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HPV IN MEN: UNVEILING THE SILENT EPIDEMIC

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ABSTRACT

Human Papillomavirus (HPV) is one of the most common sexually transmitted infections with about 1 in 3 men infected globally. Men do not develop protective immunity after an infection and consequently remain susceptible to re-infection throughout their lives, serving as a reservoir of infection. While HPV infections may be asymptomatic, persistent HPV infection may lead to the development of genital warts and increase the risk of anal cancer in men. 4- and 9-valent HPV vaccines have been approved for use in boys and men in Singapore and are efficacious and safe in preventing HPV infections and HPV-associated diseases.

Keywords: Human Papillomavirus, Vaccination, Genital Warts, Anal Cancer, Penile Cancer

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INTRODUCTION

HPV is one of the most common sexually transmitted infections worldwide. In men, HPV infections are known to cause genital warts and have been linked to increased risk of anal cancer. While routine screening and vaccination programmes for HPV are commonplace for women, no such programmes exist for men in Singapore. Men consequently continue to suffer morbidity caused by HPV and serve as a reservoir of infection. This paper is a snapshot of the current landscape for HPV infection and morbidity for men in Singapore. It also discusses the use of 4- and 9-valent HPV vaccines for men in Singapore and how a gender-neutral HPV vaccination programme can potentially reduce the burden of HPV disease in men and make women vaccination programmes more robust.

HPV BIOLOGY

HPV are small double-stranded nonenveloped DNA viruses of the *Papillomaviridae* family. They all exhibit tropism for epithelia of the human genitals and upper respiratory tract and skin.[1] More than 150 HPV types have been identified so far, of which approximately 15 high-risk mucosal types are clearly associated with cancers including cervical cancer, anal cancer, vulvar cancer, and vaginal cancer.[1]

HPV is transmitted via direct contact with infected skin or mucosa. The HPV life cycle involves several steps, including attachment, entry, replication, and release. The virus initially infects basal cells of the epithelium, where it establishes a productive infection. The viral DNA is replicated and packaged into new viral particles, leading to the release of mature virions. In some cases, the virus can also establish a latent infection in the basal cells, contributing to its persistence.[2]

The mechanism of HPV carcinogenesis mainly involves two viral genes, namely the HPV E6 and E7 oncogenes. Both oncogenes encode for proteins that bind and inactivate tumour suppressors p53 and retinoblastoma gene family proteins. This in turn permits the cell to escape normal checkpoints and lead to the malignant transformation of epithelial cells.[3]

Unlike women, few men seroconvert after a HPV infection. In the HPV Infection in Men (HIM) seroconversion sub cohort study, only 9 percent of participants between the ages of 18 and 30 had detectable HPV antibodies after a follow-up period of 36 months.[4] This fell to 8 percent in men aged 45 to 70. Even males who do develop antibodies may not be protected against subsequent infections. Pamnani et al reported incident infection rates for HPV were similar in both seropositive (incidence rate 3 to 17 percent) and seronegative (incidence rate 4 to 12 percent) men over a median follow-up duration of four years.[5] The same author reported HPV recurrence rates in male external genital skin of 3.9 to 31.2 percent with the same HPV type after prior infection,[6] with higher recurrence observed of oncogenic HPV types (HPV-16, 19.6%; HPV-45, 22.9%; HPV-52, 31.2 percent; and HPV-58, 21.4%) compared to non-oncogenic types (HPV-6, 19.9%; HPV-11, 3.9%).[6] Consequently, men remain susceptible to HPV infections throughout their lifespan.[7]

HPV EPIDEMIOLOGY IN SINGAPORE FOR MEN

A study by Bruni et al published in 2023 estimated that globally almost 1 in 3 men are infected with at least one strain of HPV.[8] In that study, the regional grouping of "Eastern and South-Eastern Asia" (represented countries include China, Japan, Malaysia, and South Korea) had the lowest pooled prevalence for both any HPV (15%, 95% CI 11-21) and high risk HPV (10%, 95% CI 7-13) compared to other regional groupings. The only study representing Southeast Asia was by Khoo et al published in 2021 to determine anogenital HPV prevalence among healthy

