An Update on HPV Vaccine

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Introduction

Cervical cancer is the third most common cancer in women worldwide, with an estimated 530 000 new cases and 275 000 deaths in 2008. More than 85% of them occurred in developing countries.[1] In 2008, there were 358 new cases and 120 deaths reported in Hong Kong.[2]

Human Papillomavirus

Infection with the human papillomavirus (HPV) is a necessary, though insufficient, cause of cervical cancer. Almost all cervical cancers are attributed to HPV infection.[3] More than 40 HPV types have been detected from the female genital tract, and 15 of them (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73 and -82) are considered high-risk types that are associated with cervical cancers. HPV-16 and HPV-18 together account for about 70% of all cervical cancers worldwide. The importance of other high-risk HPV types differs in different parts of the world. Data in Hong Kong showed that HPV-52 and -58 were found in 13.2% and 8.8% of cervical cancers respectively, while HPV-31, -33, and -45 each accounted for less than 5%.[4] Low-risk HPV types cause genital warts, among which, HPV-6 and -11 account for about 90% and 10-30% respectively.[5,6]

HPV Transmission

The majority of anogenital HPV is sexually transmitted. While up to 70% of sexually active women will become infected in their lifetime,[7] the majority of these infections are transient with over 90% spontaneously cleared within 24 months.[8] It is the persistent infection with high-risk HPV that is important in causing cervical cancer. However, there is currently no way of predicting which infection will persist.[9]

Non-sexual routes of transmission are uncommon, but possible routes include vertical transmission from mother to newborn,[10] finger-genital transmission[11] and transmission via formites and environmental surfaces.[12]

Prophylactic HPV Vaccines

Following natural infection, about 50% of women will have no measurable immune response. Those who have the response show low antibody levels, which may not be able to protect them against re-infection.[13] Prophylactic vaccination aims to prevent HPV infection by inducing high levels of serum neutralising antibodies by antigens (virus-like particles) that closely mimic the native virus structure. Adjuvants are compounds that are added to the vaccines to enhance the specific immune response to vaccine antigens.

Two prophylactic vaccines are currently available for prevention of HPV infection and the development of cervical neoplasia. The amorphous aluminium hydroxyphoshpate sulphate (AAHS)-adjuvanted quadrivalent HPV-6/11/16/18 vaccine (Gardasil®) was licensed in Hong Kong in 2006 for women aged 9-26 years. The age indication was extended to 45 years in 2010. It is also licensed for use in males aged 9-15 years for the prevention of HPV-6 and -11 related genital warts. The other vaccine, the ASO4-adjuvanted bivalent HPV-16/18 vaccine (CervarixTM) was licensed in Hong Kong in 2008 for women aged 10 to 25 years. Both products are to be delivered intramuscularly in three separate doses within six months.

Efficacy

Differences among efficacy trials of the quadrivalent and bivalent vaccines in terms of populations analysed, choice of control subjects and immunological assays preclude direct comparison of results for the two vaccines. However, both vaccines demonstrated high efficacy (>90%) against HPV-16/18 related cervical intraepithelial neoplasia grade 2 and grade 3 (CIN 2/3) and adenocarcinoma in situ (AIS), which served as the surrogate endpoints for cervical carcinoma.

Data from the quadrivalent vaccine trials showed that the efficacy against vaccine-type-related CIN 2/3 or AIS was 99% for those women aged 16-26 years who received all three doses with negative HPV-16/18 DNA and serology at baseline.[14] The efficacy against vulvar and vaginal intraepithelial neoplasia grade 2 and grade 3 (VIN 2-3/VaIN 2-3) and genital warts was 95.4% and 96.4% respectively.[15] The efficacy was also persistently high (>90%) in older age women (aged 24-45 years).[16]

For the bivalent vaccine, the efficacy against HPV-16/18 associated CIN 2+ lesions (defined as CIN 2/3, AIS and invasive carcinoma) was 92.9% for those aged 15-25 years who received all three doses and had normal or low-grade cytology at baseline.[17]

Follow-up Efficacy and Mathematical Modelling Studies

Both vaccines showed high efficacy against vaccine-type HPV associated CIN2+ for at least seven years.[18,19] There was no breakthrough CIN 2+ in the vaccine recipients during the follow-up periods. The antibody levels were persistently high and remained at or several-fold above those following natural infections after 5 to 7.3 years.[19,20]

While awaiting the long-term efficacy results of ongoing trials, mathematical modelling studies for both vaccines had predicted that the antibody titres would remain well above natural infection levels for at least 20 years.[21,22] However, since immune correlate of protection for HPV vaccination remains unknown, the actual duration of protection will only be established by long-term efficacy studies.

Cross-protection Against Non-vaccine High-risk HPV Types

Besides HPV-16 and HPV-18, which account for about 70% of all cervical cancers, other high-risk HPV types (HPV-31, -33, -35, -39, -45, -52, -58, -59 and -68) are associated with more than 20% of cervical cancers.[23] Given the polyclonal nature of the immune response to vaccination, it is postulated that anti-HPV-16 and anti-HPV-18 antibodies generated by vaccination may provide additional cross-protection associated with these non-vaccine type HPV.

