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REVIEW

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Human papillomavirus vaccination at the first opportunity: An overview

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ABSTRACT

The Advisory Committee on Immunization Practices (ACIP) has recommended human papillomavirus (HPV) vaccination for adolescents in the United States since 2006. Though recommended at a similar time to the routine recommendations for adolescent tetanus, diphtheria, and acellular pertussis vaccination (Tdap) and quadrivalent meningococcal vaccination (MCV4), HPV vaccine uptake has consistently lagged behind these other adolescent vaccines. The ACIP recommends HPV vaccination at 11–12 y, with vaccination starting at 9 y of age included as an option that is routinely encouraged by the American Academy of Pediatrics and American Cancer Society. To support efforts to increase HPV vaccination at the first opportunity, this commentary summarizes the current HPV vaccination recommendations and available evidence regarding HPV vaccination starting at 9 y – including recent studies and trials documenting the effectiveness of HPV vaccination at 9 in supporting vaccine series completion, while providing future directions for research and implementation to improve HPV vaccination.

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Since first being recommended for routine use in 2006, uptake of human papillomavirus (HPV) vaccine has remained suboptimal. There have been numerous subsequent updates in vaccination licensure and recommendation, uptake, and research to support optimal HPV vaccine delivery. One strategy for improving HPV vaccine uptake is vaccination at the first opportunity, starting at 9 yof age. This manuscript provides an overview and summary of the current state of adolescent vaccination, focused on HPV vaccination, and the opportunities and challenges around starting HPV vaccination at the first opportunity.

Adolescent vaccination licensure and recommendations

Between 2005 and 2006, the introduction of three vaccines forming the "adolescent immunization platform" was a major advance in protecting adolescents from infectious diseases. During this time, over an 18-month span, the United States (US) Food and Drug Administration licensed a quadrivalent meningococcal conjugate vaccine (MCV4) for individuals aged 11–55 y;[1] two tetanus, diphtheria, and acellular pertussis (Tdap) vaccines, one for individuals aged 10–18 y and one for individuals aged 11–64 y;[2] and a human papillomavirus vaccine for females aged 9–26 y.[3]

Following these FDA licensure decisions, the Advisory Committee on Immunization Practices (ACIP) recommended MCV4 vaccination for individuals aged 11–12 y, with catch-up vaccination through 15 y of age for those who had previously not received MCV4[1]; Tdap vaccination for individuals aged 11–18 y[2]; and HPV vaccination for females aged 9–26 y, with a preferred age of vaccination of 11–12 y[3].

This initial recommendation for HPV vaccination read: "The recommended age for vaccination of females is 11–12 years. Vaccine can be administered as young as age 9 years."[3] Notably, this 2006 recommendation for routine vaccination at 11–12 y, but with vaccine able to be administered at 9–10 y[3], was harmonized with other organizations' (e.g. American Academy of Pediatrics [AAP][4], American Cancer Society [ACS][5]) recommendations, but over the years, the recommendations of AAP and ACS have been updated following new evidence supporting vaccination at the first opportunity. One significant advance was the 2009 update to the HPV vaccine recommendation that indicated that males at high risk for HPV infection may receive HPV vaccine through age 26[6], followed by a 2011 update for routine HPV vaccination for males aged 9–21 y, and an allowance for vaccination of males aged 22–26 y[7]. These age differences, which may have impacted perceptions of need for HPV vaccination for males, have been addressed through the most current HPV vaccine recommendations. The current ACIP recommendation reads "HPV vaccination is routinely recommended at age 11 or 12 years; vaccination can be given starting at age 9 years. Catch-

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up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated."[8] with no distinction by sex, as earlier recommendations had made[3,9,10]. More recently released recommendations from the AAP ("… recommends starting the [HPV vaccine] series between 9 and 12 y, at an age that the provider deems optimal for acceptance and completion of the vaccination series.")[11] and ACS ("… recommends routine HPV vaccination for females and males between the ages of 9 and 12 years.")[12,13] maintain a consistency with the ACIP in that 11–12-y-olds are included in the main recommendation, but the AAP and ACS recommendations also more clearly indicate vaccination at the first opportunity, which is recommended by ACIP but not as directly. Subtle wording changes, as shown here, are associated with a negative impact on willingness to recommend HPV vaccination at the first opportunity[14].

