CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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The Need to Optimize Adolescent Immunization

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abstract

The adolescent period heralds the pediatric patient's transition into adulthood. It is a time of dynamic development during which effective preventive care measures can promote safe behaviors and the development of lifelong health habits. One of the foundations of preventive adolescent health care is timely vaccination, and every visit can be viewed as an opportunity to update and complete an adolescent's immunizations.

In the past decade, the adolescent immunization schedule has expanded to include 2 doses of quadrivalent meningococcal conjugate vaccine, 1 dose of tetanus, diphtheria, acellular pertussis, absorbed vaccine, 2 or 3 doses of human papillomavirus vaccine, depending on the child's age, and an annual influenza vaccine. In addition, during adolescent visits, health care providers can determine whether catch-up vaccination is needed to meet early childhood recommendations for hepatitis B; hepatitis A; measles, mumps, rubella; poliovirus; and varicella vaccines. New serogroup B meningococcal vaccines are now available for those at increased risk for meningococcal disease; in addition, these serogroup B meningococcal vaccines received a Category B recommendation for healthy adolescents, where individual counseling and risk–benefit evaluation based on health care provider judgements and patient preferences are indicated. This clinical report focuses on the epidemiology of adolescent vaccine-preventable diseases by reviewing the rationale for the annual universally recommended adolescent immunization schedule of the American Academy of Pediatrics, the American Academy of Family Physicians, the Centers for Disease Control and Prevention, and the American Congress of Obstetricians and Gynecologists. In addition, the barriers that negatively influence adherence to this current adolescent immunization schedule will be highlighted.

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Immunization is a key preventive cornerstone of pediatric care.[1,2] An updated harmonized immunization schedule of the American Academy of Pediatrics (AAP), American Academy of Family Physicians, and Centers for Disease Control and Prevention (CDC) is released each February (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/

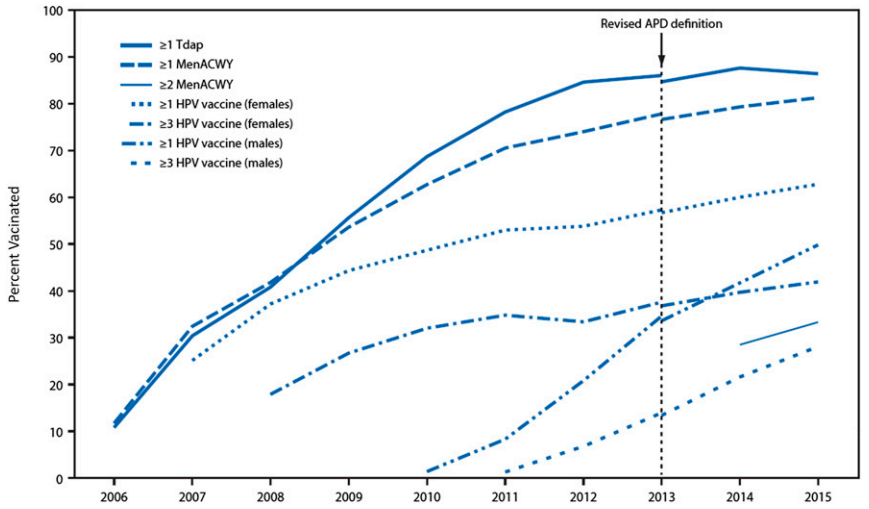

FIGURE 1

Immunization rates for Tdap, MenACWY, and HPV. * Tdap: ≥ dose Tdap at or after age 10 years; ≥ 1 MenACWY: ≥ 1 dose MenACWY or meningococcal-unknown type vaccine; ≥ 2 doses MenACWY: ≥ 2 doses MenACWY or meningococcal-unknown type vaccine, calculated only among adolescents aged 17 years at the time of the interview (does not include adolescents who received their first dose of MenACWY at or after 16 years of age); ≥ 1 HPV vaccine: ≥ 1 dose HPV vaccine, 9-valent (9vHPV), quadrivalent (4vHPV) or bivalent (2vHPV); ACIP recommends 9vHPV, 4vHPV or 2vHPV for females and 9vHPV or 4vHPV for males (the routine ACIP recommendation was made for females in 2006 and for males in 2011); ≥ 3 HPV vaccine: ≥ 3 doses HPV vaccine. †NIS-Teen implemented a revised APD definition in 2014 and retrospectively applied the revised APD definition to the 2013 data. Estimates using different APD definition may not be directly comparable. APD, adequate provider data; NIS-Teen, National Immunization Survey - Teen. (Source: Centers for Disease Control and Prevention. National and state vaccination coverage among adolescent aged 13-17 years - United States. *MMWR Morb Mortal Wkly Rep.* 2016;65(33):850-858)

immunization/Pages/Immunization-Schedule.aspx; www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html). It currently is formatted as a single schedule for children ages 0 through 18 years, with footnotes that highlight vaccine recommendations for individuals in specific circumstances, including those with high-risk conditions.

The recommended schedule for healthy adolescents[3] includes:

- quadrivalent meningococcal conjugate vaccine (MenACWY): 1 dose at 11 through 12 years of age, with a booster dose at 16 years of age;
- serogroup B meningococcal vaccines (MenB): 16 through 18 years of age (category B recommendation; A Category B recommendation indicates individual counseling and risk benefit evaluation that depends on provider judgment);
- tetanus, diphtheria, and acellular pertussis, absorbed vaccine (Tdap): 1 dose at 11 through 12 years of age; pregnant adolescents should receive 1 dose during each pregnancy at 27 through 36 weeks of gestation;
- human papillomavirus (HPV) vaccine: 2 doses at 9 through 14 years of age for persons at 0 and 6 to 12 months; 3 doses for persons 15 through 26 years of age and 9 through 26 years of age for immunocompromised at 0, 1 to 2, and 6 months;
- influenza: 1 dose every year.

