



SCCPS Scientific Committee Position Paper on HPV Vaccination

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Obstetrical & Gynaecological Society of Singapore (OGSS)
Society for Colposcopy and Cervical Pathology of Singapore (SCCPS)
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The aim of this guideline is to provide information, based on clinical evidence where available, on the use of the HPV vaccine.

In Singapore, the HPV vaccine is licensed for use in females and males aged between 9 and 26 years. There is recent evidence that clinical utility is not limited to this age group. However, it must be emphasized that there should be detailed counseling to aid an informed decision before the use of the vaccine in such situations.

Introduction

Cervical Cancer is the 10th most common cancer among women in Singapore. ¹ Almost 100% of cases have been attributed to oncogenic Human Papilloma Virus (HPV) infection, of which types 16 and 18 are found in up to 70% of all cervical cancers. ² Oncogenic HPV is also implicated in the development of other cancers including tumors of the vulva, vagina, anus, penis and the head and neck. HPV types 6 and 11 though non-oncogenic account for 90% of genital warts.

Types of Vaccines

Currently 3 vaccines are available in Singapore: Gardasil®, Cervarix® and Gardasil®9.

All 3 vaccines are prepared from HPV type-specific empty shells or virus-like particles (VLPs). VLPs do not contain any viral DNA and therefore are able to stimulate an immune response without infecting the host.

Gardasil® is a quadrivalent vaccine containing VLPs for 4 HPV types – 6, 11, 16 and 18. It is licensed in Singapore to be used in girls and boys aged 9 to 26 years of age.

Cervarix® is a bivalent vaccine containing VLPs of 2 HPV types – 16 and 18. It is licensed for girls aged 9 to 25 years of age.

Gardasil®9 is a nonavalent vaccine containing VLPs of 9 HPV types –

6, 11, 16, 18, 31, 33, 45, 52 and 58. It is licensed for boys and girls aged 9 to 26 years.^{3,4}

Vaccination Schedule and Recommendations

Currently the National Childhood Immunization Schedule and the Health Promotion Board Singapore recommend the HPV vaccination for females age 9 to 26 years old on the following schedules:^{5,6,7,8}

Gardasil® and Gardasil®9:

- 3-dose schedule: 0, 2 and 6 months for individuals 9-26 years of age.

OR

- 2-dose schedule: 0 and 6 months for individuals 9-14 years of age.

Cervarix®:

- 3-dose schedule: 0, 1 and 6 months in females 9-25 years of age.

OR

- 2-dose schedule: 0 and 6 months in females 9-14 years of age.

The need for boosters for any of the vaccines has not been established.

Efficacy

The efficacy for the bivalent and quadrivalent vaccines has been demonstrated in large Phase III randomized controlled trials involving healthy young women.^{9,10} The vaccines are highly efficacious against HPV 16/18 related pre-cancerous lesions.

The national HPV immunization programme introduced in England in 2008 using the bivalent vaccine had shown substantial declines in HPV 16 and 18 infections in young women 8 years after its introduction.¹¹ This was further corroborated in a Dutch and a Scottish study showing no waning protection 6 to 7 years after vaccination with the bivalent vaccine.^{12,13,14}

The efficacy of the nonavalent vaccine has similarly been proven in

large randomized controlled trials, demonstrating non-inferiority in the reduction of cervical, vulvar and vaginal high-grade disease compared to the quadrivalent vaccine in young females aged 16 to 26 years. ^{15, 16, 17} Non-inferiority of the nonavalent vaccine was also demonstrated in in boys and girls aged 9 to 15 years. ¹⁸ All available data for seroconversion and seropositivity show non-inferiority of the 2-dose compared with the 3-dose schedule in young females as the antibody responses were comparable as shown by a recently published Cochrane review. ^{3, 15} Long-term observational studies are needed to determine the effectiveness of reduced-dose schedules against HPV-related cancer endpoints, and whether adopting these schedules improves vaccine coverage rates. ¹⁵

Safety

All three vaccines continue to have a high safety profile and are well-tolerated. No serious adverse events have been documented. ⁸ Local side effects such as pain, swelling, itching and redness at the site of injection are common. Post vaccination syncope has also been reported and can be avoided with appropriate care.

