



Foreword

Human Papillomavirus Infection and Related Cancers in Sub-Saharan Africa: Burden and Tools for Prevention

1. Introduction

Cancer of the cervix is the most common cancer among women in sub-Saharan Africa (SSA) [1]. Of the over half a million women who develop cervical cancer each year, nearly 85% reside in developing countries, where the majority of cervical cancer deaths occur [2]. Human papillomavirus (HPV) is an extremely common sexually transmitted virus that has a strong causal relationship with cervical cancer globally [3,4]. Recent studies exploring HPV genotyping in invasive cervical cancer confirmed the high prevalence of HPV16 and 18 in the African region, and confirmed that these are the most common HPV types identified [5,6].

The documented regional variations in cervical cancer incidence in Africa are associated with a number of factors, including differences in the underlying prevalence of high-risk HPV infection in women, as well as disparities in the availability of effective cervical cancer diagnosis, treatment, and prevention. Historically, it has proven impossible to initiate and sustain cytology-based cervical cancer screening programs in SSA, resulting in a very high incidence of the disease, late presentation, and high mortality. With the introduction of primary prevention of HPV infection through vaccination, a new paradigm for cervical cancer prevention has been created; however, the use of and widespread implementation of the prophylactic vaccines pose many challenges in the context of SSA, which will be addressed in this Regional Report. The countries considered in this Regional Report are listed in Fig. 1.

2. Cervical Cancer and sub-Saharan Africa

Sub-Saharan Africa accounts for 14.5% of the world population and almost all of the 54 countries are in the lowest rank of the Human Development Index (HDI) and highest Human Poverty Indices (HPI) [7]. Africa has a population of more than 250 million women aged 15 years and older who are at risk of developing cervical cancer. Current estimates are that in 2008, there were 75,000 women diagnosed with cervical cancer in SSA and over 50,000 women died from the disease [1]. In his evaluation of 341,658 cases of cancer survival in developing countries, Sankaranarayanan *et al.* [8] found that the 5-year survival was lowest among Africans. Moreover, access to cutting edge cancer management (anti-cancer therapies) is very limited in almost all African countries, with only 22% of African countries having access to such therapies (e.g., chemotherapy, radiation or surgical oncology), compared to 91% in Europe [9,10]. Furthermore, there is a shortage of cancer management experts in most African countries. This is not

unrelated to the fact that there are few facilities for training in cancer diagnosis and management in SSA and those that exist are found mainly in Northern and Southern Africa. The lack of trained personnel is exacerbated by the well known 'brain drain' of trained health care personnel from Africa to more attractive opportunities in countries outside of the African continent. Adding to these challenges facing SSA are environmental disasters, endemic civil strife, war, lack of safe water and sanitation and competing health needs such the human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS) epidemic, tuberculosis, malaria and maternal mortality to name a few.

The immense disease burden and fragile health care systems are embedded in the broader context of poverty, under-development, poor governance, political instability, internal conflict, and insecurity of lives and properties. Several African countries have been faced with sociopolitical challenges since the post-colonial era and this has adversely affected all sectors of the economy. For instance, food insecurity, poverty, housing, unemployment, and a host of other necessities for human survival have remained an albatross in many countries in Africa. On top of these mundane necessities, the continent has suffered setbacks from poor governance, high levels of corruption and various layers of internal conflict and all of these have made sustainable development a mirage over the years.

However, the current World Bank report shows that Africa, despite her numerous problems, is beginning to enjoy international investment opportunities and better fiscal policies. These new developments have improved the annual gross domestic product growth rate of some African countries by about 5 percent in the last 7 years and this has been forecasted to increase further in the next decade. Over the same period, inflation has either stabilized or reduced in many countries, with only a handful having some increase, all related to increasing political stability. The net effect of an improved macro-economy will favor development, including that of the health care sector. A prosperous Africa will have the resources and capacity to focus on cutting edge medical services, such as cancer management and prevention [11].

3. Epidemiology of HPV in Africa

Genital HPV infection is a commonly diagnosed sexually transmitted infection (STI) in young, sexually active populations worldwide [12,13]. Most sexually active women will acquire HPV infection over a lifetime, albeit most will be transient infections with no significant clinical consequences. Infections with oncogenic types of HPV represent 50–75% of all HPV infections [13].



Fig. 1. Countries included in the Regional Report “Comprehensive Control of HPV Infections and Related Diseases in the Sub-Saharan Africa Region”.

List of included countries: Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Cape Verde; Central African Republic; Chad; Comoros; Congo; Côte d'Ivoire; Democratic Republic of Congo; Djibouti; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea Bissau; Kenya; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mauritius; Mayotte; Mozambique; Namibia; Niger; Nigeria; Réunion; Rwanda; Saint Helena; Senegal; Seychelles; Sierra Leone; Somalia; South Africa; South Sudan; Sudan; Swaziland; São Tomé and Príncipe; Togo; Uganda; United Republic of Tanzania; Zambia; Zimbabwe.