Figure 1 compares immunization rates for Tdap, MenACWY, and HPV vaccine. The Healthy People 2020 goals for immunization coverage specify target immunization rates of 80% for ≥1 Tdap dose, for ≥1 MenACWY dose, and for 3 HPV vaccine doses (the recommended schedule before October 2016).[4] As of 2015, in 43 states and the District of Columbia, ≥80% of adolescents 13 through 17 years of age had received Tdap,[5] but in only 23 states and the District of Columbia, ≥80% of adolescents 13 through 17 years of age had received MenACWY.[6] Uptake of HPV vaccine lags far behind both of these vaccines, however, for both boys and girls, as does uptake of influenza vaccine: for the 2015–2016 influenza season, the influenza vaccination rate for adolescents 13 through 17 years of age was 46.8%.[7]

Vaccination rates also vary considerably by vaccine and by state.[5,6] The National Immunization Survey (NIS)–Teen showed the immunization rates of adolescents receiving at least 1 dose of Tdap ranged from 70% to 97%, whereas rates for at least 1 dose of MenACWY ranged from 55% to 98%. Completion of the 3-dose HPV vaccine series ranged from 24% to 68% in girls and from 16% to 58% in boys.[8]

Although HPV vaccination rates are improving slowly, they continue to be far behind Tdap and MenACWY vaccination rates for both boys and girls. Compared with 2014, national vaccination rates in 2015 have increased to 81% for MenACWY but decreased to 86% from 88% for Tdap. Meanwhile, only 63% of girls received at least 1 dose of HPV vaccine, and 42% completed the 3-dose series. Rates for boys were even lower, with 50% of boys having received at least 1 dose of the HPV vaccine series and only 28% having completed the 3-dose series.[8] In addition, there are distinct missed opportunities to administer adolescent vaccines, particularly HPV vaccine. If HPV vaccine had been administered during the same visit at which another recommended vaccine, such as Tdap, was given, the vaccination rate of 13-year-old girls

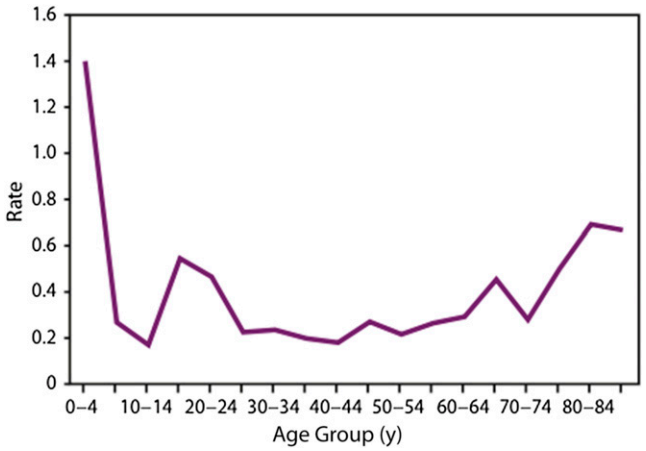

FIGURE 2

Rate of meningococcal disease by age group. Source: Centers for Disease Control and Prevention. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62(RR-2):1-28.

born in 2000 for at least 1 dose of HPV vaccine would have been 91%.[9]

Current data demonstrate a need for improvement in adolescent immunization rates.[10] Understanding the epidemiology and current vaccine recommendations in the adolescent schedule is important to optimize health care for adolescents.[11,12] Although barriers to optimizing immunization rates persist, familiarity with this information should enable health care providers to create better implementation strategies to enhance vaccine coverage. The increased flexibility created by the recent shift to a 2-dose schedule for HPV vaccine for persons initiating the series at 9 through 14 years of age is anticipated to increase completion rates, but additional efforts will be needed to reach the Healthy People 2020 goal of 80%.

EPIDEMIOLOGY OF ADOLESCENT VACCINE-PREVENTABLE DISEASES

Meningococcal Vaccines

Meningococcal disease affects all age groups, with increased infection rates seen among infants, adolescents, and the elderly (Fig 2). Complications of meningococcal disease include neurologic sequelae, limb amputation, and death.[13,14] The case/fatality ratio of meningococcal disease ranges from 10% to 40%.[15] Although the incidence of meningococcal disease has been declining, outbreaks do still occur.[16] Adolescents and their families should be informed about the threat of infection and its complications.

Two polysaccharide-protein conjugate vaccines are currently licensed and recommended as part of the routine immunization schedule for the prevention of meningococcal disease in US adolescents: MenACWY-D (Menactra [Sanofi Pasteur, Swiftwater, PA]) and MenACWY-CRM (Menveo [Novartis Vaccines and Diagnostics, Cambridge, MA]). Both vaccines provide protection against meningococcal serogroups A, C, W, and Y. These vaccines also are indicated for groups at increased risk (ie, those with asplenia, complement deficiencies, or travel to an area where meningococcal disease is prevalent). There is no preferential recommendation for one MenACWY over the other.

In 2005, the Advisory Committee on Immunization Practices (ACIP) recommended immunization against meningococcal disease with a MenACWY conjugate vaccine for individuals 11 through 12 years of age, primarily because the increased incidence of disease begins in late adolescence. In August 2011, the CDC recommended a booster dose of meningococcal vaccine 5 years after primary immunization for all adolescents because of serologic evidence of waning immunity and several cases of breakthrough disease.

