



衛生防護中心
Centre for Health Protection

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

**Joint Consensus Recommendation on the Use of 9-valent
Human Papillomavirus Vaccine in Prevention of
Cervical Cancer in Hong Kong**

Introduction

Persistent infection with high-risk (HR) types of human papillomaviruses (HPV) can cause cervical cancer. Worldwide, HPV-16 and 18 accounted for about 70% of cervical cancer cases, whereas HPV-31, 33, 45, 52 and 58 accounted for an additional of about 20%. In recent years, there has been increasing scientific evidence showing the well proven effects of HPV vaccination in prevention of infections with HR-HPV and thence cervical cancer.

2. In the updated position paper on HPV vaccine¹ published in May 2017, the World Health Organization (WHO) reiterated the recommendation that HPV vaccine should be included in national immunisation programmes as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. Cervical cancer should remain the priority for HPV immunisation. Prevention of cervical cancer is best achieved through the immunisation of girls, prior to sexual debut.

**Epidemiology and Disease Burden of HPV Infections and
Cervical Cancer**



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The Centre for Health
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¹ Available online:

<http://apps.who.int/iris/bitstream/handle/10665/255353/WER9219.pdf;jsessionid=9E9F1FE0AFE06A20D4AAE8D5065B2F42?sequence=1>

3. Epidemiological and clinical studies that have incorporated highly sensitive molecular biology techniques detected HR-HPV in practically 100% of cervical cancer cases. HR-HPV viral DNA was also detected in the majority of precursor lesions or intraepithelial lesions of high degree such as cervical intraepithelial neoplasia (CIN)2 and CIN3. Worldwide, HPV-16, 18, 45, 31 and 33 were the five most prevalent HR-HPV identified in cervical cancer cases. For low-risk HPV, the majority of anogenital warts are associated with HPV-6 and 11 infections.

4. In Hong Kong, HPV-16, 18, 31, 33, 45, 52 and 58 accounted for about 90% of cases of cervical cancer. All the above seven genotypes are included in the 9-valent HPV vaccine. Of note, HPV-52 and 58 are more prevalent and contribute to a higher proportion of cervical cancer and high-grade squamous epithelial lesions in Eastern Asia (including Hong Kong) when compared with other regions. These two genotypes are only included in the 9-valent HPV vaccine but not the 2-valent (covering HPV-6,11) and 4-valent (covering HPV-6,11,16,18) vaccines.

5. In 2015, cervical cancer was the seventh most common cancer among females in Hong Kong with 500 new cases, accounting for 3.3% of all new cancer cases in females. The median age at diagnosis was 54 years old. The age-standardised incidence rate (ASIR) was 8.4 per 100,000 standard population. In 2016, cervical cancer was the ninth leading cause of female cancer deaths with 151 registered deaths, accounting for 2.6% of female cancer deaths. The age-standardised mortality rate (ASMR) was 2.2 per 100,000 standard population. Comparing with some Asian countries with organised cervical screening programmes (including Korea, Japan and Singapore), Hong Kong had lower ASIR and ASMR for cervical cancer in 2012. Compared with Western countries such as United Kingdom (UK), United States (US) and Finland, the local ASIR was higher while the ASMR was comparable.

Vaccine Efficacy and Duration of Protection

6. Overseas studies including randomised control trials (RCT) have showed that the 2-valent and 4-valent HPV vaccines had high efficacy of protection against persistent HPV infection and cervical precancerous lesions. Immunogenicity and follow-up studies using clinical outcomes as endpoints

have showed that the vaccine efficacy has been maintained for more than 10 years.

7. A double-blind RCT comparing the efficacy and immunogenicity between the 4-valent and 9-valent HPV vaccines showed that the risk reduction of high-grade cervical, vulvar, vaginal diseases related to the five additional HPV types (i.e. HPV-31, 33, 45, 52 and 58) was 97.4% and the vaccine efficacy was sustained for up to six years. Besides, the antibody responses to HPV-6,11,16,18 by the 9-valent vaccine were similar to the 4-valent vaccine.² Subgroup analyses of Asian participants (including Hong Kong) also showed that the 9-valent HPV vaccine is efficacious, immunogenic, and well tolerated in Asian participants.