Studies for both vaccines showed roughly similar efficacy pattern against persistent infection (≥ 6 months) and CIN lesions associated with these non-vaccine HPV types, except HPV-45, for which the bivalent vaccine but not the quadrivalent vaccine appeared to have a clear effect. The highest level of protection was against HPV-31 (70-90% against CIN 2+). The efficacy against a combination of HPV-31/33/45/52/58-associated CIN 2+ in women who were negative for high-risk HPV DNA at baseline was 53% and 32.5% respectively for the bivalent and quadrivalent vaccines.[17,24] While HPV-52 and -58 are more prevalent in Asia including Hong Kong,[4,25] data from a quadrivalent vaccine trial showed that the efficacy was about 20%.[24]

Head to Head Immunogenicity Comparison of the Two Available HPV Vaccines

A recent trial directly comparing the two vaccines demonstrated that the bivalent vaccine showed a significantly higher neutralising antibody level than the quadrivalent vaccine at 24 months after the first dose (2.4-5.8-fold higher for HPV-16 and 7.7-9.4-fold higher for HPV-18). Moreover, it also showed higher anti-HPV-16/18 neutralising antibodies in cervicovaginal secretions and higher circulating HPV-16/18 specific memory B-cell frequencies compared with the quadrivalent vaccine.[26]

However, there are no data correlating antibody titres or memory B-cell response with clinical efficacy. Since both vaccines have shown high efficacy in the follow-up studies, the clinical significance of the differences in magnitude of immune response between the two vaccines remains to be elucidated.

Safety and Adverse Effects

Both vaccines are generally well tolerated and serious adverse effects are rare. There were previous concerns about serous adverse events including deaths after administration of the quadrivalent vaccine. However, after investigation of over 23 million doses in the United States, they were not causally linked with the vaccine and they were not greater than the expected background rate.[27]

The most common side effects include local injection site reactions, headache, syncope, nausea, vomiting, diarrhoea, abdominal pain, itchiness, rash, urticaria, myalgia, arthritis, fatigue and fever.[26] However, they are transient and will resolve spontaneously without sequelae. A study in Hong Kong for the bivalent vaccine also confirmed similar safety profiles.[28] The compliance rates with the three-dose schedules were consistently high (84%) for both vaccines.[26]

Data on both vaccines administered during pregnancy did not indicate any adverse outcome, but they were insufficient to recommend use during pregnancy.

Booster Dose

The necessity for booster vaccination largely depends on whether the immune memory can outpace the disease pathogenesis.[29] Since the immune correlate of protection for HPV vaccination remains unknown and the pace of HPV pathogenesis is uncertain, the requirement for booster vaccination remains to be determined.

Target Population

Since the benefit of protection is greatest in pre-sexually active adolescents who have not been exposed to the virus (efficacy about 40-70% against CIN 2+ irrespective of causative HPV types),[15,17] HPV vaccination has been included in some national immunisation programmes including the United Kingdom and Australia. However, it has not been included in the Hong Kong Childhood Immunisation Programme yet.

Women who are sexually active (who might have already been exposed to the virus) can also be protected from catch-up programmes. The efficacy was about 20-30% against all CIN 2+ irrespective of causative HPV DNA.[15,17]

Given that HPV infections may be transient and antibody levels are unable to correlate protection, HPV

DNA and serology testing are not recommended before vaccination. Patients with a past history of abnormal Pap test or cervical lesion are not precluded for vaccination since they might not be infected with any or all of the vaccine-type HPV. However, these women should be informed that the efficacy of vaccination could be diminished.

Public Health Implications

Studies showed that the vaccines significantly reduced the number of all Pap test abnormalities, colposcopy referrals, cervical excisional procedures and all procedures for external genital lesions (genital warts, VIN 1-3 or VaIN 1-3).[15,17] These reductions might be translated to a reduction of preterm births and other adverse pregnancy outcomes because these outcomes have been shown to be associated with the treatment of CIN.[17]

Despite all the benefits, vaccinated women should continue cervical screening since current HPV vaccines do not protect against all oncogenic HPV types. However, the current cervical cancer screening programme may require modifications in the future, such as starting screening at an older age and increasing the screening interval.[30]

The quadrivalent vaccine is also licensed for use in males aged 9-15 years for prevention of HPV-6 /11 related genital warts. A study showed a significant reduction (67.2%) of genital warts in 16-26 years old males regardless of their baseline HPV DNA and serology status.[31] It has also been postulated that vaccination in males might further protect females from HPV-16 and HPV-18 infection by inducing herd immunity.[32]

Conclusion

With the availability of high efficacy HPV vaccines, a well-organised HPV immunisation policy coupled with an effective cervical screening programme will probably be the mainstream strategy in the near future in reducing the global burden of cervical cancers.

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