Concurrent administration of meningococcal vaccine (MenACWY-CRM) with Tdap and quadrivalent HPV vaccine (4vHPV) yielded similar immune responses when compared with the response of each individual vaccine given independently. There also was no increase in adverse effects when all 3 vaccines were administered together.[17] Similar results have been found for the 9-valent HPV vaccine (9vHPV).[18] This finding has important implications in the clinical setting, encouraging simultaneous administration of these 3 vaccines during the same office visit and thereby increasing timely protection of adolescents against these vaccine-preventable diseases.

With the use of MenACWY vaccines in adolescents and young adults, serogroup B now causes 40% of all meningococcal disease cases in this age group. Most children survive serogroup B meningococcal disease without major sequelae. However, approximately one-tenth have major disabling deficits, and more than one-third have 1 or more deficits in physical, cognitive, and psychological functioning, with the additional burden of memory deficits and executive function problems.[19] In recent years, ~50 cases of serogroup B meningococcal disease have occurred annually among 11- through 23-year-olds.[20] Approximately one-third of cases of serogroup B meningococcal disease among 18- through 23-year-olds occur in college students, and there have been 10 university-based outbreaks attributable to this serogroup since 2008.[21] Two MenB

vaccines have been licensed in recent years, as described below.

During 2013 to 2014, outbreaks of serogroup B meningococcal disease occurred at 2 universities, with a combined 13 cases and 1 death reported. In response, vaccination campaigns were conducted at both universities using a MenB vaccine (Bexsero [Novartis Vaccines and Diagnostics, Cambridge, MA]), which at the time had been investigational in the United States[22] but already had been licensed in Europe, Canada, and Australia. It is not known whether the available MenB vaccines reduce the number of secondary cases.[23]

Bexsero was licensed[24] in the United States in January 2015 for use in individuals 10 through 25 years of age. Trumenba (Wyeth Pharmaceuticals, a subsidiary of Pfizer, Philadelphia, PA) was licensed[25] in the United States for use in the same age group in October 2014. The ACIP currently recommends the use of either MenB vaccine for people 10 years and older at increased risk for meningococcal serogroup B disease, including people with persistent complement component deficiencies, people with anatomic or functional asplenia, people receiving eculizumab, microbiologists who work with *Neisseria meningitidis*, and people in outbreak settings. These MenB vaccines were approved under the surrogate marker of complement-dependent killing of organisms by vaccine-induced antibodies. This surrogate marker has not been established with serum from persistent complement component-deficient subjects, and it is unknown whether such people can expect protection. Bexsero is a 2-dose series administered 1 month apart; Trumenba is approved as a 3-dose series administered at 0, 2, and 6 months and a 2-dose series given at 0 and 6 months.[26] Only the 3-dose series of Trumenba should be used for those at increased risk for meningococcal serogroup B disease or those for whom immediate protection is optimal, such as during an outbreak. Although there is no preference for one MenB vaccine over the other, the same product must be used to complete the series. In June 2015, the ACIP made a Category B recommendation for use of MenB vaccines in 16- through 23-year-old individuals for short-term protection against meningococcal B serogroup strains. Bexsero or the 2-dose Trumenba series can be used. The preferred ages are 16 through 18 years. A Category B recommendation indicates individual counseling and risk benefit evaluation that depends on health care provider judgment and patient preferences. It is covered by the Vaccines for Children (VFC) program and by insurance companies under the Patient Protection and Affordable Care Act (Pub L No. 111-148 [2010]), with no patient out-of-pocket costs. International studies may be useful to consider when evaluating the Category B recommendation in the United States.

Acellular Pertussis Vaccines

There has been increased clinical recognition of pertussis and its associated morbidity and mortality over the past 30 years. Increased awareness, evolving diagnostics,[27] vaccine refusal, and, most importantly, a more rapidly waning immunity after vaccination with acellular products compared with whole-cell pertussis vaccines have contributed to the marked recent increase in pertussis cases in the United States.[28–30] In 2015, 20 762 cases of pertussis were reported among all ages, with 32% of these cases occurring in adolescents 11 to 19 years of age and 9 reported infant deaths.[31,32] The incidence of pertussis peaked in 2012, with ~48 277 cases across all ages and 20 reported deaths attributable to pertussis.[33]

Adolescents serve as an important reservoir for pertussis and are known to transmit the infection to the most vulnerable population: young infants.[28] In 2015, almost 7000 cases of pertussis were reported in the population of adolescents 11 to 19 years of age.[32] Healthy People 2020 has created a goal to have no more than 2000 cases of pertussis in adolescents by 2020. Although most of the deaths are among young infants, older people, including adolescents, experience considerable morbidity attributable to pertussis. Prolonged cough, paroxysms of cough, pneumonia, shortness of breath, a choking sensation, vomiting, rib fractures, and scleral hemorrhages can occur. Adolescents need to be vaccinated to reduce adolescent disease morbidity and to minimize transmission of the disease to infants.

Two Tdap products, Boostrix (GlaxoSmithKline, Research Triangle Park, NC) and Adacel (Sanofi Pasteur), were licensed in the United States in 2005 for use in adolescents to improve pertussis immunity. The ACIP recommended a single Tdap dose at ages 11 through 12 years, with catch-up vaccination at ages 13 through 18 years.[34] The Tdap booster is recommended regardless of the interval since the last immunization with a tetanus or diphtheria toxoid–containing vaccine.[35] Tdap has also been recommended as a single dose for adults, replacing 1 Td booster.[36] Beginning in October 2012, the ACIP recommended a dose of Tdap for every pregnant woman during each pregnancy, regardless of immunization history.[37] Tdap administration is preferred for pregnant women between 27 and 36 weeks of gestation, with an emphasis on earlier weeks during this preferred period, to enable high titers of the antibody to cross the placenta to provide the longest duration of passive protection to the young infant. The available data do not suggest any increased risk or

adverse events in pregnant women who receive Tdap.[38]