8. Due to the longer track records of the 4-valent and 2-valent HPV vaccines, the duration of protection of the 9-valent HPV vaccine may only be inferred from observations related to the 4-valent HPV vaccines given the results of the non-inferiority (immunogenicity) studies and the fact that the same adjuvant is formulated in the two vaccine preparations.

Safety and Adverse Effects

9. HPV vaccines are generally well tolerated and serious adverse effects are rare. The most common side effects include local injection site reactions, headache, syncope, nausea, vomiting, diarrhoea, abdominal pain, itchiness, rash, urticaria, myalgia, arthritis, fatigue and fever. However, they are transient and will resolve spontaneously without sequelae. A local study of the 2-valent and 4-valent vaccines also confirmed similar safety profiles.³

10. There were previous concerns about serious adverse events including anaphylaxis, syncope, Guillain-Barré syndrome (GBS), complex

² Huh WK, Joura EA, Giuliano AR, *et al.* Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *Lancet.* 2017 Nov 11;390(10108):2143-2159.

³ Nelson EA, Lam HS, Choi KC, *et al.* A pilot randomized study to assess immunogenicity, reactogenicity, safety and tolerability of two human papillomavirus vaccines administered intramuscularly and intradermally to females aged 18-26 years. *Vaccine.* 2013 Jul 25;31(34):3452-60.

regional pain syndrome (CRPS)⁴, postural orthostatic tachycardia syndrome (POTS)⁵, premature ovarian insufficiency, primary ovarian failure (POF), venous thromboembolism and deaths after administration of HPV vaccine. The regulatory authorities in North America and Europe, as well as WHO, have issued updated reports and position statements reassuring the safety of HPV vaccines.

11. In June 2017, the WHO Global Advisory Committee on Vaccine Safety (GACVS) had reviewed studies assessing safety concerns of HPV vaccine related to anaphylaxis, syncope, GBS, CRPS, POTS, premature ovarian insufficiency, POF and venous thromboembolism, as well as data from Japan that assessed cases with diverse symptoms (including pain and motor dysfunction). The Committee concluded that there was no evidence to suggest a causal association between HPV vaccines and these conditions. Besides, a risk of >1 case of GBS per million doses of vaccine was excluded. The local data on adverse events following immunisation for the 9-valent HPV vaccine (i.e. Gardasil 9) also did not detect any signal of autoimmune disorders, and no cases of CRPS, POTS or premature ovarian insufficiency have been reported.

Local Economic Analyses on 9-valent HPV Vaccination for Female Adolescents

12. The School of Public Health of the University of Hong Kong had carried out a modelling study to evaluate the cost-effectiveness and cost-benefit of routine 9-valent HPV vaccination for girls at 12 years on cervical cancer burden in Hong Kong.⁶ The threshold vaccine cost (TVC), which is the maximum cost for fully vaccinating one girl at which routine female adolescent 9-valent HPV vaccination is cost-beneficial or cost-effective, was estimated. It was found that when vaccine uptake was 75% and the vaccine provided only 20 years of protection, the TVC was US\$444 (95% confidence interval \$373 -

⁴ A chronic pain syndrome affecting a limb

⁵ A condition where the heart rate increases abnormally on sitting or standing up

⁶ Choi HCW, Jit M, Leung GM, *et al.* Simultaneously characterizing the comparative economics of routine female adolescent nonavalent human papillomavirus (HPV) vaccination and assortativity of sexual mixing in Hong Kong Chinese: a modeling analysis. *BMC Med.* 2018 Aug 17;16(1):127.

506) [HKD\$3,463 (\$2,909 - 3,947)] and \$689 (\$646 - 734) [HKD\$5,374 (\$5,039 - 5,725)] in the cost-benefit analysis and cost-effectiveness analysis respectively, increasing by approximately 2-4% if vaccine protection was assumed lifelong. TVC is likely to be far higher when non-cervical diseases (e.g. cancers of the other anogenital regions) and non-cancer diseases (e.g. anogenital warts) are included. The study concluded that routine HPV vaccination of 12-year-old females is highly likely to be cost-beneficial and cost-effective in Hong Kong.

