

# Cervical cancer screening – The challenges of complete pathways of care in low-income countries: Focus on Malawi

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## Abstract

Cervical cancer is the fourth most common cancer among women globally, with approximately 580,000 new diagnoses in 2018. Approximately, 90% of deaths from this disease occur in low- and middle-income countries, especially in areas of high HIV prevalence, and largely due to limited prevention and screening opportunities and scarce treatment options. In this overview, we describe the opportunities and challenges faced in many low- and middle-income countries in delivery of cervical cancer detection, treatment and complete pathways of care. In particular, drawing on our experience and that of colleagues, we describe cervical screening and pathways of care provision in Malawi, as a case study of a low-resource country with high incidence and mortality rates of cervical cancer. Screening methods such as cytology – although widely used in high-income countries – have limited relevance in many low-resource settings. The World Health Organization recommends screening using human papillomavirus testing wherever possible; however, although human papillomavirus primary testing is more sensitive and detects precancers and cancers earlier than cytology, there are currently costs, infrastructure considerations and specificity issues that limit its use in low- and middle-income countries. The World Health Organization accepts the alternative screening approach of visual inspection with acetic acid as part of 'screen and treat' programmes as a simple and inexpensive test that can be undertaken by trained health workers and hence give wider screening coverage; however, subjectivity and variability in interpretation of findings between providers raise issues of false positives and overtreatment. Cryotherapy using either nitrous oxide or carbon dioxide is an established treatment for precancerous lesions within 'screen and treat' programmes; more recently, thermal ablation has been recognized as suitable to low-resource settings due to lightweight equipment, short treatment times, and hand-held battery-operated and solar-powered models. For larger lesions and cancers, complete clinical pathways (including loop excision, surgery, radiotherapy, chemotherapy and palliative care) are required for optimal care of women. However, provision of each of these components of cancer control is often limited due to limited infrastructure and lack of trained personnel. Hence, global initiatives to reduce cervical mortality need to adopt a holistic approach to health systems strengthening.

## Keywords

cancer screening, cervical cancer, human papillomavirus, low-income country, Malawi, thermal ablation, treatment options

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## The burden of cervical cancer in low-income countries and possible interventions

Cervical cancer is the fourth most common cancer among women worldwide, with the highest incidence in low-income countries (LICs), particularly in sub-Saharan

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Africa and with almost 90% of cervical deaths occurring in resource-constrained countries. Cervical cancer is a very painful cancer, affecting the poorest and most vulnerable women disproportionately through their child-bearing and economically productive years. As world population and life expectancy increase, the World Health Organization (WHO)<sup>1</sup> predicts the number of new cancer cases will increase significantly in LICs, unless effective interventions are introduced.

Cervical cancer is largely preventable through interventions such as human papillomavirus (HPV) vaccination for girls and screening of adult women with prompt treatment of precancerous lesions. When performed well and with high population coverage, these interventions could lead to cervical cancer being a disease of the past, at least in well-resourced countries. While primary prevention of all HPV-induced cancers by vaccination must be the ultimate goal globally, secondary prevention by screening is required for the generation of women too old for vaccine, but at highest risk of developing cervical cancer. However, HPV vaccines do not cover all high-risk (HR)-HPV types, and vaccine availability and uptake are highly dependent on resource and infrastructure for delivery.

Cervical screening has traditionally been based on the detection of cytological abnormalities in superficial cell scrapes from the transformation zone (Pap tests). The United Kingdom implemented call-recall population-based cytology screening in the 1990s. Most high- and several middle-income countries (HMICs) also offer screening by cytology, but often use it opportunistically with excessive screening of those at lower risk and inadequate screening of those at highest risk.<sup>2</sup> Cytology is subjective, time intensive, requires considerable training, quality assurance, maintenance of skills and is dependent on repeat testing (every 3–5 years).<sup>3</sup> Screening methods adopted by HMICs have little relevance for the poorest countries, yet the medical and scientific worlds have been slow to accept that alternative models, potentially with lesser efficacy, can be made to work and delivered in population-based programmes to reduce the current and immense challenge of cervical cancer. Visual inspection with acetic acid (VIA) is recommended by WHO for cervical screening in LIC because it is cheap, non-invasive and can be executed in low-tech health facilities with instant results. To date, a VIA-based screening strategy has been adopted by 26 countries.<sup>4</sup>

