



## Cervical cancer screening and treatment in Uganda



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### ABSTRACT

Cervical cancer is the leading cause of cancer death among women in Uganda. Given the high prevalence of genital human papillomavirus infection, the current unavailability of radiotherapy, and the absence of a national cervical cancer prevention and control program, these deaths will likely increase. Efforts to organize an effective cervical cancer screening and treatment program will require adequate financial resources, the development of infrastructure, training needed manpower, and surveillance mechanisms of the targeted women. Screening with VIA (visual inspection with acetic acid) and HPV DNA testing on self-collected samples with processing at a specific site could, for the first time, make national, large-scale population-based screening feasible in Uganda. Combining screening efforts with timely treatment of all screen positives for HPV infection can prevent progression to invasive cervical cancer. To date, this is the most effective intervention in closing the current prevention gap.

Training of health professionals, ongoing construction of new radiotherapy bunkers, and opening of regional centers are all geared towards improving cervical cancer care in Uganda. The Uganda Cancer Institute Bill establishes the Institute as a semi-autonomous agency mandated to undertake and coordinate the prevention and treatment of cancer. Its implementation will be a milestone in cervical cancer prevention and control. However, execution will require political will and an increase in domestic and international investment.

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### 1. Introduction

Cancer of the cervix uteri is the fourth most common cancer among women worldwide and the leading cause of gynecologic cancer death in low- to middle-income countries. In 2012, there were an estimated 527,624 new cases and 265,672 deaths due to cervical cancer. 85% of these deaths occurred in sub-Saharan Africa (Ferlay et al., 2013). In Uganda, cervical cancer is the number one cause of cancer-related death in women. The WHO estimates that in 2014 approximately 3915 Ugandan women were diagnosed with cervical cancer and that

2160 died from the disease (ICO Information Centre on HPV and Cancer (HPV Information Centre), 2016).

A 33.6% prevalence of human papillomavirus (HPV) among women in Uganda combined with low screening uptake has resulted in the country having one of the highest cervical cancer incidence rates in the world of 47.5 per 100,000 per year (ICO Information Centre on HPV and Cancer (HPV Information Centre), 2016). Furthermore, in our experience at the Uganda Cancer Institute (UCI), 80% of the women who present with cervical cancer have advanced stage disease. In order to prevent deaths due to cervical cancer in Uganda, a multidisciplinary approach must be taken. Of utmost importance is the effective identification and treatment of cervical precancerous lesions and early disease. Unfortunately, the baseline lifetime screening rate for cervical cancer in Uganda is reported to be between 4.8% and 30% (Campos et

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al., 2016; Ndeje et al., 2016). Data suggests that increasing baseline screening coverage in a lifetime leads to comparable or better cancer risk reductions than a multiple screenings in a single lifetime with lower baseline coverage in Uganda (Campos et al., 2016). Therefore, it has been suggested that increasing access to those previously un-screened women should be of priority.

The Ministry of Health in Uganda has a division dedicated solely to Non-Communicable Diseases (NCDs). This Division is charged with managing the healthcare delivery for all NCDs, including cancer in the country, and has been fairly successful in implementing a palliative care program. It has also played a significant role in developing a contemporary strategic plan for cervical cancer prevention and control in Uganda. A national HPV vaccination program for prevention of cervical cancer was initiated and is currently ongoing. However, efforts by the Ministry of Health have been uncoordinated and with limited success.

The UCI is the only center for comprehensive cancer care in Uganda. In November 2016, the Prime Minister, after approval from Parliament, passed the UCI Bill. The Bill establishes the UCI as a semi-autonomous agency apart from the government and mandates the Institute to undertake and coordinate the prevention and treatment of cancer and cancer related diseases as well as to conduct cancer research in Uganda. Specifically, the UCI Bill includes provisions for human resources, infrastructure, medications, and financing, and is anticipated to greatly impact cancer prevention and control in Uganda. Increased autonomy of the UCI will aid in more effective implementation of cervical cancer screening, treatment and prevention programs in Uganda.

## 2. Screening, treatment and prevention of cervical precancers

Over the past 50 years, use of the Pap test to screen for early signs of disease has resulted in a dramatic decline in cervical cancer deaths in developed countries. Uganda, like most developing countries, lacks the infrastructure and trained personnel needed for a technician-dependent, multi-visit testing approach. Scarce health care resources in Uganda should be directed toward cost-effective prevention strategies for which quality can be assured. Studies have shown that in low-resource settings screening using either a single round of HPV testing or visual inspection with acetic acid (VIA), followed by immediate treatment of precancerous lesions has the greatest impact and is the most cost-effective cervical cancer prevention strategy (Sherris et al., 2009). For countries that have the resources, the WHO recommends triaging screening with HPV testing first, followed by VIA to identify women that can be treated immediately with cryotherapy.

