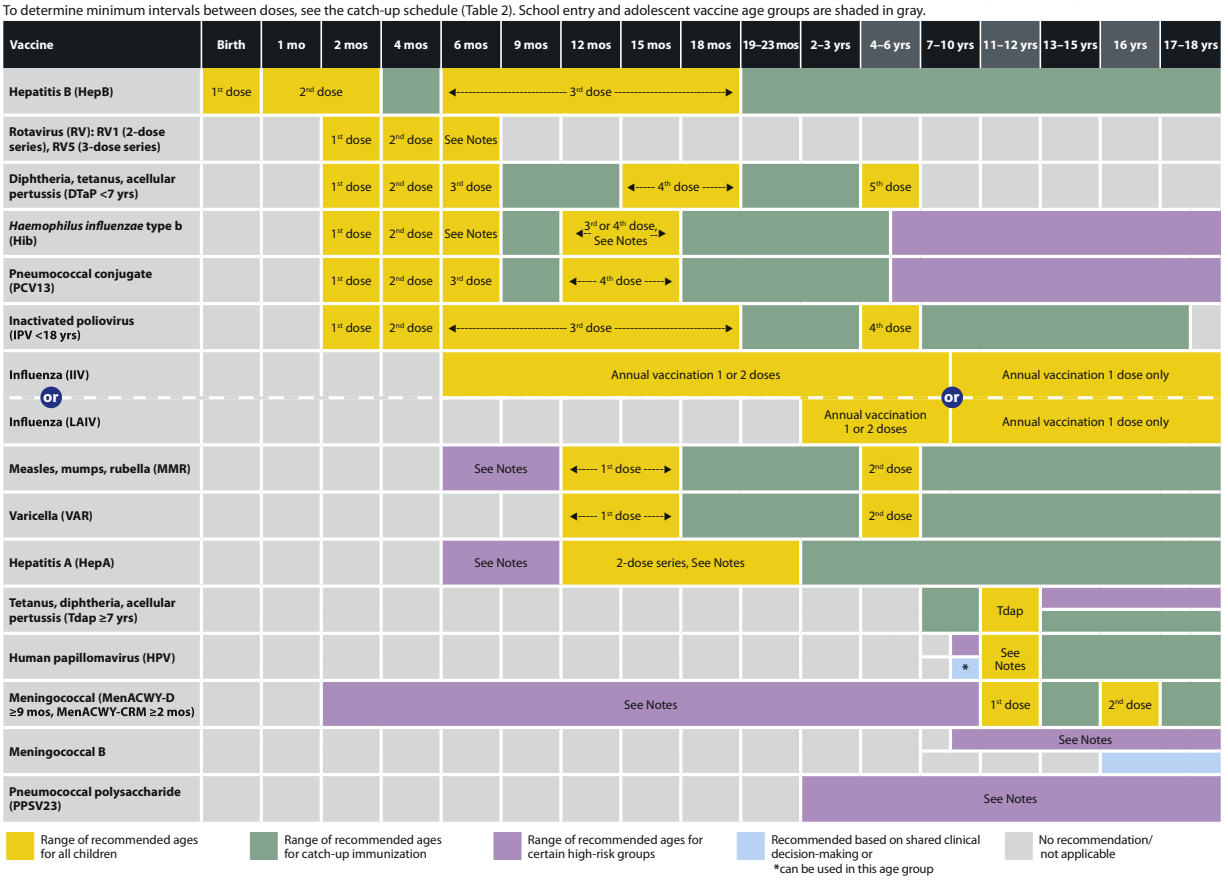

TABLE 1. Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2020. Reproduced from Centers for Disease Control and Prevention.[6] LAIV = live attenuated influenza vaccine. To view the notes mentioned mentioned in the table, access the original source referenced.

early 1990s led to the universal adoption of a second dose at 4 to 6 years of life to address the need to achieve a herd immunity of more than 90%.[16] In 2017 in the United States, 91.5% of children 19 to 35 months of age had received the first dose of MMR,[18] and 94.7% of those entering kindergarten had received the two doses due.[19]

Recent developments in the prevention of measles include both global efforts to eradicate measles as well as efforts in the United States and other developed nations to address vaccine hesitancy.[11,20] Before the 1980s, perhaps 2 million children died each year worldwide from measles.[21] Beginning in the 1980s, the WHO has led efforts to ensure worldwide measles vaccination. Global vaccination efforts have been hampered by the temperature lability of the vaccine and the need to maintain the cold chain from manufacture through shipping and onsite storage before administration. Since 2015, 85% of the children across the world have received one dose of a measles-containing vaccine but only 61% have received two doses. A reported 254,928 children died of measles in 2015 worldwide, remarkably far less than the 2 million a year pre-1980s.