Adolescent vaccine uptake

Despite introduction within approximately 18 months of each other, a lower proportion of adolescents is vaccinated against HPV than against MCV4 and Tdap. In 2021, 77% of US adolescents aged 13–17 y initiated the HPV vaccine series, with 62% completing the series.[15] This stands in stark contrast with uptake of Tdap (90%) and MCV4 (89%),[15] and also falls behind the Healthy People 2030 goal of 80% of 13–15-y-old adolescents who have received all recommended doses of the HPV vaccine.[16] Additionally, disparities in HPV vaccine uptake have been noted, with lower coverage in the southern US compared to the Northeastern US, lower coverage among males compared to females, and lower coverage in rural areas compared to metropolitan statistical areas. Notably, one traditional health disparity – vaccination coverage by race and ethnicity – has been reversed for HPV vaccination, with higher coverage among racial and ethnic minorities compared to non-Hispanic White adolescents as well as among adolescents living below poverty compared to those living at or above poverty.[15]

The goal of HPV vaccination recommendations is for the HPV vaccine series to be completed prior to the thirteenth birthday.[17] A 2021 study of 11 y of NIS-Teen data (2008–2018), focused on the 13-y-old cohort in each years' survey evaluated vaccination at aged 9–12 y, documented vaccine series initiation and completion by 13 y of age. While increases occurred over time, the level of increases differed by vaccine series initiation and completion. In 2008, 17% of 13-y-olds had initiated HPV vaccination, rising to 63% in 2018. However, the gains were not as pronounced for HPV vaccine series completion among 13-y-olds, rising from 14% in 2008 to 33% in 2018.[18] The most recent NIS-teen data from 2021 indicate that on-time completion (by age 13) of the HPV vaccine series was 49.4%.[15]

One method that has been employed to encourage completion of the HPV vaccine series by age 13 has been the implementation of a Centers for Disease Control and Prevention (CDC) I*mmunization* for *Adolescents Combination 2 (IMA-2)* quality measure incorporated into the Healthcare Effectiveness Data and Information Set (HEDIS), used to assess the quality of healthcare delivery. The measure specifically focused on evaluating receipt of one dose each of Tdap and MCV4 and completion of the HPV vaccine series by the thirteenth birthday.[17] The most recent data, for 2020, highlights continued gaps in HPV vaccination by the thirteenth birthday. Across the three types of healthcare delivery (commercial health maintenance organization [HMO], commercial preferred provider organization [PPO], and Medicaid HMO), MCV4 coverage by 13 y ranged from 78.4% to 83.4%; Tdap coverage ranged from 83.2% to 88.2%; and HPV vaccine series completion ranged from 29.2% to 39.9%. With an additional emphasis on monitoring all adolescent vaccines by age 13, we have better benchmarks for comparison to support efforts to improve adolescent vaccine uptake.

Taken together, these recent analyses of adolescent vaccine uptake in the US show that gaps in HPV vaccine coverage have not yet been sufficiently addressed, leaving large numbers of adolescents and young adults unprotected from HPV-related cancers.

Initiating HPV vaccination at the first opportunity

AAP and ACS recommend routine HPV vaccination at 9–12 y of age, and the ACIP states that that HPV vaccination "can be administered" starting at 9 y of age. These recommendations offer an opportunity to improve HPV vaccine uptake with starting vaccination at the first opportunity. This approach can be successful in increasing adolescent HPV vaccine coverage.

First, a practice-based quality improvement initiative, which changed electronic medical record alert prompts to indicate a need for HPV vaccination starting at 9 y of age, led to an 8-fold increase in vaccination prior to 11 y of age (4.6% to 35.7%) during the 6 months following the start of the initiative and a 13-fold increase (to 60.8%) within 18 months of the start of the initiative.[19] This offers a relatively low effort action that can be taken to give a larger number of pre-teens an opportunity to be vaccinated.

Second, in a retrospective, population-based review of medical records in a regional health system, adolescents who initiated HPV vaccination at 9–10 y of age were more likely to have completed the series by 13.5 y of age, compared to those who initiated at 11–12 y of age (97.5% versus 78%, respectively).[20]

Third, a provider-focused multi-level intervention in pediatric and family medicine offices serving primarily low-income and minority populations increased HPV vaccination at 9–10 y of age by 13% points. Notably, following the initial intervention and evaluation, this increase continued to grow in the post-intervention period, yielding a 27% point uptick in HPV vaccination at ages 9–10.[21] Two of these practices were followed for 4 y, 2016–2020, spanning the pandemic and showed long-term sustainability of the intervention with increases of on-time series completion by 13th birthday from 62% to 88%.[22] Another study, started in 2014, conducted in a different population but using a similar intervention, documented increases in HPV vaccine uptake that were sustained through 2021.[23] These two studies, taken together, provide preliminary evidence that this type of multi-level intervention may be generalizable for use in a variety of populations to achieve high and sustained HPV vaccine uptake.

These studies, while not encompassing the full and ever-evolving state of the literature on age at HPV vaccination,[19–25] show that when a concerted effort to vaccinate at 9–10 y of age is put into place, it is followed by increases in a variety of measures of HPV vaccination, including vaccine series initiation and completion.

Provider and parent attitudes toward HPV vaccination at the first opportunity

Some healthcare providers routinely recommend HPV vaccination starting at 9–10 y of age. A 2021 survey of 1,047 primary care professionals in the US documented that 21% routinely recommend HPV vaccination at 9–10 y of age. While relatively low, an additional finding in this survey – an additional 48% of healthcare professionals were somewhat or more willing to start recommending HPV vaccination at age 9 – indicates a willingness on the part of pediatric health care providers to vaccinate against HPV at the earliest opportunity.[26] Additionally, a recent study found that 65% of federally qualified health center providers strongly recommend HPV vaccination starting at ages 9–10 y.[27]

This is critical because adolescents are less likely to attend primary care visits for routine checkups as they get older.[28] In the 2021 NIS-Teen,[29] 82% of adolescents had a well-child checkup at ages 11–12, indicating that adolescent healthcare visits are occurring; this is also borne out by the high coverage of Tdap and MCV4 vaccines. However, as documented by Rand and Goldstein, the proportion of children having a well-child visit at 9 y of age is similar to that for 11–12 y-olds.[28] This presents an opportunity for additional recommendations for HPV vaccination starting at age 9.