National School-Based HPV Vaccination Programme

In April 2019, Ministry of Health launched the school-based HPV vaccination programme as an opt-in scheme to all Secondary 1 female students (ages 12 to 13 years old).

The bivalent vaccine (Cervarix) is the chosen HPV vaccine to be used for the programme. It was selected following an assessment which included considerations on efficacy, price and stock availability. A catch-up HPV vaccination programme was introduced as well to Secondary 4 students.

Frequently Asked Questions (FAQs)

Can sexually active women younger than 26 years of age be vaccinated?

Yes. They can be offered HPV vaccination.

All 3 HPV vaccines are prophylactic vaccines. For optimal benefit, the vaccine should be given before the onset of sexual activity, as it does not protect against pre-existing HPV infections. However, sexually

active women can be vaccinated.

Women who are sexually active risk exposure to HPV infection, hence these women should be advised that the vaccine may be less effective compared to women who have had no previous HPV exposure at the time of vaccination. ^{19, 20, 21, 22}

Can women older than 26 years of age be vaccinated?

Yes. Women older than 26 years of age can be offered HPV vaccination. The Advisory Committee on Immunization Practices (ACIP) recommends shared decision-making regarding HPV vaccination for adults aged 27 to 45 years who are not adequately vaccinated. ²³ Women should be provided with information to make an informed decision about the costs and benefits of vaccination. Since October 2018, Gardasil®9 has been approved by FDA to be given to women and men from 27 to 45 years old. ²⁴ HPV vaccines are not licensed for use in adults aged more than 45 years.

Studies have shown that a large proportion of HPV infections in women aged 27 to 45 years are the result of new exposure or infection, hence indicating likely benefits in vaccinating this population. ²⁵ Data also shows significant efficacy against a combined endpoint of persistent vaccine-type HPV infections, anogenital warts and CIN grade 1 or worse as well as high post-vaccination seroconversion rates even up to 10 years in individuals aged 27 to 45 years. ^{26, 27}

Women between the ages of 27 to 45 years of age who request HPV vaccination should be counseled that vaccination in this age group is not licensed in Singapore. The benefit received from HPV vaccination in women older than age 27 also may be limited compared to HPV vaccine naïve populations if they have been exposed to HPV infection e.g. sexually active, evidence of abnormal cervical cancer screening results, previous treatment for high-grade CIN.

Is HPV testing recommended before vaccination?

Testing for HPV DNA is not necessary prior to vaccination. Serologic tests for HPV are currently not available commercially. ^{28, 29}

Should women who have been vaccinated be encouraged to have cervical cancer screening?

The HPV vaccine is not a substitute for cervical cancer screening. It must be emphasized that women aged 25 years and above, who are sexually active or who have ever had sex, must continue with cervical cancer screening (HPV DNA test or PAP smear) regardless of their HPV vaccination history.⁵

Can women who have had an HPV infection or a history of CIN be vaccinated?

Women with current HPV infection, current CIN or previously treated CIN can be given the HPV vaccine. Vaccination in addition to local treatment of HPV-related disease appears to reduce recurrent or subsequent HPV-related disease.³⁰

However, these women must be informed that the HPV vaccine is not therapeutic and does not treat existing infection or CIN, and the benefits of the vaccination may be limited to the prevention of future HPV infection. Clinical follow-up according to Cervical Screen Singapore guidelines must continue in these women.

Can women who are immunocompromised be vaccinated?

Vaccination can be given to women who are immunocompromised e.g. those who are on steroids, immunosuppressant medications or are HIV-infected.

However, these women should be informed that their immune response to the vaccine may be lower compared to immunocompetent women.^{31,32}

It is recommended that the 3 dose regime is given to any women who are immunocompromised and are suitable or request for the HPV vaccine regardless of age.

