



Role of Human Pappillomavirus and Cervical Cancer in Developing Countries: A Current Trend in Africa

*Hayatudeen, M.R. and Bashir, A.

Department of Microbiology, Faculty of Natural and Applied Sciences, Umaru Musa Yar'adua University, Katsina, Katsina State, Nigeria.

*Corresponding author: Hayatudeen.muhammad@umyu.edu.ng (+2348138652564)

Abstract

Cervical cancer is a relatively rare disease in countries that have instituted and maintained national screening programs, with call and recall of women at various intervals and built-in quality control with appropriate monitoring and evaluation. Unfortunately, this process has failed in most areas of the world where more than 80% of new cases of cervical cancer are diagnosed. Cervical cancer is the fourth most common cancer affecting women, with worldwide annual incidence and mortality rates of 528,000 and 266,000, respectively. It is well established that cervical cancer is predominantly caused by a persistent human papillomavirus (HPV) infection of cervical cells. Increasing numbers of studies have investigated HPV and cervical cancer, contributing greatly to the global knowledge and unraveling some of the critical questions regarding HPV transmission, infection, and prevention. Treatment of cervical cancer in Africa is hampered by the lack of diagnostic and treatment facilities, lack of healthcare infrastructure and poor pathology services. Furthermore, there is a significant brain drain of trained healthcare workers in Africa that exacerbates the problem. Cancer is becoming an increasingly important public health problem as more people live longer. It is time to develop programs for the prevention, early detection, treatment, and palliation of cancer sufferers in Africa. Therefore, this review describes the current status of HPV in developing countries, presenting some of the existing challenges in implementing cervical screening and HPV vaccination programs.

Keywords: Africa, Cancer, Challenges, Screening, Treatment, Virus, and Women,

INTRODUCTION

Papillomaviruses are ubiquitous and are members of a family *Papillomaviridae* of DNA viruses that infect humans and animals (AMC, 2014). Human papillomaviruses (HPVs) are small non-enveloped viruses that contain a double-stranded, closed circular DNA genome, and this genome comprises approximately 8,000 base pairs with at least eight open reading frames that separate the genome into three regions. The first region, called the long control region, regulates the replication and transcription of the viral genome. The second region is called the early region (E) which contains six structural proteins E1, E2, E4, E5, E6, and E7 that are involved in viral replication and oncogenesis. The third region is called the late region (L). It encodes the L1 and L2 structural proteins, which form the major and minor capsid proteins, respectively. HPVs are a group of more than 200 related viruses. More than 40 HPV types can be easily spread through direct sexual contact, from the skin and mucous membranes of infected people to the skin and mucous membranes of their partners (Saeed *et al.*, 2017). They can be spread by vaginal, anal, and oral sex (Satterwhite *et al.*, 2013). Other HPV types are responsible for non-genital warts, which are not sexually transmitted. More

than 120 subtypes of HPVs have been classified based on their oncological potential of transforming cells as Low-risk HPVs, which do not cause cancer but can cause skin warts (condylomata acuminata) on or around the genitals and anus. For example, HPV types 6 and 11 cause 90% of all genital warts. HPV types 6 and 11 also cause recurrent respiratory papillomatosis, a disease in which benign tumors grow in the air passages leading from the nose and mouth into the lungs. High-risk HPVs, which can cause cancer (Louie *et al.*, 2009). HPV types 16 and 18 high risks, are responsible for most HPV cancers (Auvert *et al.*, 2009). In fact, the Centers for Disease Control (CDC) estimates that more than 90% and 80%, respectively, of sexually active men and women will be infected with at least one type of HPV at some point in their lives (CDC, 2012). Around one-half of these infections are with a high-risk HPV type (Auvert *et al.*, 2009). Virtually all cases of cervical cancer are caused by HPV, and just two HPV types, 16 and 18, are responsible for about 70% of all cases (Botha *et al.*, 2015). About 95% of anal cancers are caused by HPV mostly by HPV type 16 while about 70% of oropharyngeal cancers are caused by HPV.

