The HPV vaccine - What the family practitioner needs to know

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Abstract

This article reviews the impact of human papilloma virus infection on the development of cervical cancer and the efficacy of newly developed HPV vaccines. These vaccines may have a major impact on the reduction of these common malignancies.

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Introduction

The Human Papilloma Virus (HPV) is a non-enveloped double stranded DNA virus with more than 100 subtypes having been described. About 30–40 subtypes can infect the anogenital tract in men and women. These fall into two groups:

(a) High-risk HPV types, of which HPV 16 and 18 and their relatives are the most important in causing anogenital cancer, of which by far the most important is cervical cancer
(b) Low-risk types mainly HPV 6 and 11 which cause genital warts[1]

Even though HPV infection of the anogenital tract is very common, it appears that only once persistent infection has set in will the HPV lead to the development of premalignant conditions of the cervix, vulva, vagina, anus and in males, the penis. Fortunately persistent infection is not common and the overwhelming majority of infections, particularly in women < 35 years, will regress spontaneously and don't persist.[2]

Epidemiology

HPV Infection is most common after the onset of sexual activity with a lifetime risk for sexually active men and women said to be at least 50%, and probably closer to 80% by 50 years of age. It is estimated that about 630 million people globally will be infected annually but that in the overwhelming majority, the infection is transient and clears due to the cell-mediated immune response of the body. In the majority of cases, HPV infection produces no or minimal changes of clinical significance and people don't even know they have the infection and as a result may spread it unknowingly. However, a small subset of patients will have persistent disease and develop pre-malignant lesions or invasive anogenital malignancies of which cervical cancer is the most important.[3]

HPV infection is most common in young patients. The five year cumulative risk of getting HPV infection in girls or young women 15–19 years of age who are sexually active, is about 43%. This decreases to about 35% in women 20–24 years of age, to about 20% in women 25–29 years of age and to about 24% in those of 30–44 years. In women > 45 years there is still an appreciable risk of about 12%.[4]

Discussion

HPV needs to invade actively dividing cells to survive. The superficial cells of the cervix have undergone differentiation and are no longer actively dividing. The cells within the cervix that are actively dividing are those within the basal layer. The HPV gains access to the basal layer via micro abrasions which commonly result from sexual intercourse. It can also gain access through naturally occurring accessible areas i.e. the transformational zone found in the cervix and anus. Although HPV infection is frequently transient, especially in young women, with about 70–90% infections clearing within 24–36 months, persistent infection with high-risk types is strongly associated with the development of cervical intra-epithelial neoplasia (CIN) and cervical cancer. With integration of the virus into the replicative mechanisms of the basal cells, the impact of the E_6 and E_7 produced by the virus inhibits the P53 tumour suppressor encogene and the retinoblastoma gene respectively of the host cells. This results in desegregation of the chromosome during mitosis, chromosomal aberrations and impaired apoptosis which culminate over the years into cervical intra-epithelial neoplasia and finally invasive cervical cancer. Recently is has been reported that the risk of developing CIN or invasive cancer 10 years after the HPV infection is about 17% for HPV 16 and 13.5% for HPV 18. Exposure and persistence are more frequent with HPV 16 than with the other HPV types.[5]

Cancer of the cervix in women is nevertheless a rare consequence of HPV infection with oncogenic HPV detected in over 99% of cases. Globally, it appears that HPV 16 is found in 50–60% of cases and HPV 18 in 7-20% of cases worldwide. It is the second most common cancer in developing countries, based on age-standardised incidence rates. About 490 000 new cases of invasive cervical cancer are diagnosed annually on a global basis with about 80% occurring in the developing world. Unfortunately, as most of the patients will only be diagnosed when their disease is already advanced, about 275 000 will die annually. In Sub-Saharan Africa, cervical cancer is the most frequently diagnosed cancer and the leading cause of cancer mortality leading to about 55 000 women dying each year from this type of cancer. In South Africa each year about 7 000 women will develop cervical

cancer of which about 4 000 will die within the year. It is the most common cancer in South African black women accounting for about 32% of all cancers in this group of women. The lifetime risk of cervical cancer amongst South African women is about 1 in 26. It is a disease that affects relatively young women and hence is an important cause of loss of years of life. From a global point of view it was estimated that cervical cancer caused the loss of 2.7 million years of life during 2000 – the biggest single cause of loss of years of life from cancer in the developed world.[6]

High risk HPV infection is also associated with the development of other malignancies including oral, vulval, vaginal, penile and anal cancer and naturally the respective premalignant conditions of each of the above sites. Infection with low-risk types primarily HPV 6 and 11 may lead to genital warts, and recurrent respiratory papillomatosis (RRP). Genital warts may be found on the vulva perineum, perianal area, vagina or cervix in women and on the penis or scrotum in men. Although they generally indicate benign cell proliferation, they may be a marker for exposure to high-risk groups of CIN. Genital warts rarely progress to malignancy, but commonly cause substantial physical and psychological morbidity because of their recurrence and resistance to treatment, particularly if larger. In young children, RRP is caused by vertical transmission of HPV infection and my lead to significant airway compromise. Repeated surgical procedures are often necessary.[7, 8]