Acceptability of HPV Vaccination in Hong Kong

13. Vaccination coverage and its acceptability are the key determinants on the impact of success of such vaccination. The acceptability had an important influence on vaccine uptake and coverage. Local studies on attitude, knowledge and acceptability of HPV vaccination for cervical cancer prevention have revealed that high vaccine cost was a deterrent for accepting HPV vaccination. Other barriers to acceptability of HPV vaccination included lack of knowledge of HPV and cervical cancer, low perceived risk of infection, concerns over side effects and efficacy, and fear of stigmatisation and disruption of intimate relationships. On the other hand, knowledge of cervical cancer and HPV, family and peer support, recommendation and assurance of the safety and efficacy of the vaccines by medical professionals are facilitators to HPV vaccination.

HPV Vaccination Programmes in Overseas Countries

14. According to the 2018 global summary of WHO's vaccine-preventable diseases monitoring system, nearly 100 countries have included or planned to include HPV vaccination in their national immunisation programme, including almost all developed countries. Most countries recommended HPV vaccination for females only for prevention of cervical cancer. A 2-dose schedule starting at 9 to 11 years is the most common regimen. From the available information, the majority of the countries have not yet included males in the recommendations. Australia and UK are two developed countries with about 10 years of experience in providing HPV vaccination for girls under their national immunisation programmes. Coverage of about 80% was achieved in their school based programmes for school girls

aged around 12-13 years.

15. Studies in UK and Australia have demonstrated marked decreases in infections of vaccine-related HPV genotypes and high grade cervical abnormalities amongst vaccine-eligible women. Moreover, there have been dramatic decreases in the incidence of genital warts in young women after commencement of the immunisation programmes. The decline has occurred not only in vaccinated women but also in unvaccinated women and heterosexual men, suggesting substantial herd protection from a female-only vaccination programme with high coverage. No genotype displacement was observed since the introduction of the vaccination programme in UK (since 2008).

Recommendations on the Use of HPV Vaccine in Hong Kong

16. Based on the review of the scientific evidence on the efficacy and effectiveness of HPV vaccines in prevention of pre-cancerous cervical abnormalities and thence cervical cancer, safety of HPV vaccines, local epidemiology of cervical cancer, local studies on acceptability and cost-benefit analysis, as well as overseas experiences and practice, the Scientific Committee on AIDS and STI and the Scientific Committee on Vaccine Preventable Diseases have made the following recommendations:

- (a) HPV vaccines are safe and efficacious in preventing infection with HPV genotypes covered by the vaccines, which are responsible for the majority of cervical cancer cases. HPV vaccination is recommended to be included in the Hong Kong Childhood Immunisation Programme as a public health programme for cervical cancer prevention for girls of suitable ages before sexual debut according to the prevailing recommended schedules.
- (b) The 9-valent HPV vaccine has been shown to be equally efficacious as the 2-valent and 4-valent HPV vaccines against HR-HPV-16 and 18 infections which together account for about 70% of cervical cancer. The 9-valent vaccine, in view of its efficacy against HPV-31, 33, 45, 52 and 58, could potentially increase the protection of cervical cancer to around 90% in Hong Kong. In this regard, 9-valent HPV vaccine should preferably be used for better protection against cervical cancer.

- (c) Overseas experiences and studies on the cost-effectiveness of HPV vaccination among males are still limited. The Centre for Health Protection of the Department of Health is recommended to continue to closely monitor the latest scientific evidence on HPV vaccination among males.
- (d) HPV vaccination cannot offer a 100% full protection from cervical cancer and cannot replace cervical cancer screening. In this connection, regular cervical cancer screening remains an important public health strategy for secondary prevention of cervical cancer, which should continue to be promoted to achieve a high participation rate among the target population in Hong Kong.
- (e) An ongoing surveillance on adverse events following immunisation for HPV vaccines is essential after the commencement of the universal HPV vaccination programme.

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