However, the real cause of cervical cancer is persistent HPV infection, and there is substantial evidence<sup>5,6</sup> to show that HPV as the primary screening modality is more sensitive than cytology and detects cancers and significant disease cervical intraepithelial neoplasia grade 2+ (CIN2+) earlier, thus allowing the screening interval to be increased. HPV as the primary test for mass cervical screening has already been implemented in the Netherlands and Australia, and is gradually being introduced in screening programmes in a number of other developed countries, including the United Kingdom. Recently, Kuhn and Denny<sup>7</sup> presented

accumulated evidence to show that HPV testing was more effective than VIA in reducing the prevalence of cervical intraepithelial neoplasia (CIN) grades 2, 3 or cancer (CIN2+) and the increasing availability of lower cost; rapid HPV tests which could make HPV-based screening approaches more cost-effective have been highlighted.<sup>8</sup>

## Challenges of screening in LICs, with particular focus on Malawi

Malawi currently has the second highest rate of cervical cancer in the world (age-standardized (world) rate of 72.9/100,000) and the highest mortality (age-standardized (world) rate of 54.5/100,000) figures.<sup>9</sup> As in many other countries, the Malawian Ministry of Health Strategic Plan includes cervical screening services using the VIA, but delivery and treatment of early lesions are often challenging.<sup>10,11</sup> There is considerable interest in HPV testing in Malawi, but choice of HPV test is a difficult issue and one must question whether this is currently the right approach for low- and even middle-income countries. Primary prevention will in time change the need for population-based screening. To this end, Malawi completed a successful HPV vaccine demonstration programme in two areas in 2014, but has found it challenging to scale up to the national level. In January 2019, the first dose of quadrivalent vaccine (Gardasil®) was offered to 9-year-old girls in school, and while the programme is expected to continue, it remains to be seen whether a second dose is offered to these girls or all resources are focussed on the next age cohort during January 2020.

## Clinical screening using VIA

As its name suggests, VIA involves identification of abnormalities by inspection of the cervix without the benefit of magnification. The application of acetic acid turns abnormal cervical cells white allowing an immediate assessment. The main advantages of VIA are its low use of resources – it can be undertaken by trained nurses and midwives, it does not utilize laboratories and it gives an immediate result allowing screening and treatment to be completed in a single visit. However, VIA is subjective, with often considerable variability between providers even in settings where quality measures have been introduced. Loss of skill set and misinterpretation of temporarily acetowhite lesions lead to false positives and overtreatment. This has been well-documented in studies from Malawi as well as other sub-Saharan African countries.<sup>12–15</sup>

## Findings from Nkhoma cervical cancer screening programme

The Nkhoma cervical cancer screening programme (CCSP) was initiated in 2013 in Nkhoma Church of Central Africa Presbyterian (CCAP) Hospital and 10 surrounding health

centres as a hub and spokes model to deliver same-day screening and treatment using VIA as per Malawian guidelines and an alternative treatment, thermal ablation (previously called cold or thermal coagulation), to the cryotherapy recommended by the WHO and the Malawian Government as the gas for cryotherapy was frequently unavailable. From the outset, this was to be a quality-assured VIA programme, where all providers had to have documented evidence of completing a theoretical Ministry of Health training course, supplemented by experiential practice at Nkhoma, regular continuous professional development (CPD) sessions and annual competence assessment of performance by an independent clinician. Local ownership of the programme and peer learning have contributed to the success of this approach. In 2015, over 7000 previously unscreened women had attended VIA clinics. Overall, VIA positivity was 6.1%. In women infected with HIV, the VIA positivity rate was higher at 10.4%. In addition, 1.4% of attendees had suspicious or advanced cancers, with the majority of early/treatable lesions occurring in the age range 20–39 years, while cancerous lesions were more frequent in women aged 30–59 years and also in those who were HIV+. <sup>11</sup> At the end of 2016, the number screened had risen to >18,000, the VIA positive rate was 6.5% and in HIV+ women was 8.1%. <sup>16</sup> In the mid-2018, >27,000 women had attended for screening and VIA positivity was comparable at 6.3% and 8.3% in HIV+ women (manuscript in preparation), suggesting consistency in interpretation and maintenance of the necessary skill set. These rates of VIA positivity and suspicious cancers are comparable to results from other studies. <sup>17–19</sup> Over 80% of VIA positive women received treatment on the same day; another 8%–10% were referred to the Nkhoma for treatment and received treatment with approximately 4–6 weeks <sup>11</sup> and Beatrice Kabota (unpublished). Five-year coverage for the catchment area reached around 25%, and women who have never been screened continue to come. While the known HIV positive proportion was 6%, a further 34% did not know their HIV status. Efforts are now in place to ensure that voluntary counselling and testing (VCT) is offered to women attending VIA screening in the Nkhoma catchment area. We conclude that quality-assured VIA with adequate support is a relatively inexpensive and acceptable screening solution for LIC which could enable much higher coverage than more resource-intensive screening options. In our experience, this has enabled provision of screening to reach rural women and those infected with HIV more readily. The WHO <sup>4</sup> also recognizes the role of VIA in the most resource-constrained settings.

