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Human Papillomavirus Vaccination in Males: The State of the Science

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Abstract Human papillomavirus (HPV) is an extremely prevalent sexually transmitted infection that is typically acquired soon after onset of sexual activity. The burden of HPV-related malignant and nonmalignant disease is high in men and women. High-risk or oncogenic types of HPV cause cervical, vaginal, and vulvar cancer in women. These types have also been shown to cause penile cancer in men and a substantial proportion of oropharyngeal and anal malignancy in men and women. Low-risk types of HPV cause anogenital warts. Prevention of penile, anal, and oropharyngeal cancers and anogenital warts represents potential benefits of the HPV vaccine in men. This review focuses on HPV disease in men, existing data on HPV vaccination in men, and various factors associated with the decision to vaccinate boys and young men, as well as the timing of vaccination.

Keywords Human papillomavirus · HPV · Quadrivalent vaccine · Vaccination · Cervical dysplasia · Cervical cancer · Anal dysplasia · Anal cancer · Oropharyngeal dysplasia · Oropharyngeal cancer · Penile dysplasia · Penile cancer · Cancer · Anogenital warts · Condyloma acuminata · Sexually transmitted infections · Human immunodeficiency virus · HIV · Acquired immunodeficiency syndrome · AIDS

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Introduction

HPV was first established as a causative agent of cervical cancer. Further evidence has emerged that the virus is associated with cancer in males, including anal, penile, and oropharyngeal cancer. The incidence of these cancers is increasing [1, 2]. In particular, anal cancer rates are increasing, especially among the subpopulation of HIV-positive men who have sex with men (MSM) [2].

In 2006, the quadrivalent HPV vaccine was licensed for use in women aged 9 to 26 to prevent infection with HPV serotypes (6, 11, 16, 18) in the vaccine. Serotypes 6 and 11 cause 90% of genital warts, whereas serotypes 16 and 18 cause 70% of cervical cancers [3, 4]. In 2009, the vaccine approval was extended to boys and men aged 9 to 26 based on prevention of infection with serotypes 6 and 11, and subsequent prevention of genital warts. In 2010, the vaccine received an additional indication for prevention of anal cancer in men and women.

Epidemiology of HPV

HPV is estimated to be the most common sexually transmitted infection. The virus exists as more than 100 different serotypes, with different serotypes displaying distinct tissue tropism. Certain serotypes display mucosal tropism and are therefore more often sexually transmitted, whereas others display tropism towards keratinized epithelium and are spread through casual contact.

Several studies indicate that HPV prevalence is high among men, with rates approaching 20% to 65% depending on the collection site and method used [5]. One cross-sectional study found an anogenital HPV prevalence of 40%, with no difference between men and women [6]. The largest cohort study of HPV prevalence in men is the HPV in Men (HIM) study [7]. This study examined a broad cohort of 1160 men from Brazil, Mexico, and the United States and found genital HPV infection in 65%. Multiple HPV infections were found in 25% of this population and 20% had active infections with at least one of the vaccine strains. Other studies have found that HPV infection is nearly ubiquitous in HIV-positive MSM populations, with active anal infection rates exceeding 90% [8, 9]. The most common serotype is this population is HPV 16 [10], occurring in about 40% of infections as defined in one cohort.

Noncervical Dysplasia Caused by HPV

In the past decade, the association between HPV non-cervical cancers was better defined. These include not only squamous cell carcinoma of the vagina and vulva, but also of the penis, oropharynx, and anus. HPV causes about 5% of cancer worldwide [11, 12], virtually 100% of cervical cancers [13], more than 90% of anal cancers, 40% of penile cancers, and between 12% and 60% of oropharyngeal cancers [11]. HPV subtypes 16 and 18 cause a high proportion of noncervical disease, accounting for 60% to 90% of disease.

Despite the high proportion of disease caused by HPV, the absolute incidence of cancer varies widely among different anatomic sites and different populations at risk. Furthermore, although screening programs have drastically reduced the incidence of cervical cancer, the incidence of oropharyngeal cancer and especially the incidence of anal cancer are rising sharply [14, 15]. The disease burden at these sites represents potential benefits to men from the vaccine.