In developing countries, complications in immunocompromised HIV patients due to HPV and other sexually transmitted diseases are a major cause of mother and child mortality and morbidity during pregnancy (Saeed *et al.*, 2017). Also HPV is known to increase the incidence of cervical cancer in HIV/AIDS patients (Ferlay *et al.*, 2007). According to the World Health Organization, 2014 85% of cervical cancer cases occur in developing countries, and these cases generate a worldwide burden. Their latest report indicated that the incidence of cervical cancer cases in developing countries is more than half a million, with half of these women dying from the disease (Jemal *et al.*, 2011). Therefore, this review also discusses the challenges facing developing countries combating sexually transmitted infections, especially HPV because it is the major cause of cervical cancer, and attempting to establish effective cervical screening programs.

Aim of the review

The aim of this review is to appraise the incidence, mortality, state of prevention and treatment of cervical cancer in Africa. This is with the objectives of appreciating and understanding the state of the disease so as to reinvigorate responses through the development of treatment, preventive and control programs that will lessen the burden and mortality from this disease in Africa. It will also highlight the need to consider cervical cancer as a public health problem in the region.

Methodology

The method used was through the synthesis of primary and secondary data derived from available surveillance and current published scientific works including proceedings, hospital and regional based cancer registry figures, reports from specific centers.

Development of cervical cancer

Nearly all cases of cervical cancer can be attributable to HPV infection, and cervical cancer is considered one of the most common gynecological malignant neoplasms worldwide (Satterwhite *et al.*, 2013). While cervical cancer development is a multistep process, the disease can only develop in the presence of a persistent HPV infection of the cervical epithelium. Although most HPV infections clear up on their own and most pre-cancerous lesions resolve spontaneously, there is a risk for all women that HPV infection may become chronic and pre-cancerous lesions progress to invasive cervical cancer (Saeed *et al.*, 2017). It takes 15 to 20 years for cervical cancer to develop in women with normal immune systems. It can take only 5 to 10 years in women with weakened immune systems, such as those with untreated HIV infection. An infection is generally initiated by the onset of viral

replication leading to low-grade cervical intraepithelial neoplasia (CIN1) (Sauveget *et al.*, 2011). If the virus persists and the neoplastic changes remain untreated, CIN2 may develop. Persistent HPV infection could then result in progression to high-grade lesions (CIN3) and to invasive cervical carcinoma. However, it appears that abnormal development occurs primarily when high-risk HPVs express the viral oncogenes E6 and E7. The HPV E6 and E7 early genes are viral oncoproteins that detrimentally disturb the cell cycle by altering the function of cell cycle regulators. These two primary oncoproteins inactivate two tumor suppressor proteins, p53 (inactivated by E6) and retinoblastoma (pRb, inactivated by E7), leading to cell cycle disruption and cellular transformation (Chesson *et al.*, 2014).

Cervical cancer in developing countries

Globally, cervical cancer was the third most common cancer ranking after breast and colorectal cancer and the fourth most common cause of cancer death ranking below breast, lung, and colorectal cancer (Louie *et al.*, 2009). Report indicated that the global cervical cancer incidence was highest in Asia (54%), followed by Africa (19%), then Central and South America (13%) and Europe (11%), and lowest in North America (3%). The same pattern was detected for mortality rates, with Asian countries, especially the lower-income countries, having the highest mortality rate worldwide (54%), followed by African countries (22%), Central and South America (11%), Europe (9%) and, as expected, North America having the lowest mortality rate (3%), which is likely attributable to effective early cervical screening, awareness, and vaccination programs. The cervical cancer burden in developing countries creates a genuine threat to the world because infectious diseases do not recognize borders (Saeed *et al.*, 2017). Unfortunately, developing countries have neither screening programs nor facilities to implement them, and some of these countries continue to rely on primitive detection techniques. Global efforts should be initiated to provide these countries with the latest technologies to establish successful screening, vaccination, and public education programs to halt sexually transmitted infections, especially HPV (Ferlay *et al.*, 2013).

Cervical cancer in African countries

In Africa, which has a population of 267.9 million women aged 15 years and older at risk of developing cervical cancer, approximately 80,000 women are diagnosed with cervical cancer per year, and just more than 60,000 women die from the disease (Arrossi *et al.*, 2010).

