A Second Look

Understanding the Two-Dose HPV Vaccine Schedule

Kate T. McNair

Holly B. Fontenot

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Kate T. McNair, BSN, RN, is a student in the MSN-PhD program at the W. F. Connell School of Nursing at Boston College and a registered nurse at the Dimock Center in Roxbury, MA. Holly B. Fontenot, PhD, RN, WHNP-BC, is an assistant professor at W. F. Connell School of Nursing at Boston College in Chestnut Hill, MA, and a nurse practitioner at Fenway/Sidney Borum Jr. Health Center in Boston, MA. The authors report no conflicts of interest or relevant financial relationships. Address correspondence to: holly.fontenot@bc.edu.

Abstract Recent advances in human papillomavirus (HPV) science have led to updates to national HPV vaccine recommendations. This column takes a second look at two recent studies that provide evidence to support the current two-dose HPV vaccination schedule for youth ages 9 to 14 years. This short review will help nurses and other clinicians understand the health and economic benefits of the current dosing recommendation. Nurses are leaders in national vaccination efforts; therefore, it is vital that they remain up to date on the latest
evidence that supports vaccination practice as well as health counseling and HPV vaccine recommendations.

**Keywords** adolescent health | HPV | human papillomavirus | two-dose schedule | vaccine

Nearly 80 million persons in the United States are infected with human papillomavirus (HPV); 14 million new infections occur each year, and persistent infection leads to more than 30,000 new HPV-associated cancer diagnoses among men and women each year (Centers for Disease Control and Prevention [CDC], 2016a). The primary HPV-related cancer affecting women is cervical cancer, and the primary HPV-related cancer affecting men is oropharyngeal cancer (CDC, 2016a). Research has documented that HPV vaccination can reduce the incidence of HPV infection, especially in countries that have achieved high vaccine uptake. Maximal reductions of nearly 90% of the HPV types in the previous 4-valent vaccine (types 6, 11, 16, and 18) and 85% of high-grade cervical cytologic abnormalities have been reported (Garland et al., 2016). U.S. data have begun to reflect declines in HPV infection prevalence (Markowitz et al., 2013); however, greater adolescent vaccination rates are needed to fully realize the health benefits of HPV vaccination in the United States (Garland et al., 2016; Rimer, Harper, & Witte, 2014).

There have been recent advances to the HPV vaccine characteristics, dosing, and guidelines. The most superior and currently available HPV vaccine in the United States is the 9-valent (9vHPV) vaccine. This updated HPV vaccine first received recommendation from the Advisory Committee on Immunization Practices (ACIP) in 2015 with a three-dose schedule,
the same as the preceding 4-valent vaccine. It has documented safety and efficacy and protects against nine viral strains, seven of which account for more than 90% of HPV-causing cancers (types 16, 18, 31, 33, 45, 52, and 58) and two of which account for 90% of anal/genital condylomas (types 6 and 11) (Petrosky et al., 2015). Then, in 2016, the ACIP updated the 9vHPV dosing guidelines and approved a two-dose schedule for children and early adolescents ages 9 through 14 years (Meites, Kempe, & Markowitz, 2016). This two-dose change was based on more recent evidence (Dobson et al., 2013; Krajden et al., 2011; Romanowski et al., 2011) and follows patterns in the international community led by dosing changes made by the World Health Organization in 2014. Current HPV vaccine guidelines in the United States as set by the ACIP and the CDC are summarized in Box 1.

The purpose of this column is to review two recently published studies important to women’s health nursing. The two studies chosen contributed to the scientific evidence that supported the most recent CDC 9vHPV vaccine recommendation to move from a three-dose to a two-dose vaccination schedule for early adolescents. Review of these studies will provide nurses a clear understanding of the health and economic benefits of this switch in the United States. In the first study, Iversen et al. (2016) examined the immunogenicity—that is, the vaccine’s ability to provide protection—of the two-dose versus the three-dose 9vHPV vaccine among males and females. This study provides Level II-1 evidence (see Box 2). In the second study, Laprise, Markowitz, Chesson, Drolet, and Brisson (2016) showed the potential health and economic impact of this schedule change using a cost–utility analysis (Level II-3 evidence, see Box 2). Understanding recent changes and rationales for changes in vaccine guidelines
will help nurses provide comprehensive up-to-date care and enhance nurses’ abilities to be strong advocates for and recommenders of HPV vaccination for all youth.

