A SELECTION OF TEN READINGS ON TOPICS RELATED TO ADVANCING HPV PREVENTION IN SINGAPORE: FROM AWARENESS TO ACTION, 2024

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Selection of readings made by A/Prof Goh Lee Gan

READING 1 – SURVEILLANCE OF HUMAN PAPILLOMAVIRUS THROUGH SALIVARY DIAGNOSTICS

Wijesekera A,[1] Weeramange CE,[2] Vasani S,[3] Kenny L,[4] Knowland E,[5] Seneviratne J,[6] Punyadeera C.[7] Surveillance of human papillomavirus through salivary diagnostics - A roadmap to early detection of oropharyngeal cancer men. Tumour Virus Res. 2024 Mar 3;17:200278. PMID:38442788.

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted disease. Certain strains have the potential to cause malignancy in multiple anatomical sites if not cleared by the immune system. In most infected people, HPV is cleared within two years. However, HPV may persist in susceptible individuals with certain risk factors, eventually leading to malignancy.

New evidence suggests that over 75% of all oropharyngeal cancers (OPC) are directly attributable to HPV. It is estimated that prophylactic HPV vaccination alone may take at least 25 years to have a significant impact on reducing the incidence of OPC. The temporal link between detection of oral HPV, persistence of the infection, and the subsequent development of OPC have been well established. Moreover, men are at a threefold higher risk than women for acquiring HPV-OPC. This comprehensive review focuses on OPC development in men, highlighting the risk factors associated with malignant transformation of HPV-OPC.

Current evidence is insufficient to determine whether early identification of at-risk demographics, screening, and prompt diagnosis result in improved outcomes. Hitherto, the effectiveness of an oral HPV screening programme in this regard has not been investigated. Nevertheless, the potential to emulate the success of the cervical screening programme remains a very real possibility.

READING 2 – AWARENESS, PERCEPTIONS, AND ACCEPTANCE OF HUMAN PAPILLOMAVIRUS VACCINAT ON AMONG PARENTS IN HONG KONG

Kun KY,[1] Li DFH,[1] Wan WY,[1] Lam EWH,[1,2] Ngan HYS,[1,3] Chan PKS.[1,4] Awareness, perceptions, and acceptance of human papillomavirus vaccination among parents in Hong Kong. Hong Kong Med J. 2023 Aug;29(4):287-294.

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ABSTRACT

INTRODUCTION: This study investigated the awareness, perceptions, and acceptance of human papillomavirus (HPV) vaccination for children among parents in Hong Kong. It also explored factors associated with, and differences in, vaccine acceptance and hesitancy between parents of girls and boys.

METHODS: Parents of boys or girls in Primary 5 to 6 were invited to participate in an online survey through an established health and lifestyle e-platform.

RESULTS: Overall, 851 parents completed the survey: 419 (49.2%) had daughters, 348 (40.9%) had sons, and 84 (9.9%) had children of both sexes. Parents who enrolled their children into the Childhood Immunisation Programme were more likely to accept HPV vaccination (79.7% vs 33.7%, odds ratio [OR]=7.70; 95% confidence interval [CI]=5.39-11.01; P<0.001); parents of girls were more likely to accept than parents of boys (86.0% vs 71.8%, OR=2.40; 95% CI=1.67-3.46; P<0.001). Among parents of girls and boys, the main reasons for HPV vaccination acceptance were prevention of cancers (girls: 68.8% and boys: 68.7%), prevention of sexually transmitted diseases (girls: 67.3% and boys: 68.3%), and optimal timing before initiation of sexual activity (girls: 62.8% and boys: 59.8%). Vaccine hesitancy was mainly associated with concerns about serious side-effects (girls: 66.7% and boys: 68.0%) and the belief that their children were too young (girls: 60.0% and boys: 54.0%).

CONCLUSION: Parents in Hong Kong are hesitant about HPV vaccination for their sons. This barrier could be removed by providing information to correct vaccine safety misconceptions and offering a gender-neutral vaccination programme through the school-based Childhood Immunisation Programme.

READING 3 – HUMAN PAPILLOMAVIRUS IN THE SETTING OF IMMUNODEFICIENCY

Hewavisenti RV,[1] Sasson SC,[1] Arena J,[1,2] Ahlenstiel CL.[1,2] Human papillomavirus in the setting of immunodeficiency: Pathogenesis and the emergence of next-generation therapies to reduce the high associated cancer risk. Front Immunol. 2023 Mar 7;14:1112513. PMID: 36960048; PMCID: PMC10027931.

