

A Short Review on Human Papillomavirus Vaccines

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Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide and this is the commonest cancer in women in some of the developing countries where 83% of all cases occur¹. Globally, it was estimated that about 493 000 cervical cancer cases were developed in the year 2000 and 274 000 deaths were due to this disease. Mortality from cervical cancer ranged from about 30% in developed countries to about 70% in developing countries where most of the cervical cancers were coming from²⁻⁴. The higher mortality rate in developing countries was probably contributed by late diagnosis and difficulties in accessing quality care. Women who survived cervical cancer would suffer a lot from psychosexual problems as a result of the disease and the treatment. The expenditure for this disease is a challenge to most of the health care systems. In Hong Kong, we had 439 new cases of cervical cancer in 2004 and the age-standardised rate was 9.4, which is relatively high when compared to some other developed countries⁵.

Cervical Cytology Screening

Since its introduction in the mid-20th century, cytology-based cervical cancer screening has been the most effective method in preventing cervical cancer. Cervical cancer screening is a mode of secondary prevention, which reduces the incidence and mortality of cervical cancer by detection and treatment of pre-cancerous cervical lesions. The success of a screening programme depends on the coverage. Some countries are performing better than the others due to the difference in policies, input of resources, and the call/recall systems⁶. Patients having abnormal cervical cytology would be subjected to colposcopy examination. High-grade

cervical intraepithelial neoplasia (CIN) if found could be treated by ablative or excisional procedures. Despite the effectiveness in preventing cervical cancer, the psychosocial impact to women arising from colposcopy or complications from local excisional procedures could be very distressing and should not be overlooked^{7,8}.

Human Papillomavirus

It is now widely accepted that human papillomavirus (HPV) is the cause for cervical cancer based on the fact that HPV DNA was detected in 99.7% of the cervical cancer samples⁹. Human papillomaviruses are small DNA viruses that infect epithelial tissues. Human papillomavirus consists of 8000 base-pair long circular DNA molecules wrapped into a protein shell, which is composed of two molecules including the L1 and L2. More than 100 types of HPV have now been molecularly characterised and about 40 types are able to infect the genital tract. A subset of mucotrophic high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82) belonging to the alpha genus is associated with more than 99% of the cervical cancer⁹. Among the high-risk HPV types, HPV-16 and -18 accounted for about 70% of all the cervical cancers¹⁰. Together with another six high-risk HPV types, including 31, 33, 35, 45, 52, and 58, they are the eight most common HPV types accounting for about 90% of the cases. However, the relative importance of HPV types 31, 33, 35, 45, 52, and 58 appeared somewhat different

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among different continents¹¹. Based on the knowledge on HPV and its causative effect on cervical cancer, HPV vaccines were developed to prevent this disease.

Human Papillomavirus Vaccines

Role of Human Papillomavirus Vaccines

The role of the HPV vaccine is to prevent anogenital cancers especially cervical cancers by inducing immunity against high-risk HPV types.

Types of Vaccines

There are prophylactic and therapeutic vaccines. Two prophylactic vaccines were developed to prevent HPV infections by two drug companies. One of them has been licensed in 2006.

Therapeutic vaccines aim at the elimination of persistent HPV infections. Phase 1 and 2 studies are now being conducted. Currently, the use of therapeutic vaccines is only within the context of a clinical study.

How Does the Prophylactic Vaccine Work?

Virus-like particles (VLPs) containing the L1 capsid protein are created through recombinant DNA technology. This antigen presented to the immune system would induce the production of neutralising antibodies. The early evidences of protection from HPV infection by antibodies came from animal studies^{12,13}. The protective effect was believed to be conferred to the IgG, which is present in the epithelium neutralising the virus particles and prevent infection. The VLPs do not contain genetic materials and therefore they are non-infectious and would not cause genital infection. The antibodies induced by the VLPs are type-specific and therefore they prevent infection of the relevant viruses only. However, some evidences from recently published data did suggest that there was cross protection against other HPVs of the same phylogenetic subtype, which share the same conformational epitopes¹⁴.