### Primary screening with HPV

Which HPV test to use is a difficult issue for low- and middle-income countries (LMICs). A recent study concluded that the ‘HPV test global market is one of the most confusing, least regulated and with the most divergent

products on the market’, <sup>20</sup> with around 200 commercially available HPV tests, mostly oriented towards Western markets and not validated according to internationally approved diagnostic standards. Not all HPV tests are suitable for primary screening, where ease of use and rapid turnaround time may be more important than detailed genotyping or maximum analytical sensitivity. <sup>21,22</sup> Cost of HPV tests is a major consideration, but there are many other challenges to delivery of reproducible and timely clinical results. These include massive infrastructure challenges affecting all kinds of molecular tests and additional challenges specific to HPV testing, listed in Table 1.

### Findings from Nkhoma studies

The Nkhoma CCSP also considered HPV testing as a potential replacement for or adjunct to VIA screening. Our aim was to introduce a reproducible assay which was simple to perform after minimal training, had with a short turnaround time to allow a same-day ‘screen and treat’ programme and which could possibly be used in the clinic rather than over-stretched laboratory staff. We chose Xpert<sup>®</sup> HPV, a qualitative test for detection of HPV in specimens collected in PreservCyt<sup>®</sup> cytology medium which can be completed in 1 h. The test detects DNA of 14 HR-HPV types through three channels which provide partial genotyping: HPV 16, HPV 18 and 45 together, and other HR-HPV types in a single result, but which can be broken down into three subgroups: (31, 33, 35, 52, 58), (51/59) and (39, 56, 66, 68). <sup>23,24</sup>

Almost 2500 Xpert HPV tests were performed in the small laboratory at the Nkhoma Hospital. HR-HPV prevalence was found to be 21.2% with HPV 31+ significantly more prevalent than HPV 16/18/45, <sup>25</sup> comparable to previously published results based on 750 routine screening results. <sup>24</sup> Quality measures included regular use of internal quality control (IQC) samples and reproducibility was assured through both intra- and inter-laboratory testing. Manufacturer’s instructions were followed except that a range of collection media and devices were tried. Xpert HPV proved simple to perform. Training of laboratory staff proved straightforward and could be cascaded to lower-skilled personnel. Hands-on time per sample was only a few minutes. Multiple IQC samples showed high reproducibility and few errors were reported, with valid HPV results available from 98.3% of sampled women. Our work in Malawi has shown that the Xpert HPV is a feasible test for screening in LMIC, confirming other recent reports from Cameroon <sup>26</sup> and South Africa. <sup>27</sup>

In Nkhoma, we showed that HPV results could be returned to the clinic within 2 h of sample collection. Most of our work related to provider-taken samples which mean that HPV positive women have to be examined twice. However, we also found that self-taken vaginal swabs taken by women as soon as they arrived at the clinic were

**Table 1.** General challenges in introducing HPV tests to laboratories across LICs.

Infrastructure challenges	HPV test-associated challenges
Many labs are not physically suitable to run nucleic acid-based tests	<i>Sample collection</i> There are a confusing number of collection brushes and swabs
Equipment for high throughput assays takes up considerable space and is usually expensive or dependent on purchase of guaranteed numbers of tests	Sample transport media may be proprietary and designed for cytology, with high alcohol or formaldehyde content and large volume
Lack of local agents makes access to technical support and maintenance difficult and impacts on regular delivery of supplies	Sample transport may need temperature control and limited storage before testing
Disposal of clinical waste and associated plastics can be problematic	<i>HPV test</i>
Temperature control and transportation of samples to testing laboratories can be difficult	HPV tests often have several manual steps, leading to cross contamination and other errors
IT systems may be limited and Internet connectivity intermittent	Internal quality control and external quality assurance are additional issues, especially for small runs where the proportionate cost of controls can be high
Lab staff may not be knowledgeable nor trained to deliver molecular tests; even when staff have had training, there is often not the resource for regular competence assessment	Turnaround times greater than 2 h render many HPV tests unsuitable for point-of-care use and therefore for use in 'screen and treat' programmes
	Reproducibility in specific setting needs to be tested, and information on failure rates is essential

