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Review Article

Commonly asked questions on human papillomavirus vaccine

關於人類乳頭瘤病毒疫苗的常問問題

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Recently, human papillomavirus (HPV) vaccine has been attracting the attention of the media and the medical profession. It is the first vaccine that is proven to be safe and effective against a sexually transmitted infection though it is marketed as a vaccine for cancer prevention. Whenever there is any promotion of a vaccine in the media, the interest of the local people and also the medical profession will be aroused. A monograph will be required in order to comprehensively review the whole subject but it is out of scope of the current short review. This review article summarises the questions that have been encountered by the authors during professional communication on various occasions in the past year. It aims at providing readers with a quick reference on the subject and hence facilitating better communication between doctors and their clients.

最近，人類乳頭瘤病毒疫苗受到傳媒及醫學界的廣泛注意。雖然這種疫苗是防癌疫苗，但它亦是第一種可以安全而有效地預防性傳染病的疫苗。但凡有疫苗推出，都會引社會及醫學界的關注。全面地論述本專題需要一部專論，惟本短篇綜述篇幅所限，祇能集中探討筆者於過往一年中所被問及的問題，望能為讀者提供快捷的參考，以便和病人有更好的溝通。

Keywords: Cervical cancer, HPV, vaccine

關鍵詞：子宮頸癌，人類乳頭瘤病毒，疫苗

What is the nature of the currently available human papillomavirus (HPV) vaccines?

To date, there are two commercially available vaccines in Hong Kong. Gardasil™, a quadrivalent HPV vaccine developed by Merck and Co., Inc. (MSD), was first licensed in the US in early June 2006. The vaccine consists of synthetic L1 capsid proteins of each of the four target HPV types 6, 11, 16 and 18. The proteins are produced using recombinant technology and are assembled as non-infectious virus-like particles (VLPs) in a yeast cell line. The same system has been used for producing hepatitis B vaccine by the same manufacturer. The vaccine is non-infectious as they do not contain any live organisms.

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The VLPs are co-formulated with and hence delivered in an amorphous aluminium hydroxyphosphate sulfate adjuvant.

The other commercially available vaccine, Cervarix™, was developed by GlaxoSmithKline plc (GSK). This is a bivalent vaccine containing VLPs of HPV type 16 and 18 produced in an insect cell line. The VLPs are co-formulated with a proprietary adjuvant containing aluminium hydroxide and monophosphoryl lipid (AS04).

These two vaccines are referred to as prophylactic vaccines and have been shown to prevent HPV infections by inducing antibodies that neutralise extracellular viruses. They are not therapeutic vaccines that elicit cellular immunity which is essential for the clearance of established infections/lesions. Therefore both Gardasil™ and Cervarix™ are not effective for treating established infection or their complications.

How effective are the HPV vaccines?

These two vaccines are highly effective in preventing the vaccine related types of HPV in young women who have not been previously exposed to HPV. These vaccines target HPV types (type 16 and 18) that cause about 70% of all cervical cancers worldwide, as well as in Hong Kong.[1,2] Data from large international randomised double-blind placebo-controlled multi-centre trials have shown that the efficacy is more than 90% in protecting against high grade cervical squamous epithelial lesions caused by the vaccine related HPV in the vaccinees (females aged 16-26 years for Gardasil™, 15 to 25 years for Cervarix™).[3-6]

Gardasil™, in addition, offers protection against two low-risk HPV types (type 6 and type 11) that are found in about 90% of external genital warts and a proportion of low-grade cervical intraepithelial neoplasia.

Both Gardasil™ and Cervarix™ have also been shown to be effective in preventing low grade lesions related to the vaccine HPV types. A substantial portion of these women will eventually end up in the colposcopy clinic. The anxiety of having these low grade lesions and the need to undergo repeated cervical smears or even colposcopy cannot be underscored. Therefore the potential benefit of these new vaccines is more than cancer prevention.

Are the HPV vaccines safe?

Safety data derived from these large international vaccine trials have been available for about 5 years. Mild local reactions such as erythema, pain and swelling were the most commonly reported local side effects for both vaccines. The most common systemic adverse experiences were fever, headache and nausea but the proportion in the vaccine group and placebo group were similar.

Post marketing adverse effect surveillance mechanism in the US has recorded a potential increase in the number of syncopal attacks as well as Guillain-Barre Syndrome (GBS) after receiving Gardasil™. The Immunization Safety Office of USCDC, after conducting concerned investigation and review, concluded that the casual relation between HPV vaccine (here refers to Gardasil™) and GBS cannot be established. Some vaccinees may experience excessive pain and even syncope after vaccination.[7]

In conclusion, there is good evidence to show that the vaccines are safe at least in the short term, and up to about 4 to 5 years with the short development history.

