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"Gender-Neutral Human Papillomavirus (HPV) Vaccination: Expanding Population Protection Against HPV Related Oropharyngeal Cancer."

A Joint Consensus Statement by the Asian Society for Pediatric Infectious Diseases (ASPID), World Society for Pediatric Infectious Diseases (WSPID), Asia Pacific Pediatric Association (APPA), Hong Kong Chinese Medical Association (HKCMA), Indonesian Pediatric Society, Malaysian Pediatric Association (MPA), The Hong Kong Society for Paediatric Immunology, Allergy and Infectious Diseases, Hong Kong Society for Infectious Diseases, The Centre for Health Education and Health Promotion, The Chinese University of Hong Kong, Macau Pediatric Society, The Hong Kong Society for Microbiology and Infection, The Hacettepe University Faculty of Medicine, Department of Pediatric Infectious Diseases, Ankara, Türkiye, The Hong Kong Association of Oral and Maxillofacial Surgeons, Asia Pacific Paediatric Nurses Association, Hong Kong College of Paediatric Nursing, College of Nursing Hong Kong, Hong Kong Paediatric Nurses Association, Hong Kong School Nurses Association, and Asian Medical Expert Academy

Human papillomavirus (HPV) is a common sexually transmitted infection in both men and women and is a well-established cause of cervical cancer, with evolving evidence supporting its causal role in other cancers, including anogenital and oropharyngeal cancers. Sexually active people may potentially be infected at some point in their lives. More than 200 HPV types have been identified. Approximately 40 infect the anogenital mucosa, of which a subset is classified as high-risk or oncogenic. While most HPV infections are asymptomatic and transient, persistent infection with certain high-risk genotypes, most frequently types 16 and 18, as well as other high-risk genotypes including types 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59, may increase the risk of progression to precancerous lesions and cancer.¹⁻³ HPV-related cancers may involve the cervix, vulva and vagina in females; the penis in males; and the oropharyngeal and anogenital regions in both males and females. Low-risk genotypes, particularly HPV6 and HPV11, are mainly associated with benign anogenital lesions such as condylomata acuminata, or genital warts, and may also involve mucous membranes, causing recurrent respiratory papillomatosis. Other HPV genotypes are more commonly associated with

cutaneous warts, including plantar and filiform warts.⁴

HPV is transmitted primarily through sexual contact, including vaginal, anal and oral sexual exposure. Non-sexual transmission has also been described, particularly perinatal transmission through an infected birth canal, which may be relevant to conditions such as recurrent respiratory papillomatosis.⁴ Separately, factors associated with an increased risk of HPV acquisition include multiple or new sexual partners and other high-risk sexual behaviours. Higher HPV prevalence has also been reported in some populations, including HIV-positive men who have sex with men.^{5,6} Studies have reported higher HPV prevalence among children with a history of sexual abuse; however, HPV detection in a child is not diagnostic of sexual abuse and should be interpreted in the context of clinical, epidemiological and safeguarding assessments.⁷⁻¹⁰ The burden of HPV-related disease extends to both sexes. Although cervical cancer continues to account for a large proportion of HPV-attributable cancers globally, HPV also causes substantial morbidity in males, including anal, penile and oropharyngeal cancers. This broader disease burden provides an important rationale for considering gender-neutral HPV vaccination.

Global burden of HPV-related cancers and diseases

It is estimated that 730,000 cases of HPV-related cancer are diagnosed in males and females around the world each year. Cross-sectional studies estimating the burden of cancer cases attribute these cancers to at least 1 of 25 HPV types (types 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70 and 74).¹¹⁻¹⁵ HPV DNA detection showed that HPV infection is unequivocally linked to almost all (approximately 95%) cervical cancer and a large proportion (approximately 88%) of anal cancer cases. HPV is also causally associated with a varying percentage of cancers of the vulva, vagina, penis, and a subset of head and neck cancers, particularly tonsillar cancer.¹⁶ Meanwhile, low-risk HPV types are non-oncogenic and can cause benign or low-grade cervical cell abnormalities, anogenital warts and respiratory tract papillomas.²

The global profile of HPV-related disease is increasingly recognised as extending beyond cervical cancer alone. Worldwide analyses show that HPV is attributable to cancers of the cervix, anus, penis, vulva, vagina and oropharynx, with substantial geographic variation in burden and HPV genotype distribution.^{17,18,19} In many high-income and middle-income settings, non-cervical HPV-associated cancers, particularly

oropharyngeal squamous cell carcinoma, represent an increasingly important component of the overall HPV-related cancer burden.

Strategies in the prevention of cervical cancers

Prevention strategies should include education on reducing behaviours that increase the risk of acquiring HPV infection, together with health programmes that provide screening, diagnosis and treatment of precancerous lesions and cancer.²⁰ Access to quality cervical screening and treatment services should be improved. **HPV vaccination before girls become sexually active and exposed to HPV infection is the most effective primary prevention intervention and does not eliminate the need for screening later in life.**

HPV vaccination has demonstrated long-term effectiveness and immunogenicity in adolescents and young adults.²¹⁻²⁴ HPV vaccination has also been associated with reduced risk of invasive cervical cancer in a nationwide population-based study.²⁵

When considered in a non-communicable disease context, **it is crucial that resources in cancer prevention programmes be directed towards targeted prevention of infections, particularly in high-risk populations.** Such interventions can markedly reduce the increasing cancer burden and associated mortality.