Penile Cancer

Penile cancer remains rare, with an incidence of 0.81 per 100,000 in the United States [16]. About 40% are caused by HPV, with high-risk serotypes 16 and 18 being the most common [17, 18]. Incidence varies widely with race—it is highest in Hispanics, equal in Caucasian and African Americans, and lowest in Asians; incidence increases with age [16]. Risk factors include lack of neonatal circumcision, smoking, a history of phimosis, and other penile conditions [18–20]. Given multiple etiologies and the low incidence of penile cancer, vaccination will likely provide marginal benefit on a population level. Nevertheless, the vaccine should decrease penile cancer caused by HPV 16 and 18, which are the most common subtypes. Vaccination is likely to have a more substantial benefit for benign HPV-related diseases of the penis, such as condyloma acuminata, which are far more common.

Anal Cancer

Anal cancer represents one of the most prevalent HPV-related cancers, and thus one of the greatest potential benefits of vaccinating men. Historically, the male-to-female ratio has been skewed towards women (1:1.6), but this has recently begun to normalize (1:1.2), largely as a result of the HIV epidemic [21]. Incidence varies widely depending on risk factors, from 1 per 100,000 in general populations, increased 37-fold in HIV-positive men, to as high as 75- to 100-fold in HIV-positive MSM, which exceeds the incidence of cervical cancer anywhere in the world [9].

Furthermore, the incidence of anal cancer is increasing among HIV-infected individuals in the era of effective antiretroviral therapy (ART). With effective ART, HIV-infected individuals are far less likely to die from AIDS-related complications and life expectancy has improved dramatically. This allows time for areas of anal dysplasia to progress to invasive cancer. Immune reconstitution from effective ART does not cause high-grade anal dysplasia to regress; therefore, the improved survival of HIV-positive patients is accompanied by a parallel increase in anal cancer rates [22•, 23].

A history of anal-receptive intercourse is not necessary for anal HPV infection. One study of healthy men from the general population found that 20% had anal HPV infection [5]. Studies of non-MSM HIV-infected men have found that, although lower, anal HPV infection and resultant dysplasia remain problematic, with rates of 46% and 34%, respectively [24]. Anal cancer rates are also increased among organ transplant recipients, highlighting the role that immunosuppression plays in the disease [25].

Because of the pathophysiology of HPV and the slow progression of changes, rates of infection far exceed dysplasia, whereas dysplasia rates far exceed cancer. Rates of anal HPV infection among HIV-positive MSM are extremely high, exceeding 90% in most studies, and infection with multiple serotypes is the norm [8, 9]. The most common serotype is HPV 16, found in 40% [10]. Anal dysplasia rates are high, with 7% of HIV-negative MSM patients having any degree of dysplasia [26] and up to 50% of HIV-positive patients having high-grade dysplasia [27].

Data supporting the progression of high-grade anal intraepithelial neoplasia (HGAIN) to anal cancer are largely indirect. The populations with the highest incidence of anal

intraepithelial neoplasia (AIN) also have the highest incidence of anal cancer; and the epidemic increase in anal cancer incidence has paralleled an increase in AIN among immunosuppressed individuals. Long-term follow-up of cohorts with HGAIN shows malignant transformation in about 5% of individuals and high rates of recurrence [28, 29]. The most direct data come from a retrospective chart review of anal cancer patients from San Francisco with available biopsy reports. Previous HGAIN was found at the current anatomic location of anal cancer in 21 of 27 patients, and there was a history of HGAIN but no recent biopsy in the remaining six [30]. The strong epidemiologic association between AIN and anal cancer, coupled with limited direct retrospective evidence of HGAIN preceding anal cancer, serve as strong evidence for the paradigm of high-risk HPV infection proceeding to high-grade AIN, which in turn proceeds to anal cancer.

Oral Cancer

Oropharyngeal cancer has multiple causes; certain subtypes are associated with HPV, but others remain independent of HPV. Alcohol and tobacco use are established risk factors for the majority of oropharyngeal cancers, although HPV was recently discovered as a cause for a subset. On average, about 35% of oropharyngeal and 23% of anterior oral cancers are associated with HPV, but this number varies highly depending on anatomic location. The posterior oropharynx, particularly the base of the tongue and the tonsils, tend to have higher proportions of HPV-associated squamous cell carcinomas, up to 63% in some studies [31]. Most HPV-associated oral and oropharyngeal cancers are caused by HPV 16 [31].

