

9vHPV vaccine: Prevention of oropharyngeal cancer

Most clinicians and many parents know that the 9vHPV vaccine prevents cervical cancer. Less well known is that the 9vHPV vaccine was approved in 2020 to prevent oropharyngeal cancer.



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Surprisingly, in the United States, the most common cancer associated with human papillomavirus (HPV) is oropharyngeal squamous cell cancer (SCC), with one study reporting 15,479 cases among men and 3,428 cases among women in 2015.¹ In the same year, the investigators reported 11,788 cases of cervical cancer.¹ A public health concern is that cases of oropharyngeal SCC are increasing, while cases of cervical cancer are decreasing. From 1999 to 2015, the rate of oropharyngeal SCC increased annually among both men and women, at rates of 2.7% and 0.8% per year, respectively. By contrast, the rate of cervical cancer decreased by 1.6% per year.¹

Although the incidence of HPV-negative oropharyngeal SCC (cases associated with cigarette smoking) has declined by 50% from 1988 to 2004, the incidence of HPV-positive oropharyngeal SCC has increased by 225%, with much of the increase occurring among young, white men.² HPV infection is a major cause of

oropharyngeal SCC at the base of the tongue and tonsils, but not in the soft palate or oropharyngeal walls.³

Most physicians and parents recognize that the 9-valent (9v)HPV vaccine prevents the majority of cervical cancers and precancers in women. Far fewer people realize that there is an important opportunity to prevent a large number of oropharyngeal cancers by improving 9vHPV vaccination in men and women.

Which HPV types are associated with oropharyngeal cancer?

HPV16 is the most common HPV type associated with oropharyngeal SCC. Among these cancer types, greater than 80% harbor HPV16, with greater than 90% harboring HPV16 or 18 and less than 10% of tumors associated with HPV types 31, 33, 45, 52, or 58.⁴⁻⁷

The high prevalence of HPV16 in patients with oropharyngeal cancer raises the question of the HPV status of the intimate partner of the index patient. In one study of 164 people with HPV detected in their oropharyngeal,

the partner of the index patient had a low prevalence of high-risk HPV types (1.2%) in oral rinse and gargle samples, similar to the rate in the general population (1.3%).⁷ This finding is reassuring and suggests that intimate partners of patients with HPV-positive oropharyngeal cancer effectively clear high-risk HPV virus from the oropharynx. The HPV status of the genital tissue of the intimate partner of an index patient with oropharyngeal SCC has not been adequately studied.

Men are more likely than women to harbor oral HPV

Among a sample of 5,501 men and women aged 14 to 69 years from the National Health and Nutrition Examination Survey, oral rinses were obtained and analyzed for the presence of HPV.⁸ The prevalence of any oral HPV and any oral high-risk HPV was 6.9% and 3.7%, respectively. Oral HPV-16 was detected in 1.6% of men and 0.3% of women. The prevalence of HPV was higher among current smokers, heavy alcohol drinkers,

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9vHPV vaccine: Indications and immunization schedule

In 2020, the US Food and Drug Administration (FDA) approved the 9-valent human papillomavirus (9vHPV) vaccine for the prevention of oropharyngeal cancer. The 9vHPV vaccine contains inactive L1 capsid proteins for 9 HPV types, including types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The vaccine stimulates the production of neutralizing antibodies to the capsid protein.

9vHPV is approved for females aged 9 to 45 years to prevent cancers and precancers of the cervix, vulva, vagina, and anus caused by HPV types 16, 18, 31, 33, 45, 52, and 58.¹ It is also approved for males aged 9 to 45 years to prevent cancer and precancers of the anus caused by those viral types. **In 2020 the 9vHPV vaccine was approved by the FDA to prevent oropharyngeal cancer in males and females.** Of note, the FDA reported that, “the oropharyngeal and head and neck cancer indication is approved under accelerated approval based on effectiveness in preventing HPV-related anogenital disease. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.”²

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of girls and boys, 11 to 12 years of age.¹ Children with a history of sexual abuse or assault can start the vaccine at 9 years of age. Catch-up vaccination is recommended for all females and males through age 26 years. The ACIP recommends shared clinical decision-making regarding vaccination for some adults 27 to 45 years of age. Gynecologists with routine exposure to HPV may have occupational risk that warrants HPV vaccination³ (see “As a gynecologist, should you receive the 9vHPV vaccine?”).