However, cervical cancer incidence in Africa also varies considerably by region with the highest rates in Africa are found in Eastern and Southern Africa (Denny and Anorlu, 2012). In addition, there are marked variations within regions themselves as for Southern Africa (Parkins *et al.*, 2010), where the highest incidence is found in Lesotho and Swaziland, 2 countries that have neither screening programs nor any anticancer treatment facilities and who have 1 and 2 doctors per 10,000 population, respectively. African countries and their estimated current population (in millions) with Nigeria has the highest population of over 170,000,000 but unfortunately, fewer than 50 articles examining HPV and cervical cancer have been published (Iliyasu *et al.*, 2010; Manga *et al.*, 2015; Isa *et al.*, 2013). However, cervical cancer ranked second (8.9%) of all cancers for women in the sub-Saharan African countries with the highest incidences (34.6%) and mortality rate (25.3%) in eastern and western Africa according to the International Agency for Research on Cancer 2008 (Jemal *et al.*, 2011). Still, the total number of cervical cancer cases registered in African countries is the lowest in the world, and this may be attributed to differences in sexual practice, lifestyle, and genetic predisposition. Despite the lower number of registered cases, what is alarming is that most women with cervical cancer in African countries do not seek treatment until later stages of the disease (Denny and Anorlu, 2012). Indeed, almost half of all patients arrived at the hospital with regional or distant metastasis stages, decreasing the survival rate. This is especially unfortunate because cervical cancer is the most preventable cancer and has a high survival rate when detected in early stages (Denny *et al.*, 2006). However, because cervical cancer is not among the most prioritize diseases in the most of the African countries, the cost-effectiveness of implementing HPV vaccination programs is debatable. Further evaluation will be required, especially given the current changes in socioeconomic status, lifestyles, and reproductive patterns of individuals in the Africa.

Incidences and Mortality of Cervical cancer in African Countries

Globally there are over 500,000 new cases of cervical cancer annually and in excess of 270,000 deaths, accounting for 9% of female cancer deaths 85% of cases occur in developing countries and in Africa it is the commonest cancer in women with incidence frequently equating with mortality in the absence of healthcare facilities to deal with the condition (Andrus *et al.*, 2008). Cervical cancer incidence and mortality rates have declined substantially

in Western countries following the introduction of screening programmes (Manga *et al.*, 2015). Screening programmes in Africa, are however, often rudimentary or non-existent. The burden of cervical cancer is quite low in the developed countries of the world (Ferlay *et al.*, 2013). The situation is quite the reverse in developing countries where it constitutes a major health problem. While the incidence is decreasing in the former, it is on the increase in the later. This is a source of great concern considering the fact that cervical cancer is preventable and curable at low cost with currently available methods. The magnitude of the problem has been under-recognized and under-prioritized compared with the competing health priorities of infectious diseases such as HIV/AIDS, tuberculosis, and malaria. Sub-Sahara Africa is the region with the highest incidence of cervical cancer in the world with concomitant high mortality affecting women at their prime (Ibrahim *et al.*, 2011). There are no screening programs for early detection of precancerous lesions within the countries of Sub Sahara Africa. Most screening activities are done as pilot or research projects which are discontinued on completion. South Africa is the only country in the region with a national cytology based screening program since 2001 but then coverage remains poor and the impact on invasive cervical cancer is unknown (Louie *et al.*, 2009). The onset of HIV/AIDS epidemic that is highest in the sub region has elevated the problem of cervical cancer to a serious level. To compound the problem is the widespread lack of resources associated with the region.

Cervical cancer occurs worldwide but the highest incidence and mortality rates of cervical cancer are in Eastern, Western, and Southern Africa, as well as South-Central Asia and South America. Rates are lowest in Western Asia, Australia/New Zealand. In sub-Saharan Africa cervical cancer accounts for 22.2% of all cancers in women and it is also the most common cause of cancer death among women (Parkin *et al.*, 2003). Cervical cancer is however the second common cancer among women after cancer of the breast in some areas like Ibadan in Nigeria (Adebamowo *et al.*, 1999). About 60%-75% of women in sub-Saharan Africa who develop cervical cancer live in rural areas. Many of these women go untreated, mostly due to lack of access to health care. Women in sub-Saharan Africa lose more years to cervical cancer than to any other type of cancer. Unfortunately, it affects them at a time of life when they are critical to the social and economic stability of their families (Parkin *et al.*, 2002).