Although recent evidence suggests that the prognosis for HPV-associated cancers of the oral cavity is better than non–HPV-associated subtypes [32], the incidence of HPV-associated cancers has been increasing while the non–HPV-associated types are decreasing [14]. In contrast to cervical and even anal HPV-associated disease, the natural history of oral disease is poorly understood. HPV oral infection rates are lower in the oropharynx [33], although infection is associated with oral-genital contact and number of sexual partners, similar to HPV infection in other anatomic sites [31]. HIV infection is associated with increased oral HPV infection, although persistence of oral infection is only increased in the subset of HIV-positive patients with low (<500) CD4 count [33].

Given the high proportion of HPV-related oral cancers caused by HPV 16, HPV vaccination has the potential to impact the morbidity and mortality of a significant subset of oropharyngeal cancers. Although the efficacy of vaccination for prevention of oral HPV infections, dysplasia, or neoplasia has not been studied, future studies of vaccine efficacy and current surveillance of oropharyngeal cancers in the backdrop of increasing HPV vaccination rates will further elucidate these important questions. In the meantime, although speculative, the potential of the vaccine to impact oropharyngeal cancer incidence should be considered.

Nonmalignant HPV Disease

A substantial burden of HPV disease is caused by non-oncogenic serotypes that are covered in the quadrivalent vaccine, namely HPV 6 and 11. These serotypes are responsible for about 90% of condyloma acuminata in the anogenital region. In men, these occur primarily on the penile shaft, but warts on the foreskin, scrotum, perineal skin, and perianal mucosa (especially, although not necessarily, in MSM subgroups) may also occur. Anogenital warts cause substantial morbidity through decreased quality of life, depression, and associated stigma [34]. Genital warts have also been demonstrated as a risk factor for HIV acquisition [35]. Treatment requires multiple physician visits, and warts often recur, resulting in significant cost. HPV 6 and 11 are also associated with recurrent respiratory papillomatosis, a rare disease of the upper respiratory tract that causes substantial morbidity from recurrent airway obstruction caused by bulky, warty lesions that often require multiple surgeries [36].

HPV Vaccine Studies in Men

The quadrivalent HPV vaccine was shown to be safe and well tolerated in male patients. The most direct data involve HPV-related external genital lesions, for which the vaccine was highly efficacious. The largest study involved a randomized, double-blind, placebo-controlled trial of 4055 males aged 16 to 26 [37••, 38••]. Of this group, 3457 were heterosexual men aged 16 to 23 years and 598 were MSM aged 16 to 26 years. The primary end point was development of HPV-associated external genital lesions in men aged 16 to 26 years. Per-protocol efficacy was defined as the subgroup that was seronegative and HPV DNA-negative to all four serotypes upon enrollment, completed the vaccination series, and remained infection-free during the vaccination series. External genital lesions cases were then counted after the completion of vaccination, which occurred at month seven. There were 34 cases of external genital lesions, 31 of which were genital warts (all caused by HPV 6 or 11), and three cases of penile intraepithelial neoplasia (PIN). Of the genital warts, 28 cases occurred in the placebo group and three cases in the vaccination group, resulting in 89.3% efficacy. Although all three cases of PIN occurred in the placebo

group, the small group sizes resulted in a lack of statistical significance.

A second analysis included all men who received at least one dose of the vaccine; all cases of external genital lesions were counted after the first dose of vaccination. This group also included men who were exposed to HPV at baseline or who became exposed before completing the vaccination series. In this group, there were 104 cases of external genital lesions, 95 of which were warts positive for HPV 6 or 11. In this analysis, 24 cases occurred in the vaccine group and 71 cases occurred in the placebo group, for an efficacy of 65.5%.

Among 598 MSM aged 16 to 26, the vaccine prevented 95% of persistent anal infections with vaccine types (39 placebo cases vs 2 vaccine cases, 95% CI: 80%–99%) and 84% at a single time point (95% CI: 69%–93%) [39]. The vaccine also prevented 75% of HGAIN due to vaccine types in the per-protocol analysis (95% CI: 9.9%–95%) and 54% in the intent-to-treat analysis (95% CI: 18%–75%) [40].

The study also established the immunogenicity of the vaccine in men, with a robust immune response in both age groups (9–15 and 16–26). Immunobridging studies show that boys aged 9 to 15 show two- to threefold higher antibody titer to vaccine strain than the 16 to 26 age group, demonstrating a noninferior immune response in boys [41]. Given the noninferior vaccination response in the lower age group and the fact that the vaccine shows no protection against a given strain once infection is established, vaccination should target the lower age group (9–15) in order to complete vaccination before the age of sexual debut. The immune response has also been studied in HIV-positive men, who also show robust antibody titers similar to HIV-negative patients [42•].

