衞生防護中心
Centre for Health Protection

Scientific Committee on Vaccine Preventable Diseases and Scientific Committee on AIDS and STI

Consensus Statement on the use of Human Papillomavirus (HPV) Vaccine in prevention of cervical cancer

Introduction

Human Papillomavirus (HPV) vaccine is the first vaccine that has been successfully developed to prevent a sexually transmitted virus infection, the persistence of which predisposes to cervical cancer. In 2013, Scientific Committee on AIDS and Sexually Transmitted Infections (SCAS) and Scientific Committee on Vaccine Preventable Diseases (SCVPD) of the Centre for Health Protection jointly reviewed the applicability of HPV vaccination in Hong Kong, the conclusions of which were published in their subsequent recommendations. By 2016, additional studies and new evidence concerning the efficacy of HPV vaccines have become available, urging SCAS and SCVPD to revisit the situation.

2. This consensus statement summarizes the latest scientific knowledge on HPV infection, its epidemiology and association with cervical cancer, efficacy and safety of HPV vaccines, the synthesis of which led to the consensus on the approach to the prevention of HPV infection and cervical cancer, focusing on the situation in Hong Kong. This document replaces "Recommendation on the use of Human Papillomavirus (HPV) vaccine" issued by SCAS and SCVPD in 2013.

Background

3. Human Papillomavirus (HPV) causes cervical cancer and anogenital warts. More than 100 HPV genotypes are known today, which can be broadly categorized as high risk (HR-HPV) and low risk (LR-HPV) types. Genital HR-HPV include genotypes 16,18,31,33,35,39,45,51,52,56,58,59,and 68. They are potentially oncogenic[1, 2] and can cause premalignant and malignant cancers of cervix, vagina, vulva, anus, penis and upper aerodigestive tract. LR-HPV including genotypes 6,11,42,43 and 44 mainly cause genital warts. Majority, around 90%, of HPV infections are cleared or become suppressed within 1 to 2 years of infection by the host's own immunity. Persistent infection of HR-HPV is a prerequisite for the increased risk of pre-malignant lesions and progression to malignant cervical cancer.[3]

4. HPV, a highly transmissible virus, is acquired from infected persons through mainly sexual, particularly vaginal and anal, intercourse. High number of sex partners is a salient risk factor for HPV transmission.[4] It is estimated that the incidence of HPV infection among initially uninfected women could reach as high as 60% over a 5-year follow-up period[4] and that the probability of HPV transmission per coital act ranged from 5% to 100% with a median of 40%.[5]

5. There is no published study to support the transmission of genital HPV through toilet seats, kissing on the mouth, hugging, holding hands, poor personal hygiene, sharing food or utensils, swimming in pools or hot tubs.

Epidemiology of HPV infection and diseases

6. By incorporating advanced molecular techniques, epidemiological and clinical studies have reported the detection of HR-HPV in practically 100% of cervical cancer tissues.[6] HR-HPV viral DNA was also detected in a majority (70-90%) of pre-cancer lesions or high-grade intraepithelial lesions (CIN II-III)[6] and in a smaller fraction (20-50%) of lower grade lesions (CIN I).[6]

7. Worldwide, HPV-16 and HPV-18 are the most frequent HR-HPV genotypes, amounting to an estimated 53.5% and 17.2% of cervical cancer respectively.[6] They are followed by HPV-45 (6.7%), HPV-31 (2.9%), HPV-33 (2.6%), HPV-52 (2.3%) and HPV-58 (2.2%).[6] Overall, the cumulative percentage of cervical cancer related to HPV-16 and HPV-18 is 70.7%, rising to 87.4% when all these seven HPV are included.

8. LR-HPVs are associated with condylomata acuminata (genital warts) mainly or papillomatosis. Over 90% of the genital warts have been reported to be associated with HPV-6 and HPV-11 infection, and rarely with HPV-42.[6, 7]

HPV situation in Hong Kong

9. In 2013, 503 new cases of cervical cancer were reported to the Hong Kong Cancer Registry administered by the Hospital Authority, making it the seventh in ranking among all cancers diagnosed in females and the cervical cancer accounted for 3.6% female cancer in Hong Kong. According to statistics from Department of Health, cervical cancer ranked number nine in cancer mortality in females in Hong Kong, with 131 (2.3%) reported deaths in 2014.