In summary, but more specifically in line with the HPV vaccines that are now available i.e. the bivalent which has HPV types 16 and 18 in it and the quadrivalent, which has HPV types 6, 11, 16 and 18 in it, it is important to bear in mind that HPV types 6 and 11 account for about 90% of genital warts in women and men and about 10% of low grade cervical lesions. HPV types 16 and 18 account for about 25% of low grade cervical lesions, 50% of high-grade cervical lesions, 70% of cervical cancers and about 70% of other genital cancers. Worldwide distribution of HPV types in cervical cancer support that high-risk HPV 16 and 18 account for about 70% of cervical cancers, whilst HPV types 31, 33, 35, 45, 52 and 58 account for a further 10%.[9,10]

Until the advent of the HPV vaccines, our primary strategy in combating cervical cancer has been through screening programmes. The aim of this secondary preventative measure is to identify premalignant conditions and then to subject these patients to conservative ablative or excisional strategies with the intention to decrease the likelihood of invasive disease and hence its accompanying morbidity and mortality.

Screening for cervical cancer

The traditional method of screening has for years been cervical cytology. Although the South African Screening strategy has only had 1 pap smear every decade from about 25 years of age onwards for 3 decades as its cornerstone, it has proved very unsuccessful to counteract or decrease the incidence of invasive cancer or mortality related to the cancer. The developing world in general has had screening programmes that have been opportunistic, haphazard and particularly unsuccessful in combating cervical cancer. Liquid based cytology, HPV testing and visual assessment of the cervix after acetic acid or Lugol's iodine application have all been proposed as possible options to overcome our present appalling state of affairs in screening for cervical cancer. Although a number of developed countries have managed to implement and maintain a screening protocol that has very successfully decreased incidence of invasive cervical cancer and mortality from the disease within their countries, it has required significant effort and input to establish and obtain resources, facilities, finances, education and political buy-in. In the overwhelming majority of developing countries where screening programmes are non-existent or have failed miserably, primary prevention utilising HPV vaccinations may be an option that merits serious attention.[11]

Vaccines that prevent viral diseases such as polio, measles, smallpox and hepatitis B have provided some of the most successful strategies to reduce infectious disease associated morbidity and mortality. For example, prophylactic vaccination has reduced the incidence of infection by 72% for hepatitis B, 99,9% for measles, diphtheria and rubella and has almost completely eradicated polio and smallpox. The fact that cervical cancer is caused by high risk HPV, provides an exceptional opportunity to use vaccination as a tool for cancer prevention.[12]

The HPV vaccination has the potential to greatly reduce HPV associated disease and its accompanying burden worldwide which would include the pre-malignant lesions of the cervix, vulva and vagina and hence malignant lesions in the long-term as well as preventing condylomatous lesions of the lower anogenital tract.

Formulations of HPV vaccines

Prophylactic HPV vaccines are formulations of the major capsid proteins LI of the natural HPV particle. LI monomers in yeast, insects or mammalian cells self-assemble into virus like particles (VLPs) which closely mimic the structure of natural HPV virons. These VLPs are not toxic and don't contain infectious genetic material. Because these VLPs are recombinant proteins, they are not oncogenic and don't have disease producing potential. They are ideal for vaccination. Administration of these VLPs in the form of vaccinations produces neutralising antibodies that bind to natural HPV virons, preventing their entry into cells.[13]

The results of the first double-blind efficacy trial utilising HPV VLPs vaccines were published in 2002. This study randomly assigned 2 392 women, aged 16–23 years, to receive 3 doses of vaccine or placebo, given at months 0, 2 and 6. Women were followed for a medium of 17 months after their 3rd dose. Of the 768 women who received the vaccine, none developed persistent infection (100% protective) compared with 41 cases in the 765 women in whom persistent infection was noted and who had received placebo. Furthermore, 99.7% of all women vaccinated seroconverted with antibody levels between 50–100 fold higher than those produced in response to natural HPV 16 infection. The vaccine was shown to be safe and well tolerated.[14]

More recently two multivalent vaccines have been developed and used in a number of large studies. GlaxoSmithKline have produced the bivalent vaccine CERVARIX®, formulated to protect against HPV 16 and 18, while Merck have developed the quadrivalent vaccine, GARDASIL®, to protect against HPV 6 and 11, 16, 18. Based on epidemiological data, an HPV 16 and 18 vaccine would be expected to prevent about 25% of all low grade SIL and about 50% of high grade SIL and about 70% invasive cancers. GARDASIL® would be expected to prevent an additional 12% of low grade SIL and nearly all cases of genital warts in line with it containing also HPV 6 and II VLPs.