The true incidence of cervical cancer in many African countries is unknown as there is gross under-reporting. Only very few countries have functional cancer registries and recordkeeping is minimal or non-existent in many countries. Some of the figures quoted in the literature are hospital-based, which represents a small fraction of women dying from cervical cancer, as most women cannot access hospital care and die at home. A mortality rate of 35 per 100,000 is reported in Eastern Africa. The reported mortality rates in developed countries with successful screening programs seldom exceed 5 per 100,000 women (Chokunonga *et al.*, 2002).

Strategies for Prevention of Cervical Cancer in Africa

A global conference, organized by Oxford University's Africa-Oxford Cancer Consortium and Cardiff University, was held in Oxford University on March 26th and 27th, 2009 to set down a strategy for preventing cervical cancer in Africa and issue an international call for action in combating the disease. The conference was attended by health ministers from African nations, African doctors, and advisors, the World Health Organization, representatives from the pharmaceutical industry, leading international oncologists, and major global cancer organizations and charities.

The main communique resolved is to look at the possibilities for international community support funding for HPV vaccination programmed. The delegates made a tremendous effort to provide a means of lowering down the cost of the vaccine for easy affordability to African countries whose budget cannot sustain the current cost of the vaccine. There was also complete among delegates to develop a broad partnership among research institutions, international organizations, governments and pharmaceutical companies to effectively prevent, detect and treat the rising number of cervical cancer in Africa as reported by many African literatures (Denny and Anorlu, 2012; Isa *et al.*, 2013; Manga *et al.*, 2015; Louie *et al.*, 2009).

Current diagnostic methods for Cervical Cancer

Given the high prevalence of HPV as well as the persistence of HPV infections and the long latency for the development of cervical cancer, effective screening for the presence of HPV infection and for cervical cancer at the population level is critical to provide better outcomes for patients worldwide and especially in developing countries. The techniques that have been extensively used for HPV and cervical cancer screening include testing for

the presence of HPV as well as visual inspection, conventional cytology, liquid-based monolayer cytology, or histological examination of the cervix (Skomedal *et al.*, 2012). Briefly, the Pap test is considered the gold standard for cervical cancer screening. After its introduction into standard clinical practice in the 1950s, cervical cancer decreased by 60% in women under the age of 55 (Gichangi *et al.*, 2003). HPV infection is primarily diagnosed using molecular biological methods because culturing the viruses are unfeasible and serological methods are insufficiently sensitive (Ibrahim *et al.*, 2011). Nucleic acid-based screening tools, such as PCR, quantitative reverse transcription PCR, microarray, and next-generation sequencing, are now widely used to facilitate the detection, quantification, and gene expression of HPV viruses (Chirenje *et al.*, 2001). Next-generation sequencing is a high-throughput technique that has been shown to be a useful tool for HPV detection and genotyping. Although high-throughput next-generation sequencing is becoming the dominant technology in the discovery and experimental validation of HPV sequences, it may still be too expensive for practical routine use. Therefore, the molecular methods, including DNA-based assays and RNA-based assays may be most practical in terms of accuracy and speed. Currently, more than five such assays have been approved by the US Food and Drug Administration for HPV detection, including the Digene HC2 HPV DNA Test by Qiagen, the Cobas HPV test by Roche Molecular Diagnostics, and the Cervista HPV HR, the Cervista HPV 16/18, and the Aptima HPV (Rajikaart *et al.*, 2012)

Treatment of Cervical Cancer in African Countries

Women who are fortunate enough to access treatment for cervical cancer in Africa will most often receive radiation therapy, either with curative or more commonly, palliative intent. Based on GLOBOCAN data from 2002, Barton and colleagues (AMC, 2014) estimated that 55% (range 47-61%) of new cases of cancer diagnosed in Africa had an indication for radiotherapy. Radiation facilities are not available at all in many African countries (Chirenje *et al.*, 2001). In those countries where radiation facilities do exist, there is usually one machine per several million people—for example, in Nigeria in 2007 there were only 5 radiation facilities for a population of more than 150 million people (Iliyasu *et al.*, 2010). In most cases, radiation is delivered using cobalt machines that are a lot cheaper and easier to maintain than linear accelerators.