The vaccine hesitancy specific to the MMR vaccine has been driven by large part around the world from false claims made

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by Andrew Wakefield and others regarding the safety of the MMR vaccine and claims it causes or aggravates autism spectrum disorder.[22] Dozens of studies conducted across the world over the past 2 decades since the claim was first made has shown no such association; the most recent of these studies was published in 2019, a Danish cohort study of 657,461 children.[23] In the United States, outbreaks have begun with international travel, of primarily unvaccinated travelers, and have been sustained primarily in communities with lower rates of measles vaccination.[11] Education alone has been found to be futile or even counterproductive in battling vaccine hesitancy.[24-26] Evidence instead supports population health management strategies including school and daycare mandates and clinical efforts with strong provider recommendations.[27]

MUMPS

Mumps infection can range from causing no symptoms at all to a vague, brief febrile illness, to a severe acute febrile illness characterized by parotitis and other glandular inflammation.[8] Before the vaccine era, it was reported that 15% to 27% of persons infected with mumps did not show any symptoms or signs of infection.[8] Whether symptomatic or not, affected individuals can spread the illness through salivary secretions. Complications include orchitis, mastitis, oophoritis, and meningitis. Sequelae include hypoplasia of the testes and decreased sperm count. Few infected require hospitalization. The infection is highly contagious with a similar infectivity as influenza. Before universal vaccination, many children developed mumps in the first 10 years of life. Maternal immunity from the wild form of the virus provided passive immunity that protected most infants until their second year of life.

Universal vaccination began in 1967 and resulted in a dramatic reduction of childhood cases.[8] Up until recently, cases in the United States only occurred among the unvaccinated.[28] Current recommendations call for all infants to undergo immunization against mumps, starting the two-dose series at 12 to 15 months of life, when maternal immunity has waned to the point that it does not interfere with the vaccine's immune response.[13] The child should receive the second dose at 4 to 6 years of age before beginning elementary school. One dose is thought to be 78% effective and two doses 88% effective.[8] Studies show, unlike measles, that waning is common and in recent outbreaks most of the college-aged individuals acquiring mumps have had two doses previously.[29]

The vaccine is a live, attenuated viral vaccine generated from the Jeryl-Lynn strain of mumps.[14] One manufacturer is licensed in the United States to make the mumps-containing vaccines—Merck & Co. Thus, mumps-containing vaccine is available in the form of the MMR and MMRV vaccines previously mentioned.[14,15]

Recent developments in the prevention of mumps concern the substantial number of outbreaks involving dozens or hundreds of individuals.[30] Since 2015, approximately 150 outbreaks of mumps have occurred in the United States resulting in at least 16,000 cases, primarily among adolescents and adults in athletic events, schools, and universities.[30] These cases were routinely occurring among those who previously received two doses of mumps-containing vaccine. Complications from mumps among those previously vaccinated occurred at lower rates than reported in the pre-vaccine era. In contrast, a recent outbreak in previously unvaccinated adults resulted in high rates of complications, more typical of the pre-vaccine era.[31] In the past year, between September 1, 2018, and August 22, 2019, nearly 900 adult migrants detained in 57 US facilities in 19 states had confirmed or probable mumps.[30] An additional 33 detention center staff members also contracted the disease. A third dose among those previously vaccinated has been used in outbreaks, and records show a reduction of cases following the introduction of the third dose.[29] However, only in one study was this reduction found to be statistically significant. Studies of antibodies produced from the third dose indicate the increase in

seropositivity was short lived and measured antibody levels returned to baseline in approximately 1 year after vaccination. Current recommendations limit the use of a third MMR dose for the prevention of mumps to only be used in local outbreaks when directed by public health authorities for those at increased risk for exposure.

RUBELLA

Rubella causes a mild, acute febrile illness characterized by a faint maculopapular rash beginning on the face and progressing down the body.[8] Fifty percent have no symptoms at all, and the infection often goes undiagnosed.[8] The infectious illness carries the name of German measles because of similar characteristics to measles, but it is a much less severe illness. The primary concern with rubella is that it can cause a severe congenital infection resulting in miscarriage, stillbirth, or congenital rubella syndrome including blindness, deafness, and cognitive impairments. Before routine vaccination, most children acquired the condition and subsequent exposures of non-immune, pregnant women led to congenital rubella syndrome.

Current recommendations call for all infants to receive vaccination against rubella with the combination MMR vaccine given at 12 to 15 months of age and then again at 4 to 6 years of age.[13] A single dose is 97% effective, and following two doses 91% to 100% still have measurable antibody 12 to 15 years later.