Is there any harmful effect on pregnancy by HPV vaccination?

Both Gardasil™ and Cervarix™ are classified under pregnancy category B and are not recommended for use in pregnant women. In the clinical trial (FUTURE II) for Gardasil™, pregnancy was reported in 1053 subjects in the vaccine group and 1106 in the placebo group. Moreover, in the clinical trial for Cervarix™, pregnancy was reported in 870 subjects in the vaccine group and 867 in the placebo group. A causal relationship between adverse pregnancy outcome and HPV vaccine was unable to be established. Women who accidentally got pregnant during the course of vaccination should consult their gynaecologist/ obstetrician for advice.[3,6]

Who should get the HPV vaccine?

USCDC recommends the HPV vaccine for all 11 and 12-year-old girls. The vaccine can be given to females from age 9 to 25.[8] In Australia, Cervarix™ has been licensed for use in women up to 45 years of age.[9] In Hong Kong, as there are no local data regarding the age of sexual debut and the cumulative risk of acquiring the vaccine related types of HPV after sexual debut, no evidence based recommendation can be made. The following factors need to be taken into account whenever a doctor recommends HPV vaccination to his/her female clients: 1) younger people in general can mount a higher antibody response which however may wane with time; 2) the duration of protection has not yet been defined; the longest follow up is about 5 to 6 years although there is some evidence that protection can still persist up to 5-6 years after vaccination; 3) the need to have booster vaccination some years later after vaccination is still not yet defined.

What are the basis for approving the use of HPV vaccine in different age groups?

A young female adult group 16-26 years was recruited for the phase 3 clinical trial for Gardasil™, and 15-25 years was recruited for Cervarix™. These trials used cervical intraepithelial neoplasia (CIN) 2/3 as the efficacy analysis endpoint, which is recommended by WHO as a surrogate endpoint for cervical cancer vaccines. Both vaccines showed high efficacy, and therefore have been approved for use in this age group.[3,6]

The efficacy results obtained from the young adult group are inferred to teenagers from 9-15 years for Gardasil™ and 10-15 years for Cervarix™, based the observation that higher levels of antibody were produced in teenagers (9-15 years) compared to the young adults (15-26 years). In other words, the approval for teenagers (9-15 years for Gardasil™ and 10-14 years for Cervarix™) was based on the concept of immunobridging, rather than efficacy data generated using CIN as the endpoint. This is understandable as it will take more than 15 years to observe the development of any CIN from these teenagers.

At the time of writing (January 2008), MSD has submitted data to the US FDA for consideration of granting approval to the use of Gardasil™ in adult females older than 26 years of age.

GSK has applied the immunobridging concept to demonstrate the effect of Cervarix™ in adult female older than 25 years. Australian authorities and a number of other countries have the following interpretation: "As observed with other vaccines, the immune response to Cervarix™ decreases with increasing age. This is not unexpected since this reflects the senescence of

the immune system. It was observed that the geometric mean titres (GMTs) remained in the same range or higher as those observed in the plateau phase of the long term follow up in the efficacy study in female aged 15-25 years". On the basis of immunogenicity data, the efficacy of Cervarix™ is inferred from 10 to 45 years (or 10-55 years in some countries).[9]

At the time of writing (January 2008), the registered age range in Hong Kong for Gardasil™ and Cervarix™ are 9-26 years and 10-25 years respectively.

Will sexually active females still be benefited from these vaccines?

Females who are already sexually active will still be benefited from the vaccines. Firstly, they may still be naïve to the HPV types contained in the vaccines. Secondly, they may have been infected but have cleared the infection. However, these natural HPV infections do not result in subsequent protection. Thirdly, they may be infected and are still carrying the virus. While, a majority of these women will clear the infection in about 1-2 years, they are still susceptible to future repeated infections. Therefore, in all these three possible scenarios, vaccination will offer protection for future infection though these females may not get the full benefit of the vaccine.

There is a theoretical risk of delaying the clearance of pre-existing HPV infection if the vaccine is delivered to those already infected with the vaccine containing HPV types. This is because of the potential of suppressing cell mediated immune response essential for clearance of established infection by the humoral response induced by the vaccine. A study involving 2189 women randomly assigned to receive either 3 doses of bivalent HPV-16/18 vaccine (i.e. the GSK vaccine) or a hepatitis A vaccine (the control group) with HPV DNA detection from cervical specimen as the endpoint have shown that in women positive for HPV DNA, the vaccine did not accelerate or delay clearance of the virus of concern at 6 and 12 months of follow up (33.4% vs. 31.6% at 6 months in the vaccine and control group respectively; 48.8% vs. 49.8% at 12 months in the vaccine and control group, respectively).

