

## **Review Article**

### **Human papillomavirus related cervical cancer and anticipated vaccination challenges in Ethiopia**

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#### **Abstract**

Cervical cancer is the leading cause of cancer deaths among women in Ethiopia. This may be due to the high prevalence of high-risk human papillomavirus (HR-HPV) genotypes in the population. So far, few studies have been done that showed the presence of HR-HPV genotypes. The HR-HPV-16, -18, -52, -56, -31 and -58 were the most common genotypes reported in Ethiopia. The introduction of HPV vaccines in Ethiopia is likely to go a long way in reducing cervical cancer deaths. However, there are few challenges to the introduction of the vaccines. The target population for HPV vaccination is at the moment not well-defined. Besides, the current HPV vaccines confer only type-specific (HPV-16 and -18) immunity, leaving a small proportion of Ethiopian women unprotected against other HR-HPV genotypes such as 52, 56, 31 and 58. Thus, future HPV vaccines such as the nonavalent vaccine may be more useful to Ethiopia as they will protect women against more genotypes.

**Keywords:** Cervical cancer, Human papillomavirus, Vaccination challenges, Ethiopia.

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## Introduction

The human papillomaviruses (HPVs) are a big group of highly ubiquitous, small, non-enveloped double-stranded circular DNA viruses that infect cutaneous and mucosal surfaces and induce squamous epithelial tumors (warts and papillomas) in many different anatomical sites. <sup>(1)</sup> More than 140 HPV genotypes have been identified. <sup>(2, 3)</sup> They are classified into high-risk (HR), probable high-risk (PHR) and low-risk (LR) types. <sup>(4)</sup> Approximately 50 of these genotypes are known to be oncogenic or HR types, which cause cancer of the cervix. <sup>(2,3,5)</sup> Of these, fifteen HR-HPV genotypes: HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, and -82 cause more than 95% of all cases of cervical cancer (CC). <sup>(5, 6)</sup> HPV-16 is the type that is responsible for 50-60% of all CC worldwide <sup>(7,8)</sup> and HPV-18 is followed by an incidence of 10-20%. <sup>(7)</sup> Thus, HPV-16 and -18 are considered as the types responsible for approximately 70% of CC worldwide. <sup>(9-11)</sup> Currently, public knowledge of HPV and CC is poor in Ethiopia. <sup>(12, 13)</sup>

## The burden of cervical cancer in Ethiopia

Ethiopia has a population of 27.19 million women ages 15 years and older who are at risk of developing CC. <sup>(14)</sup> Nationally, the Ministry of Health, Maternal, Newborn and Child Health (MNCH) directorate has the primary responsibility of providing health care services to the majority of the population, including maternal and reproductive health services such as prevention and treatment of CC. CC is the second most common cancer among women globally and the leading cause of cancer deaths in women in low income countries. <sup>(6,15)</sup> It causes 530,000 new cases and 280,000 deaths annually in adult women, of which 88% occur in low income countries where access to pre-cancer screening and treatment is limited. <sup>(16, 17)</sup> By 2020, it has been estimated that CC will be diagnosed in over 665,035 women worldwide, and 357,852 will die as a result. <sup>(18)</sup> The incidence and mortality in sub-Saharan Africa are among the highest in the world and accounts for over 70% of the global CC burden with 70,000 new cases annually. <sup>(18,19)</sup> In Ethiopia, CC is an important reproductive health problem and is a major cause of mortality and morbidity in women than any other cancers. <sup>(14)</sup> Its incidence is 35.9 per

100,000 women with 7619 annual number of new cases and 6081 deaths every year. <sup>(12, 14, 20)</sup> Thus, CC ranks as the second most frequent cancer among women in Ethiopia. Despite this fact, very few women receive screening services. <sup>(20)</sup>

## HPV genotypes among women Ethiopia

In Ethiopia, few studies have been done to evaluate high-risk HPV genotypes present in women. Firstly, a cross-sectional study (n= 537) was done to assess the cervical HPV prevalence, genotype distribution and associated correlates among female hospital outpatients in Gurage zone, rural Ethiopia. <sup>(21)</sup> Using the second generation Hybrid Capture assay (HC2), HPV DNA was detected in 17.3% of any of the cervical samples. The prevalence of any of the HR-HPV genotypes: HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -53, -56, -58, -59, -66, -68, -73 and -82 was 16%. Among HC2 HR-HPV positive infections (n = 86), the most common genotype was HPV-16 (24.4%), followed by HPV-52 (11.6%), -56 (10.5%), -31 (10.5%), -51 (7.0%), -35 and -39 (both 5.8%), -45, and -68 (both 4.7%), and -18 (3.5%). The LR-HPV genotypes: HPV-6, -11, -43, -70, and -73 were detected in 4% of the samples. Overall, 17 different HR and 3 different LR-HPV genotypes were identified, amounting to a total of 92 HR or LR infections. In this study, multiple infections with LR and/or HR-HPV genotypes were found in 23.7% of the cases. In this group, 49 (53.3%), 19 (20.7%) and 12 (13.0%) HPV infections were attributed to species  $\alpha 9$  (HPV-16, -31, -33, -35, -52, -58, and -67),  $\alpha 7$  (HPV-18, -39, -45, -59, -68, and -70) and  $\alpha 6$  (HPV-53, -56, -66), respectively, based on their phylogenetic classification. <sup>(22)</sup> Furthermore, in this group, 24 (26.1%) and 52 (56.5%) HPV infections would be targeted by a current bivalent (types 16 and 18) and an impending next generation nonavalent (types 6, 11, 16, 18, 31, 33, 45, 52 and 58) HPV vaccine, respectively. <sup>(23)</sup>

