Point/Counterpoint

The Case for a Gender-Neutral (Universal) Human Papillomavirus Vaccination Policy in the United States: Point

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Published data to date indicate that human papillomavirus (HPV) prevention vaccines are safe and efficacious in reducing HPV persistence and cervical intraepithelial neoplasia grade 2/3 lesions of the cervix (1-5). The U.S. Food and Drug Administration licensed the quadrivalent HPV vaccine Gardasil (HPV 6, 11, 16, and 18; Merck & Co.) in 2006 for females ages 9 to 26 years. The Advisory Committee on Immunization Practices at the Centers for Disease Control and Prevention recommended broad dissemination of this vaccine as licensed (6). A second HPV prevention vaccine, bivalent directed against HPV 16 and 18, will likely receive Food and Drug Administration approval in early 2008.

One of the most important policy questions under consideration is whether males should also be included in a HPV vaccine dissemination program. Although vaccine efficacy trials are currently in progress in men internationally (7), it is important to start considering the arguments for male vaccination in preparation for trial results that should be available by 2009. Final U.S. policy decisions will be dependent on the outcome of this trial, as there is concern the HPV vaccine will have efficacy limited to females as was observed in the HSV-2 trials (8). However, data from studies of male and female adolescents ages 9 to 15 years show robust antibody responses in males as well as in females (9, 10) and efficacy in reducing external genital lesions in females as well as vulvar precancerous lesions (6, 11), an epithelium similar to that of the penile skin. Therefore, there is a strong reason to suspect that the HPV vaccine will show efficacy in males and a need to consider the public health benefit of including males in a HPV vaccine dissemination strategy in the United States.

Several important questions emerge from this argument. Is there an added public health benefit to vaccinating both sexes compared with vaccinating only females should the vaccine show efficacy in males? What is the cost-effectiveness of a broad dissemination approach compared with a targeted one? To answer these questions, this article will review (*a*) HPV-associated disease burden in men and women, (*b*) whether HPV in men influences disease risk in women, (*c*) the burden of HPV infection in men, (*d*) estimates of female HPV-related disease reduction and cost-effectiveness if males are also vaccinated, and (*e*) lessons learned from gender targeting of other vaccines.

HPV-Associated Disease Burden in Men and Women

Cervical cancer is the second most common cancer among women worldwide accounting for 15% of female cancers in developing countries and 3.6% of all newly diagnosed cancers in developed countries (12). Anogenital cancers and their precursor lesions are strongly associated with infection with the sexually transmitted HPV among men and women (13-15). HPV 16 infection is also strongly associated with anal cancer in men and women (16). In the United States, anal cancer has increased by more than 35% among men and women in the past 20 years (17, 18). Forty percent to 50% of cancers of the vulva, vagina, and penis are attributable to HPV infection as well as ~12% of oropharyngeal cancers, 3% of cancers of the mouth, and 90% of anal cancers (13, 19, 20). Worldwide, ~28,100 male cancers annually are attributable to HPV 16/18 infection (20). Approximately 5,000 cases of cancer annually among U.S. men are attributed to infection with HPV. In addition to cancer, HPV causes genital warts (~1 million cases per year among each sex in the United States) and recurrent respiratory papillomatosis in both males and females.

Invasive cervical cancer is preventable through routine cytology screening, diagnosis, and treatment of preneoplastic lesions. In the United States, 50 million Papanicolaou smears are done annually, 2.8% to 5.0% or 1.4 million to 2.5 million of which will be abnormal (e.g., mild, moderate, and severe dysplasia; refs. 21, 22). The annual costs of repeat Papanicolaou screening in the United States total $150 million, and colposcopy, biopsy, and treatment add $6 billion annually (21, 22). Broad dissemination of a HPV vaccine has the potential to decrease health-care costs and patient burden. Although routine Papanicolaou screening is still necessary, the costs associated with colposcopy, biopsy, and treatment should be reduced.