For most individuals who start the vaccine series before age 15, two doses of 9vHPV vaccine are recommended, with the second dose 6 to 12 months following the first dose. For teens and adults aged 15 to 26 years, 3 doses of 9vHPV vaccine are recommended, with the second dose 1 to 2 months later and the third dose 6 months following the first dose. Immunocompromised individuals 9 to 26 years of age, including those with HIV infection, should receive 3 doses of the vaccine.

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and people with a history of a greater number of sexual partners. In men and women reporting more than 20 lifetime sexual partners, the prevalence of oral HPV was 20%.

In a study of 2,627 men and women aged 18 to 33 years, the prevalence of oral HPV 16/18/6/11 was lower among those vaccinated versus those unvaccinated (0.11% and 1.6%, respectively; $P = .008$).⁹ Among men, oral HPV 16/18/6/11 was lower among those vaccinated versus unvaccinated (0.0% and 2.13%, respectively; $P = .007$).⁹ The results of this observational study support the important role of vaccination in reducing oral HPV infection.

Vaccinate boys and girls to prevent cancer

Most population studies report that males are less likely to receive an HPV

vaccine than females. For example, based on the National Health Interview Survey of people aged 18 to 26, the percentage of women who self-reported receiving at least one dose of HPV vaccine was 37% in 2013 and 54% in 2018.¹⁰ By contrast, among men, the rates of self-reported vaccination were much lower—8% in 2013 and 27% in 2018.¹⁰

The percentage of women who received the recommended number of doses of HPV vaccine (see “9vHPV vaccine: Indications and immunization schedule”) was 26% in 2013 and 35% in 2018.¹⁰ For men, these percentages were 2% in 2013 and 9% in 2018.¹⁰ These data indicate that, compared with women, men are less likely to receive an HPV vaccination and far less likely to have received the recommended number of doses.

It is heartening that there has been a slow and steady increase in

the prevalence of HPV vaccination. In fact, increasing the HPV vaccination rate among both boys and girls has the potential to markedly reduce the incidence of oropharyngeal cancer.

The reasons for the female-male gap in vaccination rates are not fully characterized. For one, parental awareness of the importance of HPV vaccination to prevent cancer among men is limited, and represents an important opportunity for additional public health education. In a qualitative interview study of mothers with children aged 11 to 19, the investigators reported that most mothers were aware that HPV vaccination could prevent cervical cancer in women, but most mothers did not know that HPV causes cancer of the mouth and that vaccination could prevent oropharyngeal cancer in boys and girls.¹¹ Because of this lack of knowledge,

As a gynecologist, should you receive the 9vHPV vaccine?

Surgical treatment of tissues infected with human papillomavirus (HPV) often involves the use of laser or electrocautery devices that generate smoke, which is known to contain HPV nucleic acid sequences and may contain infective virions.¹ It is known that HPV nucleic acid sequences are present in surgical smoke. In one study plantar warts were treated with a carbon dioxide laser or electrocautery. The vapor produced from the surgery was collected with a dry filter apparatus. Five of 8 laser-derived vapors and 4 of 7 electrocautery-derived vapors were positive for HPV DNA. The concentration of HPV DNA was greater with laser than with electrocautery treatment.²

It is not known if surgical smoke derived from treatment of HPV-infected tissues contains infective HPV virions. In an experimental bovine model, smoke generated by laser ablation of fibropapillomas was collected. Injection of the contents of the smoke caused cutaneous papillomavirus lesions when inoculated into calves, suggesting that the smoke contained infective HPV virions.³ Although this animal experiment is a proof of principle that surgical smoke generated from treatment of HPV-infected tissue contains virions, it is unclear if surgical smoke generated in gynecologic practice contains HPV virions.

