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Mini Review

Vaccines for Prevention of Cervical Cancer

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Abstract

The characteristics of two prophylactic Human Papilloma Virus HPV vaccines and ethical issues related to HPV vaccination are reviewed in this paper. These vaccines have the potential of substantially reducing HPV-related morbidity and mortality, and in particular cervical cancer. The vaccines cannot treat women with current HPV infection or HPV-related disease. They should be administered before the commencement of sexual activity. The ideal age group is adolescent girls between the ages 9-13. Both vaccines are highly efficacious and immunogenic and induce high levels of serum antibodies after three doses for all vaccine-related HPV types. School-based vaccination is considered as a cost-effective method for its delivery. Adequate education of both clinicians and patients is an essential to ensure effective implementation when considering a national vaccination program.

Key words: Cervical cancer, HPV vaccines, ethical issues.

Introduction

Cancer of the cervix remains a problem worldwide in women and is not only the fourth most common cause of cancer, but also the fourth most common cause of death in women.[1] In women between the ages of 15-44, cervical cancer is the eighth most common cancer whilst it is also the eleventh most frequest cancer in Saudi women.[2] The WHO predicts that 6.5 million women 15 years and older may be at risk of developing cervical cancer.

One hundred and fifty two women are diagnosed with cervical cancer each year in Saudi Arabia and 55 of these women will die each year.[3] That HPV is the cause of and is responsible for the development of pre-invasive and invasive lesions of the cervix, vagina and ano-genital region is already an established fact.[4]

The HPV is a double-stranded DNA (dsDNA) virus, non-enveloped, small in size with 7.9 kiliobases.[5] HPV can infect cutaneous or mucosal surfaces of epithelial cells. There are approximately 189 HPV genotypes which have been classified and sequenced according to their phylogenetic position and oncogenic potential.[6,7] Furthermore, 30-40 types from α-genus of HPVs have been identified which have oncogenic potential and infect the human genital tract; these have been divided into low and high-risk types. Low risk types are HPV 6 and 11 and are associated with benign anogenital warts or condylomata. There are at least 12 high-risk HPV (HRHPV) which include HPV 16 and 18 which cause anogenital cancers as well as precursor neoplastic lesions.[6,8,9]

Recent advances have contributed largely to our knowledge of HPV oncogenesis and how it causes cervical cancer, so much so, that persistent HPV infections can be detected using new technologies now and are been used for managing persons who are infected. In addition to this, the future of HPV infections and disease will change dramatically in the future due to the availability of vaccines against this virus.

Females are the primary candidates to receive HPV vaccine, and in particular those who have not come in contact with vaccine-related HPV types in the past. Therefore young adolescent girls between 9 to 13 years of age before becoming sexually active are the main candidates to receive the vaccine.[10] High vaccine coverage is the main objective in this group to get maximum benefit and a long term reduction in disease burden. Older women who are sexually active are the secondary target group for this vaccine. The vaccination of males is still not clear and is under debate and therefore WHO does not recommend vaccinating this population group currently, due to cost-benefit ratio.[11]

The Ideal Age for Vaccination

Immunogenicity over a wide age range has been demonstrated in boys and girls aged between 9 and 15 years with greatest immune response in pre-pubertal children.[12] Immunogenic response was reported to be 100% in subjects who participated and who were between

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10 to 55 years in (Cervarix trial),[13] and 10-45 years in (Gardasil trial).[14] It was observed that there is a decrease in antibody response with the increase in age mainly due to convolution of the thymus and similar,[13] is also noted with HPV vaccines,[15] and that is the main reason of vaccinating older women in order to prevent new HPV infections.

Vaccines

The characteristics of the 2 currently available commercial vaccines developed for HPV prevention are summarized in Table.

Table: Characteristics of the two currently available HPV prophylactic vaccines.

