Singapore Journal Of Obstetrics & Gynaecology
2018; 49(2): 37-40

An Update on Primary Prevention of Cervical Cancer

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ABSTRACT

This article gives an update on primary prevention of cervical cancer.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women in the world with an estimated 528,000 new cases in 2012 and 266,000 deaths annually.[1] It is considered a highly preventable cancer as it is mainly caused by persistent high risk (hr) HPV infection, particularly by types 16 and 18 which account for up to 70% of all cervical cancers. The HPV is a double stranded DNA virus from the papillomavirus family and the infection is limited to the basal cells of stratified epithelium.[2] In most infected individuals, the infections do not cause symptoms and resolve spontaneously but in some, a persistent infection might cause precancerous and cancerous lesions. The discovery of the recombinant expression of L1 in a range of systems in the 1990s that yielded virus like particles (VLPs) that were devoid of the oncogenic viral genome and immunologically similar to the nativevirions led to the development of the prophylactic vaccine.[3]

BIVALENT AND QUADRIVALENT HPV VACCINE

The bivalent (2v) and quadrivalent (4v) HPV vaccines have been in use for the past decade, and has been shown to be safe and highly efficacious in preventing HPV related diseases. For maximal benefit, the vaccine should be given before the onset of sexual activity, as it does not protect against pre-existing HPV infections.[4] More than 200 million doses have been given worldwide with a good safety profile. According to various studies, the proportion of women experiencing severe adverse events such as new autoimmune disorders after vaccination were similar to controls.[5] The European Medical Agency (EMA) completed a review and supported that there is no linkage between HPV vaccination and an increased risk of developing complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS).[6] Besides cervical cancer, we also know that hrHPV is associated with vulvar and vaginal cancer in women, penile cancer in males, anal and oropharyngeal cancer in both sexes.

THE NONAVALENT HPV VACCINE

The second generation nonavalent (9v) HPV vaccine was FDA approved in December 2014 and is the only HPV vaccine available in the United States today. The vaccine was launched in Singapore in April 2017 and has been approved for use in both young men and women age 9 to 26 years. Several largeinternational trials were undertaken to demonstrate the efficacy, immunogenicity and safety prior to being FDA approved. The evidence for the 9v HPVvaccine are summarized in the following paragraphs.

In a phase III efficacy randomized trial comparing 9vHPV with 4vHPV vaccine in about 14,000 females aged 16 through 26 years, the 9vHPV efficacy for prevention of ≥CIN2, VAIN grade 2 or 3, and VIN grade 2 or 3 caused by HPV 31, 33, 45, 52, or 58 was 96.7% in the per protocol population.[7] Few cases were caused by HPV 6, 11, 16, or 18 in either

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vaccine group. The 9vHPV vaccine generated anti-HPV 6, 11, 16, and 18 immune responses that were non-inferior to those generated by the 4v HPV vaccine.[7] In the 9vHPV group, >99% seroconverted to all nine HPV vaccine types. The 9vHPV vaccine also reduced the numbers of pap test abnormalities and cervical procedures. In terms of vaccine related adverse events (AEs), the 9v HPV vaccine caused more injection site AEs compared to the 4v HPV vaccine but the systemic AEs are similar.[7] The most common injection-site AEs were pain, swelling, erythema, and pruritus whereas the most common vaccine-related systemic AE in both vaccines was headache. As with the 2v and 4v HPV vaccines, vaccination with the 9v vaccine should be postponed till completion of pregnancy. Nevertheless, current data does not indicate any increased risk of malformation or fetal/neonatal toxicity in pregnant women.

In the immunobridging study involving 2400 girls and boys age 9 to 15 years compared to 400 women 16 to 26 years, the immune responses for the adolescents were found to be non-inferior to those in women.[8] In both females and males, >99% seroconverted to all 9 types, and the geometric mean titres(GMT) in boys were non-inferior to those in girls. In another immunobridging study involving 1394 males age 16 to 26 years compared to 1075 women 16 to 26 years, the GMTs for all 9 HPV types were non-inferior in heterosexual males compared to the women but the GMTs were slightly lower in MSM compared with heterosexual males and women.[9]

With regards to giving the 9vHPV vaccine to women with prior 4v HPV vaccine (>12 months interval), a study was performed whereby 924 women were randomized to placebo or the 9v vaccine.[10] The GMTs against HPV Types 6, 11, 16, and 18 showed evidence of an immune memory response in prior 4vHPV vaccine recipients and immunogenicity was demonstrated with respect to HPV Types 31, 33, 45, 52, and 58 in prior 4v HPV vaccine recipients. Hence, the 9v HPV vaccine can be given to those with prior vaccination.

In a recently concluded study comparing the immunogenicity of the 2 dose and 3 dose regimens of the 9v HPV vaccine, the 2-dose schedule was shown not to be inferior to the 3 dose in both girls and boys age 9 to 14 years.[11] Furthermore, the HPV antibodies were found to be higher in those who receive at a 12-month interval than in those at 6-month interval. The 2-dose schedule has cost saving and pragmatic advantages that may facilitate a higher coverage.

CURRENT GLOBAL HPV VACCINE COVERAGE

More than 80 countries have introduced a national HPV vaccination program but the majority are in high or upper middle income countries. 70% of all women immunized against HPV worldwide are found in high income countries which bear only 0.14% of cervical cancer burden.[12] Recently, Gavi and WHO has provided some financial assistance to help some low-income countries to implement a national program. However, barriers still exist such as the perceived adverse effects of vaccination, low perceived risk of getting cancer, parental refusal, convenience issues such as high cost and lack of access to vaccination clinics.[13]

Preliminary findings from a recent multicenter cluster randomized study in India suggest that a single dose of 4v HPV vaccine is immunogenic and provides lasting protection against HPV 16 and 18 infection similar to 3 and 2 doses.[14] In this study, 17729 girls age 10-18 years were vaccinated and randomized to three doses vs two doses. However, 4950 (28%) only received one dose, 8431 (47%) received 2 doses and 4348 (25%) received 3 doses and they were followed up for 4 years. Long term data on the HPV vaccine single dose is lacking and more studies are needed to validate this potential cost saving schedule which could increase uptake in low resource countries where the cervical cancer burden is high.

CONCLUSION

The HPV vaccine is a safe and effective vaccine for the prevention of cervical cancer. The new 9v vaccine covers up to 90% of the hrHPV types that can cause cancer. However, barriers still exist that prevent vaccine uptake in many countries especially those with the highest burden of cervical cancer. Ongoing clinical trials on the potential of single dose vaccination may provide the solution for an increased uptake in low income countries.[15]

Approved Recommendations for the 9v HPV Vaccine

Indications:	Girls and women 9-26 years of age	Boys and men 9-26 years of age
Cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58		
Cervical	✓*	
Vulvar	✓*	
Vaginal	✓*	
Anal	✓*	✓
Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58		
Premalignant cervical lesions	✓	
Premalignant vulvar lesions	✓	
Premalignant vaginal legions	✓	
Premalignant anal legions	✓	✓
Cervical adenocarcinoma in situ	✓	
Genital warts caused by HPV types 6 and 11	✓	✓
HPV infections caused by HPT types 6, 11, 16, 18, 31, 33, 45, 52 and 58	✓	✓
Dosage: 3 dose (0, 2 and 6 months)	✓	

For 9 to 14 years of age, the 2 dose regimen can also be used at 0, 6-12 month interval.

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