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# Human papillomavirus in 2019: An update on cervical cancer prevention and screening guidelines

## ABSTRACT

The human papillomavirus (HPV) causes most cases of cervical cancer. Healthcare providers can help prevent this cancer by recommending HPV vaccination when appropriate, regularly screening women for cervical cancer, and following up on abnormal test results.

## KEY POINTS

Immunization against HPV can prevent up to 70% of HPV-related cervical cancer cases.

Gardasil 9 is the only HPV vaccine currently available in the United States and is now approved for use in males and females between the ages of 9 and 45.

In girls and boys younger than 15, a 2-dose schedule is recommended; patients ages 15 through 45 require 3 doses.

Vaccine acceptance rates are highest when primary care providers announce that the vaccine is due rather than invite open-ended discussions.

Regular cervical cancer screening is an important preventive tool and should be performed using the Papanicolaou (Pap) test, the high-risk HPV-only test, or the Pap-HPV cotest.

ABOUT 12% OF WOMEN worldwide are infected with human papillomavirus (HPV).<sup>1</sup> Persistent HPV infection with high-risk strains such as HPV 6, 11, 16, and 18 cause nearly all cases of cervical cancer and some anal, vaginal, penile, and oropharyngeal cancers.<sup>2</sup> An estimated 13,000 cases of invasive cervical cancer will be diagnosed this year in the United States alone.<sup>3</sup>

Up to 70% of HPV-related cervical cancer cases can be prevented with vaccination. A number of changes have been made to the vaccination schedule within the past few years—patients younger than 15 need only 2 rather than 3 doses, and the vaccine itself can be used in adults up to age 45.

Vaccination and routine cervical cancer screening are both necessary to prevent this disease<sup>3</sup> along with effective family and patient counseling. Here, we discuss the most up-to-date HPV vaccination recommendations, current cervical cancer screening guidelines, counseling techniques that increase vaccination acceptance rates, and follow-up protocols for abnormal cervical cancer screening results.

## ■ TYPES OF HPV VACCINES

HPV immunization can prevent up to 70% of cases of cervical cancer due to HPV as well as 90% of genital warts.<sup>4</sup> The US Food and Drug Administration (FDA) has approved 3 HPV vaccines:

- Gardasil 9 targets HPV types 6, 11, 16, and 18 along with 31, 33, 45, 52, 58—these cause 90% of cervical cancer cases and

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TABLE 1

## HPV vaccination timeline, male and female

| Age 9–14                              | Age 15–26                                | Age 21–26 (male)                | Age 27–45                                   |
|---------------------------------------|--|---------------------------------|---|
| 2-dose HPV vaccine, 0 and 6–12 months | 3-dose HPV vaccine, 0, 1–2, and 6 months | Vaccine offered, 3-dose regimen | FDA-approved, but not routinely recommended |

FDA = US Food and Drug Administration; HPV = human papillomavirus

most cases of genital warts<sup>5</sup>—making it the most effective vaccine available; Gardasil 9 is the only HPV vaccine currently available in the United States

- The bivalent vaccine (Cervarix) targeted HPV 16 and 18 only, and was discontinued in the United States in 2016
- The quadrivalent HPV vaccine (Gardasil) targeted HPV 16 and 18 as well as 6 and 11, which cause most cases of genital warts; the last available doses in the United States expired in May 2017; it has been replaced by Gardasil 9.

The incidence of cervical cancer in the United States dropped 29% among 15- to 24-year-olds from 2003–2006 when HPV vaccination first started to 2011–2014.<sup>6</sup>

### VACCINE DOSING RECOMMENDATIONS FOR PRIMARY PREVENTION

The Advisory Committee on Immunization Practices (ACIP) revised its HPV vaccine schedule in 2016, when it decreased the necessary doses from 3 to 2 for patients under age 15 and addressed the needs of special patient populations.<sup>7</sup> In late 2018, the FDA approved the use of the vaccine in men and women up to age 45. However, no change in guidelines have yet been made (Table 1).

In females, the ACIP recommends starting HPV vaccination at age 11 or 12, but it can be given as early as age 9. A 2-dose schedule is recommended for the 9-valent vaccine before the patient's 15th birthday (the second dose 6 to 12 months after the first).<sup>7</sup> For females who initiate HPV vaccination between ages 15 and 45, a 3-dose schedule is necessary (at 0, 1 to 2, and 6 months).<sup>7,8</sup>

The change to a 2-dose schedule was prompted by an evaluation of girls ages 9 to 13 randomized to receive either a 2- or 3-dose schedule.

Antibody responses with a 2-dose schedule were not inferior to those of young women (ages 16 to 26) who received all 3 doses.<sup>9</sup> The geometric mean titer ratios remained noninferior throughout the study period of 36 months.