International experience has demonstrated that HPV vaccination programmes can reduce vaccine-type HPV infection, anogenital warts and cervical precancer, with evidence of population-level and herd effects where coverage is high.²⁶ Because HPV epidemiology, genotype distribution, vaccine uptake and disease burden differ between regions, continued surveillance and region-specific research are essential to evaluate long-term programme impact and inform prevention strategies across diverse healthcare systems.²⁷

Prevent and treat cervical cancer: Global strategy

The World Health Organization (WHO) has set a global strategy to accelerate the elimination of cervical cancer as a public health problem, with the goal of achieving the 90-70-90 targets by 2030: 90% of girls fully vaccinated with HPV vaccine by 15 years of age, 70% of women screened with a high-performance test by age 35 and again by age 45, and 90% of women identified with cervical disease receiving appropriate treatment.^{28,29} Substantial progress in girls' HPV vaccination has provided an important foundation for

cervical cancer prevention. Building on these achievements, the next opportunity is to broaden protection against HPV-related diseases by considering prevention strategies that also address the burden of infection and disease in boys and men.

Cervical cancer was the seventh most common cancer among females in Hong Kong and accounted for 3.1% of all new cancer cases in females in 2021.³⁰ Local clinical commentary has also highlighted the consequences of HPV infection and the role of prevention through vaccination and cervical screening.³¹ It was the ninth leading cause of female cancer deaths in Hong Kong; in 2022, a total of 167 women died from cervical cancer, accounting for 2.6% of female cancer deaths. The crude death rate of cervical cancer was 4.2 per 100,000 females, and the age-standardised death rate was 2.1 per 100,000 standard population. The Department of Health (DH) of the Hong Kong Special Administrative Region has offered HPV vaccination to eligible primary school girls as part of the Hong Kong Childhood Immunisation Programme since the 2019/2020 school year.³² The first dose is given to Primary 5 students, typically aged 10 to 11 years, at their schools; in accordance with the recommended vaccination schedule, they receive the second dose after progressing to Primary 6 in the following school year. DH also launched the HPV Vaccination Catch-up Programme in the 2024/25 school year to offer a one-off catch-up HPV vaccination to eligible female Hong Kong residents born between 2004 and 2008.³³

Prevalence of HPV Infection in Men

Overall, males have a higher prevalence of any HPV genotype than females.³⁴ The prevalence of HPV infection varies across geographical regions; however, prevalence in males after adolescence remains significant across all age groups.^{6,35} HPV seropositivity in males is associated with age, marital status, smoking status and sexual practice. The HPV Infection in Men (HIM) study has shown that males have a low rate of seroconversion following HPV infection.³⁶ Moreover, seroconversion following natural infection in males has shown no protection against subsequent reinfections.³⁷⁻³⁹ This leaves males susceptible to recurrent reinfections,⁴⁰ which can progress to HPV-related genital warts⁴¹ or cancers. The likelihood of recurrent reinfection has been associated with higher numbers of new male sexual partners, as well as other high-risk sexual behaviours, including the number of new female sexual partners and frequency of sexual intercourse.

Other HPV-related cancers and prevention

Emerging evidence has revealed that HPV-related diseases extend beyond cervical cancer in females. HPV also causes cancers in anogenital and oropharyngeal regions in both males and females. While women and girls benefit from the HPV vaccination and well-developed cervical cancer screening and treatment programmes, HPV-related cancers in males are unfortunately difficult to detect and often underestimated.^{16,42}

Oropharyngeal cancer is a subtype of head and neck cancer that can be caused by tobacco smoking, alcohol consumption, exposure to pollutants, or infection with high-risk HPV.^{43,44} Studies have found that the prevalence of oral HPV infection is significantly higher among males than females.⁴⁵ Reports have also shown an increasing burden of HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) in Europe, North America, Australia and New Zealand.^{46,47} In recent decades, declining incidence rates, particularly for cancers of the oral cavity, hypopharynx and larynx, have been observed as a result of reduced tobacco consumption in industrialised countries. In contrast, there has been a rapid increase in the incidence of oropharyngeal cancers, particularly cancers of the tonsils and base of the tongue, which have been associated with HPV.⁴⁸⁻⁵⁰ OPSCC in males has surpassed cervical cancer in females as the most common HPV-associated cancer in the United States population overall.⁵¹

A similar trend has also been observed in Hong Kong, with an increased incidence of head and neck cancer in males.^{52,53} A retrospective study in Hong Kong showed that oropharyngeal cancer cases have persistently increased over the last three decades, with the proportion of HPV-positive oropharyngeal cancer substantially increasing over the last decade.⁵⁴ Research on methods for early detection and strategies for prevention of HPV infection in males is needed.