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community-based Malaysian men.[9] Five hundred and three men were recruited from community-based clinics and genital and anal samples were collected for HPV DNA detection and genotyping. The median age at enrolment was 40 years old. The anogenital prevalence of HPV types 6 and 11 was 3.2 percent and the prevalence of high-risk HPV types was 27.1 percent.[9] HPV 18 was the most prevalent genotype detected.[9] Given Malaysia's geographical and cultural proximity to Singapore, it would be logical to assume similar prevalence rates apply.

While genital warts caused by HPV infection are very common, the other HPV-related diseases, namely cancers, remain relatively uncommon. However, anal cancer incidence has been rising in the US and oropharyngeal cancer incidence has been steadily rising in Singapore. The crude incidence rate per 100,000 population of HPV-related diseases in Men in Singapore are as follows:[10]

Table 1: Crude incidence rate per 100,000 population of HPV-related diseases in Men in Singapore

Anal Cancer	1.24

A systematic review of the incidence and prevalence of genital warts by Patel et al published in 2013 reported new ano-genital warts incidence rates among males ranged from 103 to 168 per 100,000, with a median of 137 per 100,000 population.[11] Notably, Asian countries included in the review were China, Hong Kong, Japan, South Korea, and Vietnam. Five studies in the review reported temporal trends and all reported increases in both incidence and prevalence of anogenital warts over time. A bar graph available on Singapore's Department of STI Control (DSC) clinic's website dated 2018 listed genital warts as the fourth most common STI diagnosed.

HPV MORBIDITY IN MEN

While HPV infections may be transient and asymptomatic, persistence of HPV infection may lead to the development of genital warts, and high-risk mucosal types can increase the risk of anal cancer in men.

HPV types 6 and 11 are responsible for more than 90 percent of anogenital warts.[12] Genital warts are highly contagious, with more than 75 percent of sexual partners developing warts after being exposed.[13] Consequently, it is not surprising that the estimated lifetime risk of developing genital warts is about 10 percent.[14,15] Genital warts may persist for months or even years. About 25 percent of cases recur within several months even after treatment.[16] Pamnani et al reported a recurrence rate of 19.9 percent and 3.9 percent for HPV type 6 and 11 respectively in men with prior infection of the same HPV type over a median follow-up period of 3.7 years.[6]

Anal squamous cell carcinomas (ACC) are primarily linked to HPV infection with an estimated 80 percent of anal cancers linked to HPV types 16 and 18.[17] Like cervical cancer, HPV-related inflammation leads to dysplasia and progression to cancer. ACC develops at the anal squamocolumnar junction and arises from precancerous lesions called anal intraepithelial neoplasia (AIN). The incidence of anal cancer has increased at a rate of approximately 2.1 percent per year from 2009 to 2018 in the US.[18] Although the prevalence of anal cancer is low, Singapore has the highest incidence rate of anal cancer in men in Southeast Asia, with an age-standardised incidence rate of 0.70 per 100,000.[19] Risk factors include active HPV infection, smoking, anoreceptive sex, and immunosuppression. Anal cancer is often misdiagnosed or the diagnosis is significantly delayed. The five-year survival rate ranges from 81.9 percent in patients with localised disease to 34.5 percent for patients with metastatic disease.[21] Vaccination against HPV for primary prevention of anal cancers is recommended by American Society of Colon and Rectal Surgeons.[20]

HPV PREVENTION IN MEN

Currently, there are no clinical guidelines or recommendations for HPV screening in men. There are also no HPV tests that have been validated and approved for use in men outside of a research setting.