The current rubella vaccine virus is a live, attenuated virus generated from the RA 27/3 strain of rubella.[13] One manufacturer is licensed in the United States to make the rubella containing vaccines—Merck & Co. The vaccine is contained in the MMR and MMRV vaccines previously discussed.[14,15]

Universal vaccination against rubella in children began in the United States in 1969 to 1970.[8,32] The original live vaccines were eventually replaced in 1979 with the RA 27/3 strain, which produced more measurable antibody, a more persistent immunity, better herd immunity, and less joint symptoms.[32] This was given as a single dose at 15 months of age previously, but outbreaks of measles beginning in the late 1980s and early 1990s led to the universal adoption of a second dose at 4 to 6 years of life.[8] Endemic transmission of rubella was verified as eliminated in the United States in 2004 as a result of high levels of coverage with MMR.

As recently as 2017, however, an infection in a US resident pregnant at 19 weeks gestation demonstrates the problem with continued rubella infections worldwide where rubella is still endemic and where worldwide travel places US residents at risk.[33,34] In this case, the pregnant woman had previously refused the rubella vaccine. She had not traveled outside the country, but her brother, a 22-year-old, had traveled to India and stayed with her 4 weeks prior. He had a rash at the time that was previously diagnosed as poison ivy. Both tested positive for rubella by serology. The pregnant woman had previously tested negative in the first trimester. Fortunately, while the baby did test positive for rubella immunoglobulin M at birth, the baby's testing by physical exam, echocardiogram, skeletal radiographs, head ultrasound, audiometry, and ophthalmology exams were all normal. Countries that still vaccinate only adolescent females still have endemic rubella.[35,36] However, not every female responds to the vaccine and not every female receives the vaccine. Such outbreaks have led to cases of congenital rubella syndrome.

CHICKENPOX

Chickenpox or varicella was once a universal infection that most children living in temperate zones acquired often in school age.[8] Typically, a prodrome of fever leads to a generalized, pruritic rash characterized by papules, vesicles, and crusted-over lesions lasting 4 to 7 days. Otitis media or impetigo often complicates the infection; more rarely, pneumonia, hepatitis, or encephalitis can be complications. Most children recover completely, but the disease can cause a disseminated varicella syndrome in those who are immunocompromised by disease or medication. The infecting virus never really clears completely but establishes a latent infection in the dorsal root ganglia and re-emerges as zoster (shingles) later in life.

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The virus causing chickenpox and shingles is a member of the herpes virus family.[8] The viral infection is spread by respiratory droplets and is quite contagious. Seventy-percent of non-immune individuals will acquire the infection when exposed in the household. The patient is most contagious in the first days of the prodrome and remains contagious until all the lesions are crusted over, approximately 5 to 7 days after the rash first appears.

The vaccine is a live, attenuated vaccine using the Oka strain.[37] Although the vaccine was first developed in 1974, it was not licensed in the United States until 1995 when it was universally recommended for all children 12 to 18 months of age with catch-up through 12 years of age.[38] Outbreaks in preschool and school despite high levels of vaccination led to recognition of both primary and secondary vaccine failure and resulted in the universal recommendation of a second dose given at 4 to 6 years of age and catch-up for individuals 13 years and older who lacked evidence of immunity. Since the adoption of the second dose, chickenpox outbreaks have become a rare occurrence and a reportable condition in most states in the United States.[8] Evidence from patients vaccinated against chickenpox indicates that the vaccine not only prevents chickenpox but also adult-onset shingles.[39] As mentioned previously, MMRV combines the MMR and varicella vaccine and is routinely recommended and preferred for those 4 to 6 years of age for the second dose of varicella vaccine.[15]

A persisting concern is that, as varicella is no longer as common as a childhood infection, those who are not vaccinated and therefore not immune against chickenpox may only be exposed as adults.[40] Adults have a more severe case of chickenpox than children. Although antivirals have been proven effective in preventing infection after exposure and reducing the severity of chickenpox if it develops, it behooves health care providers to make strong recommendations for routine varicella vaccination for all of their patients who are non-immune. Furthermore, other countries have held off on routine childhood vaccination against chickenpox for fear that the reduction of subclinical exogenous exposure to varicella infection among those with latent varicella zoster infections would result in more outbreaks of herpes zoster, but studies in countries such as the United States that vaccinate in childhood against chickenpox have not shown evidence that would support that concern.[41]

HEPATITIS A

We vaccinate routinely to prevent two major forms of hepatitis — hepatitis A and hepatitis B.[1] With hepatitis B, we begin vaccination at birth to protect that infant from the development of chronic hepatitis, cirrhosis, and cancer. Hepatitis A is a very different issue for infants and preschool children.[8] Unlike hepatitis B, transmitted by blood, at parturition, or through mucosal contact, hepatitis A is transmitted by the fecal-oral route. Most infants who develop hepatitis A infection develop no symptoms or signs but can expose those caring for them during diaper changes. Adults can develop a severe infection with fever, chronic abdominal pain, nausea, vomiting, malaise, and lethargy combined with jaundice lasting weeks. Such infections resolve without risk of a chronic phase and without increasing the patient's risk for cirrhosis or hepatocellular carcinoma. Rarely the acute infection can result in fulminant hepatitis leading to death.