HPV: human papillomavirus; LIC: low-income countries; IT: information technology.

highly acceptable and indeed preferable for women and gave similar levels of HPV positivity to provider-taken samples.<sup>25</sup> There are increasing numbers of reports of the effectiveness of self-sampling with Xpert HPV testing from LMIC,<sup>28,29</sup> summarized in a recent meta-analysis.<sup>30</sup> It should be noted, however, that the Nkhoma programme was designed to test the practicalities of testing with Xpert HPV, but was not designed to be part of a clinical management algorithm.

Between 2014 and 2016, 1248 HPV results of which 290 were HR-HPV positive were linked to VIA outcomes and associated clinical information from the Nkhoma programme. As expected, HR-HPV positivity was the highest for suspicious and advanced cancers, but less than 1/3 of VIA+ were also HR-HPV+.<sup>31</sup> HPV testing gives an objective result indicating HPV infection, while clinical interpretation of disease state by VIA can be challenging. While WHO recommends HR-HPV testing followed by VIA triage to improve the specificity of HPV screening, there is a significant loss of sensitivity and the recommendation has been questioned. Recently, a study in Papua New Guinea<sup>32</sup> suggested that HPV screening followed by VIA triage may not be helpful, and that HPV testing alone, using Xpert HPV, would show better performance. In 2015, a self-sampling study in Cameroon using Abbott Real Time high risk HPV reported an HPV prevalence of 27%, VIA positivity of 12.9%, disease prevalence of 5% and the need to improve VIA performance.<sup>28</sup> In the Nkhoma study, HR-HPV prevalence was a little lower (23.2%) than in Cameroon, but VIA positivity in Nkhoma was only 6% and closer to disease prevalence, which we consider that it reflects the commitment in Nkhoma to

maintain quality assurance in VIA interpretation for all providers. With current investment in Malawi to reach high coverage of screening and treatment based on VIA and the high-resource needs (direct costs, laboratory and clinic capacities) associated with the higher sensitivity of HPV tests, HPV primary screening must be several years away.

## Treatment of early lesions

The WHO<sup>4</sup> has produced detailed guidance on treatment of lesions detected in cervical screening. Within 'screen and treat' programmes, treatment is provided soon or, ideally, immediately after a positive screening test.

## Cryotherapy

WHO current recommendations state that cryotherapy is the first-choice treatment for women who have screened positive in screen and treat settings and are eligible for cryotherapy. Cryotherapy uses either nitrous oxide or carbon dioxide to freeze cells at  $-90^{\circ}\text{C}$ . Meta-analysis of studies using cryotherapy has reported cure rates (i.e. no evidence of disease at 1 year) for CIN2–3 lesions as 85%–92% for cryotherapy.<sup>33</sup> A number of criteria are associated with eligibility for cryotherapy: screen-positive women are eligible for this treatment if the entire lesion is visible, the squamocolumnar junction is visible, and the lesion does not cover more than 75% of the ectocervix.<sup>4</sup> However, if the lesion extends beyond the cryoprobe being used, or into the endocervical canal, the patient is not eligible for cryotherapy, and LEEP (loop electrosurgical



excision procedure, also known as large loop excision of the transformation zone, LLETZ) is the recommended treatment. WHO guidance also states that all women who have screened positive with any test (including an HPV test) should be visually inspected with acetic acid to assess eligibility for cryotherapy and to rule out large lesions or suspected cervical cancer.