HPV Vaccines

HPV can be transmitted with any genital-mucosal contact. The lifetime risk of acquiring an HPV infection is >80%.[39] An estimated 79 million people in the United States are currently infected with HPV and approximately half of the 14 million new infections that occur each year are in 15- through 24-year-old individuals.[40,41] Just over 20% percent of a representative sample of the US population of 14- through 19-year-old girls who self-obtained vaginal swabs were found to be colonized with high-risk (oncogenic) HPV types.[42] High-risk HPV types are responsible for virtually all cases of cervical cancer and a large percentage of anogenital and oropharyngeal cancers in females and males.[43,44] More than 26 000 new cases of HPV-related cancers are diagnosed annually in the United States. With no vaccination among girls 12 years of age and younger, there would be an estimated 168 400 lifetime cases of cervical cancer and 54 100 cervical cancer deaths among this group.[45] In fact, comparison of prevaccine (2003–2006) and vaccine era (2009–2012) HPV prevalence showed a 64% decrease in 4vHPV type prevalence among girls 14 through 19 years of age and a 34% decrease among women 20 through 24 years of age, highlighting the impact of the HPV vaccine.[46]

The HPV vaccine has been included in the annual schedule as a 3-dose series for girls since 2007 and for both boys and girls since 2011 at ages 11 through 12 years. As of October 2016, the ACIP has revised its recommended HPV schedule to be a 2-dose series for persons initiating the vaccine series from 9 through 14 years of age.[47] Until recently, 2 HPV vaccines were available in the United States: bivalent human papillomavirus vaccine (2vHPV; Cervarix [GlaxoSmithKline]), which targets HPV types 16 and 18 and is licensed for use in females, and quadrivalent HPV vaccine (4vHPV; Gardasil [Merck & Co Inc, Whitehouse Station, NJ]), which protects against HPV types 6, 11, 16 and 18 and is licensed for use in females and males.[40] A 9-valent HPV vaccine (9vHPV; Gardasil-9 [Merck & Co Inc, Whitehouse Station, NJ]) was licensed in December 2014. All 3 licensed HPV vaccines provide primary protection against cancers related to HPV types 16 and 18, which are responsible for ∼70% of HPV-related cancers in the United States. The 9vHPV vaccine includes coverage for the original 4 HPV types (6, 11, 16, and 18) in the quadrivalent vaccine and for the high-risk HPV types 31, 33, 45, 52, and 58, which are responsible for an additional 14% of HPV-related cancers in women and 4% of HPV-related cancers in males in the United States.[48] The 4vHPV and 9vHPV vaccines also protect against types 6 and 11, which are responsible for 90% of genital warts. As of January 2017, the 9vHPV vaccine became the only available HPV vaccine in the United States.

The 9vHPV vaccine was initially licensed in December 2014 for use in females 9 through 26 years of age and males 9 through 15 years of age on the basis of trial results available at the time of Food and Drug Administration (FDA) submission. To evaluate the efficacy and safety of 9vHPV, a randomized, controlled clinical study was conducted in the United States and internationally.[49] The 9vHPV was 97% effective in protecting against cervical, vulvar, and vaginal cancer precursor lesions related to the 5 additional types, and antibody response against the 4 types in the 4vHPV vaccine was noninferior.[49] Additional data on males through age 26 years were submitted to the FDA, and in December 2015, 9vHPV was licensed for use for males through age 26 years.[50]

A 2-dose HPV vaccine schedule has the potential to improve completion rates and reduce costs. Data on antibody responses and the effectiveness of 2 doses of 2vHPV and 4vHPV suggest that protection from a 2-dose regimen would be similar to that of a 3-dose series. In 1 Canadian randomized clinical trial, 520 girls aged 9 to 13 years were randomized to receive either 3 doses of 4vHPV at 0, 2, and 6 months or 2 doses of 4vHPV at 0 and 6 months. Researchers found that antibody levels after the 2-dose schedule were noninferior to those after the 3 doses. They also found that antibody titers resulting from the 2-dose and 3-dose schedules were still comparable 36 months after receiving the vaccine.[51] Similarly, in a study with over 1500 participants, Iverson et al[52] found that antibody concentrations achieved in a clinical trial after a 9vHPV 2-dose series administered at 0 and 6 or 12 months to 9- through 14-year-old girls and boys were noninferior compared with the currently licensed 3-dose series in 16- through 26-year-old females. The immune response with a 12-month interval between the 2 doses was more robust than that measured when the interval was only 6 months. Geometric mean antibody titers against all HPV types in the 9vHPV vaccine were higher in the 9- through 14-year-old age groups than in the 16- through 26-year-old women.[52] Although these studies are being extended for 2 more years to evaluate antibody persistence,[53] current data suggesting stronger immune responses in younger individuals may result in routinely recommending HPV vaccination for individuals as young as 9 years of age. The FDA approved the 2-dose schedule for persons 9 through 14 years of age on October 7, 2016, and the ACIP revised its recommendation on October 19, 2016 to vaccinate

with 2 doses of 9vHPV vaccine.[47,50] The second dose should be administered 6 to 12 months after the first. Recommendations for completion of the vaccination series depend on the individual's age when the HPV vaccination was initiated.[47] For example, if the first dose is given at age 14 years, that individual only needs 1 more dose >6 months later to complete the series, regardless of when the second dose is given.