Cervical cancer screening guidelines in Uganda are based on a “See and Treat” algorithm (Ministry of Health & Strategic Plan for Cervical Cancer Prevention and Control in Uganda 2010–2014, 2010). The target age group is women 25 to 49 years old. Women in Uganda are screened using VIA and those with positive findings and eligible precancerous lesions are treated using cryotherapy. Screening occurs every 3 years for HIV-negative women and annually for HIV-positive women. Midwives and nurses are the primary providers of cervical cancer screening as well as treatment. Unfortunately, screening in Uganda is erratic, opportunistic, and in some places absent due to a lack of resources or lack of financial commitment. This translates to a staggeringly low screening uptake of about 4.8% in rural Uganda (Ndeje et al., 2016).

After VIA, women in Uganda with positive lesions should be routinely treated with cryotherapy according to national guidelines. Very few women undergo colposcopic-guided biopsy when invasive disease is suspected. Colposcopy is only routinely offered at three high-level government facilities, making this procedure inaccessible to most women. Additionally, there is only one government pathology laboratory that processes these specimens and a limited total number of pathologists in the country. It takes weeks to months for women to obtain their biopsy results and pathology services add an additional cost. Thus, we do not advocate for this step in routine work-up of precancerous cervical lesions in Uganda.

Cryotherapy has been shown to be a safe, effective treatment for the majority of cases of cervical precancers and is the major mode of treatment in Uganda. For cases in which cryotherapy is not appropriate, loop electrosurgical excision procedure (LEEP) and cold knife cone are performed by physicians and limited to higher-level facilities. Unfortunately, cryotherapy equipment is expensive and only two suppliers in Uganda, both within the capital city (Kampala), source the necessary materials. Due to these restraints, hubs that provide cryotherapy services have been created that treat women referred from associated health posts and clinics that offer VIA. Sometimes outreaches with mobile cryotherapy services are offered when sufficient cases have accumulated at a facility or in a community following mass mobilization (Jeronimo et al., 2014). Referral hubs create a delay between screening test and treatment, and thereby increase the chance of loss to follow-up. Perhaps, the use of new ablative technologies such as cold coagulation which can be powered by electricity as well as rechargeable batteries and does not involve the use of external gas supplies might ensure more affordable treatment of precancerous lesions.

Clearly, there is a need to develop a feasible, but comprehensive national cervical cancer control program. Previously established and accepted guidelines provide valuable technical and political support for program planning, but do not address practicalities of implementation (Ministry of Health & Strategic Plan for Cervical Cancer Prevention and Control in Uganda 2010–2014, 2010). One national prevention initiative involves HPV vaccination for girls and young women in 14 districts in Uganda, which has been met with some success (Gulland, 2012). If combined with a well-organized screening program, this could significantly reduce deaths due to cervical cancer.

Program for Appropriate Technology in Health's (PATH's) start-up demonstration project reported that HPV DNA collected from the vagina is more sensitive for detection of cervical precancers than VIA or the Pap test. Several studies have showed that women can be taught to use a soft brush to swab the vaginal wall near the cervix and to gather samples themselves (Jeronimo et al., 2014). In Uganda, vaginal sampling, including self-sampling, is an attractive option. Many Ugandan women prefer a female provider for pelvic exams, which is not always available. Vaginal self-sampling for cervical screening is desirable for many women in Uganda as it circumvents a male provider and obviates the anxiety and potential perceived discomfort of a pelvic exam. Initially, providers were skeptical of self-sampling, but quickly began to see its potential for reducing the burden of pelvic exams and expanding screening coverage. Uganda has a reported 99% acceptance of this screening method (Bansil et al., 2014).