### Thermal ablation

Thermal ablation has been increasingly adopted within 'screen and treat' cervical screening settings in recent years.<sup>34</sup> Thermal ablation uses a probe heated to 100°C–120°C to ablate cells. This technique has been used in the United Kingdom for decades, with published high rates of effective treatment.<sup>35–37</sup> A systematic review published in 2013 provided evidence of pooled data from 13 studies.<sup>38</sup> Meta-analyses of proportion cured were conducted with data stratified by lesion grade and study region: among 4569 patients, summary proportion cured of 96% (95% confidence interval (CI) 92%–99%) and 95% (92%–98%) were obtained for CIN1 and CIN2–3 diseases, respectively. However, only one study from an LMIC<sup>39</sup> was included in the meta-analysis. More recently, an updated systematic review with 34 papers was produced by Randall et al.,<sup>40</sup> of which 23 papers published between 2014 and 2017 were included in a meta-analysis and six from LMIC settings. The authors found an overall response rate for thermal ablation of biopsy proven CIN2+ lesions of 93%–95% and concluded it is a feasible, safe and effective treatment.<sup>40</sup> However, this rate was lower in some, although not all of the studies from LMIC contexts, partly due to patient populations (e.g. women living with HIV (WLHIV)), highlighting the need for careful patient follow-up. Another recent systematic review and meta-analysis comparing use of thermal ablation and cryotherapy in LMICs<sup>41</sup> found a similar cure rate for cryotherapy (82.6%) and thermal ablation (82.4%), with authors emphasizing the need for further research especially for treatment outcomes for WLHIV. Indeed, a number of trials are ongoing, including a randomized control comparison of thermal ablation with cryotherapy and with LLETZ in screen and treat clinics in Zambia; pilot phase results suggest similar outcomes at 6 months but full results are awaited.<sup>42</sup>

Thermal ablation has a number of other features that make it suitable for LMIC settings. Machines – both the traditional (WISAP) and newer hand-held models – are lightweight compared to cryotherapy equipment, and the hand-held models are also battery-operated or solar-powered (a WISAP C3 thermo-coagulator (<https://www.wisap.de/Gynecology.html>) and Liger thermo-coagulator (<http://www.curemedicalglobal.com/>)), respectively. Treatment time is short – WHO guidance recommends thermal ablation be provided at a minimum of 100°C for 20–30 s.<sup>49</sup> There is an initial cost outlay for the machine and probes, but ongoing maintenance costs are low.<sup>11,34</sup>

In our experience in Malawi, cost savings compared with cryotherapy were realized after 50 treatments. VIA-based screen and treat programmes have been in place in Malawi since the mid-1990s. However, challenges including health system capacity and cultural barriers meant that screening coverage and treatment was limited.<sup>44</sup> Indeed, in the early 2010s, only one-third of facilities offering screening were able to provide treatment due to lack of cryotherapy equipment or gas.

As noted above, a 'screen and treat' programme was begun in Nkhoma CCSP in 2013. It was quickly evident that the cost and limited availability of cryotherapy was prohibitive. Given the decades of experience in Scotland and the evidence from the Dolman systematic review, thermal ablation was chosen as the alternative treatment modality, with agreement of the Ministry of Health. Within the Nkhoma CCSP, over 1650 women received treatment with thermal ablation between October 2013 and July 2017. Recurrence rate (i.e. VIA positivity) was assessed in a cohort of over 580 treated women who returned for a 1-year review visit: among HIV negative women (n=546), 94.3% were VIA negative, that is, a treatment failure rate of approximately 5%–6%, comparable with the international literature. Among WLHIV (n=133), the figure was slightly lower with only 91% recurrence free: this is again in line with international findings and supports the need for careful follow-up in this group of women.<sup>39,45,46</sup> Thermal ablation has now been widely adopted within Malawi both within government and non-governmental organization (NGO)-supported screening services and its use is reported in other contexts.<sup>49,47,48</sup>

Critically, in 2019, the WHO<sup>43</sup> issued revised guidance for treatment of cervical precancer lesions, for the first time supporting the use of thermal ablation. This guidance recognized the challenges relating to the cost and availability of a refrigerant gas for cryotherapy (as mentioned above), and the need for an evidence-based recommendation for use of thermal ablation in LICs. In supporting the use of this treatment modality for histologically confirmed CIN2–3, or women who have screened positive in screen-and-treat strategies, WHO also emphasizes the need for post-treatment follow-up at 1 year, especially for WLHIV or of unknown HIV status.