The rationale for administering the HPV vaccine routinely at the 11- through 12-year-old visit is based on data from vaccine trials, epidemiologic studies of HPV infection, and sexual behavior as well as modeling studies of HPV infection in adolescents that indicate the greatest protection will be achieved by giving the vaccine before the adolescent becomes sexually active. There is remarkably high incidence of HPV infection after sexual initiation. The cumulative incidence of HPV infection was nearly 40% within the first 2 years after first having sexual intercourse among college women and almost 60% among college men, underscoring the importance of early immunization with all 3 HPV vaccine doses.[54,55] Data reporting that ~24% of adolescent boys and girls report having sexual intercourse by ninth grade and that 58.1% report having sex by 12th grade[56] support targeting HPV vaccination at the 11- through 12-year-old visit. Administration of either 2vHPV, 4vHPV, or 9vHPV leads to greater antibody responses in girls and boys 9 through 15 years of age, compared with those in girls and boys 16- through 26 years of age receiving the respective vaccine.[57,58] Pre- and postlicensure studies also have demonstrated safety, immunogenicity, and efficacy for the 2vHPV, 4vHPV vaccines. Each vaccine is highly effective, providing type-specific protection against the included HPV types.[59] A recent long-term study of 4vHPV recipients conducted over a period of 8 years has demonstrated safety, immunogenicity, and effectiveness in both girls and boys 9 through 15 years of age.[60]

Currently, the ACIP recommends routine vaccination with the HPV vaccine for individuals 11 through 12 years of age. The vaccine is licensed for use in children beginning at age 9 years, the age at which the World Health Organization recommends starting HPV immunization. In addition, the ACIP recommends HPV vaccination beginning at age 9 years for children and youth with any history of sexual abuse or assault who have not initiated or completed the series. Girls and boys who are victims of sexual abuse or assault should receive the HPV vaccine through the recommended ages if they have not already been vaccinated.[40] Vaccination is also recommended for 13- through 26-year-old females and 13- through 21-year-old males who have not been vaccinated previously or who have not completed the series. Persons who receive the first dose of the vaccine at 15 years of age or older, and persons who are immunocompromised, should complete a 3-dose schedule at 0, 1 to 2, and 6 months.[47] Males 22 through 26 years of age also may receive the vaccine. Men who are immune suppressed, have HIV infection, or have sex with men should be vaccinated through age 26 years. For transgender persons, HPV vaccination is recommended through 26 years for those who were not adequately vaccinated previously. A series begun with 4vHPV can be completed with 9vHPV. A study on the cost-effectiveness of additional 9vHPV vaccination (ie, receiving a full 9vHPV series after receiving a full 4vHPV series) suggests that additional 9vHPV vaccination is not as efficient as other vaccination strategies, such as primary 9vHPV vaccination.[61] Regardless, if a decision is made to give 9vHPV to a person who previously received a 2vHPV or 4vHPV series, the 2- or 3-dose regimen currently recommended for 9vHPV should be followed.[40,48]

Most female adolescents on commercial and Medicaid health plans are currently not receiving the recommended doses of HPV vaccine by 13 years of age. Medicaid plans have reported significantly higher rates of 3-dose HPV vaccine coverage compared with commercial plans, although the median of adolescent girls receiving 3 doses was only 19%.[62] According to the 2015 NIS–Teen, just over half (63%) of girls ages 13 through 17 years received ≥1 dose of HPV vaccine, and only 41.9% completed the series. The coverage is even more limited among boys of the same age range, with 49.8% having received ≥1 dose, and 28.1% having completed the series. Compared with non-Hispanic white adolescents or adolescents living at or above the federal poverty level, adolescents who are African American, Hispanic, American Indian/Alaska Native, or living below the federal poverty line have a higher rate of initiation of the HPV vaccine series.[8]

Health care provider recommendation and physician attitude play a major role in the decision to vaccinate against HPV. On the basis of 2011 NIS–Teen data, Rahman et al[63] found that health care provider recommendation independently predicted HPV vaccine initiation and completion. A strong endorsement is more influential than a weak one. Parents prefer clear, unambiguous recommendations; offering the HPV vaccine without strongly recommending it appears to confuse and frustrate parents. One of the most powerful messages that health care providers can transmit is that vaccination against HPV is a critical strategy for cancer prevention. Hull et al[64] demonstrated that mothers and adolescent daughters were more willing to

receive the HPV vaccine when it was recommended as a routine vaccine that prevents cancer. A study of the impact of maintenance-of-certification participation on HPV vaccination rates revealed that captured opportunities increased after participating health care providers chose to focus on cancer prevention, to use consistent language, and to emphasize vaccination at acute visits. These physicians had a significant relative increase in captured opportunities compared with non–maintenance of certification participants for HPV dose 1 at preventive visits and for doses 1 and 2 at acute visits.[65] Mothers also stated that they were less skeptical of the HPV vaccine when it was recommended with other vaccines than when the vaccine was singled out. The "same way, same day" slogan of the CDC promotes the recommendation of HPV vaccine with Tdap and meningococcal vaccines, grouping the 3 vaccines together to avoid singling the HPV vaccine out.[66]

Influenza Vaccines

Influenza causes annual outbreaks, the timing and severity of which are unpredictable. Both children with high-risk conditions and otherwise healthy children are hospitalized each year because of influenza. Many more require outpatient or emergency department evaluation and management of influenza. A study of influenza-associated deaths from 2004 to 2012 demonstrated that even healthy children are at risk for mortality attributable to influenza.[67] During nonpandemic seasons since the 2003–2004 season, reported pediatric deaths have ranged from a low of 37 (2011–2012 season) to a high of 171 (2012–2013 season). Higher pediatric mortality was noted during the 2009–2010 pandemic, with >344 pediatric deaths reported.[68] From 2004 through 2012, influenza A virus has accounted for 78% of pediatric influenza-associated deaths.[67]