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ABSTRACT

Human papillomavirus (HPV), a common sexually transmitted virus infecting mucosal or cutaneous stratified epithelia, is implicated in the rising of associated cancers worldwide. While HPV infection can be cleared by an adequate immune response, immunocompromised individuals can develop persistent, treatment-refractory, and progressive disease. Primary immunodeficiencies (PIDs) associated with HPV-related disease include inborn errors of GATA, EVER1/2, and CXCR4 mutations, resulting in defective cellular function.

People living with secondary immunodeficiency (e.g., solid-organ transplants recipients of immunosuppression) and acquired immunodeficiency (e.g., concurrent human immunodeficiency virus (HIV) infection) are also at significant risk of HPV-related disease. Immunocompromised people are highly susceptible to the development of cutaneous and mucosal warts, and cervical, anogenital, and oropharyngeal carcinomas.

The specific mechanisms underlying high-risk HPV-driven cancer development in immunocompromised hosts are not well understood. Current treatments for HPV-related cancers include surgery with adjuvant chemotherapy and/or radiotherapy, with clinical trials underway to investigate the use of anti-PD-1 therapy. In the setting of HIV co-infection, persistent high-grade anal intraepithelial neoplasia can occur despite suppressive antiretroviral therapy, resulting in an ongoing risk for transformation to overt malignancy. Although therapeutic vaccines against HPV are under development, the efficacy of these in the setting of PID, secondary- , or acquired-immunodeficiencies remains unclear. RNA-based therapeutic targeting of the HPV genome or mRNA transcript has become a promising next-generation therapeutic avenue. In this review, we summarise the current understanding of HPV pathogenesis, immune evasion, and malignant transformation, with a focus on key PIDs, secondary immunodeficiencies, and HIV infection. Current management and vaccine regimes are outlined in relation to HPV-driven cancer, and specifically, the need for more effective therapeutic strategies for immunocompromised hosts.

The recent advances in RNA-based gene targeting including CRISPR and short interfering RNA (siRNA), and the potential application to HPV infection are of great interest. An increased understanding of both the dysregulated immune responses in immunocompromised hosts and of viral persistence is essential for the design of next-generation therapies to eliminate HPV persistence and cancer development in the most at-risk populations.

READING 4 – GENDER-NEUTRAL HPV VACCINATION PROGRAMS

Dykens JA,[1,2,3] Holt HK,[1,3] Peterson CE,[2,3,4] Harper DM.[5,6,7] Gender-neutral HPV vaccination programs: Reconsidering policies to expand cancer prevention globally. Front Public Health. 2023 Feb 21;11:1067299. PMID: 36895694; PMCID: PMC9989021.

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ABSTRACT

Human papillomavirus (HPV) infection is responsible for many cancers in both women and men. Cervical cancer, caused by HPV, is the fourth most common cancer among women worldwide, even though it is one of the most preventable cancers. Prevention efforts include HPV vaccination; however, these programmes remain nascent in many countries.

In 2020, the World Health Assembly adopted the Global Strategy for cervical cancer elimination, including a goal to fully vaccinate 90% of girls with the HPV vaccine by the age of 15. However, very few countries have reached even 70% coverage. Increased vaccine availability in the future may allow the opportunity to vaccinate more people. This could add to the feasibility of introducing gender-neutral HPV vaccination programmes. Adopting a gender-neutral HPV vaccine approach will reduce HPV infections transmitted among the population, combat misinformation, minimise vaccine-related stigma, and promote gender equity. We propose approaching programmatic research through a gender-neutral lens to reduce HPV infections and cancers and promote gender equality.

In order to design more effective policies and programmes, a better understanding of the perspectives of clients, clinicians, community leaders, and policymakers is needed. A clear, multi-level understanding of these stakeholders' views will facilitate the development of target policies and programmes aimed at addressing common barriers and optimising uptake.

Given the benefit of developing gender-neutral HPV vaccination programmes to eliminate cervical cancer and address other HPV-associated cancers, we must build knowledge through implementation research around this topic to inform policy-makers and funders for future policy shifts.