Vaginal self-sampling for HPV testing and cervical cancer screening has the potential to dramatically increase access to screening for many women in Uganda. Clinics that provide preventive screening are often far from a woman's home making transportation difficult and thereby limiting access. Services are sometimes not offered at times or on days when women are able to take time to travel to a clinic. Long wait times for services and time spent to get to clinics are associated with high costs to the individual. Furthermore, trained VIA providers are limited and there is a significant turnover of staff in Uganda (Cervical cancer screening and treatment in low-resource settings: Practice Experience from PATH 2013 [Internet], 2013). In campaign-style situations, outreach teams give self-sampling kits to women when visiting villages. Women are then asked to return the samples to the clinic or the team collects them at the end of the outreach visit or at a return visit (Jeronimo et al., 2014). In clinics, women can be trained to collect samples themselves and be given a private place to do so, which would speed up sample collection increasing number of women screened. If a woman does not feel comfortable collecting the sample herself, a trained nurse, or nurse's assistant, can collect a vaginal sample from the woman. This frees up higher-level clinical staff's time and also increases screening rates. Such strategies could have a major impact on screening coverage in Uganda if adopted on a wider scale.

Uganda can build on existing primary health care platforms to create efficient screening and treatment services. We propose strengthening national VIA-based screening, and incorporating HPV DNA testing when it becomes affordable. 70–80% of women who present to the UCI are infected with the human immunodeficiency virus (HIV). In a few health facilities, cervical cancer screening has been integrated into existing HIV care services and family planning services. As HIV-infected women are at higher risk for cervical precancers and cancers, there is an obvious need to make preventive services more accessible to these patients (Bukirwa et al., 2015). Despite integration of screening into HIV care, uptake of screening is still very low due to misconceptions as well as competing priorities for both the women and the health workers. This calls to light the need for education of community members and health professionals with regards to the importance of screening to cervical cancer prevention. A recent study indicated that up to 96% of women in Uganda receiving HIV care had never heard of HPV. Further, almost all of these women were amenable to self-sampling for cervical cancer screening (Mitchell et al., 2017).

Women and families appreciate receiving information about screening services through both direct communication from knowledgeable experts and from mass media (Bansil et al., 2014). Sensitization workshops with key community stakeholders and other health providers early in the service introduction process—well in advance of actual service delivery—will also help promote buy-in and reduce misinformation (Cervical cancer screening and treatment in low-resource settings: Practice Experience from PATH 2013 [Internet], 2013). Community-health education must be culturally sensitive and take into account societal context to maximize effectiveness and increase acceptance from communities.

Increasing the relatively low levels of up-to-date knowledge in Uganda among health professionals on this topic must also be addressed (Mutya et al., 2006). Although, training programs of health professionals have been ongoing, these programs have been mostly project or research-related. Moreover, these programs, such as Reproductive Health Uganda, Marie Stopes Uganda and others, have not been well coordinated by the Ministry of Health. The result has been an inability to have any sustained measurable impact. As a general strategy for training a large number of health workers across the country (either to increase awareness or build clinical skills), a cascade training system with highly experienced trainers is key. One master trainer who teaches and supervises teams of lower-level trainers is a cost-effective strategy to broad dissemination of information and to ensuring high-quality, acceptable, and accessible cervical cancer preventive services (Cervical cancer screening and treatment in low-resource settings: Practice Experience from PATH 2013 [Internet], 2013). Supportive supervision is an important element for maintaining quality after initial training is complete. This allows for guiding corrections as necessary and providing continual education to health staff. Unfortunately, this component of training is largely absent due to a lack of continued financial commitment.

Improving treatment follow-up is another barrier that must be addressed. There remains a large time gap between screening and treatment. Treatment of screen-positive women is best achieved at time of screening visit. If treatment is not possible during the same clinic visit, it should be arranged as soon as possible, and as conveniently as possible for the woman, so as to reduce loss to treatment. When screening results are not immediately available (i.e. HPV testing), it is crucial to develop an effective follow-up system to provide test results and, most importantly, to offer treatment to screen-positive women. A system best suited to local conditions should be put in place.

Plans for quality control monitoring should also be considered at the beginning of the program development process. Hurdles such as chronic shortages of health workers and resources, weak referral processes, and inadequate health information systems make it difficult to track individual patients or monitor program performance. Routine monitoring of

screening and treatment will work only if a good health information system is in place.

### 3. Treatment of invasive cervical cancer

The UCI is the only center for cancer care in the country with an 80-bed capacity receiving about 6000 cases every year. Based on the Kyaddondo Cancer Registry, more than 80% of women with cervical cancer referred to the UCI present with stage III or higher disease. Initial work-up of these patients to enable staging and plan treatment is based on: complete blood count, liver and renal function tests including creatinine clearance, chest X-ray, HIV status and pelvic ultrasound. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are not routinely performed. Patients with cervical cancer are examined and staged in the outpatient clinic. Given the high demand for operating room time, patients are rarely taken to the operating room for staging.

