



## HPV vaccination disparities and strategies to prevent oropharyngeal cancer in males

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Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States (U.S.). Persistent HPV infection is associated with cancers of the oropharynx, cervix, vagina, vulva, anus and penis, as well as genital warts (CDC, 2020). Of all HPV-attributable (HPVa) cancers, oropharyngeal cancer (OPC) is the most prevalent (Senkomago et al., 2019). According to data from the American Cancer Society, an estimated 53,260 adults will be diagnosed with oral and oropharyngeal cancer in the U.S. in 2020 (estimated case numbers of OPC apart from oral cavity cancers are not provided by the American Cancer Society) (ASCO, 2020). However, OPC and other sequelae of HPV infection are largely preventable through HPV vaccination. In fact, the U.S. Food and Drug Administration (FDA) very recently added OPC to the list of official indications for the HPV vaccine (18). The Advisory Committee on Immunization Practices (ACIP) emphasizes HPV vaccination for males and females ages 11–12, although vaccination is recommended as early as 9 years of age and through age 26. The recent ACIP harmonization of catch-up vaccination in both men and women to age 26 years was specifically to address the unfortunate historical impression that vaccination was more important for females (Meites et al., 2019). HPV vaccination is generally not recommended for those older than the age of 26 who are unvaccinated, however the ACIP recently gave a permissive recommendation for unvaccinated adults ages 27–45. Vaccination at this age provides much less of a benefit than younger vaccination since most people have already been exposed to HPV by the age of 27 (CDC, 2020). The HPV vaccine does not treat existing infections; rather, it only prevents new HPV infections.

While tobacco and heavy alcohol use are risk factors for OPC, the majority of OPC cases (approximately 70%) are caused by HPV infection, particularly HPV types 16 and 18 (de Martel et al., 2017; NCI, 2017; ACS, 2018). In 2017, there were over 46,000 total new cases of oral cavity and oropharyngeal cancer in the U.S. and more than 10,000 deaths, as reported by the CDC (CDC, 2018). Interventions discouraging negative health behaviors such as tobacco and heavy alcohol use has demonstrated success in lowering the number of HPV-negative OPC

cases (ASCO, 2020; Lowy and Munger, 2010; Sturgis and Cinciripini, 2007). However, even with the reduction of these cases, overall OPC incidence has continued to increase in the U.S., driven by HPV-positive cases (Lowy and Munger, 2010; Adelstein et al., 2019). The overall 5-year survival rate for those with any type of OPC is 65%, increasing to 84% in those with early stage disease and no involvement of surrounding tissue or lymph nodes (ASCO, 2020). Still, the ideal scenario would be altogether prevention of HPVa OPC.

Prevention strategies are particularly important for men because they are disproportionately affected by HPVa OPC. Data from the Centers for Disease Control and Prevention (CDC) from 2013 to 2017 showed approximately 16,200 annual cases of HPVa OPC in males and approximately 3500 in females, demonstrating that males experienced five times the burden of OPC compared with females (CDC, 2017). Further, 71% of new OPC cases in 2017 were among males (CDC, 2018). In the U.S., rates of OPC cases in males have surpassed rates of cervical cancer cases in females. From 2013 to 2017, case numbers of HPVa OPC exceeded the number of HPVa cervical cancer cases by almost 4,000 annually (CDC, 2017). In 2017, the CDC reported 46,157 new cases of oral cavity and oropharyngeal cancer in the U.S. compared to 12,831 new cases of cervical cancer (CDC, 2018). The disproportionate OPC burden among men indicates urgent need for HPV vaccination initiatives targeting males in the U.S.

Despite broad support of the healthcare community and the vaccine's demonstrated safety and efficacy, HPV vaccination rates in the U.S. remain far below the Healthy People 2020 goal of 80% series completion (HP, 2020). Additionally, HPV vaccine uptake and completion rates among males, specifically, lag even further behind those of their female counterparts. According to 2018 National Immunization Survey-Teen data, rates of completion of the 3-dose HPV vaccination series for females and males ages 13–17 were 37.9% and 32.1%, respectively (Walker et al., 2019). Among older adolescents and young adults, a study by Boakye et al. found that only 1 in 25 males and 1 in 4 females in the 18–26 age range had completed the HPV vaccine

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series, indicating that low vaccine uptake and completion among males is prevalent across the recommended age range (Adjei Boakyee et al., 2018). The disproportionately high rates of HPVa OPC and low rates of HPV vaccination among males in the U.S. present a significant health disparity in need of attention.

In order to develop effective strategies to increase HPV vaccination among males—and subsequently prevent HPVa OPC, it is essential to better understand potential barriers to male HPV vaccination. One barrier that may explain lower uptake among males is a persisting gap in parental knowledge and awareness about the need for males to be vaccinated. When the HPV vaccine was approved for use in the U.S. in 2006, its initial recommendation was only for females; ACIP recommendations did not include males until 2011 (Markowitz, et al., 2014). Further, when the vaccine was approved for males, the ACIP recommendation was phrased as “permissive” rather than the more strongly worded “routine” recommendation for females, which likely reinforced the incorrect notion that the HPV vaccine was unnecessary for males (FDA, 2010). Additionally, there has been heavy emphasis on the HPV vaccination’s exceptional effectiveness at preventing cervical cancer. The attention placed on the vaccine’s efficacy regarding a female-specific cancer has likely only augmented impressions of the vaccine’s relevance to females almost exclusively (Liddon et al., 2010). Even almost a decade after ACIP expanded the recommendation to include males, misperceptions remain that the vaccine is only for females and/or unnecessary for males, contributing to lower uptake and series completion rates. However, the recent trends and steady increases in male HPVa OPC data indicate that it is an opportune time to promote the HPV vaccine’s applicability and importance for males.