In the 2015–2016 influenza season, there were 89 reported influenza-associated pediatric deaths.[69] Twenty-two deaths occurred in adolescents 12 through 17 years of age (24.7% of all pediatric deaths). Approximately 60% of all pediatric deaths occurred in children and adolescents who did not have any underlying high-risk medical conditions (out of 68 with known medical history).[69]

Influenza immunization rates are much lower in older pediatric patients. On the basis of 2015–2016 NIS influenza vaccine coverage data for children 6 months through 17 years of age, only 46.8% of adolescents 13 through 17 years of age received the vaccine, the lowest uptake of all pediatric age groups. In comparison, 75.3% of infants 6 through 23 months of age received the influenza vaccine in 2015 to 2016.[69]

Annual vaccination against influenza is recommended for individuals of all ages beginning at 6 months of age, with a specific emphasis on groups at higher risk for complications (eg, children <5 years, the elderly, pregnant women, and those who are immunocompromised).[70] In addition, the Committee on Obstetric Practice of the American Congress of Obstetricians and Gynecologists recommends routine influenza vaccination of pregnant women.[71]

Although vaccine effectiveness varies and is unpredictable from year to year, protection against virologically confirmed influenza illness after immunization with the inactivated influenza vaccine in healthy children >2 years generally ranges between 50% and 60% or higher, depending on the closeness of vaccine strain match with the circulating strains. Given the unpredictable nature of influenza each season, the AAP currently recommends that any licensed and age-appropriate inactivated influenza vaccine available be used. In light of the evidence for poor effectiveness of quadrivalent live attenuated influenza vaccine (LAIV4) documented during the past 3 seasons, LAIV4 should not be used in any setting during the 2016–2017 season. The interim recommendation that LAIV4 not be used in children will be reevaluated for future influenza seasons. Vaccination should not be delayed to obtain a specific product and can be simultaneously administered with another vaccine.[72]

Catch-up Immunization and Immunization in Special Circumstances

Adolescents also may require catch-up of certain immunizations, such as hepatitis B, hepatitis A, measles, mumps, rubella vaccine (MMR), and varicella. Health care providers may choose to test for antibody to hepatitis A and varicella before immunizing against these diseases. Those who are not immunized against hepatitis B should receive a 3-dose series or can receive a 2-dose series of hepatitis A–hepatitis B vaccine (Twinrix [GlaxoSmithKline]), which is licensed for children as young as 11 years old. Others who have not been immunized against hepatitis A should receive the 2-dose series with a minimum interval of 6 months. In a 2009 study, the reported rate of adolescents receiving a 1-time dose of hepatitis A was only 42%.[73] Adolescents born outside the United States in countries with a hepatitis B surface antigen (HBsAg) prevalence >2% (and those born to mothers born in countries with an HBsAg prevalence >8% who are not immunized at birth) should have documentation of negative HBsAg before immunization with hepatitis B vaccine.[72,74] Adolescents who have not received the MMR vaccine as part of the routine schedule should receive a 2-dose

series at 11 through 12 years of age. It is particularly important for all adolescents to be up-to-date with the MMR vaccine series, given the recent measles outbreaks in 16 states.[75] Furthermore, measles remains a common disease in many parts of the world, and unvaccinated individuals are at risk for becoming infected when they travel internationally.[76] Adolescents who have not been routinely immunized against varicella should receive a 2-dose series. Among adolescents with no history of varicella, the national immunization rate in 2015 was 83% for receipt of at least 2 doses.[8] Factors, such as having private insurance, frequent office visits, having received meningococcal or Tdap vaccines, higher maternal education, residence in a state with school entry requirements, and being of younger age, were associated with completion of varicella immunization.[77]

A full vaccine history should be reviewed in the context of risk factors and to be aware of whether additional vaccines may be needed. For example, an adolescent may require a vaccine not given universally (for example, pneumococcal conjugate vaccine [PCV13] and pneumococcal polysaccharide vaccine [PPSV23] in an adolescent with diabetes, nephrotic syndrome, or a cochlear implant) because of an increased risk for certain pathogens attributable to an altered immune response, anatomic abnormality, or travel.

UNDERSTANDING BARRIERS TO IMMUNIZATION

Overcoming barriers to immunization requires understanding the inherent challenges that exist in delivering vaccines to the adolescent population. One of the greatest challenges is health care provider recommendation, which often lacks consistency and urgency. Many health care providers do not universally recommend vaccines to eligible populations and do not offer concomitant vaccination with indicated vaccines during a single patient encounter.[78] In a recent study of physicians' perspectives on the HPV vaccine, only ~60% of pediatricians and family physicians strongly recommend the HPV vaccine for 11- through 12-year-old girls.[79] Aligning the vaccine messages communicated by all office personnel is challenging but important (ie, staff should have training on the delivery of vaccine information). A recent randomized clinical trial with 29 pediatric and family practices in North Carolina found that practices trained in an "announcement" (or presumptive) delivery strategy had significant increase in HPV vaccination coverage for individuals 11 or 12 years of age when compared with control practices that did not receive any training. Similar significance was not found in practices trained in a "conversational" delivery strategy.[80] From the physician perspective, the barriers are infrequent adolescent well visits or follow-ups and a lack of awareness of the need for vaccines.[81] The perception that the patient and parent lack interest is also a reported reason that affects delivery of immunizations and other clinical preventive health services.[82] Public and health care personnel have personal beliefs that also may influence vaccine delivery. In a qualitative meta-analysis of 14 years of influenza-related communications research by the CDC, public and some health care provider perceptions and beliefs were difficult and slow to change.[83]

TABLE 1 Parental Perspectives on Vaccines

Perspective	% That Strongly Agreed or Agreed With Statement
Getting vaccines is a good way to protect my child(ren) from disease.	90
Generally I do what my doctor recommends about vaccines for my child(ren).	88
I am concerned about serious adverse effects of vaccines.	54
New vaccines are recommended only if they are as safe as older vaccines.	51
Parents should have the right to refuse vaccines that are required for school for any reason.	31
Some vaccines cause autism in healthy children.	25
My child(ren) does(do) not need vaccines for diseases that are not common anymore	11

Reprinted with permission from Freed GL, Clark SJ, Butchart AT, Singer DC, Davis MM. Parental vaccine safety concerns in 2009. *Pediatrics*. 2010;125(4):656.