The median costs of radiotherapy using linear accelerators have been estimated at \$11 compared with \$4.87 per patient for cobalt machines (Arrossi *et al.*, 2010). A survey of 72 low- and middle-income countries found that 24 countries with populations greater than 1 million people did not have any radiotherapy service and the majority of these countries were in Africa (Anorlu *et al.*, 2004). Radiotherapy is still considered to be high-technology medicine in Africa and where facilities do exist e.g., South Africa, Ethiopia (one machine for a population of more than 60 million), Madagascar, Nigeria, Tanzania, Uganda, Sudan, Kenya, Ghana, Senegal, Zimbabwe, Cameroon. They are located in tertiary institutions or in the private sector and are often nonfunctional or poorly maintained. Palliation for women with advanced disease is also extremely limited in most African countries, where for instance, oral morphine is only available in 11 countries (WHO, 2014). It is estimated that 80% of cancer deaths require pain treatment lasting an average of 3 months. In 2008, the actual procurement of morphine and equivalent opioids reported by governments in Sub-Saharan Africa to the International Narcotics Control Board was 10% of the quantity required to treat terminally ill patients with cancer and HIV.

Screening of Cervical cancer

Historically, cervical cancer has been prevented by performing cervical cytology within the context of national screening programs, referring women with abnormal cytology for colposcopy and treatment and follow up thereafter. Initiating and sustaining such programs have proved to be prohibitively complex for most developing countries. In the past 15 years alternatives to cytology-based screening programs have been investigated in developed and developing countries.

The most tested approaches have been Visual Inspection with Acetic Acid (VIA) and HPV DNA testing either as primary screening tests, in combination with cytology or adjunctive to cytology. Thousands of women have participated in these trials. Cross-sectional studies have shown promising sensitivity of VIA compared with cytology (Skomedal *et al.*, 2012) and the sensitivity of VIA to detect high-grade cervical cancer precursor lesions and cervical cancer has varied from 49% to 96% and the specificity from 49% to 98%. However, many of these studies suffered from verification bias, where the true status of disease in test negative women was unknown. In a more recent publication, Sauvaget *et al.*, (2011) carried out a metaanalysis of 26 studies in which VIA was carried out on asymptomatic

women who underwent confirmatory testing and the disease threshold was CIN 2 plus. They report a sensitivity range of 80% (range 79-82%) and 92% specificity (range 91-92%) for VIA, with a positive predictive value of 10%. They conclude that in very low resource settings where the infrastructure for laboratory-based testing is not available, VIA is reasonable alternative to cytology. However, in more recent randomized studies VIA has carried out poorly in terms of test characteristics and prevention of disease. Denny and colleagues (Denny *et al.*, 2006) conducted a randomized screening trial to evaluate the safety, acceptability, and efficacy of screening women and treating those with positive tests without the intervention of colposcopy and histologic sampling. A total of 6,555 unscreened women, aged 35 to 65 years, underwent testing for high-risk types of HPV DNA and VIA, done by nurses in a primary care setting. This study found that HPV and treat "screen and treat" arm was associated with a 3.7-fold reduction in the cumulative detection of CIN 2 or greater by 36 months and VIA was associated with a 1.5-fold reduction. For every 100 women screened, the HPV and treat screen and treat strategy eliminated 4.1 cases of CIN 2 or greater compared with VIA and treat that eliminated 1.8 cases.