In a second study in Addis Ababa, the presence of HPV genotypes in cervical tissues collected from Ethiopian women (n= 170) who had CC was conducted using a line probe assay. <sup>(24)</sup> Of all the women studied, 93% had HPV DNA in cervical tissues. In this study, HPV-16 was the most prevalent genotype and was found in 91.2% of the cervical samples.

HPV-52 was found in 25.5% of the samples followed by HPV-58 (22%), HPV-18 (20.8%), HPV-45 (12.1%), HPV-33 (7.4%), and HPV-31 (6.7%). According to this study, HPV-52 was the second commonest genotypes found in Ethiopia and is not covered by the current two HPV vaccines on the market.

In a third study with 98 Ethiopian women with cervical dysplasia in Jimma, HPV genotypes were also investigated.<sup>(25)</sup> The HPV DNA using a Qiagen FFPE kit (Qiagen, Venlo, The Netherlands) was detected in 67.1% of the samples. Of these, HR-HPV types: HPV-16 (55.7%), -18 (8.2%), -56 (8.2%), -45 (4.1%), -39 (2.5%), -52 (1.6%), -31 (1.6%), -35 (1.6%), -58 (0.8%), -33 (0.8%), and -59 (0.8%) caused severe pathology as single and/or multiple infection.

Another study was conducted to determine cervical HPV prevalence with 189 women attending Attat hospital from rural Ethiopia.<sup>(26)</sup> The HPV DNA using the Digene HPV test was detected in 16% of the patients. Of the cases, the proportion of HPV high risk types was 13.2%.

A pilot study was conducted to determine the prevalence and genotypes of HPV in twenty Ethiopian women, clinically diagnosed to have cervical neoplasia in Addis Ababa.<sup>(27)</sup> Based on a reverse line blot hybridization assay, the most frequent genotype identified was HPV-16 (13/20). Mixed infection of HPV-16 with HPV-33, -35, -45 and, -58 was detected from other four study participants. Overall, these few studies mentioned above highlight the need to have HPV vaccines in Ethiopia that will cover the most prevalent genotypes. Thus, individuals living in different geographical localities should receive vaccines based on the specific genotypes circulating in the area and a vaccine targeting HPV-16, -18, -52, -56, -31, and -58 may be optimal for the control of CC in Ethiopia.

### **Risk factors of cervical cancer in Ethiopia**

Although HPV infection is not sufficient by itself to cause cervical cancer (CC), the coexistence of various viral and/or host factors that allow the transition from infection to cancer is necessary.<sup>(27)</sup> The viral factors include the genotype, viral load, persistency and viral DNA integration with the host cell genome.<sup>(28)</sup> Studies indicate persistent infection by HR-

HPV genotypes are the major cause of CC.<sup>(5,6)</sup> The host factors include age, an early start to sexual relations, low socio economic status, multiparity, multiple sexual partners, oral contraceptive use, smoking and a history of sexually transmissible diseases such as herpes simplex, *Chlamydia trachomatis* and acquired immunodeficiency.<sup>(4, 29, 30)</sup> Other factors such as race and ethnicity are also important risk factors of CC.<sup>(11)</sup> African women are at a higher risk of developing CC than their Caucasian counterparts.<sup>(31)</sup>

In Ethiopia, few studies have been done to assess the risk factors of CC among women. Firstly, a hospital-based cross-sectional study was conducted in 448 HIV-positive Ethiopian women from Southern Nations, Nationalities and People Region (SNNPR) to assess the prevalence and risk factors associated with precancerous cervical cancer lesion among HIV-infected women.<sup>(32)</sup> In this study, late initiation of highly active antiretroviral treatment, lifetime history of sexually transmitted disease and multiple sexual partners were factors associated with precancerous CC lesion.

In a second cross-sectional study (n= 537) was done to assess the cervical HPV prevalence, genotype distribution and associated correlates among female hospital outpatients in Gurage zone, rural Ethiopia.<sup>(21)</sup> The finding from this study indicated that non-married relationship and widowhood, increasing number of lifetime sexual partners, human immunodeficiency virus infection and non-traditional housing type was significantly associated with HR-HPV infection. In a third community based cross-sectional survey<sup>(12)</sup> was conducted to assess the knowledge of 633 Ethiopian women in Gondar about CC and associated factors reported that of all the respondents, 495 (78.7%) of them had heard about CC and only 195 (31%) of them were knowledgeable about the disease.

A qualitative study<sup>(13)</sup> involving focus group discussion of men, women, and community leaders in the rural settings of Jimma Zone, southwest Ethiopia on health seeking behavior for CC revealed that participants had a very low awareness of CC.