A study by Freed et al[84] reported that 11.5% of parents of adolescents refused immunization. The meningococcal vaccine was declined 31.8% of the time and the HPV vaccine was declined 56.4% of the time.[84] The majority of parents who declined either of these vaccines believed that (1) their child was at low risk for acquiring the disease; (2) the risks for adverse effects were "too great"; (3) there was not enough research on the vaccine; and (4) the vaccine had not been on the market "long enough."[84] The NIS–Teen 2008–2010 data support these findings, including the additional concern about the safety of the HPV vaccine.[85] Table 1 provides an overview of parental perspectives on vaccines. Education about these vaccines will help parents to make informed decisions about vaccinating adolescents.

Other potential barriers to immunization are Internet and media sources that give misinformation about vaccines, especially vaccine safety. Education on the importance of immunizations, infection risk and consequences, and the need to overcome peer-pressure or fear of needles should be key

focuses for adolescent patients.[86] Pediatricians provide some of the most important education and recommendations for parents and are their most trusted source of information.[87–89] Furthermore, parents and adolescents should make decisions together regarding vaccine acceptance. The health care provider should be able to answer parent and patient questions and concerns and should be able to discuss in detail the information in the pertinent vaccine information sheet (VIS).

Racial and ethnic disparities in health care, including immunization coverage, have been demonstrated in the literature.[90] For example, a 2015 study found that HPV vaccination coverage was higher among non-Hispanic black and Hispanic males compared with non-Hispanic white males.[91] Differences in the reasons for not receiving an influenza vaccination also exist between racial and ethnic groups. Black parents were more likely to be concerned about their child getting influenza from the vaccine compared with white and other or multiple-race parents.[92] Focusing on disparities and understanding the cultural needs of a given population will aid in boosting immunization coverage rates.[93,94] Different forms of written communication may be more effective among certain subpopulations. For example, HPV vaccine–specific brochures were found to be effective in increasing HPV vaccination rates among Hispanic but not among black individuals.[95] In a predominantly Hispanic population in Los Angeles, California, community support for immunization, especially HPV vaccine, strongly affects individual decisions whether to immunize.[96] In addition, outreach programs and immunization campaigns targeting patients have proven to be effective. For example, churches can be important sources of social support and health information in black communities.[97] Using medical and nonmedical settings (eg, school-based settings) for vaccine administration also may help to increase vaccine awareness.[98] Frequent electronic communications, such as recall/reminders and electronic health record prompts, also are all strategies that can be used by health care providers to improve vaccination rates. Vaccine administrations of all vaccines and in any setting should be entered into the electronic systems.

Financial difficulties affect adolescent immunizations as well. HPV vaccines constitute the most expensive series currently included in the VFC program; private-sector prices are even higher.[99] The CDC vaccine price list (www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/) reports the following prices of vaccines in the private sector: (1) $193.63 per dose for 9vHPV; (2) $113 to $120 per dose of MenACWY; and (3) $38 to $43 per dose of Tdap.[100] The limited availability of in-network health care providers in some rural jurisdictions and the persistence of some grandfathered plans that are not required to follow the Affordable Care Act preventive care provisions represent the remaining barriers to access.[99] It has been shown that federal- and state-funded vaccine programs assist in boosting rates of office visits for immunizations.[101]

Another potential barrier is having an adequate supply of all vaccines for each patient available in the office. Efforts to work with vaccine manufacturers and the VFC program to maintain an adequate inventory should be considered. Appropriate payment for health care providers also is crucial in having successful immunization programs.[102] Practices need to be up-to-date on current coding, billing, and financing strategies. The AAP has resources on vaccine financing, ordering, and supply that help practices achieve healthy financial margins (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/finance.aspx). In addition, the AAP provides specific information on the proper coding to help optimize payments for vaccines (www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunization/Pages/payment-coding-billing.aspx).

Although barriers to adolescent immunizations exist for all vaccines, HPV vaccination presents a unique set of challenges.[103] A 2009 study based in 2 clinics in a Hispanic community in Los Angeles, California with high cervical cancer rates was aimed at understanding barriers to and facilitators of HPV immunization.[96] Several parental concerns and misconceptions included (1) adolescents do not need vaccination; (2) vaccine programs like VFC were only for infants and young children; (3) the vaccine may increase sexual activity; (4) discomfort toward a new vaccine; and (5) the vaccine is not required for school.

Since the introduction of HPV vaccine, parental acceptance has evolved to become a notable challenge to the immunization of adolescents. The 2010 National Health Survey explored reasons why parents opposed HPV immunization for their child.[104] Approximately 25% of parents stated that there was no need for the vaccine, 19.3% stated concern over vaccine safety, and 16.6% stated they did not have sufficient knowledge about the vaccine.[104] Other reasons include weak or lack of health care provider recommendation and concerns over the effect on adolescents' sexual behavior. Table 2 summarizes the top reasons why parents did not vaccinate their child against HPV, on the basis of their gender. Table 3 lists barriers to HPV immunization from both health care provider and parental perspectives.