10. Worldwide, HPV-16,18,45,31 and 33 are the five most prevalent HR-HPV genotypes associated with cervical cancer. The situation is different in Hong Kong where HPV-52 and 58 are more prevalent and contribute to a higher proportion of cervical cancer than Western countries. A meta-analysis study reported that the attribution of HPV-52 and HPV-58 to cervical cancer in East Asia was 3.7-4.9 folds higher than elsewhere.[8] A study involving 1924 women in Hong Kong concluded that the overall prevalence of HPV-58 was 11.4%, and was 7.6% with invasive cervical cancer.[9]

11. A recent Hong Kong study involving 236 Chinese women who had received cervical cancer treatment revealed that the four most prevalent HPV genotypes associated with cervical cancer were HPV-16(60.2%), HPV-18(21.6%), HPV-52(11.9%) and HPV-58(9.3%).[10] Another study covering 120 cervical cancer patients in Hong Kong also showed similar findings, with

HPV-16(50.0%), HPV-18(21.7%), HPV-52(12.5%) and HPV-58(8.3%).[11]

HPV vaccines

12. Currently, three HPV vaccines (**Appendix**), namely Cervarix (2-valent vaccine against HPV-16,18), Gardasil-4 (4-valent vaccine against HPV-6,11,16,18) and Gardasil-9 (9-valent vaccine against HPV-6,11,16,18,31,33,45,52,58) have been registered in Hong Kong for the prevention of cervical cancer and/or other HPV-related diseases. All three vaccines could prevent infections from HPV-16 and 18, which account for about 70% of all cervical cancer worldwide. The 9-valent vaccine covers five additional HR-HPV, viz. HPV-31,33,45,52,58, which are associated with around 90% of cervical cancer in worldwide, including Hong Kong. The 4-valent and 9-valent vaccines could protect against two LR-HPV, HPV-6 and 11, which are associated with anogenital warts. However, the vaccines have no therapeutic effect on any existing HPV infections or diseases.

Efficacy of HPV Vaccines

13. Multiple studies had provided evidence that the first generation 2-valent and 4-valent vaccines had demonstrable efficacy in preventing vaccine genotype related HPV infection thence the cervical cancer.

14. Studies suggested the 2-valent vaccine could substantially reduce the overall burden of CIN 2+ (CIN2, CIN 3 and cervical cancer) by 70.2% - 100% in HPV-naive population up to around 6 years' follow-up.[12, 13] Another study showed that the 2-valent vaccine induced significantly higher neutralizing antibody levels as compared with 4-valent vaccine 7.3 years after vaccination.[12] In an immunogenicity study, anti-HPV-6,11,16,18 antibodies were shown to remain at high level with seropositive status maintained up to 9 years of follow-up after the first dose of the 4-valent vaccine.[14]

15. A 10-year review study published in 2016 confirmed the efficacy of the 4-valent vaccine in the prevention of vaccine-related HPV infection and cervical cancer. There was a maximal reduction of 90% for HPV-6,11,16,18 infection, 90% for genital warts, and 90% for high-grade histologically-proven cervical abnormalities.[15]

16. In December 2014, Food and Drug Administration in United States (US-FDA) approved a 9-valent HPV vaccine that protects against HPV-6,11,16,18,31,33,45,52,58, which is now available in Hong Kong. It includes the HPV genotypes in the 2-valent and 4-valent vaccine (HPV-6,11,16,18) with five additional HPV genotypes (HPV-31,33,45,52,58). As HPV-52 and 58 are relatively commoner in Hong Kong, the 9-valent vaccine could theoretically increase the cervical cancer prevention from around 70% to 90%.