Vaccination Benefits and Recommendations

Based on the study demonstrating decreased incidence of genital warts, the Food and Drug Administration (FDA) approved the use of the quadrivalent HPV vaccine in October 2009 for males aged 9 to 26 years. The Advisory Committee on Immunization Practices also supports offering the quadrivalent HPV vaccination to boys for the expressed purpose of preventing genital warts. To maximize effectiveness, vaccination should be completed before the age of sexual debut (but no earlier than age 9). No data are available on the bivalent vaccine in men.

Although decreasing the burden of genital warts and anal cancer are the only definitively proven benefit from the quadrivalent vaccine in men, it should be noted that prevention of certain oropharyngeal and penile cancers are other potential benefits. Given that persistent infection is a prerequisite for dysplasia and subsequent malignancy, there is every reason to expect that the incidence of HPV-related malignancy would sharply decrease in vaccinated cohorts. The impact on cancer incidence will likely take decades to be fully realized because of the slow progression of HPV-related dysplasia. The FDA has recently added prevention of anal cancer to the list of vaccine indications, based on the decreased incidence of AIN among vaccinated men.

Another benefit of widespread vaccination of boys is increasing herd immunity, resulting in fewer HPV infections of vaccine serotypes and fewer transmission events to susceptible females. The precise benefit of herd immunity depends on the prevalence of vaccination among females in the population, and is inversely proportional to the percentage of vaccinated females. Mathematical modeling has predicted that susceptible males could serve as a potential reservoir for HPV, decreasing the threshold for infection outbreak among susceptible females [43]. Models also predict further decreases in genital warts, cervical intraepithelial neoplasia, and cervical cancer deaths through widespread vaccination of men [44]. Of note, vaccination of men in order to increase herd immunity is not without precedent, given the widespread vaccination of children of both genders for rubella, largely to prevent transmission of the virus to susceptible pregnant females [45].

Cost Effectiveness

Cost effectiveness of HPV vaccination has been controversial. This controversy arises from wide variations in cost effectiveness caused by various assumptions regarding HPV vaccination, including vaccine efficacy, prevalence of vaccination among males and females, and accounting for noncervical HPV disease.

A recent analysis by Kim and Goldie showed cost effectiveness of quadrivalent HPV vaccine in women, but not in boys and men [46•]. In this analysis, there were wide variations in cost effectiveness depending on the assumptions in the modeling, including prevalence of vaccination, screening rates for cervical disease, and effectiveness of the vaccine against noncervical HPV-related cancers. Cost of HPV-related diseases were included in the model, including cervical disease, genital warts, and anal, oropharyngeal, and penile cancers attributable to vaccine serotypes. A conservative estimate of 50% reduction of vaccine serotype-associated noncervical cancers was used, because the precise reduction rate remains to be clinically verified. However, given the high vaccine efficacy in preventing persistent HPV infection, 50% likely represents a significant underestimation. Also of note, this analysis did not account for the effect of the vaccine on anal dysplasia and

the costs associated with widespread anal dysplasia screening. Given that HPV-induced dysplasia is far more prevalent than HPV-induced cancer, the cost of screening for and treating such dysplasia will likely have a large impact on cost-effectiveness models of HPV vaccination. Finally, the base analysis assumed a 75% vaccination rate among females, which exceeds current rates in most communities.

Another cost-benefit analysis of male HPV vaccination in Belgium showed that vaccination of boys was cost effective [47]; other models have also shown benefit [44]. Specifically, a cost-benefit analysis of the vaccine among the MSM population showed that the vaccine was extremely cost effective [48•]. As expected, the cost benefit was highest when the model assumes vaccination of the MSM population at age 12 (ie, before sexual debut); however, the benefit, although less robust, remained when the vaccine was given at ages 20 and 26, after exposure to vaccine serotype was as high as 50%. Given that selectively targeting the MSM population at age 12 is not realistic from a sociologic perspective, the continued benefit of vaccinating an older cohort is promising. This study illustrates that the precise benefit of vaccination of men depends on the subpopulation investigated and the burden of HPV disease in that population. The MSM population has higher incidence and prevalence of HPV infection, particularly anal infection. HIV-positive and immunosuppressed populations are more likely to develop persistent infection, and subsequently develop dysplasia and cancer. Therefore, certain high-risk groups are most likely to benefit from the vaccine, including organ transplant recipients, the MSM population, and especially HIV-positive MSM.