READING 5 – AN EDUCATION RESOURCE FOR HUMAN PAPILLOMAVIRUS OROPHARYNGEAL CANCER PATIENTS

Sharman AR,[1] Ferguson EM,[2] Dhillon HM,[2,3] Macleod P,[4] McCrossin J,[5] Sundaresan P,[6,7] Clark JR,[7,8] Smith MA,[9] Dodd RH.[10,11,12] An education resource for human papillomavirus oropharyngeal cancer patients: think-aloud interviews. Support Care Cancer. 2023 Feb 11;31(3):158. PMID: 36773108; PMCID: PMC9918836.

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ABSTRACT

PURPOSE: The human papillomavirus (HPV) is well recognised as a factor in developing oropharyngeal cancer (OPC). A booklet for HPV-OPC patients aimed to deliver evidence-based messages in everyday language, in a way to minimise negative psychological impacts on patients. Our study explored the suitability of the booklet for use.

METHODS: Participants were recruited through social media and interviewed via Zoom. Participants were shown the booklet and a think-aloud method elicited real-time reactions to the content. Responses were analysed for each section and coded as either for or against for content, with other responses thematically analysed using NVivo.

RESULTS: The sample comprised 24 participants: patients (n=19) who completed treatment for HPV-OPC and partners of survivors of HPV-OPC (n=5). All participants found the booklet useful, and most wished the resource had been available previously. Some indicated the information was new to them. The majority agreed the booklet would be best delivered by their specialist at point of diagnosis and would be a useful resource for friends and family. Most participants gave feedback on improvements to the booklet in terms of comprehension and design. Overall, participants found the content easy to understand. Most participants found that it helped to reduce shame and stigma associated with HPV as a sexually transmitted infection.

CONCLUSION: An evidence-based booklet for HPV-OPC patients and their partners is acceptable. Implementation may be feasible in routine clinical practice, specifically at time of diagnosis. Adapting the content will help optimise the efficacy of the booklet in facilitating communication between all stakeholders.

READING 6 – TOWARDS ELIMINATION OF CERVICAL CANCER – HUMAN PAPILLOMAVIRUS (HPV) VACCINATION AND CERVICAL CANCER SCREENING IN ASIAN NATIONAL CANCER CENTERS ALLIANCE (ANCCA) MEMBER COUNTRIES

Ong SK,[1] Abe SK,[2] Togawa K,[2] Bhandari AKC,[2] Thilagaratnam S,[3] Haruyama R,[4] Pathak R,[5] Jayasekara H,[6] Shankar A,[7] Nessa A,[8] Jugder U,[9] Agustina J,[10] Biglari M,[11] Yusuf A,[12] Tshomo U,[13] Fernando E,[14] Cairo C,[15] Kaung KK,[16] Rath B,[17] Vongdala C,[18] Pradhananga KK,[19] Kim J,[20] Chung YK,[20] Thanh Huong TT,[21] Sangrajran S,[22] Zhang Y,[23] Basu P,[24] Woo YL,[25] Sukumaran B,[26] Hwang WYK.[27] **Towards elimination of cervical cancer – human papillomavirus (HPV) vaccination and cervical cancer screening in Asian National Cancer Centers Alliance (ANCCA) member countries. Lancet Reg Health West Pac. 2023 Aug 1;39:100860. PMID: 37576906; PMCID: PMC10415801.**

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ABSTRACT

About 95% of cervical cancers worldwide are caused by human papillomavirus (HPV). Cervical cancer is preventable and curable if it is detected and treated early. We reviewed the latest national cervical cancer indicators and barriers to HPV vaccination and cervical cancer screening in 21 Asian National Cancer Centers Alliance (ANCCA) member countries.

Half (n=11, 52%) of the countries have introduced HPV vaccination for girls as part of their national vaccination programme. Three countries reported coverage of over 90%. Most ANCCA member countries have cervical cancer screening programmes; only five countries reported screening uptake of over 50%.

The barriers to HPV vaccination coverage and cervical cancer screening participation have been identified. Ensuring health service accessibility and affordability for women, addressing sociocultural barriers, and strengthening the healthcare system and continuum of care are essential to increasing HPV vaccination and cervical cancer screening coverage.

