

Prophylactic human papillomavirus vaccination against cervical cancer: a summarised resource for clinicians

South African Human Papillomavirus Advisory Board

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Introduction

Carcinoma of the cervix remains the most frequent cancer affecting women in South Africa. Twenty-three per cent of all reported cancers in women are of the uterine cervix. Cancer of the cervix resulted in an estimated 3 700 deaths in South Africa during 2002.

The human papillomavirus (HPV) has been proven a potent carcinogen. The aetiological role of HPV infection in the development of preinvasive and invasive lesions of the cervix, vagina and the anogenital region has been conclusively established. Vaccination against infection with specific high-risk HPV is commercially available, and is likely to change the future of the disease.

Epidemiology and burden of disease

The HPV types most commonly associated with the development of malignant disease include HPV16 and HPV18 and, to a lesser degree, HPV31 and HPV45. HPV types are classified as high and low risk according to their association with cancer. The five most frequent HPV types among women with cervical cancer are HPV16, HPV18, HPV33, HPV45 and HPV31.

Low-risk HPV (mainly HPV6 and HPV11) causes approximately 90% of genital warts, and there is possibly an aetiological association with recurrent juvenile laryngeal papillomatosis.

Preventing cervical cancer

Primary prevention

HPV infection is one of the most common sexually transmitted infections worldwide, affecting more than 70% of women in the USA and up to 95% of high-risk women in Africa.

Prophylactic HPV vaccines, protecting against certain oncogenic strains, are available and represent the most important advance in the fight against cervical cancer, as a primary preventative strategy.

Other factors include the reduction of smoking, both active and passive, to prevent cervical cancer. Recently, two other important additional strategies have also been shown to be of value. The use of condoms has been shown to significantly decrease the incidence of acquiring HPV infection. Condom use will decrease HPV infection by about 60%, but it will not eradicate infection totally. Of note is that HPV infection of the anogenital area does not only depend on penetrative sex, and that purely skin-to-skin contact is sufficient to cause infection. The other important strategy is male circumcision. This significantly decreases transmission of HPV from males to females.

Secondary prevention

Secondary prevention is aimed at screening the general population to identify those individuals at high risk of developing disease. Cervical cytology has been the most successful cancer prevention strategy in history, and has significantly reduced the number of new cases of invasive carcinoma. The sensitivity and specificity of a single cytology test are, however, often disappointingly low. Well-organised call and recall programmes are expensive. In South Africa, the national cytology programme has not had any significant impact on mortality statistics, and may never be successful in certain isolated populations with poor access to health care.

High-risk HPV testing offers several potential advantages over conventional cervical cytology in the setting of primary screening, but also has many limitations. HPV testing is significantly more sensitive than cytology in predicting cervical cancer and its precursors. It is apparent that HPV testing may be

a better test to use in programmes with once-in-a-lifetime testing or long screening intervals (> 5 years). Longer screening intervals are more cost-effective, overall.

Other strategies include visual inspection of the cervix after acetic acid application (VIA), which has a sensitivity of 67-79% and a specificity of 49-86%, and visual inspection of the cervix after Lugol's iodine application (VILI), which has a sensitivity of 78-98% and a specificity of 73-93%.

Prophylactic HPV vaccination

The human papillomavirus

HPV is a non-enveloped, double-stranded, deoxyribonucleic acid (DNA) virus. The genome of HPV is enclosed in a capsid shell made up of major (L1) and minor (L2) structural proteins. There are more than 100 known genotypes of HPV, and certain (oncogenic) types are associated with cell transformation that leads to cancer. Certain high-risk HPV viruses have an affinity for integrating certain areas of the viral genome into the host chromosomes.

Pathology and immunology

HPV gains access to cervical tissue via skin abrasions and invades the basal layer, where it resides for the long term. A large percentage of the population will have sustained clinical remission, but a small proportion will develop persistent infection and become HPV-DNA positive on repeated testing. Persistent infection with oncogenic strains of HPV can lead to high-grade squamous intraepithelial neoplasia or adenocarcinoma in situ (AIS). These precancerous lesions have a high probability of progressing to invasive squamous carcinoma or adenocarcinoma.