The hepatitis A vaccine is a recombinant viral protein vaccine given intramuscularly as two or three doses depending on the vaccine's formulation. In the United States, infants receive a two-dose formulation with the first dose at 12 to 24 months of life and the second dose 6 to 18 months later.[42] Merck & Co manufactures VAQTA.[43] Glaxo-Smith Kline manufactures HAVRIX.[44] While the ACIP prefers the series be completed with the same brand used for the first dose, the ACIP recommends the patient not delay in completing the series and use the brand available rather than delay. The vaccines apparently give lifelong immunity. Infants younger than 12 months have a relatively poor response to the hepatitis A vaccine. While it is recommended for international travel to countries where the disease is endemic, a single dose given between 6 to

12 months does not count toward the two dose series, which should be begun at 12 months regardless of the interval between the pre–1-year-old dose and the current dose due.[45]

In 1996, the ACIP recommended vaccination of those at increased risk for hepatitis A.[42] Programs of routine infant immunization began first in 1999 in those states and territories with higher hepatitis A rates. Later, in 2006, that was broadened to include all of the United States. Routine vaccination in the United States of 1-year-old infants has proven effective in reducing symptomatic hepatitis A among adults and dramatically reducing the number of reported cases each year as well as the number of outbreaks.[46] Rates of reported acute hepatitis A have dropped from 11.7 cases per 100,000 in the United States in 2006 to 0.4 cases per 100,000 in 2011.[47]

Hepatitis A vaccination rates lag behind other infant vaccination rates.[46] Among those US children 19 to 35 months of age in 2017, only 86.0% had received the first dose of hepatitis A vaccine compared with 91.5% who received the first dose of MMR.[18] Currently, 30 states are reporting ongoing outbreaks of hepatitis A primarily among the homeless and drug users with 27,634 cases, 16,697 hospitalizations, and 275 deaths since 2016 as of November 1, 2019.[48] New recommendations now identify homeless adults and children at risk and call for vaccination for them if not previously vaccinated.[49] The ACIP has also voted to approve catch-up of all children through 18 years of age, now official this year with the recommendation is published in the MMWR.[50]

INFLUENZA

Influenza is an upper respiratory illness characterized by an acute onset of fever, cough, and pharyngitis.[8] In the 2017–2018 season, 20.0% of children 0 to 4 years of age developed influenza as compared with 14.0% of children 5 to 17 years of age. This resulted in a medical visit for 13.4% of children 0 to 4 years of age and 7.3% of children 5 to 17 years of age. The hospitalization rate in that season for children 0 to 4 years of age was 139.3 per 100,000 as compared with 38.3 per 100,000 for the older children. The mortality rate is 0.6 per 100,000 among children 0 to 4 years of age and 0.9 per 100,000 among children 5 to 17 years of age.

The thematic review of childhood vaccinations for those younger than 12 months of age described the virus as well as the inactivated trivalent and quadrivalent vaccines licensed for infants less than 12 months of age.[1] The ACIP recommends routine vaccination for everyone every fall.[51] To assure immunity in time for exposure, health care providers should begin vaccinating against influenza by the last week in October. Children less than 9 years of age who have not previously received the influenza vaccine should receive two doses no closer than 28 days apart to assure immunity for the upcoming season. Unfortunately, here in the United States many children who are due for two doses of the influenza vaccine do not receive both doses that season. In the most recent US study published in 2011–2012, only 44.7% of children 6 to 24 months of age had received the two doses they were due.[52]

The formulation and dosing of influenza vaccine available to children 12 months through 23 months of age is identical to infants 6 through 11 months of age.[1] Starting at 24 months of age, however, children who are otherwise eligible may receive their influenza vaccine in the form of a cold-adapted, live attenuated influenza vaccine administered intranasally.[51] The only formulation of this vaccine in the United States is a quadrivalent version containing cold-adapted, attenuated viruses providing immunity against the two circulating A strains (H1N1 and H3N2) and the two B strains.[53] The cold-adaptation results in these attenuated vaccine viruses having the ability to replicate at room temperature but not at body temperature.[54] Thus, the vaccine administered intranasally cannot disseminate and cause a generalized infection. Nonetheless, limited pre-licensure testing in children and adults that excluded those at increased risk from complications to influenza has resulted in the ACIP recommending the use of the live vaccine only with precaution in children and adults 2 through 49 years of age at increased risk from complications of influenza.