Can pregnant or breastfeeding women be vaccinated?

The HPV vaccine is not recommended for use in pregnancy.

Women who become pregnant before completing the vaccination schedule should defer the subsequent doses until the pregnancy is completed.^{19,20,21,28} There is no need to restart the entire vaccination

schedule but there should not be a delay of more than 12 months between the 2nd and 3rd dose.

Lactating women can be vaccinated. The HPV vaccine is an inactivated vaccine which does not contain a whole virus, hence it does not affect the safety of breastfeeding for mothers or infants. ^{19,33}

Can males be vaccinated?

The HPV vaccine is licensed to be used in Singapore for males aged 9 to 26 years old. Singapore males are licensed to have Gardasil® or Gardasil®9 (not Cervarix®) for protection against genital warts, premalignant disease of anal cancer and anal cancer.

The nonavalent vaccine has been shown to be highly immunogenic and effective in males aged 9 to 26 years. ^{18,34} For the quadrivalent vaccine, seroconversion was shown to be high for all 4 HPV vaccine types in males aged 9 to 26 years. ³⁵ A follow-up study also showed no cases of persistent infection or disease related to any of the 4 HPV vaccine types in the boys during 6 years of follow-up after vaccination with the quadrivalent vaccine. ³⁶ Data from a phase 3 double-blind randomised study involving males aged 16 to 26 years show that the Gardasil® vaccine can protect men against genital warts. ³⁷ There is also evidence of protection against anal and penile intraepithelial neoplasia. ^{38,39} The HPV vaccines are also likely to lead to a reduction in cancers of the anus, penis and oral cavity although systematic reviews in males are lacking.

Males who do not have clinical evidence of HPV infection may benefit the most from the vaccine.

Can the HPV vaccine be given together with other vaccines?

Both vaccines may be administered concomitantly with booster vaccines containing diphtheria, tetanus and acellular pertussis with or without inactivated poliomyelitis (IPV, DTaP, DTaP-IPV vaccines), with no clinically relevant interference with antibody response to any of the components of either vaccine.

If a series was started with the bivalent or quadrivalent vaccine, can it be completed with the nonavalent vaccine?

Currently there is limited data available on efficacy or safety for a nonavalent vaccine to complete a bivalent vaccine series. The practice of mixing bivalent vaccine with either quadrivalent or nonavalent vaccine to complete a series is not recommended.

A nonavalent vaccine can be used to complete a quadrivalent vaccine series. However, patient should be clear that optimal protection has only been shown for HPV 16 and 18 and genital warts only when the regime is completed. If a patient is requesting for protection from HPV 31, 33, 45, 52 and 58, the current recommendation is to complete the recommended 2 or 3 dose regime as described above.

There is no data on efficacy or immunogenicity of one, two or three doses of nonavalent vaccine among persons who have already received only one or two doses of quadrivalent vaccine. Available data shows no serious safety concerns. ⁴⁰

Patients are strongly recommended to discuss with their doctor prior to decision to mix HPV vaccine types to complete a series.

Is additional vaccination with the nonavalent vaccine recommended for persons who have completed a series of either the bivalent or quadrivalent vaccine?

There is no recommendation for additional nonavalent doses for persons who previously completed a series of bivalent or quadrivalent vaccine. The majority of all HPV-associated cancers that can be prevented by vaccination are caused by HPV 16 or 18 and these are preventable by all 3 vaccines. The benefit of protection against the 5 additional types targeted by the nonavalent vaccine would be mostly limited to females for prevention of cervical cancers and pre-cancers as only a small percentage of HPV-associated cancers in males are due to the five additional types prevented by nonavalent vaccine. ⁴⁰ In an immunogenicity and safety clinical trial, three doses of the nonavalent vaccine given to females who had previously completed the series of the quadrivalent vaccine resulted in 98% of the vaccinees developing antibodies to all 5 additional HPV types. Available data shows no serious safety concerns. ⁴¹

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