HPV infection affects the intraepithelial layer of the mucosa, and does not elicit a marked immune response. About 50% of women infected with HPV develop detectable serum antibodies, although these antibodies are not necessarily protective against subsequent reinfection by the same HPV type.

Prophylactic HPV vaccine

HPV virus-like particles (VLP) are used in the manufacturing of the currently available prophylactic vaccines. These vaccines contain no viral DNA capable of replication and are, therefore, non-infectious and cannot lead to disease. They induce antibody titres much higher than naturally occurring infections. The VLPs are combined with a non-specific immune stimulant called an adjuvant, which leads to improved production of immunoglobulins against the vaccine

types of VLPs. These specific antibodies must be concentrated primarily within the cervicovaginal secretions to ultimately provide protection.

Currently, there are two registered prophylactic vaccines for HPV vaccination, namely Cervarix®, which contains HPV types 16 and 18, and Gardasil®, which protects against HPV16, HPV18 and low-risk types 6 and 11.

Efficacy

The quadrivalent prophylactic vaccine (Gardasil®) has been evaluated in two phase III randomised placebo-controlled clinical trials designed to investigate its efficacy. In women who had no prior evidence of infection, the vaccine was 98.2% effective at 3.6 years against HPV16 and HPV18 cervical intraepithelial neoplasia (CIN) 2 or 3 lesions and adenocarcinoma in situ lesions. Gardasil® was 100% effective against HPV6- and HPV11-related lesions. The quadrivalent vaccine also showed partial cross-protection to other vaccine types. There was also a significant reduction in colposcopy, cervical biopsy and definitive therapy.

The efficacy of the bivalent vaccine (Cervarix®) for protection against HPV16 and HPV18 CIN 2 lesions was 98.4%, and against HPV16- and HPV18-associated CIN 3 lesions it was 100%. There was also significant protection against non-vaccine oncogenic types [HPV33 (72.3%) and HPV45 (100%)]. The bivalent vaccine significantly decreased colposcopy referrals and cervical excision procedures.

Safety

The safety of the two HPV vaccines has been studied extensively during clinical trials. This has been closely monitored by governing bodies, including the Centers for Disease Control and Prevention (CDC) and the FDA (Food and Drug Administration) in the United States. The overwhelming opinion, from all the published data, is that both commercial HPV vaccines are extremely safe, without any proven serious risks.

Non-serious events associated with HPV vaccination include fainting, pain and swelling at the injection site, headache, nausea and fever. There is no increase in the incidence of autoimmune disease, vascular thrombosis or other serious side-effects. Of the deaths reported around the time of vaccination, none were considered to be associated with the vaccine.

Cost-effectiveness of population-wide HPV vaccination in South Africa

A recent calculation of the cost-effectiveness of introducing HPV vaccination in South Africa (Sinanovic,

2009) found that the price for the vaccine was the main cost driver. A price reduction of 60% or more would make vaccine-plus-screening more cost effective than the screening-only option.

Ideal age of vaccination

Most authorities have recommended that HPV vaccination should be routinely offered to females between 11 and 12 years, but it can be administered as young as nine years. Catch-up vaccination is recommended for females aged 13 to 26 years who have not been previously vaccinated.

Data are now available to support that there is significant clinical efficacy with Gardasil® vaccination in women up to 45 years of age, and immunogenic efficacy with Cervarix® in women up to 55 years of age.

Testing before vaccination

Testing for HPV exposure before vaccination is currently not recommended. In general, no additional testing is required before vaccination, except where pregnancy may be a possibility.

The HIV pandemic

Studies on HPV immunisation in HIV-infected individuals are not readily available. The efficacy of HPV vaccination in immunocompromised individuals is largely unknown.