**First Study**

*Design, Sample, and Data Analysis*

Iversen et al. (2016) conducted an open-label, noninferiority, immunogenicity trial across 52 health centers in 15 countries. The objective of the study was to determine if the HPV type-specific antibody response would be similar among boys and girls (age range = 9–14 years) who received a two-dose 9vHPV schedule versus a three-dose 9vHPV schedule among adolescent/young women (age range = 16–26 years). Youth were grouped into five categories: (a) girls (9–14 years) who received two doses 6 months apart, (ii) boys (9–14 years) who received two doses 6 months apart, (iii) girls and boys (9–14 years) who received two doses 12 months apart, (iv) girls (9–14 years) who received three doses over 6 months, and (iv) adolescent/young women (16–26 years) who received three doses over 6 months. Youth were excluded if they were pregnant, had allergies to the vaccine components, had already obtained the HPV vaccine, had a history of thrombocytopenia, and/or had a prior history of or were currently undergoing immunosuppression (Iversen et al., 2016). The primary outcome was the antibody response against the nine viral types in 9vHPV just before the first dose and then again 1 month after any dosing schedule completion. Data analysis included characteristics of the sample and a noninferiority analysis of antibody geometric mean titers at the protocol set points.

*Findings*
Overall, 1,518 youth were enrolled, 1,474 completed the study, and analysis was conducted on 1,377 youth (Iversen et al., 2016). The sample consisted of 753 girls (mean age = 11.4 years), 451 boys (mean age = 11.5 years), and 314 adolescent/young women (mean age = 21.0 years). Each of the five participant categories had approximately 300 youth. The geometric mean titer antibody levels for all nine viral types were higher in all youth (ages 9–14 years) who obtained two-dose schedules. The two-dose schedule was noninferior to the three-dose schedule. In post hoc analyses to assess long-term response of the antibodies, the ratio of antibody geometric mean titers for girls and boys (two-dose schedule) compared with those who received the three-dose schedule were maintained above the noninferiority threshold after six additional months. Furthermore, the girls who received three doses had higher ongoing antibody titer levels compared with the adolescent/young women (Iversen et al., 2016).

**Study Conclusions**

The two-dose schedule (separated by 6 or 12 months) for the 9vHPV vaccine in young girls and boys produced an immune response that was as effective and was noninferior to the three-dose schedule in the cohort of older adolescent/young women (Iversen et al., 2016). Future studies should evaluate longer-term noninferiority; the two-dose schedule has yet to be tested in youth ages 15 years or older. This study was limited by the lack of universally accepted noninferiority criteria; however, investigators followed the widely adopted approach to this work. Finally, Iversen et al. (2016) discussed the benefits of the two-dose schedule as providing flexibility, entailing fewer visits to the health center, and potentially reducing the total costs for HPV vaccination.
Second Study

Design, Sample, and Data Analysis

Laprise et al. (2016) reported on a cost-effectiveness analysis aimed at examining the potential U.S. health and economic impact of changing from the three-dose to the two-dose 9vHPV vaccination schedule. Their mathematical model used the U.S. version of HPV-ADVISE, a dynamic model used in the United States extensively to inform vaccine policy decisions, to test their schedule change scenarios. For the two scenarios tested, the investigators used extant U.S. HPV vaccine uptake data (years 2007–2014) and assumed that (a) vaccination rates would remain constant with the change to a two-dose schedule and/or (b) vaccination rates would increase by 5% to 15% because of the simpler two-dose schedule. A cost–utility analysis was performed using only direct medical costs. To be conservative in their analysis, investigators assumed that (a) the HPV vaccine efficacy was 95% for both dosing schedules and (b) the three-dose schedule would produce lifetime protection, whereas the two-dose schedule would protect between 10 years and lifetime (Laprise et al., 2016).