However, a loss of noninferiority was noted for HPV-18 by 24 months and for HPV-6 by 36 months.<sup>9</sup> Thus, further studies are needed to understand the duration of protection with a 2-dose schedule. Nevertheless, decreasing the number of doses makes it a more convenient and cost-effective option for many families.

The recommendations are the same for males except for one notable difference: in males ages 21 to 26, vaccination is not routinely recommended by the ACIP, but rather it is considered a “permissive use” recommendation: ie, the vaccine should be offered and final decisions on administration be made after individualized discussion with the patient.<sup>10</sup> Permissive-use status also means the vaccine may not be covered by health insurance. Even though the vaccine is now available to men and women until age 45, many insurance plans do not cover it after age 26.

Children of either sex with a history of sexual abuse should receive their first vaccine dose beginning at age 9.<sup>7</sup>

Immunocompromised patients should follow the 3-dose schedule regardless of their sex or the age when vaccination was initiated.<sup>10</sup>

For transgender patients and for men not previously vaccinated who have sex with men, the 3-dose schedule vaccine should be given by the age of 26 (this is a routine recommendation, not a permissive one).<sup>8</sup>

### CHALLENGES OF VACCINATION

Effective patient and family counseling is important. Even though the first HPV vaccine was approved in 2006, only 34.9% of US ado-

The ACIP recommends HPV vaccination for girls at age 11 or 12, but it can be done as early as age 9

lescents were fully vaccinated by 2015. This was in part because providers did not recommend it, were unfamiliar with it, or had concerns about its safety,<sup>11,12</sup> and in part because some parents refused it.

The physician must address any myths regarding HPV vaccination and ensure that parents and patients understand that HPV vaccine is safe and effective. Studies have shown that with high-quality recommendations (ie, the care provider strongly endorses the HPV vaccine, encourages same-day vaccination, and discusses cancer prevention), patients are 9 times more likely to start the HPV vaccination schedule and 3 times more likely to follow through with subsequent doses.<sup>13</sup>

Providing good family and patient education does not necessarily require spending more counseling time. A recent study showed that spending less time discussing the HPV vaccine can lead to better vaccine coverage.<sup>14</sup> The study compared parent HPV vaccine counseling techniques and found that simply informing patients and their families that the HPV vaccine was due was associated with a higher vaccine acceptance rate than inviting conversations about it.<sup>14</sup> When providers announced that the vaccine was due, assuming the parents were ready to vaccinate, there was a 5.4% increase in HPV vaccination coverage.<sup>14</sup>

Conversely, physicians who engaged parents in open-ended discussions about the HPV vaccine did not improve HPV vaccination coverage.<sup>14</sup> The authors suggested that providers approach HPV vaccination as if they were counseling patients and families about the need to avoid second-hand smoke or the need to use car seats. If parents or patients resist the presumptive announcement approach, expanded counseling and shared decision-making are appropriate. This includes addressing misconceptions that parents and patients may have about the HPV vaccine. The American Cancer Society lists 8 facts to reference (Table 2).<sup>15</sup>

## ■ SECONDARY PREVENTION: CERVICAL CANCER SCREENING

Since the introduction of the Papanicolaou (Pap) test, US cervical cancer incidence rates have decreased by more than 60%.<sup>16</sup> Because

TABLE 2

### Facts about the human papillomavirus (HPV) vaccine

- The HPV vaccine is safe
- The HPV vaccine causes no bad side effects
- The HPV vaccine does not cause fertility problems
- The HPV vaccine does not contain harmful ingredients
- Getting the HPV vaccine is not opening the door to having sex
- The HPV vaccine is for both males and females
- The HPV vaccine works and can help prevent cervical cancer
- The HPV vaccines last a long time, maybe forever

Information from the American Cancer Society, reference 15.

almost all cervical cancer is preventable with proper screening, all women ages 21 to 65 should be screened.

Currently, there are 3 options available for cervical cancer screening: the Pap-only test, the Pap-HPV cotest, and the high-risk HPV-only test (Table 3). The latter 2 options detect high-risk HPV genotypes.

Several organizations have screening algorithms that recommend when to use these tests, but the 3 that shape today's standard of care in cervical cancer screening come from the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP), and US Preventive Services Task Force (USPSTF).<sup>17-19</sup>

**Pap-only testing** is performed every 3 years to screen for cervical neoplasia that might indicate premalignancy.

**Pap-HPV cotesting** is performed every 5 years in women older than 30 with past normal screening. Until 2018, all 3 organizations recommended cotesting as the preferred screening algorithm for women ages 30 to 65.<sup>17-19</sup> Patients with a history of abnormal test results require more frequent testing as recommended by the ASCCP.<sup>18</sup>

**The high-risk HPV-only test** utilizes real-time polymerase chain reaction to detect HPV 16, HPV 18, and 12 other HPV genotypes. Only 2 tests are approved by the FDA as stand-alone cervical cancer screening