While condoms and other barrier methods can reduce the risk of transmission, they do not provide complete protection due to potential skin contact in areas not covered by the barrier. A study by Campbell et al found that consistent condom use by men reduces their risk of acquiring HPV by almost half (hazard ratio 0.54) compared to men who never used condoms.[21] However, even among men who had a monogamous steady sex partner and always used condoms, the HPV incidence rate over a 12-month follow-up period was still 32.0 percent. This increased to 47.8 percent in men who had non-monogamous, non-steady sex partners but also always used condoms.[21]

HPV vaccines have been found to be efficacious in men. Giuliano et al reported that 97.4 percent of healthy men aged 16-26 years seroconverted within a month of receiving the third dose of the 4-valent HPV vaccine.[22] In the per-protocol population, efficacy against external genital lesions associated with HPV types 6, 11, 16, or 18 was 90.4 percent (95% CI, 69.2 to 98.1) and did not vary according to baseline characteristics.[22] The majority of external genital lesions observed were condylomata acuminata, and the observed vaccine efficacy against this lesion type was 89.4 percent (95% CI, 65.5 to 97.9) over a follow-up study period of 36 months.[22] HPV vaccination also reduced the incidence of AIN grade 2 or 3 in men who have sex with men by 74.9 percent (95% CI, 8.8 to 95.4).[23] Long-term follow-up (up to 11.5 years; median 9.5 years) of the efficacy of 4-valent HPV vaccine in men found no new cases of HPV-related genital warts, external genital lesions,

or high-grade AIN.[24] Furthermore, seropositivity rates by IgG immunoassay at month 120 were >90 percent for all four HPV types.[24] Similarly, seropositivity rates remained high at ≥95 percent at month 126 (10 years) post-dose 3 for the 9-valent HPV vaccine administered in boys aged 9-15 years.[25] Additionally, no cases of vaccine HPV type-related high-grade intraepithelial neoplasia or condyloma were reported after 11.0 (median 10.0) years of follow-up.[25]

HPV vaccines have been found to be safe. While significantly more subjects in the vaccine group reported injection-site pain (57 percent vs 51 percent in the placebo group, p<0.001), only 1.3 percent (and 1.0 percent in the placebo group) reported the pain as "severe".[22] A similar proportion of subjects in the vaccine group (14.1 percent) and placebo group (14.6 percent) reported systemic adverse events, which included fever, fatigue, gastrointestinal disorders, dizziness, and headache.[22] No serious adverse events related to vaccination were reported.

4- and 9-valent HPV vaccines have been approved for use in men aged nine to 45 in Singapore for the prevention of premalignant lesions and HPV infections, anal cancer, and genital warts. That said, the HPV vaccine for men and boys is not part of either the childhood or adult National Immunisation Schedule. Men are also not allowed to use their Medisave funds to pay for HPV vaccines.

Vaccinating men against HPV in Singapore may contribute to lowering overall virus transmission within the local community. Routine HPV vaccination of men has been estimated to increase a vaccination programme's resilience to decline in coverage compared to female-only vaccination programmes.[26] Modelling studies predict that gender-neutral vaccination programmes would reduce the prevalence of HPV 16 by an additional 18 percent in females and 35 percent in males if 40 percent of boys were vaccinated in addition to vaccination coverage rate of 40 percent among girls, and would also result in a faster decline in the prevalence of vaccine-specific HPV types.[27]

CONCLUSION

HPV is a prevalent disease among men in Singapore and can lead to significant morbidity and even mortality. Men do not develop protective immunity after an infection and consequently remain susceptible to re-infection throughout their lives while also serving as a reservoir of infection within the community. Correct and consistent use of condoms does not significantly reduce the risk of infection. 4- and 9-valent HPV vaccines have been approved for use in boys and men in Singapore and are efficacious and safe in preventing HPV infections and HPV-associated diseases. Gender-neutral vaccination programmes have been shown to improve coverage and resilience compared to female-only HPV vaccination programmes.

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LEARNING POINTS

- **HPV is prevalent among men.**
- **HPV infections can lead to the development of genital warts and increase the risk of anal cancer in men.**
- **Most men do not develop protective immunity after a HPV infection.**
- **HPV vaccines have been approved for use in boys and men in Singapore from the age of nine to 45 and are efficacious and safe in preventing HPV infections and HPV-associated diseases.**