In 2004, the results of CERVAVIX® vaccine trial were published. In the study more than 1 000 women, 15–25 years of age, were randomised to vaccine or placebo receiving their injections at months 0, 1 and 6, and followed for up to 27 months. Overall the vaccine was shown to be 91.6% effective against incident infection and 100% against persistent infection. After a medium follow-up of 4.5 years, 98% of patients

vaccinated have maintained HPV 16 and 18 antibodies at about 50–100 fold higher than that produced by natural HPV infection and have had 96.9%, 100% and 100% protection against incident infection, persistent infection and cervical intraepithelial lesions respectively. [15]

The GARDASIL® vaccine has to date been evaluated in four placebo controlled, double blind, randomised phase II and phase III clinical studies involving over 20 500 women aged 16–26 years. These patients have been followed up for up to five years after enrollment. The vaccine prevented 100% of HPV 16 and 18 related CIN 2/3 and adenocarcinoma *in situ* of the cervix (AIS), 95% of HPV 6, 11, 16 and 18 CIN 1, CIN 2/3 and AIS and 99% of genital warts caused by HPV 6 and 11. It also prevented 100% of HPV 16 and 18 related vulval and vaginal pre-cancers (VIN 2/3 and VAIN 2/3) in women not previously exposed to the relevant HPV types. In addition, administration of the vaccine to women already with one or more vaccine related HPV types protected them from clinical disease caused by the remaining vaccine types. It did however, not obviously alter the cause of an infection that was already present. The vaccine was well tolerated and there were no vaccine related serious adverse events. When comparing HPV 6, 11, 16 and 18, immune responses in 9–15 year old girls with 16–2 6year old females it was found that the immune responses were similar in both groups. Secondary analysis revealed that the vaccine was likely to have reduced cervical precancerous lesions and cervical cancer caused by HPV 16 and 18 by about 40% and of genital warts by about 70% in the four year follow-up. Most of the cases of the CIN and genital warts seen in those vaccinated resulted from infections that were present when the women received their vaccinations.[16,17]

Administration of HPV vaccine

For optimal effect, the vaccines should be given prior to sexual activity so that recipients will be naïve to all vaccine HPV types. The primary target are young girls aged 11–12 years, although it can be given to girls 9–10 years of age and to girls 13–26 years of age. Girls who are sexually active, should however still be given the vaccine, although they must be made aware that they will only obtain protection against those vaccine HPV types to which they have not been exposed. It is nevertheless most uncommon for any sexually active female to have been infected with all vaccine HPV types. Pre-vaccination cervical cytology of HPV testing is not necessary, although it is obligatory that following vaccination, all females must continue being screened for cervical cancer. A previous abnormal pap smear or a history of having a positive HPV test does not exclude that female from receiving the vaccination.

The vaccines are administered intramuscularly and should ideally be given over 6 months, with CERVARIX® being given at 0, 1 and 6 months, and GARDASIL at 0, 2 and 6 months. The vaccines are not recommended for use during pregnancy, even though there are no data to support that they are teratogenic. If pregnancy occurs during the course of administration, it is not necessary to terminate the pregnancy, although the injection must be immediately deferred and the course completed after the pregnancy. The vaccines can be administered during lactation. Simultaneous administration with other vaccines is not contraindicated and whilst they can be given to persons with minor acute illness, they should be deferred if persons have moderate or severe acute illnesses. The vaccines are prophylactic and don't have any obvious therapeutic benefits i.e. they will not treat disease that is present. Adverse events appear to be mild and overwhelmingly confined to the site of injection, with pain, swelling or erythema being the most common. Pyrexia appears to occur in 1–4% and syncope in girls < 15 years have been described.

There is now also compelling data that both the vaccines will not only result in significantly elevated levels of antibodies to their vaccine HPV types, but also to significantly elevated antibody levels to types 31, 45 predominantly, and 33, 35, 52, 58. This cross protection does not only extend to antibody levels, but also to clinical protection to development of incident and persistent infection and to cervical intraepithelial neoplasia caused by these HPV types.

Conclusion

The data pertaining to the role of HPV vaccines in eradicating cervical cancer are remarkable, inspiring and exciting. It is overwhelmingly clear that HPV vaccines are highly effective, highly immunogenic and very well tolerated. There is real hope that cervical cancer can be substantially reduced throughout the world and particularly so in the developing world. However, despite the remarkable efficacy of the vaccines there are unfortunately many questions that remain regarding its distribution and implementation. The biggest hurdle is likely to be cost. It is likely that the cost of the vaccine will be exorbitant from a South Africa perspective, even though there has been verbal assurance on the part of the pharmaceutical companies that a differential cost between the developed and developing world will exist. Be it through coercion, innovative planning or endless negotiations, finances must be earmarked for implementing this long awaited strategy in trying to eradicate cervical cancer in Southern Africa. Implementation will unfortunately be influenced by ethical, cultural, social and religious connotations.

Awareness programmes, enlightenment and education are going to be a priority in establishing meaningful vaccination programmes. It mandates cooperation and consideration of all role players, including paediatricians, gynaecologists, family medicine practitioners, nursing staff, members of the department of health and the pharmaceutical companies. I do believe that all these issues, including cost, can be resolved.

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