The conflicting data of HPV cost effectiveness studies show that further careful studies are needed before definitive conclusions can be made regarding the cost effectiveness of vaccinating boys and young men with the quadrivalent HPV vaccine. These studies will need to take various factors into consideration, including the cost of screening for and treating anal dysplasia in high-risk populations, and the costs of other HPV cancers caused by vaccine serotypes, as well as the contribution to herd immunity. Continued cancer surveillance in the vaccination era will also contribute important information to the question of vaccine efficacy and cost effectiveness.

Because of the increasing disease burden in HIV-positive individuals, anal cancer screening with cytology followed by high-resolution anoscopy is rapidly becoming standard of care. Given the prevalence of high-grade dysplasia and the inability to predict which dysplasia will subsequently become cancer, screening requires a high amount of intervention. As screening becomes more standard, there will be a further cost benefit of vaccinating men to decrease incidence of dysplasia and the need for costly treatments. Because vaccination has no effect on existing disease, and infection must persist for months to years before progression to dysplasia, there will be a time lag between widespread vaccination and discernable benefit; therefore, vaccination should not be delayed until screening infrastructure is in place.

The cumulative data indicate that although anal cancer is very rare in the general population, it is far more common in select risk groups. These include HIV-positive MSM (the highest risk group), as well as HIV-negative MSM, HIV-positive heterosexual men, HIV-positive women, and patients with prolonged severe immunosuppression. Furthermore, anal HPV infection is fairly common in the general population, and nearly ubiquitous in some subpopulations. The HPV vaccine is most effective when given to a virologically naïve population; therefore, targeting these risk groups is difficult because they will be poorly defined before the age of sexual debut. From a practical standpoint, widespread vaccination of boys and young men may be the best long-term plan to address the growing problem of anal cancer.

Recommendations for Patients and Timing of Vaccination

Quadrivalent HPV vaccination should be offered to all males between the ages of 9 and 26. The strength of this recommendation and expected cost benefit will vary, depending on risk factors of the patient. Strong evidence exists that all men will benefit from decreased incidence of genital warts, provided that the vaccine is given before the acquisition of HPV strains 6 and 11. HPV vaccination will also prevent anal cancer caused by HPV 16 and 18. The benefit in reduction of anal cancer will be most important in high-risk groups, particularly immunosuppressed individuals (eg, those with HIV infection, organ transplant recipients) and the MSM population. Typically, these risk factors are not well defined during the age of optimal vaccine efficacy (ie, prior to sexual debut). It is likely that they will prevent penile and oropharyngeal cancer from HPV types 16 and 18.

To derive maximum benefit from the vaccine, it would be optimal to widely vaccinate boys prior to sexual activity; alternatively, maximum cost effectiveness would be obtained by targeting high-risk groups. Until more comprehensive cost effectiveness analyses are completed, the optimal policy will remain undefined. Because the vaccine has no efficacy against a viral strain once acquired, patients with known HPV disease, adult-acquired HIV infection, or several years of sexual activity are less likely to fully benefit from vaccination. Such patients, so long as they are in the given age range, should still

be considered for vaccination because they may benefit from one or more of the vaccination strains to which they may not yet have been exposed.

Conclusions

HPV causes a substantial burden of malignant and nonmalignant disease in men and women. The contribution of HPV to noncervical cancers, as well as condyloma acuminata, should change the perception of the quadrivalent HPV vaccine as only a "cervical cancer" vaccine. The benefit to men includes decreases in anal cancer and anogenital condyloma, and a likely decrease in oropharyngeal and penile cancers due to HPV 16 and 18, although the latter remains unproven at this time. Subgroups at high risk for these conditions are likely to derive maximal benefit from vaccination, but such subgroups are poorly defined at the optimal age of vaccine administration. Because of multiple variables and complex assumptions, cost-effectiveness data for wide-scale vaccination of boys are conflicting. Until more definitive data are available, the quadrivalent HPV vaccine should be offered to all boys and young men, with providers making every effort to vaccinate high-risk groups before or soon after sexual debut.

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- • Of importance
- •• Of major importance

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