### LEEP

For women not eligible for cryotherapy due to the size or location of the acetowhite lesion, as mentioned above WHO recommends LEEP as the recommended alternative treatment for lesions too large for cryotherapy (and by extension, for thermal ablation). Within Malawi, health facilities follow this recommendation and do refer women with larger lesions to central hospitals within the cities for treatment (LEEP or surgery if available). LEEP is currently (2018/2019) being introduced at the district hospital level, but faces the same challenges as other

treatments – insufficient funds to train staff, lack of adequate facilities and long distances for women to travel to access treatment. LEEP is also included in the revised WHO<sup>43</sup> guidance as above, although referred to as LLETZ, with use dependent on expertise, training, equipment and consumables available.

## Complete pathways of care for detected abnormalities

Many lesions identified through screen and treat approaches are too advanced for treatment with thermal ablation, cryotherapy or LEEP, and hence robust referral pathways for larger lesions and suspect cancers are required, including surgical options and palliative care. Provision of complete pathways of care for all women requiring treatment can be challenging. Availability of diagnostics in Malawi is limited. Pathology and biopsy services are provided in teaching hospitals in Blantyre and Lilongwe, but there is limited capacity to reach most of the country, and histology can be expensive and turnaround slow.

## Surgery

In 2016, the American Society of Clinical Oncology (ASCO) provided comprehensive guidance for the management and care of women with invasive cervical cancer, including resource stratified recommendations and dependent on the type and stage of cervical disease.<sup>50</sup> They include use of cone biopsy (where adequate follow-up facilities available), extrafascial hysterectomy ( $\pm$ pelvic lymph node dissection) and modified radical or radical hysterectomy where available, with a recognition for associated pathology and anaesthesia support.

Underlying the need for resource stratification of clinical guidance is the major challenge of a global shortage of surgical and anaesthetic care, the focus of much recent recognition, concern and strategic planning in the global health community.<sup>51–53</sup> The Lancet Commission on Global Surgery highlighted that five billion people lack access to safe, affordable surgical and anaesthetic care when needed, with less than 6% of all surgeries being performed in the world's poorest countries.<sup>54</sup> A lack of trained health providers, inadequate health system infrastructure, costly out of pocket expenses and a historic lack of prioritization of surgical care as part of national health plans are cited as contributing factors.<sup>54</sup>

The situation for cancer surgery globally mirrors the general situation. It is estimated that of the 15.2 million new incident cancers in 2015, 80% would need surgery, yet less than 25% of patients with cancer worldwide have access to safe, affordable or timely surgery.<sup>55</sup> By 2030, up to 10 million cancer patients requiring surgery will be in LMICs, and approximately 50% of admissions to hospital with cervical cancer will require surgery, with substantial economic implications at both the micro- and macro-levels

(in LMICs, about a third of patients with cancer experience financial catastrophe). The Commission also highlighted the inadequate availability of adjuvant disciplines such as imaging and pathology.<sup>54</sup>

Within sub-Saharan Africa, the provision of surgery for cervical cancer is particularly acute. Management of invasive cervical cancer requires a surgical option; however, the lack of access to cancer treatment centres and the variable quality of services provided are recognized challenges. A recent cross-sectional survey across sub-Saharan Africa, affiliated with four HIV/AIDS networks spanning 17 countries, found that less than 50% of cancer treatment centres were able to perform radical or extended hysterectomies, and the vast majority were unable to provide radiotherapy or chemotherapy.<sup>56</sup>

Another recent study provides insight into the challenge of providing sufficient gynaecology oncology training, with only six gynaecologic oncology training programmes identified across Africa.<sup>57</sup> The authors emphasized the need for flexibility in curricula design and delivery, investment in facilities and treatment facilities, and support from Ministries of Health. Others suggest laparoscopic surgery for gynaecological cancers in LMICs as a feasible and ultimately cost-effective approach to delivering the high volume of surgeries required.<sup>58</sup>

Within Malawi, there is a chronic shortage of general as well as specialist gynaecological surgical capacity.<sup>59</sup> Different approaches have been adopted or are being considered to meet both current and anticipated needs. Task shifting from surgical specialists to other clinicians (e.g. clinical officers) is being trialled in Malawi, including for hysterectomies.<sup>60,61</sup> However, radical hysterectomy surgery will likely require specialist gynaecology training. As of early 2019, there are six trained gynaecology surgeons providing radical hysterectomy surgery across Malawi, totally inadequate to meet current need. A tailored, but resource-intensive approach for rapid building of surgical capacity for radical hysterectomy through a competency-based curriculum and use of master trainers and clinical mentoring has proved effective in Malawi<sup>62</sup>, a model also adopted by others in sub-Saharan Africa.<sup>63</sup>

