Update of HPV Vaccines on Cervical Cancer

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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 occur. Globally, it was estimated that there were about 493,000 cervical cancer cases in the year 2000 causing 274,000 deaths. Mortality from cervical cancers ranged from about 30% in developed countries to about 70% in developing countries. The higher mortality rate in developing countries was probably contributed by late diagnosis and difficulties in accessing quality care. Women who survived cervical cancers 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 459 new cases of cervical cancer in 2006 and the age-standardised rate was 9.4, which is relatively high when compared to some other developed countries (http://www3.ha.org.hk/cancereg/e_cx.pdf).

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 cancers. Cervical cancer screening is a mode of secondary prevention, which reduces the incidence and mortality of cervical cancers 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 differences in policies, input of resources and the call/recall systems. Patients having abnormal cervical cytology would be subjected to colposcopy examination. High-grade cervical intraepithelial neoplasia, if found, could be treated by ablative or excisional procedures. Despite the effectiveness in preventing cervical cancers, the psychosocial impact to women arising from colposcopy or complications from local excisional procedures could be very distressing and should not be overlooked.

Human Papillomavirus

It is now widely accepted that human Papillomavirus (HPV) is the cause for cervical cancers based on the fact that HPV DNA was detected in 99.7% of the cervical cancer samples. Human Papillomaviruses are small DNA viruses that infect epithelial tissues. HPV consists of 8,000 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 cancers. Among the high-risk HPV types, HPV-16 and -18 accounted for about 70% of all the cervical cancers. Together with another six high-risk HPV types including 31, 33, 35, 45, 52 and 58, they are the eighth 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 among different continents. Based on the knowledge on HPV and its causative effect on cervical cancers, HPV vaccines were developed to prevent this disease.

HPV Vaccines

Role of HPV Vaccines in Cancer Prevention

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

Only prophylactic HPV vaccines are available in the market. Currently, the use of therapeutic vaccines is only within the context of clinical studies.

How Does the Prophylactic Vaccine Work?

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

**Current Available HPV Vaccines**

Two prophylactic vaccines have been developed by the drug companies. Gardasil® (Merck and Co., Inc.) is a quadrivalent HPV-6, -11, -16, -18 vaccine. It consists of purified L1 VLPs of HPV types 6/11/16/18 at 20/40/40/20 μg per dose formulated on 225μg of aluminium adjuvant hydroxyphosphate sulfate. The product is to be delivered by intramuscular injection as a 0.5ml dose at 0, 2 and 6 months. Cervarix® (GlaxoSmithKline Biologicals) 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 AS04, an adjuvant containing 500μg of aluminium hydroxide and 50 g of 3-deacylated-monophosphoryl lipid A. This product is to be delivered intramuscularly as a 0.5ml dose at 0, 1 and 6 months. Age indications for Gardasil® and Cervarix® are 9 - 26 and 10 - 25 respectively.

**Areas of Protection:** Both vaccines offer protection against 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.

**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 (one 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 outcome has been evident.

**Immunogenicity:** Both HPV vaccines are highly immunogenic causing seroconversion in more than 98% of subjects. The peak antibody titres were found to have achieved one 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. Moreover, protection against HPV infection or HPV related diseases were observed in a wide range of antibody titres.

**Efficacy:** Clinical trials for both vaccines have used the precancerous lesions including cervical intraepithelial neoplasia (CIN) grade 2-3 and cervical adenocarcinoma in situ (AIS) as the primary end point for analyses. The vaccines were more than 90% effective in preventing cervical precancerous lesions caused by the corresponding HPV types. A recent publication on Cervarix®, it showed that there were potential cross protection against HPV -31, -33, -45 and -58, which are phylogenetically closely related to HPV -16 and -18. However, the extent of this potential cross protection and their contribution to cervical cancer/precancerous lesion prevention have to be elucidated.

**Duration of Protection:** Currently, the duration of protection provided by the HPV vaccines is not known. However, long term follow up studies have shown that efficacy is maintained for at least five years. Up to this moment, the necessity for booster injections is still unclear.

**Target Population for the HPV Vaccines:** To achieve better protection, vaccines have to be delivered before exposure to the viruses. Since HPV is mainly transmitted sexually, the vaccines should be given before sexual exposure. As better immune response was found in pre-pubertal subjects with higher antibody titres, injection before puberty may achieve better results.

**Gender:** Genital warts do concern both men and women but not cervical cancers. Penile cancer occurs in men but with a much lower incidence when compared with cervical cancer. From the mathematical models, vaccination for men could further reduce the incidence of cervical cancers. However, the cost-effectiveness is a major concern to most 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, those who are pregnant or contemplating pregnancy are advised against vaccination.

**HPV 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 (CIN):** 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, a history of CIN or abnormal cytology is not a contraindication for vaccination but one should bear in mind that the efficacy of the vaccines could be diminished.

**Cervical Cancer Screening after Vaccination**

HPV vaccine does not provide 100% protection from cervical cancer. It is very important to note that whoever has 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

HPV 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 cancers 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 results should not be overlooked. In countries with poor resources and those without an organised cervical cancer screening programme, HPV vaccines may help to alleviate the impact of cervical cancers. Although a lot of data has 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.

References