READING 7 – ASSOCIATION OF NASOPHARYNX CANCER WITH HUMAN PAPILLOMAVIRUS

Hung SH,[1,2,3] Yang TH,[4,5,6,7,8] Cheng YF,[6,8,9,10] Chen CS,[8,11] Lin HC.[12,13] Association of Nasopharynx Cancer with Human Papillomavirus Infections. Cancers (Basel). 2023 Aug 13;15(16):4082. PMID: 37627110; PMCID: PMC10452438.

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ABSTRACT

This population-based study aims to examine the association between nasopharyngeal carcinoma and human papillomavirus infections. This study included 2,747 individuals aged 20 years and older who were diagnosed with nasopharynx cancer as cases and 13,735 propensity-score-matching controls.

Multivariate logistic regression models were employed to quantitatively assess the association of nasopharynx cancer with human papillomavirus infections while considering age, sex, monthly income, geographic location, and urbanisation level of the patient's residence as well as diabetes, hypertension, and hyperlipidaemia.

Our chi-squared test indicated a significant dissimilarity in previous human papillomavirus infection rates between nasopharynx cancer patients and controls (12.7% vs. 7.2%, $p<0.001$). The adjusted odds ratio (OR) for prior human papillomavirus infections was found to be significantly higher for nasopharyngeal carcinoma cases compared to controls at a value of 1.869 with confidence interval ranging from 1.640 to 2.128. Among female participants, compared to controls, the adjusted OR of prior human papillomavirus infections was 2.150 (95% CI=1.763-2.626) in patients with nasopharynx cancer. In male participants sampled in this study, we observed a statistically significant association between prior human papillomavirus infections and nasopharynx cancer (adjusted OR=1.689; 95% CI=1.421-2.008).

Our study indicates a noteworthy association between previous human papillomavirus infections and nasopharyngeal carcinoma.

READING 8 – HUMAN PAPILLOMAVIRUS-ASSOCIATED OROPHARYNGEAL CANCER: GLOBAL EPIDEMIOLOGY AND PUBLIC POLICT IMPLICATIONS

Ndon S,[1] Ha PK,[1] Xu MJ,[1] Singh A,[2] Aswani J,[3] Chan JY.[4] Human Papillomavirus-Associated Oropharyngeal Cancer: Global Epidemiology and Public Policy Implications. Cancers (Basel). 2023 Aug 13;15(16):4080. PMID: 37627108; PMCID: PMC10452639.

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ABSTRACT
Global trends in human papillomavirus (HPV)-associated head and neck cancers (HNC), specifically in the oropharynx subsite, have been dynamically changing, leading to new staging and treatment paradigms.

Epidemiologic studies have noted regional variations in HPV-associated oropharyngeal squamous cell carcinoma (OPSCC). While HPV vaccination remains the main preventative approach, vaccination policy in relation to gender neutrality is heterogeneous and particularly sparse in low- and middle-income countries, where the burden of global cancer cases and HPV-associated HNC are not well-characterised in certain regions.

This review summarises the existing literature on regional variations of HPV-associated OPSCC and gender-neutral vaccine policies. Based on available data, the incidence of HPV-associated OPSCC is highest in North America, Europe, and Oceania. As of 2022, 122 of 195 (63%) World Health Organization (WHO) member states had incorporated HPV vaccinations nationally; of these, 41 of 122 (34%) member states have introduced gender-neutral vaccine coverage.

Future research is needed to describe continued evolving trends in HPV-associated OPSCC, understand underlying risk factors leading to regional variation in disease, and implement gender-neutral policy more broadly.

READING 9 – ECONOMIC BURDEN OF CERVICAL AND HEAD AND NECK CANCER IN TAIWAN FROM A SOCIAL PERSPECTIVE

Wu YH,[1] Chien L,[1] Pan YC,[1] Feng C,[1] Lai CH,[2,3] Chang CJ,[2,4,5,6] Lin YJ.[4] Economic Burden of Cervical and Head and Neck Cancer in Taiwan from a Societal Perspective. Int J Environ Res Public Health. 2023 Feb 20;20(4):3717. PMID: 36834412; PMCID: PMC9967678.

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ABSTRACT
BACKGROUND: Head and neck cancers (HNC) are increasingly recognised as important human papillomavirus (HPV)-related malignancies in addition to cervical cancer (CC). However, data on the socioeconomic impact of HNC and CC in Taiwan are limited.