To investigate the prevalence of nasal HPV DNA among gynecologists, 700 physicians in Zhejiang Province, China, completed a questionnaire and provided a nasal swab for HPV DNA analysis.⁴ Among gynecologists who performed or did not perform LEEP, the prevalence of HPV DNA in the nose was 10% and 3%, respectively. The most common HPV types detected were HPV16 (76%), HPV31 (10%), HPV58 (5%), HPV55 (5%), HPV56 (2%), and HPV59 (2%).⁴ Among gynecologists who performed LEEP procedures, the prevalence of HPV DNA was 19% for those who did not use a surgical mask, 8% for clinicians who used a standard surgical mask, and 0% for those who used an N95 filtering facepiece respirator, suggesting that an N95 respirator provides the greatest protection from surgical smoke.⁴ Over 24 months of follow-up, all the gynecologists who had initially tested positive for HPV DNA no longer had detectable nasal HPV DNA. In this study, no gynecologist was diagnosed with an HPV-associated oropharyngeal disease. The investigators concluded that surgical masks, especially an N95 respirator, should be used by gynecologists performing LEEP procedures.

Investigators also have evaluated for the presence of HPV DNA in matched samples from the cervix of 134 patients undergoing loop electrocautery excision procedure (LEEP) for cervical dysplasia, as well as the smoke generated during the procedure and nasal swabs from the surgeon performing the LEEP.⁵ HPV DNA was detected in 95% of the cervical samples, 30% of the surgical smoke samples, and 1.5% of the surgeons' nasal swabs.⁵ At 6 months of follow-up, the two surgeons who initially had HPV-positive nasal swabs no longer had detected HPV DNA.

Of concern is that otolaryngologists have reported sporadic cases of oropharyngeal squamous cell cancer⁶ and laryngeal papillomatosis⁷ in health care workers with frequent and repetitive exposure to HPVs. For example, in one case report, a 53-year-old male gynecologist, nonsmoker, presented to his physician with a lump on the neck.⁶ The gynecologist had performed more than 3,000 laser ablation or LEEP procedures of dysplastic cervical, vaginal, and vulvar lesions over a span of 20 years.⁶ Most of the procedures were performed without wearing a mask and in a poorly ventilated procedure room. A computed tomography scan demonstrated a 2.2-cm soft tissue lesion in the right tonsil extending to the right soft palate and a level-2 lymph node. A biopsy of the tonsil confirmed invasive squamous cell carcinoma containing HPV16. He was treated with 35 fractions of radiotherapy and adjuvant cisplatin. Treatment adverse effects included dysphagia and xerostomia, and the patient lost 40 pounds.

Available interventions to reduce exposure of clinicians to HPV virions that may be present in surgical smoke include:

- wearing a fit-tested N95 respirator
- routinely using a smoke evacuation device, and
- ensuring sufficient ventilation in the procedure room.

A new recommendation is to consider 9vHPV vaccination for clinicians who are routinely exposed to HPV virions.^{8,9} **In February 2020, the American Society for Colposcopy and Cervical Pathology recommended that clinicians who are routinely exposed to HPVs consider 9vHPV vaccination.**⁸ This recommendation pertains to all members of the clinical team in the procedure room, including physicians, nurses, and staff. Based on the available data, gynecologists who have not been vaccinated will need to weigh the benefits and costs of receiving a 9vHPV vaccine to protect themselves against an occupational exposure that may adversely impact their health.

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the mothers did not think their sons needed to have an HPV vaccine. The research report is aptly titled, “I don’t think he needs the HPV vaccine cause boys can’t have cervical cancer.”¹¹

Clinicians are highly influential in guiding parents to accept HPV

vaccination of their children. Offering consistent messaging to parents that HPV vaccination prevents cancer in both women and men, and reducing the out-of-pocket cost of vaccination surely will result in an increase in the vaccination rate of boys and girls. ●



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