Starting HPV vaccination at 9 y of age simplifies vaccination at older ages. When the first HPV vaccine dose is given at 9 y of age, the second HPV vaccine dose can be given at the next year's well-child visit, completing the series at 10 y of age. This allows for the provision of only two routine vaccines at the 11-y-old checkup (Tdap and MCV4), while providing space for provision of influenza and COVID-19 vaccines as needed. This is important because both parents[30] and healthcare providers[30,31] see the appeal in the opportunity to receive fewer adolescent vaccines per visit. Additionally, healthcare providers have reported that giving HPV vaccine recommendations before 11 y of age is associated with lowered parental concerns about sexual activity after HPV vaccination.[31] While that concern has been shown to be unfounded in multiple studies,[32–36] it may still be a prevalent concern for parents, and one that can be addressed by recommending HPV vaccine starting at age 9.

Finally, numerous studies have highlighted that starting HPV vaccine recommendations at 9 y of age can lead to easier and shorter discussions with parents, particularly when mention of sex or sexual activity are less of an issue.[25,31,37]

Next steps for HPV vaccination at the first opportunity – data needs and implementation challenges

Starting recommendations for HPV vaccination at ages 9–10 has been shown to improve vaccine acceptance in research trials, but this evidence is limited in scope, and broader implementation of these recommendations faces several challenges.

First, the impact of the COVID-19 pandemic on HPV vaccine uptake is only now beginning to be understood, and pandemic-related declines in vaccine delivery highlight a need for greater efforts to conduct both catch-up and routine vaccination. The parents of adolescents aged 13–17 y are surveyed for NIS-Teen, but because most adolescent vaccines are recommended at 11–12 y of age, vaccination status measured in 2021 may reflect vaccines received years before the onset of the COVID-19 pandemic. Thus, we may not see the full impact of the COVID-19 pandemic until we have additional years of NIS-Teen data reporting. This highlights the need for vaccine uptake monitoring through a variety of sources, including state-level immunization information systems, health system and managed care organization data, and insurance claims data, to better triangulate the drivers of coverage and the impact of the COVID-19 pandemic.

Second, more granular analysis and reporting of age at vaccination, preferably by birth cohort, is needed to understand the dynamics of HPV vaccine recommendations and receipt. Analyses, such as those done with the annual NIS-Teen, combine estimates from 13–17-y-olds, and make it difficult to disentangle coverage by birth cohort, or make comparisons by birth cohort over multiple years' NIS-Teen reports. Given the reporting delays for NIS-Teen described above, this is an opportunity for state-level immunization information systems to increase the breadth and depth of the data analysis and reporting from these systems. While there has been some increase in this type of data analysis, this has been an underutilized resource.[38–40]

Third, most implementation studies of programs to improve HPV vaccination at 9–10 y of age have been limited in scope, both in terms of geography and number of clinics and providers. Several have included vaccination at age 9 as one part of multi-component interventions, limiting the ability to separate the effects of age change alone from other intervention effects. Additional trials are underway focusing on the impact of changing only the age at which HPV vaccines are recommended. More comprehensive intervention research, including a focus on drivers of successful implementation,[41] is needed to expand our evidence base for appropriate methodology and systems to improve delivery of HPV vaccination at the first opportunity.

Fourth, for primary care practices that have been successful in delivering high levels of timely HPV vaccination and getting adolescents fully vaccinated as part of bundling programs with Tdap and MCV4, these efforts should be supported and continued. The discussions contained here are not to say that all pediatric and adolescent providers should shift to recommending HPV vaccination at 9 y of age, but that for practices where these successes have not materialized, starting HPV vaccination at the first opportunity offers an option to increase coverage.

Finally, providers and parents may still have some hesitancy around the rationale for HPV vaccination starting at 9 y of age.[31,42] Widespread dissemination of communications tools and outreach activities (such as those available through the

National HPV Vaccination Roundtable)[43] are needed to address these gaps, as well as to help providers see that parents are accepting of HPV vaccination, in general[30] and at age 9.[31]

Conclusions

Since the introduction of three adolescent vaccines almost two decades ago, coverage has surpassed national goals for Tdap and MCV4 vaccine. HPV vaccine coverage remains far below those goals, despite substantial progress. Given the structure of current HPV vaccine recommendations, starting HPV vaccination at the first opportunity – age 9 – is within the scope of these recommendations and should be considered for clinical practice as an aid to improving HPV vaccine uptake.[44]

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Disclosure statement

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