These data suggest that primary screening with HPV DNA, followed by treatment will be associated with a significant reduction in cervical cancer and cervical cancer precursors. HPV DNA testing however remains a laboratory-based test and current tests are not yet affordable in developing countries. The ideal test for HPV DNA detection would provide a result at the time of examination and screening that is a point-of-care test that has not yet been developed. New technologically more accessible and easier HPV DNA tests are being developed such as care HPV, which is able to detect 14 high-risk types of HPV in around 2.5 hours at a much lower cost compared with current commercially available HPV DNA tests. Other tests being developed include detection of high-risk E6/E7 mRNA that have the potential to greatly increase the specificity of HPV DNA testing and reduce the rate of overtreatment (Botha *et al.*, 2015).

Human Papilloma Virus Vaccine

HPV vaccination can reduce the risk of infection by the HPV types targeted by the vaccine. The Food and Drug Administration (FDA) has approved three vaccines to prevent HPV infection: quadrivalent (Gardasil, Merck & Co., Inc) and 9-valent (Gardasil, Merck & Co., Inc) vaccines, and HPV bivalent (Cervarix, GlaxoSmithKline Biologicals).

These vaccines provide strong protection against new HPV infections, but they are not effective at treating established HPV infections or disease caused by HPV (Richter *et al.*, 2014). All three vaccines prevent infections with HPV types 16 and 18, two high-risk HPVs that cause about 70% of cervical cancers and an even higher percentage of some of the other HPV-associated cancers (Thomas *et al.*, 2004). Gardasil also prevents infection with HPV types 6 and 11, which cause 90% of genital warts (Parkin *et al.*, 2008). Gardasil 9 prevents infection with the same four HPV types plus five additional high-risk HPV types (Haesebaert *et al.*, 2012). In addition to providing protection against the HPV types included in these vaccines, the vaccines have been found to provide partial protection against a few additional HPV types that can cause cancer, a phenomenon called cross-protection. None of the currently available HPV vaccines protects against all HPV infections that cause cancer, it is important for vaccinated women to continue to undergo cervical cancer screening. There could be some future changes in recommendations for vaccinated women. After a vaccine is licensed by the FDA, the Advisory Committee on Immunization Practices (ACIP), a group of 15 medical and public health experts that develops recommendations on how to use vaccines to control diseases in the United States, makes additional recommendations to the Secretary of the U.S. Department of Health and Human Services and the Director of the CDC on who should receive the vaccine, at what age, how often, the appropriate dose, and situations in which it should not be administered. ACIP has developed the following recommendations regarding HPV vaccination: 1. initiation of routine HPV vaccination at age 11 or 12 years (the vaccination series can be started beginning at age 9 years). 2. Vaccination of females aged 13 through 26 years and of males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose vaccination series. Males aged 22 through 26 years may be vaccinated. 3. Vaccination through age 26 years of men who have sex with men and for immunocompromised persons if not vaccinated previously. 4. When the HPV vaccine product previously administered is not known or unavailable or the provider is switching to use of Gardasil 9, any available HPV vaccine product can be used to continue or complete the series for females; Gardasil 9 or Gardasil may be used to continue or complete the series for males.

Widespread vaccination with Cervarix or Gardasil has the potential to reduce cervical cancer incidence around the world by as much as two-thirds, while Gardasil 9 could prevent an even higher proportion. In addition, the vaccines can reduce the need for medical care, biopsies, and invasive procedures associated with follow-up from abnormal cervical screening, thus helping to reduce health care costs and anxieties related to follow-up procedures. Awareness and health education campaigns are important and cost-effective interventions that should be implemented in developing countries prior to the initiation of vaccination and screening programs. Large-scale media campaigns offer substantial exposure, increasing public awareness and health education as well as enhancing public perception and response to campaigns to effect greater positive health behavior changes.

Challenges

Almost all African countries have the lowest ranked Human Development Index (HDI) and highest Human Poverty Indices. With a total population estimated in 2008 of 812 million (404 million men and 408 million women), only 7.2% were covered by medically certified causes of death and 8.3% by population-based registries. Moreover, access to anti-cancer therapies are very limited in almost all African countries and a World Health Organization (WHO) study in 2001 found that only 22% of African countries had access to anti-cancer drugs, compared with 91% in Europe (WHO, 2014).