Findings

The model predicted that a two-dose schedule, if protection lasted 20 years or longer, would provide substantial reductions in HPV-associated diseases, including reductions of at least 68% in ano-genital warts, 76% in cervical intraepithelial neoplasia (dysplasia) Grades 2 or 3, 78% in cervical cancer, and 69% in all other HPV-associated cancers after 100 years of vaccination versus no vaccination. The model also predicted cost savings in all scenarios tested, with savings ranging from approximately $118,700 to $2,042,200, depending on duration of protection (Laprise et al., 2016). Additionally, the authors suggested that if the
two-dose vaccination increased coverage by even 5%, the three doses would be more expensive and less beneficial. In this scenario, the additional benefits of the third dose would be small (Laprise et al., 2016).

Study Conclusions

According to Laprise et al. (2016), as long as the two-dose schedule provides at least 20 years of protection, receiving two doses of 9vHPV would reduce HPV disease and reduce national health care costs by millions. To address study weaknesses, particularly associated with uncertainty related to duration of protection between the two dosing schedules, the investigators tested several assumptions related to duration of protection in their model. Plus, the investigators referenced current research that has highlighted long-lasting immunogenicity for both dosing schedules. However, in this model, if the two-dose schedule provided less than 20 years of protection and the three-dose schedule still provided lifetime protection, then the results would be reversed, and the two-dose schedule would be less effective in long-term reductions in HPV diseases at the population level and would not be cost effective (Laprise et al., 2016).

Comments on These Two Studies

Authors of these two recent studies provide evidence to support the new HPV vaccine dosing guidelines set by the ACIP and CDC. It is important for nurses to understand this background to facilitate health education about the benefits associated with the recent changes in HPV dosing guidelines. Together, these studies provide evidence for two-dose efficacy (Iversen et al., 2016) and cost effectiveness (Laprise et al., 2016).
Ongoing research should continue to evaluate the duration of vaccine protection for the two- and three-dose schedules. In addition, research should explore the impact of the two-dose schedule on U.S. vaccination rates. Authors of previous research highlighted the fact that parents believed that a 9vHPV two-dose schedule would be easier, more convenient, and less expensive and would facilitate vaccine dosing completion (Fontenot, Domush, & Zimet, 2015). However, despite these benefits, it is possible that nurses and other health care providers may experience difficulties transitioning from the three-dose to the two-dose schedule. This change may cause confusion among clinicians and consumers.

Implications for Nursing Practice

It is vital that nurses remain up to date on the latest evidence that supports clinical practice changes. Providing consistent HPV vaccine education and messaging is necessary to eliminate concern or confusion among patients and parents. Studies confirm that a health care provider’s recommendation is the strongest predictor of vaccine acceptance by consumers (Gold, Naleway, & Riedlinger, 2013; Lau, Lin, & Flores, 2012; Rahman, Laz, McGrath, & Berenson, 2015; Rosenthal et al., 2011; Ylitalo, Lee, & Mehta, 2013). Additionally, how a health care provider communicates accurate information is important to parental vaccine acceptance. Parents want health care providers to show high levels of confidence in and knowledge about the HPV vaccine (Fontenot, Domush, & Zimet, 2015). The CDC (2016b) recommends that all health care providers use clear, simple language when recommending the HPV vaccine. Recommendations should be direct and discussed in the same way and on the same day as all other routinely recommended adolescent vaccinations (e.g., Tdap and
meningococcal vaccines). An example of a clear recommendation is provided by the CDC: “Now that your son is 11, he is due for vaccinations today to help protect him from meningitis, HPV cancers, and pertussis” (CDC, 2016b, para. 1).