Will the girls/women who have been vaccinated still need cervical cancer screening?

Yes, they will still need to have cervical cancer screening and to follow the latest recommendations for the following reasons: 1) the vaccine will NOT provide protection against all types of HPV that cause cervical cancer, so women will still be at risk for other HPV types that can cause cervical cancers; 2) women may also not get the vaccine's full benefits because some may have not completed the full 3 doses course or according to the dosing schedule; 3) women may develop CIN or invasive cancer due to infections that have already been established before vaccination.

Can the vaccine be used in male?

There is no published data on the efficacy of the vaccine in boys or men. Studies are now being done to find out whether the vaccine works in males. One of the factors that explain why the neutralising IgG antibodies induced by systemic immunisation are effective against a mucosal infection is that these IgG antibodies will be transudated into the female genital tract and hence render protection against HPV infection. This may imply a better protective effect of the vaccine in female than male. On the other hand, protection against vulval intraepithelial lesions caused by the vaccine related HPV is observed. In short, because there is no concrete data suggesting its efficacy, these vaccines are not to be recommended to males at this moment.

Should the potential vaccinees be tested for past or current HPV infection before they are vaccinated with the HPV vaccines?

No. The USCDC has specifically said no to this question. The purpose of vaccination is to protect an individual from future infection. Past or current HPV infection does not result in immunity against future HPV infection. Up to now, there is no data to indicate that the response to vaccine differs according to the presence of past or current HPV infection.

Furthermore, there is no reliable test for detecting anyone who has already been exposed or has had past infections. Nucleic acid amplification tests from genital specimen will only detect current infection but not past remitted infection. Serology test is not sensitive enough to rule out past infection as natural infection only elicits a low level of antibody response. In addition, these sophisticated tests are not generally available outside the research settings.

Nevertheless, one should note that there is only a small percentage of sexually active women having infection due to HPV types covered in the vaccines.[10] Vaccination does not alter the outcome of concurrent infections, but it may offer protection to future infections. It may not be cost-effective to carry out screening for HPV for all potential vaccinees.

Should the potential vaccinees received cervical screening before they are vaccinated with the HPV vaccines?

Vaccination and cervical screening complement each other in combating cervical cancer. Cervical screening can provide an early detection of cervical diseases as a result of previous HPV infections. Vaccination can prevent future infections. For women who are receiving regular cervical screening, it is not necessary to have an extra screening before vaccination. Nevertheless, doctors should take this opportunity to emphasise the importance of regular cervical screening.

Should the vaccinees receive HPV antibody test after completing the course of vaccination?

No. The response rate to HPV vaccination is very high. Furthermore, reliable HPV antibody tests are not generally available outside the research settings.

A man with penile warts may ask: "Should his female sex partner be vaccinated to prevent transmission?"

Protection against infection in this situation will be very doubtful. Most likely, the female contact has already been exposed to the HPV before the index case develops clinical disease. The reason of having a clinically unaffected partner may be because either the infection is subclinical (it is estimated that less than 1% of those infected will develop clinical lesion) or the disease is still "incubating". Therefore vaccination in this circumstance will not offer any protection against the incident type. Nevertheless, one may still bet on getting protection against the vaccine HPV types that they have not yet acquired; however, it should not be viewed as "post-exposure prophylaxis".

Will HPV vaccine help women who have already had vulval warts or cervical intraepithelial lesion?

The current vaccines are not therapeutic vaccines and hence will not treat existing clinical disease. Although protection against future infection is theoretically possible, the current efficacy data of the vaccines are derived from

those without concurrent wart or cervical intraepithelial neoplasia.

How and when is the vaccine delivered?

The vaccine is administered intramuscularly in a series of three injections over a six-month period (0, 2 and 6 month for Gardasil™ and 0, 1 and 6 month schedule for Cervarix™). There is no data on the effect of switching from one formulation to the other and therefore switching is not generally recommended.

What is the cost?

According to the manufacturers, it ranges from about HKD $900 to $1,500 per dose in the private clinics. The HPV vaccines may be supplied at lower cost to public institutions such as the Family Planning Association of Hong Kong.

Finally, as a clinician, please do not forget

It is important to remind and recommend regular cervical screening to your female clients who are sexually active irrespective of whether they have sexually transmitted diseases or not. Vulval warts will not usually become cancerous but the affected female may have already been exposed to the high risk HPV types as well; the wart is merely a surrogate indicator for other hidden, yet potentially more dreadful sexually transmitted diseases. Moreover, it is advisable to screen other concomitant sexually transmitted infections in those who practise high risk sexual behaviour and educate on safer sex.

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