

IPPF Medical Bulletin

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IMAP Statement on cervical cancer prevention and the potential role of human papilloma virus (HPV) vaccine

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Introduction

Cancer of the uterine cervix is the second most common cancer among women worldwide and is the primary cause of cancer-related deaths in women in developing countries. Of the estimated 500,000 annual incident cases worldwide and the 250,000 deaths attributed to cervical cancer, over 80% occur in low-resource countries. Cervical cancer accounts for 15% of female cancers, with a risk before age 65 years of 1.5% in developing countries, but only 3.6% of new cancers, and a cumulative risk (ages 0-64) of 0.8%, in developed countries.

Human papilloma virus (HPV) is a sexually transmitted virus, recognised as the necessary cause of 99% of all cervical cancers. Cervical cancer is detectable at an earlier stage by well-organised screening programmes. Regular cervical screening and early treatment of precancerous lesions have led to a substantial decline in cervical cancer in developed countries, but are limited or unavailable in many less developed countries.

Epidemiology and natural history of cervical cancer

Human papilloma viruses are DNA viruses that infect skin or mucosal cells. There are more than 100 known HPV genotypes that can infect the genital area of men and women, including the skin and mucosal cells of the penis, vulva and anus, and the lining of the vagina, cervix and rectum.

Genital HPV is sexually transmitted through penetrative and non-penetrative genital contact, and causes the most common sexually transmitted infection (STI) among women. The virus is endemic in all populations, and, in some, as many as 60% of women become infected with at least one type of HPV following onset of sexual activity. The prevalence of HPV infection can be up to 44% among asymptomatic women. There are an estimated 292 million women with HPV DNA worldwide; and about 105 million women have an HPV-16 or HPV-18 infection at least once. HPV prevalence in men (7.9%) is lower than in women (17.9%), as penile tissues may be less receptive to certain HPV types.

The duration of infectivity is an important component of the rate of spread of an STI in a population: infections of longer duration have a potentially greater impact. HPV infections among men usually have a short course, and most infections are not detectable

after one year. Rates of HPV infection in young women are high following sexual debut, and the risk increases with the acquisition of each new sexual partner.

Most HPV infections have no symptoms, and over 90% of HPV infections clear within two years without developing recognisable symptoms or complications. Nevertheless, genital HPV infection is a public health concern because persistent infection with certain types can lead to cervical cancer in some women.

Over 40 types of HPV can infect the genital epithelium. Two common genital HPV types (HPV-16 and -18) are classified as "high-risk" because of their strong association with cancer of the cervix, vulva, vagina and anus in females. HPV infection may lead to low-grade or high-grade intra-epithelial lesions. High-grade lesions may progress to invasive cervical carcinoma if not treated. Other high-risk types, including HPV-31, -33 and -45 are also important, although the proportion of cancers caused by each type varies in different regions.

The stepwise development of invasive cancer (HPV acquisition, HPV persistence, development of cancer precursors, and invasion) takes an average 20 years, but can be more rapid. The relatively slow development of cancer following initial HPV infection has contributed to the success of cytology-based cervical screening programmes. Not all persistent HPV infections progress to precancerous (high-grade) lesions and not all high-grade lesions develop into cancer. However, the longer an HPV infection persists, the less likely it is to clear. Co-infection with HIV and HPV substantially increases the development of invasive cervical cancer.

Two other common genital types (HPV-6 and -11) are classified as "low-risk" because they are associated with low-grade cervical dysplasia and genital warts, a benign condition of the external genitalia, which may, however, cause significant morbidity.

Unprotected sexual intercourse is the primary route of genital HPV infection, including skin-to-skin transmission of genital warts between sexual partners. While oral and digital infection with genital HPV types may occur, the risk of transmission by digital-genital or oral-genital contact appears to be minimal. Perinatal transmission of HPV also occurs, but is rare and unlikely to result in persistent infection.