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Furthermore, ACIP lists as a contraindication for theoretical reasons the use of the live vaccine in those who are pregnant or immunocompromised. It was not tested in either group. Testing in infants younger than 2 years of age showed that the vaccine did not create sufficient immunity. Similar testing in adults older than 49 years showed the same. Furthermore, testing in children younger than 5 years of age with a history of asthma or wheezing showed an increase in outcomes of acute bronchospasm and thus the vaccine is contraindicated in those with asthma or a history of wheezing among those less than 5 years of age. Asthma is a condition that increases the risks for complications from influenza. Precautions in using this vaccine include asthma among those 5 years and older for theoretical reasons. Empirical evidence did not demonstrate problems among individuals with asthma.[55]

Most influenza vaccines used are generated using chicken eggs including the live attenuated influenza vaccine.[51] The ACIP states that persons with egg allergies of any severity may receive any of the egg-based influenza vaccines including the live attenuated influenza vaccine. The ACIP recommends those individuals with severe egg allergies should be vaccinated in outpatient or inpatient settings supervised by health care personnel skilled in managing a severe allergic reaction.[51] However, the data show no increased risk of allergic reaction to the influenza vaccine no matter the severity. The data include 28 studies of 4315 egg-allergic individuals including 656 who had severe egg allergies.[56] The Influenza Vaccine and Egg Allergy Practice Parameter Workgroup was commissioned by the Joint Task Force on Practice Parameters, and both hold that the evidence is strong that egg allergic patients regardless of the severity can receive egg-based influenza vaccines and that no special precautions should be taken, even with those with severe egg allergies, as such precautions would pose unnecessary barriers to timely vaccination.[56] The American Academy of Pediatrics holds the same position.[57]

Before the 2009 pandemic, the live attenuated influenza vaccine appeared to outperform the inactivated influenza vaccine at least in children for H1N1, H3N2, and B strains and performed as well in young adults.[58] But post-pandemic in 2012−2013 and 2015−2016 seasons, the vaccine did not appear to consistently perform as well as the inactivated influenza vaccine especially for pandemic H1N1.[58] The US ACIP did not recommend the live attenuated influenza vaccine in 2016−2017 and in 2017−2018 because of those data.[58,59] The manufacturer made changes both to the viral strain used for the pandemic H1N1 strain as well as to the manufacturing process, and a randomized controlled trial comparing the new formulation to the older formulation showed improved immunogenicity.[60,61] Data from previous seasons through 2015−2016 as well as a systematic review showed that the live attenuated influenza vaccine performed comparably to the inactivated influenza vaccines for the H3N2 and B strains.[60,62] That combined with the data from the aforementioned trial led to the ACIP reinstating its recommendation without preference in 2018−2019 and again in 2019−2020.[51,60,62]

Despite years of having a recommendation for universal, annual influenza vaccination, the United States fails each year to meet its national goals. For children 6 months through 17 years of age, that goal is 70%.[63] We are making progress, however. In the 2018−2019 season, 62.6% of children 6 months to 17 years of age received one dose of vaccine compared with 51% in the 2010−2011 season.[64]

HUMAN PAPILLOMAVIRUS

Oncogenic strains of human papillomavirus (HPV) cause an asymptomatic infection of the mucosal tissue that can persist for months to years, usually resolving in 1 to 2 years, during which it is contagious.[8] Infrequently the infection does not resolve but persists and over years causes cellular dysplasia and eventually cancers. The most common sites of infection are the anogenital area including foremost the cervix in females and the oropharyngeal area. Thus, the cancers that the infection causes include cervical

cancer, oropharyngeal cancer, anal cancer, penile cancer, vulvar cancer, and vaginal cancer. Other strains of HPV can result in warts including the genital mucosa surfaces.

Viral infections with the oncogenic strains of HPV are common.[8] An estimated 79 million individuals in the United States currently have an anogenital HPV infection. For most individuals these infections last a few years. Each year 14 million individuals develop new infections. Half of these new infections occur among individuals 15 to 24 years of age.[8] Forty percent of individuals are infected within 24 months of their first sexual intercourse.[8,65] Again, while most of those infected clear the infection in a couple of years, some go on to develop dysplastic changes leading to cancers.