In SSA, about 22.5% of women in the general population are estimated to harbor cervical HPV infection at any given time, and 70% of invasive cancers are attributed to HPV types 16 and 18 [5,6,14,15]. There is considerable regional variation in cervical cancer incidence and mortality in Africa with the highest age-standardized incidence rates (ASIR) found in Eastern (34.5/100,000 women), Western (33.7/100,000), Southern (26.8/100,000) Africa compared to Middle Africa (23/100,000) and Northern Africa (12.1/100,000) [1]. The documented regional variations in cervical cancer incidence have been associated in part with the differences in underlying prevalence of high-risk HPV types. Consistently, of women tested for HPV infection in Africa, the highest prevalence (adjusted estimates) was found in Eastern Africa, where 751 women with normal cytology had been tested and 33.6% had HPV infection; corresponding values in other regions were as follows: 19.6% of 4,469 cases analyzed in Western Africa; 17.4% of 2,485 cases analyzed in Southern Africa; and 9.2% of 863 cases analyzed in Northern Africa (there was no data for Middle region) [14,15]. In this Regional Report we will thoroughly review the burden of HPV and related diseases in the region (see de Vuyst H *et al.* Vaccine, this issue [16]).

4. Additional factors affecting burden of HPV infection and associated diseases in Africa: The HIV/AIDS pandemic

HIV/AIDS infection has had a major impact on the burden of HPV associated diseases. The United Nations estimated that in 2009, 22.5 million of the 33.3 million individuals living with HIV/AIDS worldwide resided in SSA, representing 67% of the global burden of HIV, and 72% of the world's HIV-related deaths occurred in SSA [17]. It is now well known that the HPV infection is more common in HIV-positive individuals, including persistent infection with high-risk types, multiple infections, and higher incidence of anogenital cancers and their precursors [18–21]. The HIV pandemic has had

a major impact on disease burden in SSA, and it has also diverted considerable health resources away from diseases such as HPV-related cancers and benign manifestations of HPV. However, there are encouraging signs that the epidemic is stabilizing and large numbers of men and women are receiving effective antiretroviral therapy, including in SSA. The impact of antiretroviral therapy on HPV infection in women is not clear from the published literature, but it is well documented that women who are treated with antiretroviral therapy will live longer and therefore increase their risk of developing cervical cancer over time.

5. Prevention and treatment of cervical cancer - the available options

The worldwide burden of HPV infection suggests that it is of significant public health importance. Preventive strategies need to be holistic. The natural history of HPV infection allows for intervention to either prevent HPV infection *de novo* with primary prevention or through the detection of intraepithelial cancer precursors prior to the development of invasive disease, so-called secondary prevention, followed by appropriate treatment.

The most effective primary prevention strategy against HPV infection is the use of prophylactic vaccination, although lifestyle modifications are also of value and should be promoted. These nonspecific interventions will promote greater sexual and general health and at the same time reduce the risk of HPV infection within the population [22]. Health promotion strategies, such as sexuality education, lifestyle modification, campaigns against smoking, stopping early initiation of sexual debut and encouraging the use of condoms, should complement the other preventive strategies.

Historically, secondary prevention of cervical cancer relied on cytology and women with abnormal smears were sent for colposcopy and treatment and subsequent follow-up. This approach has proven far too expensive and challenging to initiate or sustain in SSA. In the past 15 years, a large number of studies have evaluated alternative approaches to cytology. Visual Inspection with 3–5% dilute acetic acid (VIA) and HPV testing are the two alternative screening methods that have been most studied [23]. These studies are heterogeneous in design, many were cross-sectional and they had varying degrees of verification of the final diagnosis. VIA is particularly suitable to low-resource settings; however, its efficacy in reducing cervical cancer is likely to be significantly lower than HPV testing. Two randomized controlled trials of screening and treating women with positive tests have shown significant reduction in cervical cancer precursors and cervical cancer in women screened with HPV and treated if positive, compared to VIA and cytology [24,25]. In this Regional Report we will address the infrastructure needed for vaccine implementation and for different screening alternatives and also the ongoing trials evaluating different strategies in the region (see Sankaranarayanan R *et al.* Vaccine, this issue [26], Adefuye PO *et al.* Vaccine, this issue [27]).

6. Prophylactic vaccines

Vaccination is now a recognized primary prevention approach against HPV infection and at the moment, there are two available vaccines namely; Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) - a bivalent vaccine effective against HPV16 and 18, and Gardasil® (Merck & Co., Whitehouse Station, NJ, USA) - a quadrivalent vaccine effective against HPV6, 11, 16, and 18. Both vaccines have been tested in randomized controlled trials and have been shown to be safe, immunogenic, and efficacious at preventing disease associated with HPV types found in the vaccines [28–31]. The two vaccines are currently licensed for use by many countries of the world. These vaccines have the potential to prevent over 70%

of cervical cancers in addition to the effects of the quadrivalent vaccine on reducing genital warts.