Does HPV in Men Influence Disease Risk in Women?

The question of whether males should be vaccinated against HPV arises from the recognition that male HPV infection significantly contributes to infection and

Cancer Epidemiol Biomarkers Prev 2008;17(4):805–8
Received 8/10/07; revised 10/2/07; accepted 10/12/07.

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doi:10.1158/1055-9965.EPI-07-0741

subsequent cervical disease in women (23-26). Case-control studies of women with cervical cancer and their husbands have shown that men's sexual behavior affects women's risk for cervical neoplasia even when controlling for female sexual activity (23-28). In areas with a high incidence of cervical cancer, the male partner's sexual behavior is in itself a risk factor for cervical neoplasia (27). Among men with a history of multiple sexual partners, male circumcision was associated with a reduced risk of penile HPV infection and a reduced risk of cervical cancer in their current female partners (28).

HPV Studies of Sexual Partners

Several small cross-sectional HPV partner studies among heterosexual couples have been published (29). In a study comparing HPV status in the cervix and the semen of heterosexual sex partners, 75% of women whose partners were HPV positive had HPV DNA in their cervix, whereas only 39% of the men whose partners were HPV positive carried HPV DNA in their semen (30). In another study, 76% of male partners of women with HPV were HPV DNA positive (31). Among women whose sexual partners had penile condyloma, 76% had genital HPV infections, including 36% with abnormal cervical cytology and 28% with cervical HPV DNA detected (32). HPV type concordance within sexual partners is variable, with one study reporting 57.8% concordance (33) and another reporting 22.7% concordance (34). Unfortunately, many of these studies examined HPV prevalence in men from a single anatomic site or a semen sample, which we know today to be an incomplete method for estimating male HPV prevalence (35). Recently, Burchell et al. estimated the probability of heterosexual HPV transmission to be between 5% and 100%, with a median probability of 40% (36). Altogether, these data indicate that HPV infection in males is common and that there is a relatively high rate of transmission of HPV from males to females.

Epidemiology of HPV Infection in Men

Reported rates of HPV infection in men vary widely in part because of the use of different analytical methods and the populations studied. HPV infection rates as high as 70% have been reported in men (29). In more recent published reports from the United States, where HPV detection was systematically evaluated in several anatomic sites and specimens in men, 51.2% of men were positive for at least one oncogenic or nononcogenic HPV type and another 14.3% were positive for an unclassified HPV infection (37). Among asymptomatic heterosexual men the penile shaft, coronal sulcus/glans penis (including prepuce in uncircumcised men), and the scrotum are the sites that contribute to >95% of genital HPV infection detected (35). HPV type distribution in males appears to differ from females with a higher proportion of non-oncogenic infections detected compared with oncogenic infections in men. In men, sexual activity is positively correlated with HPV infection (38). Men appear to have a lower HPV seroprevalence of HPV 6, 11, 16, and 18 antibodies compared with women, and titer levels appear to be lower in men than in women. The significance of lower titer levels and lower antibody prevalence in men is not clear. However, one may speculate that lower HPV antibody prevalence and titer levels in men may be associated with reacquisition of infection throughout the lifespan. The published literature supports this concept. Unlike in women, HPV prevalence in men is not associated with age (37, 39-42).