Predisposing factors

The predisposing factors that lead HPV infection to persist and progress to cancer are not well understood, but the following probably play a role.

Several aspects of sexual behaviour such as earlier sexual debut, short interval between menarche and sexual debut and multiple sexual partners increase the likelihood of acquiring an HPV infection. A higher number of pregnancies have shown an association with an increased risk of invasive cervical cancer, independent of number of sexual partners and age at first intercourse.

Biological factors, such as cervical immaturity, inadequate production of protective cervical mucus and the increased chance of cervical ectopy may make young girls more susceptible to infection.

The use of combined oral contraceptives for more than five

years is associated with a slightly increased risk of cervical cancer (1.3–1.8 fold), but this may be balanced by the reduced risk of cervical cancer attributable to parity. Women using combined oral contraception should be provided with clear information and should be screened for cervical cancer at regular intervals.

Certain sexually transmitted infections, such as Herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis*, play a role in the pathogenesis of cervical cancer. The use of condoms prevents the transmission of these STIs, which may contribute to the development of cervical cancer after the acquisition of HPV. HIV-positive women are at increased risk of HPV-associated cervical cancer compared with age-matched, HIV-negative counterparts. Tobacco smoking is also associated with an increased likelihood of acquisition of HPV infection.

Comprehensive cervical cancer prevention strategy

Effective strategies include primary and secondary prevention.

Primary prevention

Health promotion: To reduce the risk of HPV infection and cervical cancer, service providers should disseminate information and advice on healthy sexual behaviour, for example, delaying sexual debut, limiting the number of sexual partners, using condoms correctly and consistently, and avoiding tobacco use. Awareness-raising activities should include information on the significance of cervical cancer screening for the detection of precancerous lesions.

Genital HPV infections are transmitted through contact with skin or mucosal surfaces during penetrative and non-penetrative sex. Correct and consistent use of male condoms reduces the risk of heterosexual genital HPV transmission in women. Female condoms also provide limited protection against HPV infection.

HPV vaccine: HPV quadrivalent vaccine (Gardasil) is licensed in nearly 80 countries. Another, bivalent, HPV vaccine (Cervarix) has approval in Australia and is awaiting approval in the USA, the European Union and other countries. As both vaccines are prepared from virus-like particles (VLPs) and do not contain any live biological product or DNA, they are non-infectious. Each vaccine includes VLPs specific to HPV-16 and HPV-18, which account for nearly 70% of all cervical cancers worldwide. In addition, quadrivalent vaccine incorporates VLPs specific to HPV-6 and HPV-11, the types associated with most genital warts. Both vaccines are prophylactic, designed to prevent primary HPV infection. The quadrivalent vaccine demonstrated more than 90% efficacy in preventing persistent infection, and 100% in preventing precancerous cervical lesions due to these two types, in females who completed the vaccination regimen. The vaccines are not therapeutic, so they do not appear to alter the course of infections existing at the time of vaccination.

Both vaccines are administered at 0, 1 or 2, and 6 months in a series of three 0.5 ml intramuscular injections, which can cause transient pain, swelling, slight fever and erythema at the injection site. The clinical trials protocols excluded pregnant women. There are no data yet on safety or efficacy in immunocompromised persons. Preliminary data indicate that HPV vaccines may be cost-effective in developing countries by decreasing morbidity and mortality associated with cervical cancer and saving health-care costs, including treatments for genital warts, pre-invasive cervical lesions, and cervical cancer.

Challenges for universal HPV prophylactic vaccination: The need for a prophylactic vaccine is greatest in developing countries with a high incidence of cervical cancer and an extreme shortage of screening and treatment facilities. However, for these settings, the cost of a vaccine, administration in three doses at specific intervals, and strict cold chain storage requirements pose barriers to easy access.

The HPV vaccines are prophylactic so they must be administered

before first sexual activity, to provide maximum protection. This requires the vaccination of girls aged nine to 14 years. Public acceptance of the vaccine depends upon educating parents and young people about HPV infection, cervical cancer, and how vaccination at an early age prevents the disease occurring decades later.

