

MODEL HPV VACCINE RECOMMENDATIONS FOR SUB-SAHARAN AFRICA

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(Manuscript N° C86. Received 15/11/2008. Accepted in revised form 29/05/2009) **Clin Mother Child Health 2009; Vol 6, N° 1:1047-1052****1. INTRODUCTION**

Cervical cancer (CC) is the second leading cause of cancer death in women globally and the first in women in many developing countries [1,2]. In sub-Saharan Africa cervical cancer is the most common cancer in women and there are over 200 million women aged 15 years or older who are at potential risk of cervical cancer.³ Nearly 71,000 cervical cancer cases are diagnosed and approximately 62,000 deaths are caused by cervical cancer each year in sub-Saharan Africa.³ Experts believe that essentially all cases of cervical cancer are caused by infection with oncogenic types of human papillomavirus (HPV) [4-6].

HPV is a very common infection that is readily transmitted during sexual contact. Therefore, most men and women become infected with HPV soon after they become sexually active. In most countries in the world, 70% to 80% of men and women will be exposed to HPV infection at some point in their lives [7]. Condoms are only partially effective in preventing HPV infections [8,9]. A recent meta-analysis suggests that the overall prevalence of HPV is higher in sub-Saharan Africa than in other regions of the world with Eastern Africa having the highest adjusted HPV prevalence (31.6%) [10]. The prevalence and incidence of HPV infection also vary between countries in the region due to different sexual behaviours and societal norms. Even when women only become sexually active at the time of marriage and have only one lifetime partner, they are likely to acquire the infection from their husbands if these men had sexual experience before marriage.

There are more than 100 types of HPV infection that infect many parts of the body, and a subset of these cause genital infections [11]. Some genital HPV types (referred to as oncogenic types of HPV) cause cancers of the cervix [12], vulva [13,14], vagina [13], penis [15-16] and anus [17]. Irrespective of global geographic region, the most common HPV types found in association with anogenital cancers are types 16 and 18.[7]. Cancer of the cervix is by far the most common genital cancer and HPV is the necessary cause. Studies have identified HPV in almost 100% of invasive cervical cancer cases, 89% of high-grade squamous intraepithelial (HSIL) lesions and 73% of low-grade squamous intraepithelial (LSIL) lesions [18]. The most potent cervical cancer causing HPV types are HPV 16 and 18, which together cause approximately 70% of

invasive cervical cancer cases [19] and are the predominant HPV types identified in HSIL and LSIL lesions [18]

Other genital HPV types are less likely to cause cancer but can cause other HPV-related diseases [20, 21]. For example, HPV types 6 and 11 cause approximately 90% of genital wart cases.[22]. Decreasing the incidence of HPV-related cancers, in particular cervical cancer morbidity and mortality, by means such as vaccination should therefore lead to a reduction in the human and financial burden of such diseases.

Most cervical HPV infections resolve spontaneously within 2 years [23], but in some women invasive cervical cancer develops after one or more decades of persistent infection with an oncogenic type of HPV [24]. Intermediate stages in the development of cervical cancer include abnormal Pap smears, low-grade and high-grade cervical lesions as well as carcinoma in situ. These predate the onset of invasive cancer.[24]. Why some women do not clear the HPV they have been exposed to and go on to develop cervical lesions, is not well understood.

Secondary prevention methods such as visual inspection with acetic acid (VIA), see-and-treat management of cervical dysplasia, Pap testing and HPV DNA testing will allow for detection of intermediate lesions which are amenable to treatment and hence prevention of most cases of cervical cancer in regularly screened women [25]. Effective prevention using these methods requires high levels of screening in the population, an effective infrastructure to deliver the screening, cultural acceptance of screening, the availability of effective treatment, access of the population to screening and treatment, and effective follow-up. Although wealthy and middle income sub-populations of women have access to this type of care in sub-Saharan Africa, most women in these countries have never received effective screening for cervical cancer prevention.

Highly safe, immunogenic and effective vaccines have recently been developed that can prevent infection with HPV types 16 and 18 with or without 6 and 11. These vaccines have now been licensed by the national control authorities in more than 80 countries [26]. National immunisation programmes (NIPs) (with other childhood vaccines) in sub-Saharan Africa are improving their vaccine coverage, and routine immunisations reach

more than 70% of infants [27]. However, most NIPs do not have vaccines for administration to adolescents and the older population. School and community-based programmes are therefore thought by many experts to be the correct setting for HPV vaccine administration. School and community-based adolescent vaccination programmes have been shown to have high completion rates (>80%) [28,29], and are ideally suited for the implementation of HPV vaccination schedules. Ideally, both HPV immunisation and cervical cancer screening programmes should be in place to have maximal impact in preventing cervical cancer.