Recommendations for implementation of HPV vaccines in SA

Population-wide HPV vaccination

In South Africa, an HPV immunisation programme should be planned, in order to reduce the cervical cancer epidemic. A coverage rate of over 70% is needed to impact on cervical cancer incidence. While this is a public health issue that should be addressed by Government, the South African Human Papillomavirus Advisory Board makes the following recommendations:

- Universal immunisation of young girls before the age of sexual debut.
- Vaccination should be between nine and 12 years.
- Both available vaccines require a multi-dosing schedule; three doses are recommended at months 0, 1-2 and 6.

Individual HPV immunisation before population-wide HPV vaccination

- *Teenaged females:* Immunisation of young females, up to the age of 26 years, on an ad hoc basis is

recommended. The prerequisites for this practice include a consenting, well-informed patient, financial affordability, and information on cervical screening in future.

- *Adult females:* Neither HPV DNA testing of the cervical area, nor serological HPV antibody testing, proves non-contact with HPV. The entire adult female population should not be a primary target group for vaccination, although individuals may benefit from vaccination.
- *Males:* Routine vaccination of the male population is not currently recommended. However, individuals may benefit from vaccination and, in future, cost-effectiveness may be shown for disease prevention in men and/or women.
- *High risk subgroups:* It is difficult to define and identify high-risk individuals. Not all individuals who are at high risk of HPV infection may benefit from HPV vaccination, although some individuals may. These groups should be targeted for genital cancer screening.
- *HIV-positive individuals:* Individuals who are infected by HIV are at an increased risk of developing HPV-related cancers. A patient with an intact immune system can potentially benefit from vaccination, and this is considered a safe approach. However, in women with AIDS, the immune response will probably be insufficient. The importance of regular screening is obvious.
- *Post-exposure vaccination:* Unless proven ineffective in further studies, immediate vaccination of rape survivors should be strongly considered.

Contraindications to vaccination

The safety of HPV vaccination in pregnancy has not been established. While initial trials reported no adverse effects, single reports on vaccine reactions and side-effects are appearing in the literature. These vaccines are, however, regarded as extremely safe.

Prophylactic vaccines used for therapeutic effect

There is insufficient evidence of a therapeutic benefit of the available prophylactic HPV vaccines in individuals with established infection or disease, and this usage is currently not recommended.

Cervical cancer screening tests in conjunction with HPV vaccination

Continued cervical cancer screening will be needed for many decades to come. Not only will sufficient

population coverage take many years to be achieved, but all women, and particularly immunocompromised women, will require ongoing screening in an ideal health care system.

The public health sector should, as a matter of urgency and priority, continue to implement the current cytological screening programme. It is also recommended that the age of first smear should be shifted to the left, probably to age 25. The South African Human Papillomavirus Advisory Board previously also recommended that Government should explore alternative screening strategies, including HPV testing.

Cytology and HPV vaccination

HPV vaccination in women with existing cytological anomalies has no benefit. Cytology, as a prerequisite

before vaccination, is also not recommended. Cytological screening of HPV-vaccinated women is recommended and required, as protection is not 100%.

HPV testing and HPV vaccination

HPV DNA or antibody testing prior to vaccination is not recommended to prove or disprove prior HPV exposure. HPV antibody testing has no current clinical application and need not be performed to prove an immune response.

The use of HPV DNA testing as a primary screening test may be more appropriate in the vaccine era and, as triage with cytology, will still be an applicable screening option in the post-vaccination era. (See recommendations by the South African Human Papillomavirus Advisory Board).

The South African Human Papillomavirus Advisory Board was established in August 2005 as an independent advisory group of clinicians and scientists, considered to be opinion leaders in the field of gynaecological oncology and cervical cancer epidemiology and screening. The Board is affiliated to SASOG and SASGO and is supported logistically by several companies with an interest in HPV-related disease. The members of the Board do not declare any conflict of interest. The opinions and recommendations expressed in this document do not reflect the policy of any company or the opinion of any individual board member, and is not meant to be prescriptive or legally binding.

These guidelines are intended and presented as summarised information for health care providers

and managers, interpreted with South African data and conditions in mind, on which to base clinical decision making. This document represents the first major revision of the vaccine document published in 2008 and will continue to be revised. For the references of this guideline summary, please consult the webpage of SAJGO.

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