Current Prophylactic Human Papillomavirus Vaccines

Two prophylactic vaccines have been developed by the drug companies. Gardasil® (Merck and Co., Inc., Whitehouse Station [NJ], USA) is a quadrivalent HPV-6, -11, -16, -18 vaccine. It consists of purified L1 VLPs of HPV types 6/11/16/18 respectively at 20/40/40/20 µg per dose formulated on 225 µg of aluminum adjuvant hydroxyphosphate sulfate. The product is to be delivered

by intramuscular injection as a 0.5 ml dose at 0, 2, and 6 months. Gardasil® has been licensed in the United States, Europe and other countries in 2006. Cervarix™ (GlaxoSmith Kline Biologicals, Rixensart, Belgium) is a bivalent HPV-16, -18 vaccine. This vaccine consists of purified L1 VLPs of HPV types 16/18 at 20/20 µg per dose formulated on ASO4, an adjuvant containing 500 µg of aluminum hydroxide and 50 µg of 3-deacylated-monophosphoryl lipid A. This product is to be delivered intramuscularly as a 0.5 ml dose at 0, 1, and 6 months.

There have been comparisons between the two prophylactic vaccines based on the published data¹⁴⁻¹⁸. The comparisons concentrated mainly on the areas of protection, safety, immunogenicity, and efficacy:

1. **Areas of protection:** Both vaccines offer protection against anogenital cancers especially cervical cancers through the prevention of HPV-16 and -18 infections. Gardasil® also offers protection against anogenital warts through the prevention of HPV-6 and -11 infections.
2. **Safety:** Details of the safety data were obtained prospectively during the clinical trials. The most commonly reported adverse events were pain, redness or swelling over the injection sites. Fever was also common (1 in 10 subjects) but most of these were low-grade. No significant increase in serious adverse events was found in the vaccine group when compared to the placebo group. Data on pregnancy including the foetal outcome are now being collected in ongoing studies. So far, no vaccine-related adverse foetal outcome has been evident.
3. **Immunogenicity:** Both HPV vaccines are highly immunogenic causing seroconversion in more than 98% of subjects. The peak antibody titres in the phase 2 trials were achieved 1 month after the completion of all the three doses of vaccination and then started to decline. After a follow-up period of 4.5-5 years, the antibody titres were still found to be higher than the antibody titres caused by a natural infection for both vaccines. Although comparisons have been made between the two vaccines regarding the antibody titres, this was considered invalid since the assay methods used in the trials of both vaccines were different. Moreover, protection against HPV infection or HPV-related diseases were observed in a wide

- range of antibody titres.
4. **Efficacy:** Clinical trials for both vaccines have used different primary and secondary end points for analyses. If analysis was confined to the according-to-the-protocol cohort, the vaccines were 100% effective in preventing cervical precancerous lesions caused by the corresponding HPV types up to 4.5-5 years of follow-up. For the analysis of the intention-to-treat cohort, the efficacy in the prevention of persistent HPV infections or cervical precancerous lesions was about 90%. For the Cervarix™, preliminary data from the phase 2 trials showed that there were potential cross protection against HPV-31 and -45, which are phylogenetically closely related to HPV-16 and -18, respectively. However, the extent of this potential cross protection and their contribution to cervical cancer/precancerous lesion prevention has to be elucidated.

Target Population for the Human Papillomavirus Vaccines

Mathematical models have been created in order to define the target population to be included in the vaccination programme as part of the public health policy making it most cost-effective¹⁹. The two most important factors included for evaluation were the age and the gender:

1. **Age:** From the data of the published phase 2 trials^{14,15} and the unpublished data on 'safety and the immune response in young children' (<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm>) for the Gardasil®, it was recommended by the United States Food and Drug Administration that this drug could safely be used in women aged 9-26. To achieve better protection, vaccines have to be delivered before exposure to the viruses. Since HPV is mainly transmitted sexually²⁰, the vaccines should be given before sexual exposure. As better immune response was found in pre-pubertal subjects with higher antibody titres (<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm>), injection before puberty may achieve better result. However, one should also bear in mind that adolescent is not an easy group to target in any vaccination programme. Besides, this must be balanced with the possibility of

waning protective effect with time for we only have the data for 5 years regarding the efficacy. Up to this moment, the necessity for booster injections is still unclear.