The discovery, development and testing of the new HPV vaccines is a major medical achievement. The vaccine is a virus-like particle (VLP) made by recombinant DNA technology similar to the hepatitis B vaccine: the gene for the L1 coat protein of the virus is inserted into another cell (yeast or insect cell) which is grown in great quantities in fermentation or tissue culture [25, 30]. The L1 coat protein of the virus is then purified and self-assembled into hollow VLPs that are highly immunogenic but non-infectious since they do not contain nucleic acid. The vaccines, which contain aluminium salts or the AS04 adjuvant (in the GSK vaccine), are highly immunogenic and induce an immune response in almost 100% of recipients of all ages tested to date (9 to 55 years of age) [31]. The immune response has been shown to last more than 6.4 years [32-34], and anamnestic responses to booster doses of vaccine have been documented [35]. The duration of protection of the vaccine is at least 6.4 years [34], but the full duration of protection is not yet known.

The vaccines have been shown to be highly effective in preventing HPV infection and resultant disease states [32]. Two vaccines are currently available – a bivalent and a quadrivalent – both of which contain VLPs of types 16 and 18 to prevent cervical cancer. In addition, one of the vaccines (quadrivalent) contains VLPs of types 6 and 11 to prevent genital warts. In HPV naive women, studies with both HPV vaccines have been shown to have more than 95% efficacy in preventing HPV infection and the development of lesions caused by the HPV types present in the vaccines for up to 6.4 years of follow-up [36]. It is important to understand that the current HPV vaccines are not therapeutic and will have no effect on the disease process of currently infected women. However, the vaccines may prevent infection with vaccine-targeted HPV types in women infected with other types of anogenital HPV.

Cost-effectiveness studies in industrial countries have shown the vaccine to be highly cost-effective when used as a routine vaccine in pre-adolescent girls,

adolescent girls and young women [37]. Few studies have been done in developing countries, but studies in Brazil have shown the vaccine to be cost-effective with a lower vaccine cost [38]. Studies show that immunisation of males and females is less cost-effective than immunisation of females alone when the measured outcome is cervical cancer prevention. However, HPV infection in males can result in other HPV-related diseases (e.g. anal and penile cancer) [15] which are a significant burden on the health care system [39].

Vaccination of males could therefore reduce transmission of HPV to females, resulting in a lower incidence of HPV and fewer cases of cervical cancer, and prevent male HPV-related diseases. There is concern that a female-only strategy will be less culturally acceptable in many countries. Male vaccination could therefore be a consideration in some countries.

Expert committees in many countries have issued recommendations for the use of these vaccines [40, 41]. This document provides model recommendations that should be modified for use in individual countries in sub-Saharan Africa.

2. IMMUNISATION STRATEGIES

2.1 Primary immunisation strategy

Most countries that have issued official recommendations from expert groups have recommended that the primary immunisation strategy should be to immunise pre-adolescent girls in the range of 9 to 13 years of age (see Table 1) [42]. This is to ensure that the immunisation is given before the onset of sexual activity, and because this group is easier to reach with the existing immunisation infrastructure. School-based programmes are most effective if most girls are in school at the recommended age of vaccination and if school health programmes are operational [42, 43]. Community-based immunisation is also used in some countries [44]. Some countries have allowed immunisation of both males and females (e.g. Austria) but so far none has implemented universal vaccination of boys [41]. Moreover, the impact of immunising males has not yet been demonstrated in clinical studies (which are pending). Ideally, routine immunisation of pre-adolescent females should be done as part of the national immunisation programme and funded by the health care system. This will ensure high coverage and is the most important strategy that will lead to control of cervical cancer at a population level.

2.2 Catch-up immunisation strategy

Most countries also recommend a catch-up immunisation strategy to ensure that the benefits of immunisation are

available to older children and young women. The age of the recommended catch-up varies from country to country and ranges from 13 to 26 years[25] and Government funding of the catch-up is included in most countries that currently provide universal access to these vaccines (see Table 1). This strategy will ensure that cost will not be an impediment to high coverage. Even though some girls will be sexually active at these ages, they may still receive benefit from the vaccine since very few will have already been infected with the HPV types found in the vaccines.

2.3 Immunisation of women older than 26 years of age

Initial clinical trial results have demonstrated efficacy in preventing HPV infection and clinical disease in women over 26 years of age and up to the age of 45 years [45, 46].

Women in this age group continue to become infected with HPV and develop clinical disease and cancer. 'Bridging' studies have shown the bivalent vaccine to be highly immunogenic up to the age of 55 years [31]. Mass vaccination of this age group is not currently cost-effective[47]. It is therefore the decision of the individual female to seek vaccination if she wishes. Some countries (e.g. Australia) have made recommendations that allow for the immunisation of women over the age of 26, although this is not publicly funded, and other countries are waiting for cost-effectiveness studies to be completed before they issue recommendations concerning this age group.

2.4 Individual elective immunisation

While primary and catch-up immunisation may be funded and delivered by national immunisation programmes, and recommended age ranges will vary from country to country, any woman who wishes to be immunised should be offered the HPV vaccine. Women should be encouraged to discuss HPV immunisation with their health care providers, and together they can decide if immunisation is appropriate.