Notably, local evidence suggests that the HPV genotype distribution in Hong Kong OPSCC may differ from that reported in Western populations. In a recent territory-wide study, HPV16 remained the predominant genotype, accounting for approximately 80% of HPV-positive OPSCC cases; however, HPV58 was identified as the second most common genotype, despite being only rarely detected in OPSCC cohorts from Western countries. This observation is consistent with the known epidemiology of HPV-associated malignancies in East Asia and highlights the importance of considering regional HPV genotype distribution when evaluating preventive strategies.⁵⁴

Hong Kong data indicate a growing burden of HPV-associated OPSCC, with territory-wide analyses showing a marked increase in OPSCC incidence over recent decades and a rising proportion of HPV-positive tumours, particularly in the tonsils. Similar regional patterns have been reported elsewhere in Asia. In Korea, HPV positivity was detected in a high proportion of OPSCC cases and increased over time, with HPV-positive OPSCC occurring in younger patients and showing more favourable disease-free survival.⁵⁵ In Taiwan, HPV-positive oropharyngeal cancer accounted for approximately one-third of cases in large retrospective cohorts, with HPV16 as the predominant genotype and HPV58 also detected among HPV-positive tumours; incidence estimates also suggested an increasing burden over time.^{56,57} The detection of HPV58 in regional OPSCC cohorts is clinically relevant because HPV58 is among the additional oncogenic types included in the 9-valent HPV vaccine but is not covered by the 2-valent or 4-valent formulations. These findings therefore underscore the importance of local genotype-distribution data when considering vaccine strategies and formulation choice for HPV-related disease prevention.

Although no clinical studies have yet evaluated the efficacy and safety of 4-valent or 9-valent HPV vaccines in preventing or reducing head and neck cancers, evidence shows herd protection against vaccine-type oral HPV infection in a sample of unvaccinated US men aged 18 to 59 years.^{58,59} Moreover, prophylactic HPV vaccination in US young adults has been shown to reduce the prevalence of oral⁶⁰ and oropharyngeal⁶¹ HPV infection, and a significant proportion of vaccinated individuals developed IgG antibodies in oral fluid after vaccination.⁶¹ An ongoing phase 3 trial is investigating the efficacy of HPV vaccines in preventing oral persistent infection in men.⁶²

Gender-neutral HPV vaccination

Given the low seroconversion rate in men after natural infection and the rising incidence of HPV-related cancers, including cervical, penile and oropharyngeal cancers, particularly among men, **some countries advocate gender-neutral HPV vaccination to reduce HPV transmission and minimise the burden of HPV-related cancers.**⁶³ A study in mainland China identified key factors influencing HPV vaccination intentions among young men, including personal health beliefs and altruistic beliefs based on the Health Belief Model: perceived susceptibility, perceived benefits, perceived gender barriers and perceived benefits of male HPV vaccination for female partners.⁶⁴

A review of modelling studies estimated the effect of gender-neutral vaccination (GNV) strategies on HPV prevalence compared with female-only vaccination (FOV). The study showed that GNV programmes would reduce the prevalence of HPV16 by an additional 21% in females and an additional 36% in males after 70 years, and concluded that vaccinating boys in addition to girls produced a slightly faster decline in vaccine-type-specific prevalence among women and men.⁶⁵

A dynamic transmission model adapted to Hong Kong was used to estimate the potential health and economic impact of a routine GNV approach compared with the current FOV strategy. In the base-case analysis, the incremental cost-effectiveness ratio was HK\$248,354 per quality-adjusted life year for routine GNV. Compared with FOV, routine GNV fell below the cost-effectiveness ceiling of HK\$382,046 per quality-adjusted life year for Hong Kong. Routine GNV with the 9-valent HPV vaccine is predicted to provide greater reductions in cumulative HPV-related disease incidence and mortality, as well as lower HPV-related treatment costs. These results highlight the potential value of a routine GNV programme with the 9-valent HPV vaccine among 12-year-olds in Hong Kong to reduce the public health and economic burden of HPV-related diseases.⁶⁶

Conclusion

The global burden of HPV-attributable cancers and diseases is substantial for both males and females. Evidence supporting the clinical effectiveness of HPV vaccines is underpinned by more than 20 years of clinical development and real-world experience. HPV vaccination in early adolescence, particularly at ages 9–14 years and before exposure to HPV, can help protect both males and females against certain HPV-related cancers and diseases later in life. The participating societies support gender-neutral HPV vaccination programmes where feasible, affordable and sustainable, while maintaining high vaccination coverage among girls aged 9–14 years as the primary target population. Gender-neutral vaccination provides direct protection to boys and men and may further reduce HPV transmission and the burden of HPV-related diseases and cancers at the population level. Decisions on implementation should consider local disease burden, existing vaccination coverage, cost-effectiveness, vaccine supply, equity and health-system capacity. Continued surveillance of HPV infection, genotype distribution, vaccine uptake and HPV-related disease trends will be essential to monitor programme impact and guide policy refinement. Further regional research, including health economic

evaluations and studies on HPV-related cancers beyond the cervix, is also warranted to inform implementation strategies across diverse settings.

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