Until recently, surgery, radiotherapy, and chemotherapy as well as palliative care services were all available in Uganda for the treatment of invasive cervical cancer. However, in March 2016 the UCI's only radiotherapy machine providing external beam radiation stopped working. This machine provided radiation therapy to patients from as far as Sudan, Rwanda, Burundi, Congo and Western Kenya. 40% of the 2000 patients per year receiving radiation at UCI were cervical cancer patients. The Ugandan government has embarked on constructing bunkers at the UCI to cater to the large number of patients in need of radiotherapy and to increase the capacity of health workers engaged in cancer care. The old bunker is also undergoing renovation and it is hoped to be functional again within 6 months.

With a current inability to treat cervical cancer patients with radiation in Uganda, there is an urgent need for alternatives to managing these patients. Currently, the Ugandan government is supporting a small number of patients to receive radiotherapy in neighboring Kenya. The majority of patients remain in need of treatment. In low-resource settings, where access to radiotherapy is limited or lacking, few alternative treatment strategies have been reported (Sherris et al., 2009). Interest in neoadjuvant chemotherapy (NACT) for cervical cancer arose from the desire to avoid long-term toxicity related to radiation, maintain fertility, and improve survival in advanced stages of disease. However, NACT has been embraced as a temporal and alternative treatment strategy for cervical cancer in Uganda based on ASCO resource-stratified clinical practice guidelines as we await availability of radiation therapy (Chuang et al., 2016).

The Gynecologic Oncology team at the UCI and Mulago National Referral Hospital (MNRH) developed a modified protocol based on the ASCO guidelines and have since been managing patients on NACT followed by surgery with or without adjuvant chemotherapy and/or brachytherapy (Chuang et al., 2016). This has resulted in an increase in demand for limited operating room space and even more limited personnel who are skilled in carrying out the appropriate surgery. Cancer surgery is only provided at the UCI and MNRH, which are in close proximity. Due to logistical challenges, the gynecologic oncology services at the UCI and MNRH have only ten days of operating room time annually in which to perform surgery. This leads to long wait times for surgery by a gynecologic oncology specialist. Several patients seek suboptimal surgery, thereby contributing to their morbidity and mortality. A multidisciplinary group of specialists at the UCI discuss each case and determine which protocol each patient is to receive. Currently the modified NACT protocol is being applied for stages 1B2 (bulky disease) to IIIA. Stages IIIB to IV are being managed on high-dose vaginal brachytherapy with or without chemotherapy and palliative care.

Palliative care services are now available in 57 districts in Uganda under the leadership of the Ministry of Health and the Palliative Care Association of Uganda. A national morphine production program has been developed. Since 1993, liquid oral morphine has been made available through the Ministry of Health. In 2004, the statute was changed to allow nurses and clinical officers trained in palliative care to prescribe

oral morphine, and thus far more than 133 clinical palliative care nurses have been trained so that they can prescribe this medication (Downing, 2016). Each cervical cancer patient is linked to the palliative care team who manages her alongside other physicians.

Clearly, the UCI and MNRH do not have sufficient capacity to treat all cervical cancer patients nationally. Plans are underway to establish regional cancer centers where screening will take place and a visiting gynecologic oncologist will be available regularly to offer cancer management, including surgery for early-stage disease. While infrastructure for gynecologic oncology services is being established, most cervical cancer patients are being managed by general gynecologists. Training and specialized skill acquisition of health professionals in the effective management of cervical cancer, and more generally manpower, are desperately needed.

Collaborations between the UCI and the University of British Columbia, University of California San-Francisco, Duke University, and the Fred Hutchinson Cancer Research Center have led to some improvements in care. From these collaborations, local gynecologists have been trained in basic management of cervical cancer and a Gynecologic Oncology Tumor board has been established. With funding from Africa Development Bank, the Ugandan government is in the final stages of establishing a Gynecologic Oncology fellowship program at the UCI under the hospice of the East Africa Oncology Institute. The inception of a fellowship program in Uganda represents a milestone in producing gynecologic oncology specialists who will improve quality of care. These oncologists will train other gynecologists in regional referral hospitals to care for cancer patients and offer supportive supervision. Uganda awaits the availability of newly trained gynecologic oncologists.

#### 4. Conclusions

Due to challenges with infrastructure in Uganda, regional centers for cervical cancer screening, diagnosis, and early treatment should be considered in public health efforts against cancer. Cervical cancer prevention efforts should be prioritized to avoid the late presentation of women with advanced cervical cancer. Of urgent necessity is the appropriate radiotherapy equipment for the treatment of cervical cancer.

#### Conflicts of interest and financial support

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