It is also important to promote 9vHPV vaccination at the recommended age of 11 to 12 years. Evidence supports greater immune response to all HPV types for early adolescents (Meites et al., 2016; WHO, 2014). If adolescents do not obtain the vaccine at the recommended age, it is important to provide catch-up vaccination. Adolescents ages 13 to 14 years can be caught up with a two-dose schedule; however, if vaccination is delayed even longer (initiated at age 15 years or older), older adolescents will need to receive three full doses to achieve immunity. See Box 3 for important points to remember and Box 4 for select online resources.

Finally, nurses can play a significant role in ensuring vaccine series completion. To aid in vaccine dosing completion, appointments for additional doses should be made on the same day as the initial dose (CDC, 2016b). Additionally, office-based reminder systems and bundling of vaccination with other office visits may also have positive outcomes (Fontenot et al., 2016; Vadaparampil et al., 2014).

**Conclusion**

Evidence supports the current ACIP and CDC routine recommendation for youth at ages 11 to 12 years to obtain the 9vHPV in two doses. Authors of current research showed that two doses given at least 6 months apart for youth between the ages of 9 and 14 years were as good, if not better, than 3 doses. Older adolescents and adults (ages 15–26 years) still need to obtain three
doses over a 6-month time frame; however, if the vaccination dosing schedule is interrupted or the patient presents to care late, vaccine doses do not need to be repeated (CDC, 2016a). The new two-dose schedule seems to be cost-effective and acceptable to parents. Nurses have an opportunity to take the lead as strong advocates for this cancer prevention vaccination.
Box 1. Current U.S. Recommendations for HPV Vaccination

- Vaccination with 9vHPV in a two-dose series (at 0 and at 6–12 months) is routinely recommended for youth (boys and girls) ages 11 to 12 years. Youth could be given the two-dose series as early as age 9 years.
- For adolescents who do not obtain the vaccine by the recommended age, catch-up vaccination through age 14 years in a two-dose series is recommended; however, late adolescent/young adult women ages 15 to 26 years and men ages 15 to 21 years still need a three-dose series (at 0, 1–2, and 6 months).
- Routine three-dose vaccination is also recommended for all youth and young adults (ages 9–26 years) who are immunocompromised.
- HPV vaccination is recommended for men who have sex with men and for transgender persons through age 26 years.

Note. 9vHPV = 9-valent human papillomavirus; HPV = human papillomavirus.

Source: Meites et al. (2016).
Box 2. Levels of Evidence

The quality of evidence for a study is based on a grading system that evaluates the scientific rigor of a design, as developed by the U.S. Preventive Services Task Force. The levels are as follows:

I:  Evidence obtained from at least one properly randomized controlled trial.

II-1:  Evidence obtained from well-designed controlled trials without randomization.

II-2:  Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3:  Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III:  Opinions of respected authorities, based on clinical experience: descriptive studies and case reports or reports of expert committees.

Box 3. Important Points to Remember

Dosing

- It is recommended that all children ages 11 to 12 years obtain the 9vHPV two-dose schedule (two doses at least 6 months apart)
- Catch up all children who missed vaccination, through age 14 years, with a 9vHPV two-dose schedule
- Catch up all youth ages 15 years or older with a 9vHPV three-dose schedule (three doses at 0, 1–2, and 6 months)

Examples of clear, simple language regarding HPV vaccination:

- The HPV vaccine is important because it prevents infections that can cause cancer.
- As with all vaccines, we want to give HPV vaccine earlier rather than later.
- Studies continue to prove that HPV vaccination works extremely well.

For more information see Talking to Parents About HPV Vaccine, available at www.cdc.gov/hpv/hcp/for-hcp-tipsheet-hpv.pdf

Note. 9vHPV = 9-valent human papillomavirus; HPV = human papillomavirus.
Box 4. Select Online Resources

For Consumers

Centers for Disease Control and Prevention
https://www.cdc.gov/hpv/parents/index.html

YouTube
https://www.youtube.com/watch?v=1b0lJTC6K7o&list=PL807F3A190A32DF2E

For Nurses

Centers for Disease Control and Prevention
https://www.cdc.gov/hpv/hcp/index.html
https://www.cdc.gov/hpv/hcp/answering-questions.html
References