HPV vaccines produce levels of neutralising antibodies that are considerably higher than those encountered in natural infections, and the responses last for up to five years. Further research is needed to determine the factors influencing the protection provided by HPV vaccines. Extended follow-up of clinical trials may also evaluate the need for a booster dose.

A moderate level of cross-protection is demonstrated by the quadrivalent vaccine against new infections by HPV-45 and HPV-31. These two HPV types are responsible for 10% of cervical cancers globally, and there are ongoing studies to evaluate cross-protection against clinical diseases associated with them.

Secondary prevention

HPV vaccines can complement, but not replace, existing cervical cancer screening programmes. The vaccines are unlikely to benefit women who have already been exposed to the relevant virus type. Screening should continue after vaccination, in order to detect the low-risk HPV types that cause 30% of cervical cancer.

The World Health Organization (WHO) recommends cervical screening for women aged 25 to 65 years, particularly from 35 to 45 years, in limited-resource settings. If resources are available, screening intervals should be three years for those aged 35 to 49 years and five years for women aged 50 years or older. Screening is unnecessary for women aged 65 years or more, with two previous screening results showing no abnormal changes, those aged under 25 years, or who have never had sexual intercourse.

The current screening methods are: cervical cytology, which includes Pap smear and liquid-based cytology, HPV DNA test, and visual inspection with acetic acid (VIA) or visual inspection with Lugol's iodine (VILI).

The Pap smear is currently the best method for detecting precancerous lesions of the cervix, provided there is a good quality detection programme that includes sample-taking, evaluation and follow-up. Cells are scraped from the cervix, fixed and stained on a glass slide, and assessed by a trained cytologist. Good screening programmes with wide coverage have reduced cervical cancer by up to 80%.

In liquid-based cytology (LBC), the cervical smear is transferred from a brush to a preservative solution, from which a slide is prepared in the laboratory. It is an expensive method, requiring additional supplies and sophisticated equipment, but involves fewer unsatisfactory specimens, and a short interpretation time.

HPV DNA screening methods are based on the detection of high-risk HPV DNA in vaginal or cervical specimens, which are collected by the service provider or client, placed in a preservative solution and processed in the laboratory. The technical resources, cost, and infrastructure requirements can make this test difficult to implement in low-resource settings. The detection of HPV DNA indicates the presence of an HPV infection only, not cervical cancer. It is also a triage tool to assess borderline Pap results, such as "atypical cells of undetermined significance" (ASC-US), if the woman needs to be referred for colposcopy.

Abnormalities can be identified by visual inspection of the cervix, without magnification, after the application of dilute acetic acid (vinegar) in VIA, or of Lugol's iodine in VILI. Vinegar temporarily turns abnormal cervical tissue white, allowing an immediate assessment of a positive (abnormal) or negative (normal) result. Iodine makes precancerous and cancerous lesions appear well-defined, thick, and mustard or saffron-yellow colour, squamous epithelium brown or black, but columnar epithelium retains its normal pink.

VIA and VILI, which do not need laboratory services, are alternatives to cytology in low-resource locations. A recent study indicates that VIA screening, based on good training and sustained quality assurance, is effective in low-resource settings. The visual methods can be useful for all pre-menopausal women, but not older clients because the transition zone, which is inside the endocervical canal in post-menopausal women, is invisible during speculum examination. The test has a low positive-predictive value, with numerous false positive results, leading to excessive diagnosis, treatment and unnecessary anxiety, and there is no record of the test that can be reviewed later. In most countries, colposcopy is used to evaluate women with abnormal cytology, but the use of colposcopy as a primary screening test is not recommended.

All women should be offered the same cervical cancer screening options, irrespective of HIV status. This is particularly important where HIV is more prevalent. HIV-infected women have more persistent HPV infections and a greater incidence of cervical intra-epithelial neoplasia, that can progress to invasive cervical cancer.