**With effective counseling, patients are 9 times more likely to start the vaccine series, and 3 times more likely to complete the series**

TABLE 3

**Cervical cancer screening recommendations, ACOG, ASCCP, USPSTF**

|                           | ACOG <sup>17</sup>          | ASCCP <sup>18</sup>         | USPSTF <sup>19</sup>        |
|---------------------------|-----------------------------|-----------------------------|-----------------------------|
| <b>Pap only</b>           | Every 3 years               | Every 3 years               | Every 3 years               |
| <b>Pap-HPV cotest</b>     | Every 5 years,<br>age 30–65 | Every 5 years,<br>age 30–65 | Every 5 years,<br>age 30–65 |
| <b>High-risk HPV only</b> | Every 3 years,<br>age > 25  | Every 3 years,<br>age > 25  | Every 5 years,<br>age 30–65 |

ACOG = American College of Obstetricians and Gynecologists; ASCCP = American Society for Colposcopy and Cervical Pathology; HPV = human papillomavirus; USPSTF = US Preventive Services Task Force

tests—the Roche Cobas HPV test approved in 2014 and the Becton Dickinson Onclarity HPV assay approved in 2018. Other HPV tests that are used in a cotesting strategy should not be used for high-risk HPV-only testing because their performance characteristics may differ.

In 2015, the Addressing the Need for Advanced HPV Diagnostics (ATHENA) study showed that 1 round of high-risk HPV-only screening for women older than 25 was more sensitive than Pap-only or cotesting for stage 3 cervical intraepithelial neoplasia or more severe disease (after 3 years of follow-up).<sup>20</sup> Current guidelines from ASCCP<sup>18</sup> and ACOG<sup>17</sup> state that the high-risk HPV test can be repeated every 3 years (when used to screen by itself) if the woman is older than 25 and has had a normal test result.

If the HPV test result is positive for high-risk HPV 16 or 18 genotypes, then immediate colposcopy is indicated; women who test positive for one of the other 12 high-risk subtypes will need to undergo a Pap test to determine the appropriate follow-up (Figure 1).<sup>18,21</sup>

In 2018, the USPSTF updated its recommendations, noting that for women age 30 to 65, Pap-only testing every 3 years, cotesting every 5 years, or high-risk HPV-only testing every 5 years are all appropriate screening strategies, with the Pap-only or high-risk HPV-only screenings being preferred.<sup>19</sup> This is in contrast to ACOG and ASCCP recommendations for cotesting every 5 years, with alternative options of Pap-only or HPV-only testing being done every 3 years.<sup>17,18</sup>

**Is there a best screening protocol?**

The USPSTF reviewed large randomized and observational studies to summarize the effectiveness of the 3 screening strategies and commissioned a decision analysis model to compare the risks, benefits, and costs of the 3 screening algorithms. The guideline statement notes both cotesting and high-risk HPV testing offer similar cancer detection rates: each prevents 1 additional cancer per 1,000 women screened as opposed to Pap-only testing.<sup>19</sup>

Also, tests that incorporate high-risk HPV screening may offer better detection of cervical adenocarcinoma (which has a worse prognosis than the more common squamous cell carcinoma type). However, both HPV-based screening strategies are more likely to require additional colposcopies for follow-up than Pap-only screening (1,630 colposcopies required for each cancer prevented with high-risk HPV alone, 1,635 with cotesting). Colposcopy is a simple office procedure that causes minimal discomfort to the patient.

The USPSTF guideline also differs in the recommended frequency of high-risk HPV-only testing; a high-risk HPV result should be repeated every 5 years if normal (as opposed to every 3 years as recommended by ACOG and ASCCP).<sup>19</sup> The 5-year recommendation is based on analysis modeling, which suggests that performing high-risk HPV-only testing more frequently is unlikely to improve detection rates but will increase the number of screening tests and colposcopies.<sup>19</sup>

No trial has directly compared cotesting with high-risk HPV testing for more than 2 rounds of screening. The updated USPSTF

**All 3 cervical cancer screening methods are highly effective, so providers should choose the one that best fits their practice**