17. It has been shown from study that the 9-valent HPV vaccine could result in a 96.7% risk reduction of high grade cervical disease including cervical cancer and 96% risk reduction of HPV persistent infection.[16]

HPV Vaccine Safety

18. The common side effects of HPV vaccines generally include mild local reactions following injection, such as erythema, pain and swelling, and systematic adverse effects such as muscle aches, fever, headache and nausea. These side effects often subside within days. The vaccine is contraindicated in persons with a history of immediate hypersensitivity to yeast or any of the vaccine components. Because of limited data, vaccination during pregnancy is not recommended.

19. Drug Office of Department of Health (DH) has examined the safety of all HPV vaccines by reviewing the safety reports collected in Hong Kong (Department of Health, Hong Kong pharmacovigilance system) and international organisations including World Health Organization Global Advisory Committee for Vaccine Safety (WHO-GACVS); European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA-PRAC); Health Canada; United States Centers for Disease Control and

Prevention (US-CDC); United States Food and Drug Administration (US-FDA) and United States Vaccine Adverse Event Reporting System (US-VAERS). It is considered that the benefits from HPV vaccination, such as prevention of cervical cancer, outweigh the risks of potential side effects. An ongoing post-marketing surveillance on safety and effectiveness of the HPV vaccines is essential.

Approach to prevention of HPV infection as a mean to prevent cervical cancer in Hong Kong

20. To date, the scientific evidence supports that vaccination against the HPV is effective for individual protection against HPV infections, by the genotypes covered by the respective vaccine, and thence cervical cancer. The public health strategy for HPV vaccination in Hong Kong shall be formulated based on an integration of clinical evidence available internationally, epidemiological understanding, coupled with the projected population benefits derived from local studies.

21. The registered first generation HPV vaccines, i.e., the 2-valent and 4-valent vaccine, protects one from high risk HPV-16 and 18 infection, which together account for about 70% of cervical cancer. The registered second generation 9-valent HPV vaccine has been shown to be equally efficacious or not inferior than the first generation vaccines against HPV-16 and 18 infection and their consequent cervical cancer. The 9-valent vaccine, in view of its efficacy against HPV-52 and 58, could potentially increase the protection of cervical cancer to around 90% in Hong Kong, the likelihood of which would need to be confirmed by longitudinal clinico-epidemiological studies.

22. Transmission of genital HPV infection is primarily through sexual contact (both vaginal and anal sex) with an infected person. HPV transmission can be minimized through the practice of safer sex involving the use of condom, as well as reducing the number of sex partners. The ideal age of vaccination, if administered, should be timed before the commencement of sexual debut. The vaccines have no therapeutic effect on any pre-existing HPV infections.

23. Of the three HPV vaccines available in Hong Kong, their benefits in preventing HPV infection and cervical cancer far outweigh their risks or side effects.

24. HPV vaccines cannot offer a 100% full protection from cervical cancer. In this connection, regular cervical cancer screening remains an important public health strategy which should continue to be recommended to achieve a high population coverage. HPV vaccination does not replace the cervical cancer screening.

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Appendix

The attributes and dosing recommendations of the three registered HPV vaccines available in Hong Kong

Vaccines	**Cervarix (2-valent) (HK-56180)**	**Gardasil-4 (4-valent) (HK-54934)(Vial) (HK-54935)(Prefilled Syringe)**	**Gardasil-9 (9-valent) (HK-64239)**
Against HPV	HPV-16,18	HPV-6,11,16,18	HPV-6,11,16,18,31,33,45,52,58
Indicated age	From the age of 9 years (ONLY Female)	From the age of 9 years (Both Female & Male)	From the age of 9 years (Both Female & Male)
Diseases prevention caused by related HPV - Cervical cancer - Genital Warts	 Yes No	 Yes Yes	 Yes Yes
Approved dose regimen in HK	9-14 years old: 2 doses 15 years old and above: 3 doses	9-13 years old: 2 doses 14 years old and above: 3 doses	9 years old and above: 3 doses (before 31st Oct 2016) ********** 9-14 years old: 2 doses 15 years old and above: 3 doses (on or after 31st Oct 2016)