TABLE 2 Top 5 Reasons for Not Vaccinating Adolescents Against HPV

Reason	Parents of Girls		Parents of Boys	
	%	(95% CI)	%	(95% CI)
Lack of knowledge	15.5	(13.0–18.5)	15.5	(13.7–17.6)
Not needed or necessary	14.7	(12.5–17.3)	17.9	(15.9–20.1)
Safety concern/side effects	14.2	(11.8–16.8)	6.9	(5.6–8.5)
Not recommended	13.0	(10.8–15.5)	22.8	(20.6–25.0)
Not sexually active	11.3	(9.1–13.9)	7.7	(6.4–9.2)

Source: Centers for Disease Control and Prevention. Human papillomavirus vaccination coverage among adolescents, 2007–2013, and postlicensure vaccine safety monitoring, 2006–2014—United States. *MMWR Morb Mortal Wkly Rep.* 2014;63(29):620-624. CI, confidence interval.

TABLE 3 Barriers to HPV Immunization: Perspectives of Parents and Health Care Providers

Barriers Stated by Parents	Barriers Stated by Providers
Vaccines are not offered	Prefer not to give multiple vaccines
Vaccines are optional or unnecessary	Do not strongly recommend HPV vaccine
Providers do not encourage vaccination	Cannot predict onset of sexual activity
Providers do not discuss vaccine safety	Do not have experience with HPV disease
Providers do not emphasize importance of age at vaccination	Vaccination delays can cause lack of immunization
Lack of knowledge	
Concerns about vaccine safety	

Sources: Perkins RB, Clark JA, Apte G, et al. Missed opportunities for HPV vaccination in adolescent girls: a qualitative study. *Pediatrics.* 2014;134(3):e670; and Centers for Disease Control and Prevention. Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006–2014—United States. *MMWR Morb Mortal Wkly Rep.* 2014;63(29):620-624.

Several studies have focused on whether receipt of the HPV vaccine lowers inhibition for sexual activity. Data show that vaccine receipt does not alter sexual activity. A retrospective cohort study that followed adolescent girls for 3 years after immunization at ages 11 through 12 years did not find any increase in seeking medical attention for outcomes related to sexual activity, including pregnancy, sexually transmitted infection testing or diagnosis, and contraceptive counseling.[105] HPV immunization does not change the vaccine recipient's sexual behavior, such as number of sexual partners or sexually transmitted infections.[105] Although vaccination may not affect sexual behavior, Mather et al[106] found that attitudes toward practicing safe sexual behaviors differed among vaccinated and unvaccinated women. Vaccinated women were found to have more positive attitudes about practicing safe sex. However, both vaccinated and unvaccinated women did not differ in their perceived vulnerability to cervical cancer and need for cervical cancer screening.[106]

Another prominent barrier specific to the completion of the HPV vaccine series used to be its 3-dose schedule. On the basis of 2014 NIS–Teen data, the CDC found 3-dose series completion rates among those who received ≥1 dose of HPV vaccine to be only 69.3% for girls and 57.8% for boys.[107] Coverage with at least 1 dose of HPV vaccine before 13 years of age could have reached 91.3% for girls born in 2000 if opportunities to administer the HPV vaccine when other vaccines were given had not been missed.[10] Scheduling follow-up visits for the second and third doses at the time the initial dose is given, implementing standing orders for vaccination, using every clinical opportunity to evaluate and deliver remaining vaccination doses, using electronic communication, and using recall/reminders are all strategies that can be used by health care providers to improve completion rates. More data are needed to understand the impact of the recently recommended 2-dose schedule.

Reasons that encouraged parents to accept HPV immunization include (1) family history of cervical cancer or HPV infection; (2) family and community support; (3) education on HPV vaccine; and (4) health care provider access to an immunization registry. Parents who reported Internet use to acquire health information, including on HPV, had significantly better knowledge, had fewer concerns about vaccine safety, and were more likely to accept HPV immunization.[108] Health care provider knowledge about the HPV vaccine and promotion of the vaccine as a "routine" vaccine is also an important factor in encouraging parents to get their children vaccinated.[96] The impact of health care provider promotion is illustrated by data that noted the reason why parents chose not to immunize their sons against HPV was that no physician or health care provider recommendation for the vaccine was given.[109] In another study, ~55% of parents who received a physician's recommendation for HPV vaccination had their sons vaccinated versus only 1% of parents who did not receive a recommendation.[110] Not surprisingly, health care provider recommendation was found to be the strongest predictor of HPV vaccine initiation.[111]

CONCLUSIONS

This clinical report highlights each of the vaccines routinely recommended for the healthy adolescent and summarizes the barriers that should be confronted to improve overall

rates of immunization, which fall short of the Healthy People 2020 goals. It is essential to continue to focus and refine the appropriate techniques in approaching the adolescent patient and parent in the office setting. Health care providers must continously strive to educate their patients and develop skills that can help parents and adolescents overcome vaccine hesitancy. These details are addressed in a seperate clinical report, "Practical Approaches to Optimize Adolescent Immunization."[112]

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ACIP: Advisory Committee on Immunization Practices
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
HBsAg: hepatitis B surface antigen
HPV: human papillomavirus
LAIV4: quadrivalent live attenuated influenza vaccine
MenACWY: quadrivalent meningococcal conjugate vaccine
MenB: serogroup B meningococcal vaccine
MMR: measles, mumps, rubella vaccine
NIS: National Immunization Survey
Tdap: tetanus, diphtheria, and acellular pertussis vaccine
VFC: Vaccines for Children
2vHPV: bivalent human papillomavirus vaccine
4vHPV: quadrivalent human papillomavirus vaccine
9vHPV: 9-valent human papillomavirus vaccine

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