METHODS: A retrospective cohort study was conducted to estimate the total direct medical cost and indirect productivity loss from CC and HNC between 2014 and 2015. Patient data from the Taiwan National Cancer Registry were analysed, with matched non-cancer controls from the Taiwan National Healthcare Reimbursement Database. Indirect costs due to premature deaths were calculated using public data from Taiwanese government reports.

RESULTS: In the direct cost analysis, 2,083 patients with newly diagnosed CC and 11,078 with newly diagnosed HNC (10,036 males) were identified between 2014 and 2015 and followed up through the end of 2016 or until death. The total direct medical costs incurred in 2014 and 2015 due to HNC were 11.54 times higher in males than in females, and 4.55 times higher than CC. Indirect cost analysis showed the total annual productivity loss was New Taiwan Dollar (NTD) $12 billion in 2019, and 79.99% was attributed to male HNC.

CONCLUSION: In Taiwan, the socioeconomic burden associated with male HNC is high and greater than that seen with CC. While not all HNCs are attributable to HPV infection, prevention of HNC through HPV vaccination should be considered for both sexes.

READING 10 – GLOBAL AND REGIONAL ESTIMATES OF GENITAL HUMAN PAPILLOMAVIRUS PREVALENCE AMONG MEN

Bruni L,[1] Albero G,[2] Alemany L,[2] Rowley J,[3] Arbyn M,[4] Giuliano AR,[5] Markowitz LE,[6] Broutet N,[7] Taylor M.[8] Global and regional estimates of genital human papillomavirus prevalence among men: a systematic review and meta-analysis. Lancet Glob Health. 2023 Sep;11(9):e1345-e1362. PMID: 37591583; PMCID: PMC10447222

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ABSTRACT

BACKGROUND: The epidemiology of human papillomavirus (HPV) in women has been well documented. Less is known about the epidemiology of HPV in men. We aim to provide updated global and regional pooled overall, type-specific, and age-specific prevalence estimates of genital HPV infection in men.

METHODS: We conducted a systematic review and meta-analysis to assess the prevalence of genital HPV infection in the general male population. We searched Embase, Ovid MEDLINE, and the Global Index Medicus for studies published between 1 Jan 1995, and 1 June 2022. Inclusion criteria were population-based surveys in men aged 15 years or older; HPV prevalence studies with a sample size of at least 50 men with no HPV-related pathology; and known risk factors for HPV infection that collected samples from anogenital sites and used PCR or hybrid capture 2 techniques for HPV DNA detection. Exclusion criteria were studies conducted among populations at increased risk of HPV infection, exclusively conducted among circumcised men, and based on urine or semen samples. We screened identified reports and extracted summary-level data from those that were eligible. Data were extracted by two researchers independently and reviewed by a third, and discrepancies were resolved by consensus. We extracted only data on mucosal α-genus HPVs. Global and regional age-specific prevalences for any HPV, high-risk (HR)-HPV, and individual HPV types were estimated using random-effects models for meta-analysis and grouped by UN Sustainable Development Goals geographical classification.

FINDINGS: We identified 5,685 publications from database searches, of which 65 studies (comprising 44,769 men) were included from 35 countries. The global pooled prevalence was 31% (95% CI 27-35) for any HPV and 21% (18-24) for HR-HPV. HPV-16 was the most prevalent HPV genotype (5%, 95% CI 4-7) followed by HPV-6 (4%, 3-5). HPV prevalence was high in young adults, reaching a maximum between the ages of 25 years and 29 years, and stabilised or slightly decreased thereafter. Pooled prevalence estimates were similar for the UN Sustainable Development Goal geographical regions of Europe and Northern America, Sub-Saharan Africa, Latin America and the Caribbean, and Australia and New Zealand (Oceania). The estimates for Eastern and South-Eastern Asia were half that of the other regions.

INTERPRETATION: Almost one in three men worldwide are infected with at least one genital HPV type and around one in five men are infected with one or more HR-HPV types. Our findings show that HPV prevalence is high in men over the age of 15 years and support that sexually active men, regardless of age, are an important reservoir of HPV genital infection. These estimates emphasise the importance of incorporating men in comprehensive HPV prevention strategies to reduce HPV-related morbidity and mortality in men and ultimately achieve elimination of cervical cancer and other HPV-related diseases.