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Human papillomavirus vaccination in males

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Abstract

Human papillomavirus (HPV) is one of the most common sexually transmitted diseases (STDs) and is frequently presented clinically as anogenital warts in both males and females. There is a high rate of transmission of HPV in female partners of men with pre-existing penile warts, and HPV infection in men has been shown to contribute to HPV infection and subsequent cervical disease in women. HPV is associated with significant morbidity and represents a substantial healthcare burden. Data indicate that males experienced a longer duration of genital warts and incurred greater treatment costs than women. The quadrivalent vaccine, the first vaccine to be approved for use in adolescent and young women aged 9 to 26 years for the prevention of cervical cancer and genital warts, targets HPV types -6, and -11 (responsible for genital warts), and HPV types-16 and -18 (involved in cervical cancer). Pharmacoeconomic data determined that routine administration of a prophylactic quadrivalent HPV vaccine to 12-year-old males and females in addition to catch-up vaccination of 12- to 24-year-old males and females, within the setting of organized cervical cancer screening within the US, was the most cost-effective strategy. It is also anticipated that widespread use of vaccines that offer protection against HPV-6 and -11 could potentially reduce the workload at STD clinics by approximately 10% without a substantial impact on the diagnosis and treatment of other STDs. To optimally control transmission of HPV, consideration should be given to vaccinating males as well as females.

Keywords: Male; HPV infection; Genital warts

Human papillomavirus (HPV) in men

Within the general population, human papillomavirus (HPV) infections are one of the most common sexually transmitted diseases (STDs) [1]. In the US alone, it is estimated that, annually, 6.2 million individuals aged 15 to 44 years are infected; 74% of these infections occur among 15 to 24 year olds [2]. HPV infection, in the form of genital warts, is highly contagious and is therefore easily transmitted from one sexual partner to another [1].

HPV frequently presents clinically as anogenital warts; the development of genital warts (condylomata) has been linked with HPV types-6 and -11 [3]. In men, HPV-16 has also been linked to the development of penile, anal, and head and neck cancers. Evidence from a recent study in patients with penile carcinoma ($n=49$) demonstrated that HPV was present in 77.5% of cases, and specifically HPV types 16 and 18 were present in 84.2% and 10.5% of cases, respectively [4].

In men, sexual activity is positively correlated with HPV infection. In a review of the literature, Dunne et al. [5] reported that HPV prevalence was typically ≥20% and infection rates of up to 72.9% have been documented. A recent study in 463 men aged 18 to 40 years with no history of genital warts, evaluated the prevalence of HPV infection utilizing six anogenital sites (e.g. glans/corona, penile shaft, scrotum, urethra, perianal area and anal canal) and a semen sample. Approximately half of the men (51.2%) were positive for at least one oncogenic or nononcogenic HPV type [6]. The types with the highest prevalence were HPV-16 (11.4%) and HPV-84 (10.6%). These findings suggest that there is a relatively high prevalence of HPV even in men who are asymptomatic.

Evidence indicates that there is a high rate of transmission of HPV from men with pre-existing penile warts to their female partners. A small study reported that 19 of 25 (76%) women who had been in an exclusive sexual relationship with their partners for ≥1 year had genital HPV infections, and 9 (36%) women had abnormal cervical cytology [7]. In 7 (77%) of these women, cervical HPV DNA was detected.

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Economic burden of genital warts

HPV infection in general and genital warts in particular are associated with significant morbidity and substantial healthcare costs [8]. In 2000, the direct medical costs associated with HPV infection in 15- to 24-year-old American men and women were $US 2.9 billion [9]. Insinga et al. [10] estimated the health and economic burden associated with genital warts in a sample of more than 3.6 million privately insured individuals in the US. In this study, 5095 cases of genital warts were identified, equating to 1.7 cases per 1000 person-years. Across the population sample, for individual episodes of care, men experienced a longer duration of genital warts and incurred greater costs than women (Table 1). The highest prevalence of genital warts occurred among men aged 25 to 29 years (5.0 cases) and women aged 20 to 24 years (6.2 cases). The costs per 1000 person-years (including indirect, direct and pharmacy costs) were $US 1717 in men 25 to 29 years, and $US 1692 in women aged 20 to 24 years.

HPV vaccination for males

The quadrivalent vaccine is the first vaccine to be approved for use in adolescent and young women aged 9 to 26 years for the prevention of cervical cancer and genital warts, as well as vulvar and vaginal precancerous lesions [11] targeting HPV types -6, -11, -16, and -18. In two randomized, double-blind, placebo-controlled trials (FUTURE I and FUTURE II), the vaccine was shown to be effective in the prevention of genital lesions and cervical cancer due to the vaccine HPV types [12,13].