Another cross-sectional study<sup>(15)</sup> conducted to assess the diagnostic and therapeutic facility for CC in Addis Ababa public health institutions involving 3 specialized hospitals, 5 general

hospitals and 26 health centers reported that: twelve of the health centers (46%) had general practitioners ranged from one to two and all the health centers were served by health officers and nurses. There was one hospital with no gynaecologist. Seven hospitals had no pathologist and thus could not give histopathology services. The number of general practitioners in the hospitals ranged from 12 to 200. No provision was found with the basic diagnostic and therapeutic trainings such as Visual Inspection with Acetic acid (VIA), Visual Inspection with Lugol's Iodine (VILI), colposcopy, cryotherapy, loop electrosurgical excision procedures (LEEP), and cone biopsy. Only five of the pathologists working in one of the tertiary hospitals were trained on Pap smear. CC screening and related therapeutic services like cryotherapy and LEEP were not offered in all of the public institutions. Only one hospital was found to provide histopathology service performing Pap smear and biopsy for diagnostic purpose. Radiotherapy service was available only in one of the hospitals. Moreover, none of the institutions have a cancer register. However, all the institutions had enough number of rooms to accommodate the future introduction of CC diagnosis and treatment services.

In general, low level of awareness and health seeking behavior, lack of effective screening programs, overshadowed by other health priorities (such as acquired immune deficiency syndrome, tuberculosis and malaria) and insufficient attention to women's health were the possible factors for the observed higher incidence rate of CC.

### HPV vaccination challenges in Ethiopia

Implementation of a primary prevention vaccine is likely to have a significant impact on the burden of CC, particularly where screening is non-existent or limited in scale or of poor quality. (33) Two prophylactic HPV vaccines are commercially available to prevent infection with the HPV, the primary cause of CC. (33-35) At least 110 countries have licensed the bivalent HPV vaccine (Cervarix™) that protects against HPV genotypes 16 and 18 and over 120 countries have licensed the quadrivalent vaccine (Gardasil™) that protects against HPV genotypes 6, 11, 16 and 18. (36) The primary target group for these vaccines is girls prior to sexual debut. (37) In Ethiopia, considerations

are now being made to vaccinate girls against HPV using the two recently licensed subunit vaccines, HPV2 and HPV4. Although the two vaccines can be very helpful in reducing CC mortality in the long-term, their introduction in Ethiopia is likely to meet several challenges. Since the two vaccines only target HPV genotypes 6, 11, 16, and 18, the vaccines may not be effective in protecting against other HPV genotypes that are common in Ethiopia. Studies indicated that the high risk HPV genotypes: HPV-52, (21,24) -56, (21,25) -58 (21), and -31 (21) were also found in a substantial proportion of women with CC in Ethiopia. Thus, women infected with such genotypes will not be fully protected from getting CC by the current vaccines. This challenge has also been observed in several other sub-Saharan African countries such as Kenya, (38) Sudan, (39) Benin, (40) Equatorial Guinea, (41) Tanzania, (42) Zambia, (43) Cameroun, (44) Mozambique, (45) and Senegal (46) where other non-16 and 18 genotypes were prevalent. Although cross-protection against multiple genotypes of the current HPV vaccines may occur, it is not absolute. (47, 48) The challenge, therefore confirms the importance of developing HPV vaccines for genotypes common in sub-Saharan African women. The new HPV nonavalent vaccine may be more useful in Ethiopia as it may protect against more HPV genotypes. (23)

Moreover, the target group for HPV vaccination has not yet been defined in Ethiopia. Generally, girls should be targeted for HPV vaccination before the onset of sexual activities. (37, 49) However, the age of sexual debut among Ethiopian girls is not known.

Despite the marketing of HPV vaccines as the solution to CC, the licensing of the vaccines has not translated into universal equitable access. (50) In Ethiopia, vaccine implementation for vulnerable girls and women faces multiple barriers that include high vaccine costs, inadequate delivery infrastructure, and lack of community engagement to generate awareness about CC and early screening tools. (12,13,15,32) Thus, for HPV vaccines to work as a public health solution, the quality-assured delivery of cheaper vaccines must be integrated with strengthened capacity for community based health education and screening.

## Conclusion

Cervical cancer caused by high-risk HPV genotypes accounts for substantial morbidity and mortality worldwide. In Ethiopia, studies on the HPV genotype distribution among women with cervical dysplasia are very limited. Moreover, cervical screening services, public knowledge of HPV and cervical cancer is also poor. Besides, the target population for HPV vaccination is at the moment not well-defined. Despite these limitations, the government is planning to introduce HPV vaccines in girls. Therefore, nationwide large-scale studies shall be conducted on the HPV genotype distribution among women with cervical dysplasia before introduction of the HPV vaccines in the country. Moreover, the age at which girls start sexual activities shall be determined.

## Competing interests

The author declares no competing interest.

## Authors' contributions

The author contributed to the writing of the manuscript and read and approved the final manuscript.

## Acknowledgements

The author acknowledges support from the Departments of Medical Microbiology and Immunology, College of Health Sciences, Mekelle University, Ethiopia.

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