Diagnosis and treatment

It is crucial to follow up clients who test positive on screening, to ensure that the diagnosis is correct and to manage them appropriately. The clients should be referred to the next level of care, including the management of invasive cervical cancer

Effective treatment for precancerous lesions is a critical component of a successful cervical cancer prevention programme. Cryotherapy, which destroys precancerous cells by freezing the cervix, is inexpensive and can be safely and effectively performed by non-physicians, with minimal complications. Therefore, it is a practical treatment option for low-resource settings and acceptable to women and their partners. Cryotherapy equipment is relatively simple, the procedure needs no anaesthesia or power supply and is easy to learn. Where screening test results are immediately available, women can be treated during the same visit.

Choice of contraceptives

These are the contraceptive options for women diagnosed with cervical intra-epithelial neoplasia and cervical cancer

Barrier methods: Male and female condoms and diaphragms can be used with or without spermicides.

Combined oral and injectable contraceptives: The treatment of cervical cancer generally renders women sterile, but while awaiting treatment they need effective contraception, such as combined hormonal contraceptives (oral or injectable). There is concern that this method may affect the prognosis of existing disease.

Intra-uterine contraceptive devices (IUDs): Copper-bearing and levonorgestrel (LNG)-releasing IUDs can be used by women with cervical intra-epithelial neoplasia (CIN). But there is some concern that LNG-IUDs may enhance the progress of CIN. IUDs are contra-indicated for patients with cervical cancer, due to the increased risk of infection and bleeding at the time of insertion. An IUD already in place can remain but must be removed prior to treatment.

Female sterilization: This may be an option for women with cervical intra-epithelial neoplasia. It is not recommended for those with cervical cancer.

What can Member Associations do?

Member Associations can advocate for good quality cervical screening programmes. The clients should be informed about HPV infection, routes of transmission, associated risks, and protective measures they can take to reduce the risk of HPV acquisition. Measures include delaying sexual activity, limiting the number of sexual partners, and correct, consistent use of condoms. Screening creates opportunities for reducing the fear, embarrassment and stigma related to HPV infection and cervical cancer.

HPV vaccines do not prevent infections with all types of HPV associated with cervical cancer, so cervical screening must be continued after vaccination. The vaccines are most effective if given prior to sexual debut, but do not protect against other STIs. Comprehensive prevention programmes that offer screening, early treatment and vaccination can enable Member Associations to deliver community-based education on sexual and reproductive health topics, especially to young girls.

Novel HIV prevention technologies

Gita Ramjee

The burden of HIV infections and acquired immunodeficiency syndrome (AIDS) is increasing globally and effective prevention, behavioural interventions and novel technologies are urgently needed to halt its spread. HIV/AIDS is a multifaceted phenomenon that affects the whole fabric of a community - biological, socio-behavioural and cultural. Developing countries bear the brunt, with HIV prevalence and incidence highest in some parts of Sub-Saharan Africa, and with the greater burden of new infections in young women.¹ Addressing the pandemic requires a multi-pronged approach, acceptable to everyone.

Improved understanding of the pandemic suggests several methods to reduce the spread of infection, including: male and female condoms,^{2,3,4} voluntary counselling and testing;⁵ clean needle exchange programmes;^{6,7} treatment of sexually transmitted infections (STIs);^{8,9} antiretrovirals to prevent mother-to-child transmission;^{10,11} and male circumcision.^{12,13}

The efficacy of these measures has been studied through observation or randomized, controlled trials. Education, and messages about prevention, must continue to include them, but they do not fully protect. Escalating HIV infection rates necessitate additional options.

Microbicides

Vaginal microbicides are designed to prevent HIV infections through topical application, and women control their use.