2.5 Challenges in sub-Saharan Africa

There have been concerns that the immunisation of pre-adolescents, adolescents and younger unmarried women may meet with cultural resistance among religious conservatives in a number of countries. The impact of this issue on the uptake and acceptance of vaccination will vary from country to country and communication/advocacy strategies should therefore be tailored to the needs of the individual area.

Although the infrastructure to routinely immunise adolescents does not currently exist in many African countries, this should not prevent/hinder vaccine implementation. Furthermore, African countries should seek GAVI funding to ensure HPV vaccines become available.

Table1: EPI HPV vaccine recommendations.

| Country | Target population | Catch-up population |
|--------------------|--------------------------------------|---|
| Australia[44] | 12 to 13-year-old females | 14 to 26-year-old females |
| Austria[41] | Males and females aged 9 to 15 years | Not available |
| France[41] | 14-year-old females | 15 to 23-year-old females (who have not yet become sexually active, or have been sexually active for less than 12 months) |
| Germany[41] | 12 to 17-year-old females | Not available |
| Italy[41] | 11-year-old females | Not available |
| United Kingdom[48] | 12 to 13-year-old females | 16 to 18-year-old females (from autumn 2009) 15 to 17-year-old females (from autumn 2010) |
| USA40 | 11 to 12-year-old females | Women aged 13 to 26 years |

4. RECOMMENDATIONS FOR THE USE OF HPV VACCINES IN SUB-SAHARAN AFRICA.

3.1 Target populations

- Routine vaccination with three doses of the same HPV vaccine is recommended for females from 9 to 12 years of age. The exact age of primary immunisation may however vary from country to country to fit best with the available infrastructure.
- Catch-up vaccination is recommended for females 13 to 26 years of age who have not been vaccinated previously or who have not completed the full three-dose vaccine series.
- Women over 26 years of age should be encouraged to discuss HPV immunisation with their health care

providers, and together they can decide if immunisation is appropriate.

- Male vaccination is not recommended at this time but this issue may be reassessed when data are available and high vaccination coverage in the female population has been achieved.

3.2 Co-administration

- HPV vaccine can be administered at the same visit when other age appropriate vaccines are provided. Each vaccination should, however, be administered individually during the visit.

3.3 Screening

- At present, cervical cancer screening recommendations have not changed for females who receive the HPV vaccine. All women should receive regular cervical cancer screening as recommended.

- Screening for cervical pathology or for the presence of HPV is not required prior to vaccination.

- A woman with abnormal screening/Pap smear result is still eligible for vaccination unless, of course, the woman has cervical carcinoma.

3.4 Special situations

- The HPV vaccine can be given to females who have an equivocal or abnormal Pap test result, a positive HPV DNA or Hybrid Capture II® high risk test, or genital warts.

- Vaccine recipients should be advised that the data from clinical trials do not demonstrate that the vaccine will have any therapeutic effect on existing Pap test abnormalities, HPV infection or genital warts. Vaccination of these females would provide protection against infection with vaccine HPV types 16 and 18 ± 6 and 11 if not already acquired.

- Lactating women can receive the quadrivalent HPV vaccination [49]. The bivalent HPV vaccine should be administered during breast-feeding only when the possible advantages outweigh any possible risks [50].

- Females who are immunocompromised either from disease or medication can receive the HPV vaccine. However, the immune response to vaccination and vaccine effectiveness might be less than in females who are immunocompetent [51]

3.5 Contraindications to use of vaccine

- The HPV vaccine is contraindicated for people with a history of immediate hypersensitivity to any vaccine component.

- Women are discouraged from becoming pregnant during the immunisation schedule.

- The HPV vaccine is not recommended for use in pregnancy [25]

a. If a female has not finished her three-dose vaccination course and becomes pregnant, she should not receive any other vaccine doses until after delivery, at which point the remaining dose(s) can be administered.

b. The vaccine has not been associated causally with adverse outcomes of pregnancy or adverse events to the developing foetus. However, data on vaccination during pregnancy are limited.

3.6 Precautions

- The HPV vaccine can be administered to females with minor acute illnesses (e.g., diarrhoea or mild upper respiratory tract infections, with or without fever). Vaccination of people with moderate or severe acute illnesses should be deferred until after the illness improves.

4. APPENDIX

4.1 Administration

- Each dose of the HPV vaccine is 0.5 mL and is administered intramuscularly.

- HPV vaccine is administered in a three-dose schedule. The quadrivalent is recommended in a 0, 2, and 6-month schedule; the bivalent vaccine should be administered in a 0, 1, and 6-month schedule.

4.2 Adverse events

- Serious adverse events are exceedingly rare. The most common adverse events are pain, redness and swelling at the site of the injection which are commonly mild in nature ■

5. MEMBERSHIP

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