The Centers for Disease Control and Prevention estimate that HPV causes 34,800 cancers in the United States each year.[66] These include 20,700 in females and 14,100 in males. Of the 34,800 cancers, 13,500 occur in the oropharynx, with 2200 in females and 11,300 in males. An additional 10,900 occur in the cervix. The remainder occurs in other anogenital organs.

The virus is a DNA virus that has no other hosts than humans.[67] More than 100 strains exist. Some are responsible for nonmucosal cutaneous common warts, others for genital warts, and still others for cancers. They spread by direct contact. Those that cause anogenital and oropharyngeal cancers are spread by direct mucosal contact. Immunity to these viruses are strain specific. The nonavalent vaccine currently in use in the United States is manufactured by Merck and consists of recombinant L1 particles from the virus capsid that reassemble into spheres containing no DNA or RNA.[68] Seven of the vaccine strains are directed against genital lesions, and two of the vaccine strains protect against viruses that cause genital warts. Thus, they mimic the viral shell without causing infection. The vaccine has proven highly immunogenic particularly in younger individuals and efficacious in trials and effective in experience in preventing infection, dysplastic changes, and cancers.

ACIP recommendations call for all children at 11 to 12 years of age to receive the vaccine with catch-up recommended both males and females through 26 years of age.[69-71] The recommendations provide permission to start as young as 9 to 10 years of age. Immunocompetent individuals receiving the first dose before age 15 years need only two doses 6 months apart.[70] Those beginning the series at 15 years of age or older and those who are immunosuppressed at any age need three doses to achieve immunity with the second dose 1 to 2 months after the first and the third 6 months after the first.

Uptake with the vaccine in the United States has been disappointing. While the vaccine was introduced at the same time as the adolescent-adult formulation of the tetanus-diphtheria-acellular pertussis (Tdap) and the quadrivalent meningococcal (MenACWY) vaccines also recommended routinely at 11 to 12 years of age, the uptake of the HPV vaccine has lagged.[72] In 2018, among 13- to 17-year-old adolescents across the United States, 51.1% had completed the HPV vaccine series as contrasted to 88.9% who received their Tdap vaccine due at 11 to 12 years and 86.6% who received the first dose of the MenACWY vaccine also due at 11 to 12 years of age.

Initially in 2007 the vaccine was only recommended in females.[73] It was only later recommended in males in 2012, resulting in further lags specifically with males.[72,74,75] In 2018, 53.7% of US females 13 to 17 years of age had completed the HPV vaccine series in contrast with 48.7% of US males of the same age.[72] The gap has been closing steadily.

Part of the problem with lag between HPV and the other adolescent platform vaccines is the lack of visits to health care providers made by adolescents. In a large study of 15% of all adolescents in Minnesota regardless of private or public insurance, few had preventive care visits at all.[76] One-third of adolescents 11 to 18 years of age observed for 4 or more years had no such visits and another 40% had only one. Non—preventive care visits averaged 1 a year. The second dose of MenACWY vaccine recommended at 16 years of age similarly lags. Only 38.6% of adolescents at 17 years of age have received both

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of the MenACWY vaccine doses in the series.[72] But this would not explain the relatively lower rates of HPV vaccine initiation as compared with Tdap and the first dose of MenACWY. One glaring issue is the failure for providers to recommend the vaccine.[77,78] Parents express hesitation and base plans not to vaccinate their children against HPV for concerns of the lack of provider recommendation, safety, lack of perceived need, concern for the youth of their children, and other concerns.[79]

Current work is underway across the country to identify successful measures to improve HPV vaccination rates. Only two states call for the vaccine as part of their school-mandated vaccines.[80-83] They enjoy much higher rates of HPV vaccination rivaling Tdap and MenACWY. Efforts include teaching providers to make strong recommendations as well as take advantage of other systems approaches to improve vaccine uptake including reminder recalls, point-of-care prompts, reduction in out-of-pocket expenses, and school-based delivery.[84]

MENINGOCOCCUS

Meningococcus can cause severe bacterial infections including meningitis and sepsis.[8] Although rare, the bacterial infections are life-threatening even when identified within hours of onset. Approximately 15% die from the infection and another 15% suffer permanent disability from loss of limb or other organs affected by gangrene.

Neisseria meningitidis is a Gram-negative bacilli that has only human hosts.[8] Meningococcal bacteria are spread person-to-person through droplets; thus, kissing, sharing cigarettes, and sharing drinkware are modes of contagion. Host risk factors include immunosuppression, cerebrospinal fluid leaks, and splenic dysfunction. Outbreaks typically occur among older adolescents and young adults.

The current vaccines recommended for routine use in adolescents in the United States are Menactra and Menveo, and they are directed against strains A, C, W135, and Y.[85-87] They are conjugated polysaccharide vaccines, which like the *Haemophilus influenzae* type b vaccine and the 13-valent pneumococcal conjugate vaccines, rely on conjugation of the polysaccharide antigen to a protein to generate immunity.