	Cervarix (Glaxo Smith Kline Biologicals)	*Gardasil (Merck & Co.)*
Genotypes included	16, 18	16, 18, 6, 11
Doses	0, 1 and 6 months	0, 2 and 6 months
Mode of delivery	0.5ml IM	0.5ml IM
Duration and efficacy	Up to the age of 4.5 years	Up to the age of 5 years
Availability	Yes	Yes
Cost per vaccine	SAR 600/ (160 USD)	SAR 600/ (160 USD)

The Gardasil ® was first licensed in 2006. It is a quadrivalent vaccine for HPV types 6, 11, 16, and 18 and contains VLP antigens. It is produced by recombinant technology using yeast. The vaccine gives protection to both low and high risk groups of HPV including HPV types 16 and 18 which cause cervical neoplasia and 6 and 11 which cause anogenital warts. The adjuvant used in the quadrivalent vaccine is aluminium hydroxyphosphate sulphate.

The Cervarix ® is a bivalent vaccine licensed in 2007 for HPV types 16 and 18, and also contains VPL antigens like the Gardasil vaccine. The Cervarix vaccine was developed using a recombinant baculovirus expression system. This vaccine only protects against HPV 16 and 18 which cause cervical neoplasia. The adjuvant used in this vaccine is Alluminium Sulphate.

Both vaccines are given by intramuscular injections in three doses within a period of six months. The only difference being that the recommendations for administering Gardasil is at 0, 2 and 6 months, and Cervarix to be administered at 0, 1 and 6 months. To date there is no recommendation for a booster dose. Being liquid, both vaccines need to be stored between 2 to 8^0C.

Vaccine Safety

Currently in the USA, extensive programs are underway and studies are been undertaken to evaluate vaccine safety which is part of the licensing requirements and also as part of post-licensing monitoring. The data obtained so far satisfies the requirements of a safe vaccine. There have been no reports of any effects in inadvertent vaccination of pregnant, although sufficient evidence to support this is lacking. In pregnant women who are breastfeeding who received the qaudrivalent vaccine, there have been no reports of any adverse effects.

Ethical Issues

Below are some ethical issues which need to be considered with the use of the HPV vaccine:

1. Obtrusion into an individual's privacy regarding taking the HPV vaccine whether voluntary or compulsory. At the same time considering an individual's freedom of right to choose versus community benefit.
2. In Islamic countries, non-marital sex is prohibited by strict religious laws. Therefore, the availability of a vaccine which will prevent a sexually transmitted disease could raise concerns from some religious and cultural groups sending out a wrong message regarding prevention and abstinence. Furthermore, some argue that vaccination against HPV is unnecessary since sex before marriage is totally prohibited and prostitution is forbidden. In other countries in the world, people are not willing to modify their personal sexual behavior; even if this may protect them from exposure to HPV and combat cervical cancer. While a woman may abstain from having sexual intercourse until after marriage, her partner may be promiscuous and may transmit HPV to her. There are also other factors to consider as potential risk factors for transmission of HPV such as incest or rape.
3. The benefits of HPV vaccination are by far greater than the disadvantages, because this will reduce the number of cervical cancer cases and hence reduce stress and anxiety in many women who have to regularly undergo Pap smear testing and further testing in those who get abnormal Pap smear results.
4. Despite the fact that the vaccine should be available to everyone in the community who require it, especially those from disadvantaged communities, this is not possible due to the current high price of the vaccine as well as the fact that it is not available in the public health sector, for these reasons it is not accessible to all.
5. The vaccine is currently been tested in men with the intention to increase herd immunity and thereby prevent infections in women. Although morbidity and mortality from HPV 16 and 18 occurs as a result of oral/ pharyngeal, penile and anal cancers, these cancers are less frequent than cervical cancer in women.

The greatest obstacle remains the affordability and acceptance of the vaccine by the larger public. The main aim to implement a successful national vaccination program will be to educate both clinicians as well as the general population sufficiently.

Conflict of interest: None declared.

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