Prophylactic vaccination has been introduced in Rwanda, which became the first country in Africa to introduce a national prevention program for cervical cancer. The program includes HPV vaccination for girls aged 12–15 years and HPV testing for women between ages 35 and 45 years [32]. This has been made possible by a 3-year donation of 2 million doses of the quadrivalent vaccine by the manufacturer (Merck & Co., Whitehouse Station, NJ, USA) and 250,000 HPV screening tests by diagnostics company Qiagen (Qiagen Gaithersburg, Inc., MD, USA). After 3 years, Merck have agreed to provide Rwanda with access to a discounted price for the vaccine. Moreover, the quadrivalent vaccine has received World Health Organization (WHO) prequalification and is approved for use in 112 countries, 23 of which are Global Alliance for Vaccines and Immunization (GAVI)-eligible. GAVI have officially agreed to fund HPV vaccination depending on a price to be negotiated with manufacturers of both vaccines [33].

PATH (Program for Appropriate Technology in Health) has, together with Ministries of Health of Uganda, Peru, India and Vietnam, explored vaccine acceptance and refusal [34]. The research was carried out in two phases; during formative research, each country's sociocultural environment and the capacity of the health system were investigated before introducing HPV vaccination. With the information obtained through this phase, the demonstration projects were designed, and these operated for 1–2 years in each country. In Uganda [35], 69 health facilities and 38 schools participated in the demonstration project. In 2009, 88.9% of vaccinated girls received all three doses. In the school-based program in Uganda, 6% of girls were partially vaccinated and 4% were not vaccinated at all. In the school-based programs, girls were selected by grade, but in what was known as the Child Days Plus program (also school-based), in which eligibility was determined by age rather than grade at school, 25% of 10 year-old girls did not receive any vaccine, while 21% and 13% received fewer than three doses in the first and second years, respectively. This study illustrates clearly that the many apparent obstacles to introduction of HPV vaccination in poor countries are possible to overcome and to achieve very high coverage using school-based systems for administration.

7. Challenges and prospects

Adding a new vaccine to a national immunization program requires consideration of the avertable burden of disease, relative value of the vaccine compared with alternative uses of resources, affordability, likelihood of public acceptability, political support for a vaccine against a sexually transmitted disease, and feasibility of achieving high coverage in young adolescent girls. The question of how to use screening in the context of vaccination adds an additional layer of complexity. Essentially two groups need intervention: young girls for prophylactic vaccination (and possibly boys if resources allow) and screening for older women (>30 years) who have already acquired HPV infection and its sequelae.

Creative and innovative ways of providing both interventions need to be developed and the study by PATH clearly shows that with careful planning and working with national governments, this is feasible. Similarly, the program in Rwanda, which is designed to link primary prevention with vaccination and secondary prevention by using HPV testing, is another example. For such programs, however, to be successful and sustainable, a reliable funding structure needs to be in place.

Predicting and monitoring the population-level impact of a cervical cancer prevention program is particularly complex, as the time course from infection to disease spans several decades, the best available data are based on intermediate endpoints.

Decision-makers need information on the relative value of investments in vaccination versus screening, on the synergies that might be realized with the use of both modalities, and on the “best bets” for a sustainable cervical cancer prevention program. Furthermore, immunization policy recommendations made by the WHO, and financing coordination mechanisms such as the GAVI Alliance and Pan American Health Organization Revolving Fund, require information on the financial cost requirements and cost-effectiveness of adolescent HPV16 and 18 vaccination. In this Regional Report, we show results of model-based impact and cost-effectiveness analyses of cervical cancer prevention using data from 46 countries in SSA, and particularly from Uganda and South Africa (see Kim JJ *et al.* Vaccine, this issue [35]).

The African Union published a document on Africa Health Strategy: 2007–2015 after the Third Session of the African Union Conference of Ministers of Health, Johannesburg, South Africa 9–13 April 2007 [36]. The subject of this conference was ‘Strengthening of Health Systems for Equity and Development in Africa’. This document clearly recognizes the impact of non-communicable diseases, including cancer, and states that there is good evidence that investing in reducing the burden of disease will have a significant impact on economic and development indicators. It also points out that Africa is not on track to meet many of the Millennium Development Goals (www.un.org) and that life expectancy on the continent has been reduced to 52 years, due to many factors, including HIV/AIDS. The mission of the African Union is to ‘build an effective, African driven response to reduce the burden of disease and disability, through strengthened health systems, scale-up health interventions, inter-sectoral action and empowered communities’. We strongly support this mission and, if accomplished, will have a major impact on reducing the burden of HPV-related disease in Africa (see Denny L *et al.* Vaccine, this issue [37]).

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