2. **Gender:** Genital warts do concern both men and women but not cervical cancer. Penile cancer occurs in men but with a much lower incidence when compared with cervical cancer²¹. From the mathematical models, vaccination for men could further reduce the incidence of cervical cancer¹⁹. However, the cost-effectiveness is a major concern to most of the policy-makers. For those localities having a high prevalence of genital warts, including men in the vaccination programme using the quadrivalent vaccine, which helps preventing 90% of the genital warts, would make it easier to justify.

Pregnancy

So far, there is no evidence showing vaccine-related adverse pregnancy outcomes. Nevertheless, vaccination is contra-indicated for those during pregnancy or contemplating pregnancy.

Human Papillomavirus-positive Subjects

The vaccine, which is now available, is a prophylactic vaccine. A cytotoxic and T-cell response is required to clear up the infected cells and this immune response is probably not triggered by the dose and way the VLPs are administered. Individuals who have been infected with the corresponding HPV types would lose the protection to the specific type of HPV from the vaccine. A negative serology test or HPV DNA test is not a reliable test on any prior HPV infection. Therefore, routine HPV serology test or HPV DNA test is not recommended before the use of vaccines.

History of Abnormal Cervical Cytology or Cervical Intraepithelial Neoplasia

If one has been infected by HPV types of the corresponding vaccines, leading to abnormal cervical cytology or CIN, the protective effect of the vaccines would not be as high as quoted. Unfortunately, using the currently available commercial kit, one cannot tell the causative HPV type leading to the abnormalities. Therefore, history of CIN or abnormal cytology is not a contra-indication for vaccination but one should

bear in mind that the efficacy of the vaccines could be diminished.

Cervical Cancer Screening after Vaccination

Human papillomavirus vaccine does not provide 100% protection from cervical cancer. It is very important to note that whoever received the vaccine should continue with cervical cytology screening. However, the chance of having abnormal cervical cytology or CIN may be lower when compared to the population without HPV vaccination. In the future, the mode of screening may be changed if the vaccine is incorporated in the immunisation programme. In the meantime, we do not have enough evidence to substantiate a change in our screening policy.

Conclusion

Human papillomavirus causes cervical cancer, which is a major burden to the health care system especially in the developing countries. Cervical cytology is so far the best method in preventing cervical cancer but it is unable to prevent precancerous lesions. Psychosexual impact on women with abnormal cervical cytology and the expenditure on the follow-up of abnormal cytology result should not be overlooked. In countries with poor resources and those without an organised cervical cancer screening programme, HPV vaccines may help alleviate the impact of cervical cancer. Although a lot of data

have been available on the use of vaccines, there are still a lot of uncertainties to be clarified. The effect of HPV vaccines on a community would not be seen in the near future because it works only on those women who have not been infected. It will take another few decades before results become obvious. Therapeutic vaccines, if successfully developed, may be another significant progress in cervical cancer prevention.

Below are important points to be noted when counselling women on HPV vaccination:

1. Vaccination before prior exposure to HPV, about 70% of cervical cancers could be prevented. It would better be given before sexual exposure.
2. The vaccines are safe to be used. Injection of the currently available HPV vaccine is licensed for female between the age of 9 and 26.
3. The effect of the vaccine lasts at least 4.5-5 years. The necessity for booster doses is not clear.
4. For those who have prior HPV infection, history of abnormal cervical cytology or CIN, the protection offered by the vaccine may probably be below 70%. There is no recommendation on any routine testing before the use of HPV vaccines.
5. After vaccination, cervical cytology screening should be continued.
6. Vaccination is contra-indicated for those during pregnancy or contemplating pregnancy.

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