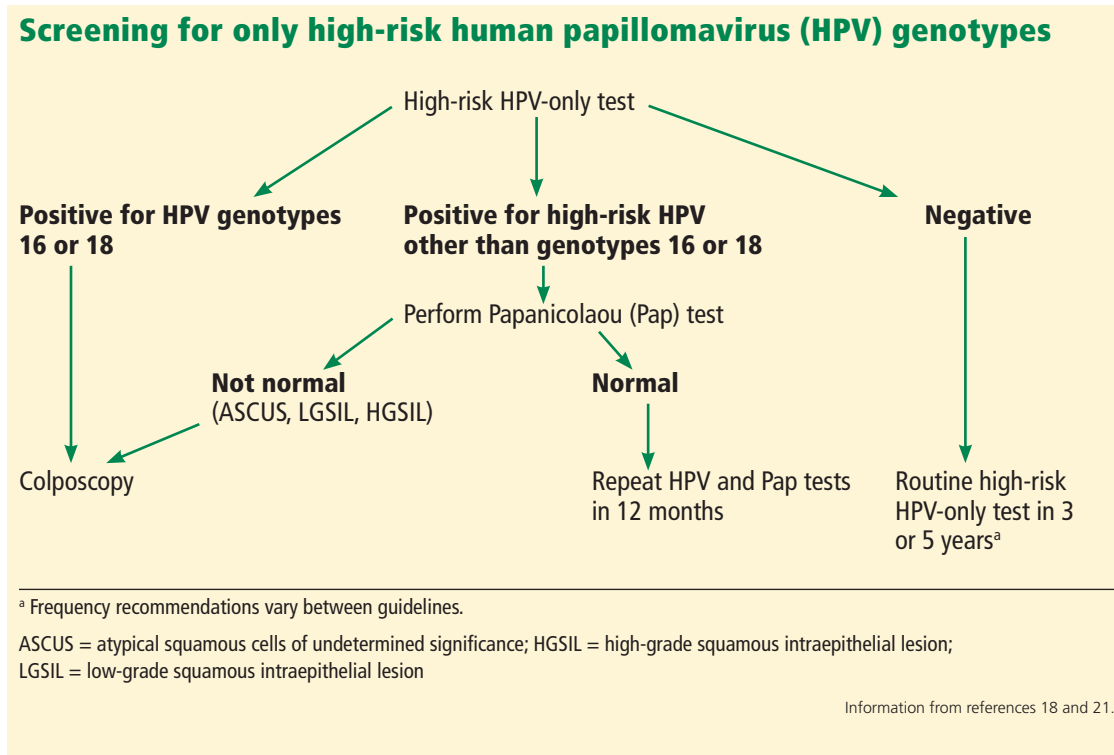


Figure 1.

recommendations are based on modeling estimates and expert opinion, which assesses cost and benefit vs harm in the long term. Also, no high-risk HPV test is currently FDA-approved for every-5-year screening when used by itself.

All 3 cervical cancer screening methods provide highly effective cancer prevention, so it is important for providers to choose the strategy that best fits their practice. The most critical aspect of screening is getting all women screened, no matter which method is used.

It is critical to remember that the *screening* intervals are intended for patients without symptoms. Those who have new concerns such as bleeding should have a *diagnostic* Pap done to evaluate their symptoms.

### Follow-up of abnormal results

Regardless of the pathway chosen, appropriate follow-up of any abnormal test result is critical to the early detection of cancer. Established follow-up guidelines exist,<sup>22,23</sup> but accessing this information can be difficult for the busy clinician. The ASCCP has a mobile phone application that outlines the action steps corresponding to the patient's age and

results of any combination of Pap or HPV testing. The app also includes the best screening algorithms for a particular patient.<sup>24</sup>

All guidelines agree that cervical cancer screening should start at age 21, regardless of HPV vaccination status or age of sexual initiation.<sup>17,18,25</sup> Screening can be discontinued at age 65 for women with normal screening results in the prior decade (3 consecutive negative Pap results or 2 consecutive negative cotest results).<sup>23</sup>

For women who have had a total hysterectomy and no history of cervical neoplasia, screening should be stopped immediately after the procedure. However, several high-risk groups of women will need continued screening past the age of 65, or after a hysterectomy.

For a woman with a history of stage 2 cervical intraepithelial neoplasia or higher grade lesions, routine screening is continued for an additional 20 years, even if she is over age 65. Pap-only testing every 3 years is acceptable, because the role of HPV testing is unclear after hysterectomy.<sup>23</sup> Prior guidelines suggested annual screening in these patients, so the change to every 3 years is notable. Many gynecologic oncologists will recommend that

**The screening intervals are for patients without symptoms; those with new concerns should have a *diagnostic* Pap test**



women with a history of cervical cancer continue annual screening indefinitely.

Within the first 2 to 3 years after treatment for high-grade dysplastic changes, annual follow-up is done by the gynecologic oncology team. Providers who offer follow-up during this time frame should keep in communication with the oncology team to ensure appropriate, individualized care. These recommendations

are based on expert opinion, so variations in clinical practice may be seen.

Women infected with the human immunodeficiency virus can have Pap-only testing every 3 years, after a series of 3 normal annual Pap results.<sup>26</sup> But screening does not stop at age 65.<sup>23,26</sup> For patients who are immunosuppressed or have a history of diethylstilbestrol exposure, screening should be done annually indefinitely.<sup>23</sup> ■

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