HPV infection in men contributes to HPV infection and subsequent cervical disease in women [14–17]. A case–control study in women with one lifetime sexual partner demonstrated that men play a role in the development of cervical dysplasia and carcinoma *in situ*. In particular, male promiscuity was associated with a 6.9-fold increased risk of cervical cancer in the female partner [14]. Another case–control study reported that women with cervical cancer were 5.3 times more likely to be married to males who had ≥20 sexual partners than women without disease [17]. The association between cervical cancer and male sexual history persisted following adjustment for the female's number of sexual partners or age at first intercourse.

The majority of HPV infections in both men and women are asymptomatic or sub-clinical. Therefore, most individuals infected with HPV are unaware of their infection, allowing for transmission to occur without knowledge of either partner. Given that HPV infection can result in genital warts, precancerous and cancerous lesions in both males and females there should be consideration given to the cost-effectiveness of including both males and females in national HPV vaccination programs. While several countries (e.g., Mexico and Australia) have licensed the HPV vaccine for use in both sexes, policy recommendation for dissemination of the vaccine in males awaits HPV vaccine trial efficacy results from the on-going international trial of the vaccine in males. In preparation of results from these trials, several groups have started to evaluate the cost-effectiveness of various vaccine dissemination strategies on the reduction of cervical precancerous lesions.

Table 1
Costs associated with individual episodes of genital warts in a sample of over 3.6 million privately insured individuals in the US (Adapted with permission from University of Chicago Press [10].)

	Men (*N*=237)	Women (*N*=299)	All (*N*=536)
Duration of episode (mean days; 95% CI)	102.6 (77.8–127.4)	84.8 (67.5–102.1)	92.7 (85.3–100.2)
Mean no. physicians visits (95% CI)	3.1 (2.8–3.5)	3.1 (2.8–3.4)	3.1 (2.9–3.3)
Cost (mean $US; 95% CI)	477 (365–590)	404 (316–492)	436 (365–508)

CI=confidence interval.

The success of vaccination programs can be attributed to both direct protection for individuals who are immunized and to indirect protection or so-called 'herd immunity' [18]. With the recent introduction of the quadrivalent HPV vaccine, it remains to be determined who should be vaccinated and at what age. Pharmacoeconomic modeling may provide the best answer to these questions. A dynamic transmission model, within the setting of organized cervical cancer screening within the US, determined that routine administration of a prophylactic quadrivalent HPV vaccine to 12-year-old males and females in addition to catch-up vaccination of 12- to 24-year-old males and females was the most effective strategy [19]. According to this model, the incidence of genital warts, cervical intraepithelial neoplasia and cervical cancer was reduced by 97%, 91% and 91%, respectively, at a cost of $US 45,056 per quality-adjusted life year.

In Australia, the quadrivalent vaccine is registered for use in females aged 9 to 26 years and males aged 9 to 15 years [20]. It is anticipated that vaccination will be of benefit to all individuals within these age groups, with the greatest benefits being derived when the vaccine is administered prior to the onset of sexual activity. However, it should be noted that sexually active individuals will still benefit from HPV vaccination; if an individual has been infected with one HPV type, he/she will still benefit from vaccination against the remaining three types.

Implications of HPV Vaccination

Genital warts are associated with a substantial healthcare burden which may be significantly reduced with the introduction of effective HPV vaccines. US-based data from a single STD clinic reported that of 66,537 clinic visits, 10.3% were related to HPV infection [21]. Genital warts were the most common presenting complaint in both males and females with HPV infection. In addition, there were a total of 10,289 follow-up visits amongst men and 25.2% (2595) were for genital warts. In women 17.3% (744 of 4285) of follow-up visits were due to genital warts. The results of this study showed that there was a distinct lack of other STD diagnoses among many of the individuals presenting with HPV infection, indicating that infection with HPV occurs outside the setting of 'risky sexual behavior'. Furthermore, widespread use of vaccines that offer protection against HPV-6 and -11 could potentially reduce the workload at STD clinics by approximately 10% without a substantial impact on the diagnosis and treatment of other STDs.

High vaccination coverage must be achieved and maintained for any vaccination program to be effective [22]. Evidence from vaccination programs targeted solely at women indicates that insufficient vaccine coverage can actually result in an increase in disease transmission. Experience with a UK-based rubella vaccination program demonstrated that following an initial decline in the incidence of rubella, a resurgence of the disease resulted from an epidemic that primarily affected young males [23]. In order to best control the transmission of HPV, vaccination efforts should be co-ordinated to include both males and females, if the vaccine trials on-going in men demonstrate efficacy.

Summary

HPV infection is widespread and, in men, is most commonly presented clinically as genital warts. There is significant HPV transmission between men and their female partners, and an increasing body of evidence to suggest that men with HPV infection may play a role in the development of cervical cancer in women as well as cancer at several sites in men. Available data lend support to the implementation of vaccination programs that target not only females but also males in the future.

Questions and answers

What is the prevalence of HPV infection in men?