Furthermore, there is a great shortage of trained healthcare personnel in Africa where there is also a "brain drain" or exodus of trained personnel to other more attractive continents. The reasons for the exodus of African healthcare workers are various and include: poor salaries in State institutions, lack of career advancement, poor institutional support in terms of infrastructure, equipment, staff, access to training, and modern technologies such as medical equipment, access to electronic libraries, internet, among others. Further, developed countries often offer many of these benefits that are lacking in many African countries. WHO estimated in 2006 that Africa has a needs based shortage of 818,000 healthcare professionals based on a country needing 2.28 healthcare professionals per 1,000 population) (AMC, 2014). Another studies estimated that for 31 African countries in 2015 the shortage of healthcare professionals will be 792,000 and the estimated wage bill necessary to eliminate the shortage is approximately \$2.6 billion (Botha *et al.*, 2015).

Adding to the complexity of the challenges facing Africa (ranging from environmental disasters to competing health needs, endemic civil strife, war, lack of safe water, and sanitation to name a few) has been the HIV/AIDS epidemic, where 70% of the world's cases of HIV are diagnosed (Auvert *et al.*, 2010). It has been well known that HIV infection increases the risk of developing certain cancers and Kaposi Sarcoma, Non-Hodgkin Lymphoma, and Cervical cancer have been classified as AIDS defining diseases since 1993 (Chirenje *et al.*, 2001). Women infected with HIV have an increased risk of being infected with HPV, of persistent infection with high-risk types of HPV, of developing cervical cancer precursors and are therefore considered at higher risk for cervical cancer. However, the expected increase in women diagnosed with cervical cancer in Africa during the HIV pandemic has not been convincingly observed, most likely due to most at-risk women dying from other opportunistic infections prior to developing cervical cancer or its precursors. From a developing country point of view introducing the HPV vaccine into the public health arena poses many challenges. The most obvious is cost, and the present price of both vaccines is unaffordable, although GAVI recently announced that it will subsidize the implementation of HPV vaccination in those countries that can show the ability to distribute the vaccine, and dependent on a price to be negotiated with the commercial companies (Botha *et al.*, 2015). However, cost is only one aspect. Firstly, few developing countries have established pubescent/adolescent health platforms or school health systems from which to vaccinate young girls (and possibly boys). This infrastructure will have to be created de novo in many countries and for this to happen, a great deal of political will, along with resource allocation, needs to be generated. Unfortunately, no studies have yet included infants, so neither vaccine will be approved for integration into the Extended Program for Immunization (EPI) that has been successfully introduced into many developing countries, with high coverage. EPI is believed to save 3 million young lives per year. It has been determined beyond any reasonable doubt that high-risk HPVs are etiological agents

for cervical carcinogenesis (AMC, 2014). This leaves clinicians and healthcare providers with the challenging tasks of establishing screening platforms for HPV diagnosis and following up when high-risk HPVs are detected. Scientists also continue to be challenged as they decipher the meaning of a high prevalence of HPV but a low number of cervical cancer cases, especially in areas or countries of concern, and determine the effects of diet, genetic predisposition, and environmental factors on the persistence of HPV infection and its progression to cancer. The challenges to both clinicians and scientists are more pronounced in developing countries that do not have established cervical cancer prevention strategies, infrastructure to support vaccination plans, health and awareness education programs, or methods of direct communication with the public. Dissemination of information is necessary to increase public awareness to overcome societal and cultural issues related to sexually transmitted infections. The cultural and religious sensitivities of some countries likely generate avoidance of HPV research and screening programs when there is a dominant belief that HPV infection is associated with unfaithful sexual behavior.

CONCLUSION

Cervical cancer and other HPV-related diseases remain global health problems. Cervical cancer is a preventable disease yet remains the commonest cause of cancer death among women in poor countries. Although advancement has recently been made in molecular detection and HPV prophylaxis, mortality from cervical cancer is still high in developing countries. Given that HPVs are known etiological agents for cervical cancer, implementation and support of national HPV immunization programs as well as cervical screening would lower the incidence of HPV and its associated diseases, improving the future health of girls and women throughout the world. Nevertheless, the strategy of recommending HPV immunization in developing countries awaits further rigorous evidence at the national level.

Conflict of interest

The researchers declare no any conflict of interest on the content and during the course of review.

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