Vaccinating Males: Estimates of Female HPV-Related Disease Reduction and Cost-effectiveness. Reduction of vaccine-preventable illnesses occurs through the direct protection conferred by those vaccinated as well as indirectly in the community through herd immunity. Therefore, models estimating the cost-effectiveness of different HPV vaccination strategies need to consider HPV transmission dynamics. Elbasha et al. (43), scientists at Merck, used a dynamic model to evaluate the effect of various HPV vaccination strategies on the reduction of female disease (cervical intraepithelial neoplasia grade 2/3 and cervical cancer) in the United States, assuming current cytology screening recommendations remain in place. Strategies that included female and male vaccination of 12-year-olds resulted in maximal cervical intraepithelial neoplasia grade 2/3 reduction, ~2-fold higher reductions than those obtained with female vaccination alone. Similarly, total reduction in cervical cancer incidence was twice as high when males were also included in vaccination programs compared with female-only strategies. From a cost-effectiveness view, including males in the vaccination program was the most cost-effective strategy, at $45,056 per quality-adjusted life year. It should be noted that only cervical intraepithelial neoplasia grade 2/3 and cervical cancer in the United States were considered for this analysis, although it is expected that other cancers caused by HPV 16 and 18 will be reduced with vaccination (43). The cost-effectiveness estimates provided by Elbasha et al. may likely vary by world region and country as they are in part dependent on the vaccine coverage in that population (43). Others have suggested that cost-effectiveness of male vaccination is most justified when vaccine dissemination rates in females are low (44). Without school entry requirements for HPV vaccination, it is unlikely that we will achieve greater than 30% dissemination among U.S. females in the near future. Current HPV vaccine recommendations include vaccination of 11- to 12-year-old girls and catch-up vaccination for females ages 13 to 26 years. Even if vaccine uptake among the primary population (11- to 12-year-olds) is extremely high, it will take decades before consecutive cohorts' age and the sexually active female population has high coverage without catch-up vaccination.

Lessons Learned from Gender Targeting of Other Vaccines

Experience from gender-based targeting of rubella vaccines in many countries provides some insight into gender-based targeting of HPV vaccination. A review of the 75 countries that were using rubella vaccine in 1996 found that 9% of countries selectively immunized women (45). Many countries started their rubella immunization policy by targeting women and later changed the immunization policy to include men (46). In the United Kingdom, for example, the rubella

immunization program was aimed at schoolgirls, healthcare workers, and susceptible adult women. The weaknesses of this approach became evident in 1993 and 1996, when resurgences of rubella were attributed to susceptibility among males (47, 48). In 1998, the measles, mumps, and rubella vaccine was introduced in the United Kingdom for all children ages 12 to 15 months (46). Plotkin et al. highlight the importance of vaccinating males when considering rubella eradication efforts (49).

However, there are some differences between rubella and HPV. HPV and rubella differ in terms of their basic reproductive rates and length of infectivity. Most importantly, HPV is a sexually transmitted infection, whereas rubella is spread through far less intimate contact including coughing and sneezing from an infected person. As a sexually transmitted infection, the sexual contact patterns of individuals are particularly important for HPV. As Garnett et al. point out, ''it would be erroneous to think of (HPV) vaccination of a single sex as achieving half the coverage of vaccinated both sexes'' (44). HPV is primarily spread across genders, whereas with rubella males and females have potentially infectious contacts within and between sexes. The two models from Garnett and colleages that have explored the effect of male in addition to female vaccination for HPV have found limited benefit from vaccinating males (50, 51). However, self-reported sexual behavior from household-based surveys used in these models have led to criticism of model assumptions and consequently limit the value of these studies in assessing the utility of vaccinating males for HPV (44).

As was found with rubella (52), control of HPV among women will be achieved through a gender-based vaccination policy only if vaccine coverage among women is extremely high. Given the likelihood for suboptimal vaccine coverage among women owing to vaccine refusal, cost, and weaknesses in our vaccine delivery system, an HPV vaccine policy including men and women may become necessary to adequately control disease.

Summary

HPV infection is common in men and is readily transmitted, influencing disease rates in both males and females. Should the HPV vaccine show efficacy in males, vaccination strategies that include both sexes may be more cost-effective in reducing HPV female disease burden than gender-targeted strategies. The efficacy of the quadrivalent HPV vaccine to reduce infection and lesions caused by HPV is being tested among young men internationally. Vaccination of males may become inevitable if and when vaccination of females fails to adequately control disease because of suboptimal vaccine uptake. From a disease transmission perspective, female-only vaccination may work well for controlling cervical cancer, but the realities on the ground may force us to consider other strategies such as vaccinating males.

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