HPV infection in men appears to be as common as in women. Worldwide the prevalence ranges from less than 10% to approximately 72% among predominantly heterosexual men. Infection is most common on the penile shaft followed by the coronal sulcus/glans penis, and scrotum. As most infections are asymptomatic in both men and women transmission likely occurs readily between sexual partners.

What is the burden of genital warts in men?

In the US the incidence of genital warts in men is estimated to be ~250/100,000. The incidence is highest among men 25–29 years of age, and has been shown to be increasing over the last few decades in the US. As genital warts often require repeated treatment and the incidence is high, the economic burden associated with warts is correspondingly high.

What are the costs associated with the treatment of genital warts?

HPV infection in general, and genital warts in particular, is associated with significant morbidity and substantial healthcare costs [8]. In 2000, the direct medical costs associated with HPV infection in 15- to 24-year-old American men and women were US$ 2.9 billion. Insinga et al. [10] estimated the health and economic burden associated with genital warts in a sample of more than 3.6 million privately insured individuals in the US. In this study, 5095 cases of genital warts were identified, equating to 1.7 cases per 1,000 person-years. Across the population sample, for individual episodes of care, men experienced a longer duration of genital warts and incurred greater costs than women (Table 1). The highest prevalence of genital warts occured among men aged 25 to 29 years (5.0 cases) and women aged 20 to 24 years (6.2 cases). The costs per 1,000 person-years (including indirect, direct, and pharmacy costs) were US$ 1,717 in men 25 to 29 years, and $US 1,692 in women aged 20 to 24 years.

Conflict of interest statement
I declare that I have no conflict of interest.

References

[1] Lacey CJN. Therapy for genital human papillomavirus-related disease. J Clin Virol 2005;32S:S82–90.
[2] Weinstock H, Berman S, Cates W. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health 2004;86(1):6–10.
[3] Greer CE, Wheeler CM, Ladber MB, Beutner K, Coyne MY, Liang H, et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. J Clin Microbiol 1995;33(8):2058–63.
[4] Pascual A, Pariente M, Godinez JM, Sánchez-Prieto R, Atienzar M, Segura M, et al. High prevalence of human papillomavirus 16 in penile carcinoma. Histol Histopathol 2007;22:177–83.
[5] Dunne EF, Nielson CM, Stome KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: a systematic review of the literature. J Infect Dis 2006;194:1044–57.
[6] Nielson CM, Flores R, Harris RB, Abrahamsen M, Papenfuss MR, Dunne EF, et al. Human papillomavirus prevalence and type distribution in male anogenital sites and semen. Cancer Epidemiol Biomark Prev 2007;16(6):1107–14.
[7] Campion MJ, Singer A, Clarkson PK, Mc Cance DJ. Increased risk of cervical neoplasia in consorts of men with penile condylomata acuminate. Lancet 1985;1:943–6.
[8] Lacey CJN, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006;24(S3):35–41.
[9] Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspect Sex Reprod Health 2004;36(1):11–9.
[10] Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. Clin Infect Dis 2003;36(11):1397–403.
[11] Gardasil®. Prescribing information. 2007. Merck & Co., Inc., Whitehouse Station, NJ 08889, USA.
[12] FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356(19):1915–27.
[13] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356(19):1928–43.
[14] Agarwal SS, Sehgal A, Sardana S, Kumar A, Luthra UK. Role of male behavior in cervical carcinogenesis among women with one lifetime sexual partner. Cancer 1993;72:1666–9.
[15] Buckley JD, Harris RW, Doll R, Vessey MP, Williams PT. Case–control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 1981;2:1010–5.
[16] Thomas DB, Ray RM, Pardthaisong T, Chutivongse S, Koetsawang S, Silpisornkosol S, et al. Prostitution, condom use, and invasive squamous cell cervical cancer in Thailand. Am J Epidemiol 1996;143:779–86.
[17] Zunzunegui MV, King M-C, Coria CF, Charlet J. Male influences on cervical cancer risk. Am J Epidemiol 1986;123:302–7.
[18] Garnett GP. Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. J Infect Dis 2005;191(Suppl 1): S97–S106.
[19] Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13(1):28–41.
[20] May J. HPV vaccination – a paradigm shift in public health. Aust Fam Physician 2007;36(3):106–11.
[21] Dempsey AF, Koutsky LA, Golden M. Potential impact of human papillomavirus vaccines on public STD clinic workloads and on opportunities to diagnose and treat other sexually transmitted diseases. Sex Transm Dis 2007;34(7):503–7 [July].
[22] Vyse AJ, Gay NJ, White JM, Ramsay ME, Brown DWG, Cohen BJ, et al. Evolution of surveillance of measles, mumps, and rubella in England and Wales: providing the platform for evidence-based vaccination policy. Epidemiol Rev 2002;24:125–36.
[23] Tookey PA, Peckham CS. Surveillance of congenital rubella in Great Britain, 1971–96. Br Med J 1999;318:769–70.