Recommendations call for the universal vaccination of all children 11 to 12 years of age against strains A,C, W135, and Y with a booster at 16 years of age using either the Menactra or Menveo vaccines.[85] As mentioned above, although we have achieved high rates of vaccination with MenACWY at 11 to 12 years of age with successful reduction of disease through the first 5 years of adolescence, we are not achieving high rates of uptake with the second dose.[72] Enforcing school mandates with the second dose will drive rates upward. Thirty-seven states have school mandates for the meningococcal vaccine, but only 17 require the booster.[88]

Work to be done includes solving the uptake problem of the quadrivalent vaccine dose due at 16 years of age. Whereas the dose at 11 to 12 years of age has reached the Healthy People 2020 goals of 80%, the booster dose lags with rates similar to initiation and completion of HPV vaccine and influenza vaccine.[72] Among adolescents 13 to 17 years of age, 86.6% have received one dose but only 50.8% of the 17-year-olds have received both doses due. Again, adolescents rarely have encounters with health care providers and when they do they are for the large part not health maintenance visits.[76] Health care providers should work hard to use every visit to recommend to the parent and adolescent the vaccines due at every visit.

Two other protein-based vaccines protect against the B strain—Trumenba and Bexsero.[89,90] These have risk-based recommendations for use but are not recommended for universal use in all adolescents.[91,92] The Trumenba and Bexsero meningococcal conjugate vaccine serotype B vaccines are not routinely recommended as the rates of meningococcal B strain disease are so rare as to not justify the use of either of these vaccines in light of our limited understanding of their efficacy and the duration of the immunity they impart.[92] Instead, the ACIP gives direction to health care providers to make parents and young adults aware of the vaccine and offer them a choice of vaccinating or not. The ACIP

directive includes patients 16 through 23 years of age with the suggestion that 16 through 18 years of age would represent the best timing of the vaccine. Bexsero is recommended as two doses 1 month apart. While Trumenba is recommended in outbreaks and for those at high risk as a three-dose series administered at 0, 1 to 2, and 6 months, for these healthy adolescents and young adults not at increased risk and not involved in an outbreak, it can be given as two doses 6 to 12 months apart.[93] The two vaccines are not interchangeable, and the series must be completed with the same brand.

TETANUS-DIPHTHERIA-PERTUSSIS

The companion review described the diseases tetanus, diphtheria, and pertussis as we begin vaccinating against those diseases in infancy.[1] Children are to receive boosters of the pediatric version of that vaccine, the same one given in infancy at 12 to 15 months and again at 4 to 6 years of age.[94] At 11 to 12 years of age they are to receive one more boosting vaccine but with a differently configured dosing with lower amounts of diphtheria toxin and pertussis antigen.

At 12 to 15 months the diphtheria-tetanus-acellular pertussis (DTaP) vaccine can be given separately as DTaP or in combination as Pentacel or DTaP—inactivated polio vaccine (IPV)/*Haemophilus influenzae* type b.[5] Experts, public health officials, health care providers, parents, and patients prefer combinations because they reduce the number of injections and therefore pain, and allow for more efficient vaccination while maintaining vaccine effectiveness and safety.[95] Because of the licensure requirement that the effectiveness of the combination be equivalent or superior to the individual components, many vaccines cannot be combined. Combinations such as Pentacel are so valued for their ability to reduce injections and dosing problems that the ACIP permits the extra-immunization with IPV that results at 6 months as the result of the combination.

Similar combinations exist for the dosing of DTaP at 4 to 6 years of age.[94] While the vaccine can be given as an individual vaccine of DTaP, two manufacturers make a combination for this age group combining DTaP with a poliovirus vaccine recommended specifically for this age group — Kinrix and Quadracel. This reduces the number of injections necessary at 4 to 6 years of age.

One more routine booster is due at 11 to 12 year of age and is accomplished with the adolescent/adult formulation of Tdap.[94] In this version, the amount of diphtheria toxoid is reduced as are the panel of pertussis antigens contained. These reductions are designed to reduce reactivity and thus permit acceptability in this older age group. This Tdap is the same dose used in the 7- to 10-years of age catch-up as well as in adults who have not previously received a Tdap dose as well as in pregnancy.

This use of Tdap at 11 to 12 years of age provides sufficient decade-long immunity against diphtheria and tetanus.[94] However, those suffering puncture wounds, deep extensive wounds, and missile injuries should get a repeat tetanus-diphtheria as part of the wound care if the patient last received the tetanus-containing vaccine more than 5 years ago. The pertussis antigens at this lower dose however only provide measureable immunogenicity for a year or so and field tests indicate the achieved immunity only lasts that long.