The need for microbicides was identified in the late 1980s, when researchers recognized a role for a "woman-controlled method" to protect from HIV infection women who are not always able to negotiate condom use. Clinical trials of several microbicides have produced disappointing results. A fully effective outcome is not expected from products currently in trials, such as fusion inhibitors, that prevent attachment of the virus to target cells in the vagina; but there is hope that products under development (Tenofovir, TMC-120 and UC781), with antiretroviral (ARV) agents, will be HIV-specific and efficiently prevent infection.

The microbicide field has gained momentum, with strong philanthropic and public support, but assessment is difficult. High pregnancy rates adversely affect microbicide trials: the women cannot continue to use the product, which impairs the statistical power of the study to demonstrate efficacy. Other challenges include coital dependency of the products (they require application in the vagina one hour before sexual intercourse), which makes adherence to product use, and assessment of the self-reported data, problematic.

Recruitment and retention are challenges in many large-scale clinical trials; novel, innovative strategies must be developed to improve retention rates. However, the standard of care offered to people found HIV positive during the screening process, or who become HIV positive during the trial, has evolved: there is now greater access to ARV treatment in many of the countries where the trials are conducted.

Vaginal diaphragms

This intervention assumes the portal for HIV is mainly through cervical and endocervical target cells, and aims to reduce the risk of infection by covering the cervix with a barrier, such as a vaginal diaphragm, which is a safe, acceptable contraceptive.¹⁴ In a phase III trial in South Africa and Zimbabwe, women were randomized to receive a vaginal diaphragm plus lubricant and male condoms, or male condoms only. Both groups received intensive safe sex counselling, general counselling and treatment for sexually transmitted infections (STIs). The data suggested that fewer condoms were used in the diaphragm arm than in the male condom-only arm, however, the two arms showed similar HIV infection rates. It was concluded that adding a diaphragm to existing HIV prevention options provided no benefit. The study was not designed to assess the impact of the diaphragm-only option on the number of new infections seen in the study.¹⁵

HSV-2 suppressive therapy

Several studies show that individuals with herpes simplex virus (HSV)-2 infection are at high risk of HIV acquisition.¹⁶ Biological and epidemiological data suggest that HSV-2 facilitates transmission and acquisition of HIV, so treatment of HSV-2 may be a strategy to reduce the infectiousness of, and susceptibility to, HIV. There are several large-scale clinical trials to test the effect of HSV-suppressive therapy on the risk of HIV susceptibility and transmission. The challenges will be similar to those mentioned above, plus the need to identify any effective dosage, and the potential for HSV-2 treatment resistance.

Pre-exposure prophylaxis (PrEP)

The theoretical concept of pre-exposure prophylaxis is not new. It has long been used to prevent malaria, and, in the last decade, mother-to-child transmission of HIV. To reduce the risk of transmission, ARVs are given to the mother during labour, and the baby at birth. The aim of PrEP is to determine whether the use of daily antiretroviral doses prevents infection in HIV-uninfected persons. There are several trials nearing completion in various parts of the world. Ethical and behavioural challenges will need to be addressed, especially the concern that the use of PrEP may encourage high-risk behaviour.^{17,18}

Vaccines

An effective AIDS vaccine would be the best way to combat the HIV pandemic. Infectious diseases have historically succumbed to general immunization programmes. Unfortunately, after 25 years, the question remains, "When will we have a vaccine to prevent HIV?"¹⁹ The search remains a daunting task. It is clear that infections with HIV or other viruses are different, as HIV replicates rapidly, rendering even the strongest immune response incapable of delaying disease progression. By January 2007, at least 24 clinical trials of experimental AIDS vaccines were under way in over 20 countries around the world.²⁰

Conclusion

The results will be available in the next few years of many trials of novel technologies to prevent HIV transmission. Many are based on proven HIV/STI treatment modalities: including proven antiretroviral therapy as future microbicides (topical and oral); as oral prophylaxis in PrEP trials; and proven HSV-2 treatment for the prevention of HIV.

The new options will enhance the integration of HIV prevention and treatment research.

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