One of the mostly frequently cited barriers to vaccination among both males and females is lacking a physician recommendation for HPV vaccination, with one study finding that 66% of patients who were not vaccinated reported not receiving a provider recommendation (Dorell et al., 2011). Dorell et al. found that 19.4% of parents did not vaccinate their daughters because of lack of knowledge of the vaccine—which implies that their provider did not inform them of it—and 13.1% did not vaccinate because their provider did not recommend it (Dorell et al., Nov 2011). Other barriers to vaccination include the inconvenience of a 3-dose requirement, concern about the vaccine safety or potential side effects, and the fear of shots (Liddon et al., 2010; Daley et al., 2006; Harper and DeMars, 2017). Some studies have also identified a tendency among healthcare providers to promote HPV vaccination more frequently for females than males (Daley et al., 2006; Kahn et al., 2005; Riedesel et al., 2005). Many parents have reported willingness to vaccinate their adolescent sons against HPV but have not due to logistical barriers, the most common being lack of recommendation from their healthcare provider (Donahue et al., 2014). There are many proposed reasons to explain this; Kahn et al. performed a qualitative study and found pediatrician preference to vaccinate girls against HPV was due to rooted beliefs that the HPV vaccine is more beneficial for girls and that the vaccine would be difficult to market to caretakers of males (Kahn et al., 2007). Daley et al. found lower rates of pediatrician intention to vaccinate males due to concerns about parental reactions to a misnomered “STD vaccine” (Daley et al., 2006). Provider awareness about the necessity of male HPV vaccination and the disparity between female and male vaccination rates is lacking. While the weight of the HPV vaccine misconceptions falls largely on the shoulders of pediatricians since it is an adolescent vaccine, the American Academy of Pediatrics (AAP) is actively working towards improving both male and female HPV vaccination rates through efforts such as the “HPV Champion Toolkit” (AAP, 2021). This is an online resource for pediatricians to learn more about the vaccine, and it provides them with ideas for practice-based changes they can make to improve vaccination rates in their own practices. The AAP was also awarded a 5-year cooperative agreement by the National Center for Immunization and Respiratory Disease at the CDC to develop programs designed to measurably increase the proportion of pediatricians who implement immunization

best practices. This involves a quality improvement projects disseminating professional education and tools designed to help pediatricians make strong HPV vaccine recommendations consistently (AAP, 2021). In addition, the AAP recommends HPV vaccination between ages 9 and 12, whereas the ACIP recommends the series be initiated at ages 11 or 12. The AAP recommends earlier initiation of the series because it provides more flexibility in introducing the vaccine, it allows patients to complete the series before other adolescent vaccines are due, and it avoids the concomitant “sex talk” parents may have with patients at age 11 or 12 (AAP, 2021). HYPERLINK "SPS:refid::bib27"

HPV vaccine recommendations should *not* be a responsibility left to solely to primary care specialties. Rather, this charge should span across a broad, interdisciplinary spectrum of healthcare professionals. One study assessed the secondary acceptance of HPV vaccination in parents who initially declined and found almost half of parents accepted the vaccine due to reasons such learning more about the HPV vaccine and receiving a provider recommendation. Parents who received follow-up counseling about the vaccine were more likely to accept the vaccine (Kornides et al., 2018). If there are more avenues available for parents to learn about the vaccine by way of multiple healthcare providers, there will be more vaccine acceptance and HPV vaccination overall. This emphasizes the need for a collaborative effort and multiple voices in healthcare working towards the goal of HPV vaccination in males. The American College of Obstetricians and Gynecologists (ACOG), the American Dental Association (ADA), and the American Academy of Oral and Maxillofacial Surgeons (AAOMS) are among several professional organizations that have already begun to take initiatives. In 2018, the ADA adopted a policy urging dentists to support the administration of HPV vaccination among their patients (ADA, 2020). However, studies have shown the need for increased health literacy about HPV-related diseases in oral healthcare providers. A recent study surveying dentists in Arizona showed that dentists did not feel comfortable answering their patients’ questions about the vaccine, but they would be willing to educate their patients if they were trained to do so (Patel et al., 2020). The enthusiasm of dental healthcare providers to be involved in HPV vaccination is present, they just need the necessary education and training. ACOG released a statement in 2019 endorsing their support of HPV vaccination as prevention of cancers in the population at large (ACOG, 2019). In 2020, the AAOMS released a position paper supporting HPV vaccination for males and females as early as 9 years old to prevent HPVa cancers including OPC (AAOMS, 2020). Regarding males, particularly, the American Academy of Otolaryngology-Head and Neck Surgery released a position statement in 2016 encouraging HPV vaccination as prevention of OPC, especially in boys, but has not released a statement since the recently expanded FDA approval (AAOHNS, 2016). Steps like these, in conjunction with the FDA’s approval of the HPV vaccine for OPC prevention, are important to reducing HPVa OPC.

While these actions are promising, more proactive measures are needed from a broader array of specialists who may treat and/or detect HPVa disease. Acknowledging that a provider recommendation is the most effective motivator for HPV vaccination, providing unified, consistent messaging from many disciplines will only lend strength to this important cancer prevention initiative. Collaborative efforts among health care providers can clearly increase education and awareness among patients and parents, which, in turn, increases vaccination rates. Male disparities in HPV vaccination specific can also be addressed by implementing efforts to educate young adult males through school awareness programs, enabling young men to self-advocate. Multilevel strategies such as these, which address providers, parents, and patients, respectively, are likely essential to attain a measurable impact. Future interventions should consider their utilization in tandem to ultimately achieve increased HPV vaccination among males and reduced rates of HPVa OPC in the U.S.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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