Future work will continue to focus on the development of a better pertussis vaccine that overcomes the problem with reactivity and achieves a longer lasting immunity against pertussis.[94]

GENERAL ISSUES

In the United States starting at 12 months of age, we vaccinate children and adolescents against eight vaccine-preventable diseases in addition to the nine vaccine-preventable diseases we began vaccination against in the first 11 months of life.[1] This includes the MMR vaccine and the varicella vaccine given at 12 to 15 months of age repeated at 4 to 6 years of age before school entry. All children are to continue boosters due from their infant series including the DTaP at 15 through 18 months of age and at 4 to 6 years of age, the pneumococcal conjugate vaccine, 13-valent at 12 through 15 months of age, and the IPV at 4 to 6 years of age. Children are to receive a dose of influenza vaccine every year before

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Table 2 Recommended Catch-up Immunization Schedule for Children and Adolescents Who Start Late or Who are More than 1 month Behind, United States, 2020

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. **Always use this table in conjunction with Table 1 and the notes that follow.**

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months ***and*** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday ***and*** second dose administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB, Comvax) ***and*** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose was administered at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose was administered between 7–11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	**4 weeks** if current age is < 4 years. **6 months (as final dose)** if current age is 4 years or older.	**6 months** (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal ACWY	2 months MenACWY-CRM 9 months MenACWY-D	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal ACWY	Not applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.**		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older.			

TABLE 2. Catch-up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More Than 1 Month Behind, United States, 2020. Reproduced from Centers for Disease Control and Prevention.[6] To view the notes mentioned mentioned in the table, access the original source referenced.

the influenza season begins. At 11 to 12 years of age children should receive the Tdap, Men ACWY, and HPV vaccines. Providers may choose, as Mayo Clinic has done, to begin the HPV vaccine series at 9 to 10 years of age. The booster dose of Men ACWY should be given at 16 years of age. Providers should make parents and young adults aware of the meningococcal conjugate vaccine serotype B vaccines best received at 16 to 18 years of age. Use of combination vaccines can reduce the number of injections at a visit. Other approaches to reduce or prevent pain with vaccinations include of course routes that avoid injection such as the nasal spray of the influenza vaccines. Vaccine providers should use evidence-based approaches to reduce pain when vaccinating. These include for preschool children sweet-tasting solutions, using less painful brands of otherwise equally effective and safe vaccines when more than one brand exists, upright rather than supine positioning, rapid rather than slow injection, and ordering the vaccines from least to most painful.[96] While caregivers might propose separating the vaccinations so that fewer injections are given at a time, such an approach will likely increase the overall amount of pain and distress the patient suffers. Furthermore, the separation leads to delays and failures to vaccinate. Expert recommendations hold that all vaccines due should be given at one visit. Children 2 years and older may benefit from a vibrating ice block applied to the vaccination site before

administration or from the application of a vapocoolant spray in a similar manner. For children struggling with injection pain, the application of 4% lidocaine cream 30 minutes before vaccination can help allay anxiety. In the United States where clinicians in primary care deliver the overwhelming majority of routine childhood vaccination in their office, clinicians should use presumptive, announcement language to signal their strong recommendations for the routine childhood immunizations due and the Corroboate About Me Science Explain/Advise (CASE) approach to address vaccine hesitancy in the office setting.[97,98] Delays in on-time vaccination increasingly occur starting in the second year of life because of missed well-child visits, intercurrent moderate or severe illnesses, as well as misunderstandings about contraindicating conditions. Clinicians should use every visit to catch their patients up on past due and due vaccine rather than rely on future office visits to be scheduled. Catch-up requires specific intervals and occasionally fewer doses (Table 2).

CONCLUSION

Of course, vaccination recommendations are not simply based on age. Forthcoming thematic reviews concerning vaccination will address additional vaccination recommendations for at-risk populations including those with immunocompromising conditions, those traveling internationally, and health care workers. An additional thematic review will address the role of vaccinations for emerging infections.

Abbreviations and Acronyms: **ACIP** = Advisory Committee on Immunization Practices; **DTaP** = diphtheria-tetanus-acellular pertussis vaccine; **HPV** = human papillomavirus; **IPV** = inactivated polio vaccine; **MenACWY** = meningococcal conjugate vaccine serotypes A, C, W, and Y; **MMR** = measles-mumps-rubella vaccine; **MMRV** = measles-mumps-rubella-varicella vaccine; **Tdap** = tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed; **WHO** = World Health Organization

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The Thematic Reviews on Vaccines will continue in an upcoming issue.

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