## Radiotherapy

The ASCO guidelines describe radiotherapy is a 'mainstay' of cervical cancer treatment, ideally for women with advanced disease concurrent with platinum-based chemotherapy;<sup>50</sup> however, these guidelines recognize that in many contexts, radiotherapy is limited or indeed non-existent. Where radiotherapy availability is limited, the guidelines support its use for palliative treatment, and shorter fractionation regimes for potentially curative intent. The National Comprehensive Cancer Network (NCCN)<sup>64</sup> issued harmonized guidance for cervical cancer in sub-Saharan Africa in 2019: it recommends

chemoradiotherapy and brachytherapy as an alternative to surgery in everyone except those who require fertility preservation in the setting of stage 1a disease with no lymphovascular invasion, with adjuvant chemoradiotherapy recommended if any of lymph nodes, margins or parametrium are involved at surgery. However, in Malawi (as in many low-resource settings), radiotherapy is not currently available, although there are active plans for provision within the next 2–3 years.<sup>65</sup>

### **Palliative care**

Many women are diagnosed with cervical cancer at a stage when curative treatment is neither available nor possible. Palliative care is an approach that addresses the physical, psychosocial, social and spiritual care of patients and of their families.<sup>66</sup> As cervical cancer progresses, women may experience weight loss, fatigue, loss of mobility, vaginal discharge/malodour, pelvic and bone pain and fistulas, and palliative care services can support patients through these. A palliative care approach can be implemented in both low- and high-resource settings, with ideally a multi-disciplinary approach that includes clinical, nursing, social services, physical therapy and spiritual support, tailored to local contexts.<sup>66,67</sup>

Use of the WHO<sup>68</sup> pain management ladder is advocated in all settings, and basic steps can be followed even in low-resource settings. However, WHO<sup>69</sup> estimates that up to 80% of the global population does not have sufficient access to opioid analgesics, one of the greatest global health inequalities. They report that oral morphine is available in only 32% of countries, with only 15% of patients within the WHO AFRO region receiving palliative care either through primary healthcare or through home-based or community palliative care. It has been suggested that integration of palliative care within HIV services in sub-Saharan Africa over the last decade has provided a framework for cancer patients,<sup>70</sup> but there is a concern that most palliative care is provided by non-governmental, faith-based or community-based organizations, and hence with little or no inbuilt sustainability mechanisms. The integration of palliative care in both national health systems and educational institutions is regarded as critical for long-term sustainability.<sup>71</sup>

In 2002, Malawi introduced a palliative care approach for people living with HIV/AIDS, recommended as a strategy that improves the successful outcome of anti-retroviral therapy (ART).<sup>72</sup> Community home-based care services, as recommended by WHO and the Joint United Nations Programme on HIV or AIDS (UNAIDS) to reduce the burden of HIV care on the healthcare system, have been introduced.<sup>73</sup> More generally, the Ministry of Health has developed comprehensive palliative care guidance, and specialist palliative care is available in selected hospitals.<sup>74–76</sup> There are efforts to integrate palliative care into

public health systems, but it is estimated that only one-third of those who need palliative care in Malawi are able to access such services.<sup>71</sup>

## **Discussion and conclusion**

### **HPV screening**

Xpert® HPV ticks the boxes for LMIC use by its simplicity and ease of use by healthcare providers with minimal training. All reagents are contained in a single cartridge which is not opened, thus minimizing contamination potential. However, it is expensive even within a variable and graded pricing structure for LMIC, uses collection systems validated for cytology and generates a considerable burden for adequate disposal. Many years ago, it was considered that an HPV test kit needed to fall to less than US\$5 to be affordable (Cusick, personal communication). This point has not been reached and additional costs of testing associated with sample collection can add a further US\$2 approximately. We have tried alternative collection media, with comparable results<sup>25</sup> and we understand that manufacturers now recognize the needs of LMICs and that affordable, validated collection systems are in the pipeline. Self-collected samples add to the feasibility and are surely the way of the future.

Who would pay for this screening test? In countries where there is insufficient funding for healthcare, preventive measures are a lower priority even though there would be long-term economic benefit. In Malawi, the majority of the population live on <US\$4 per day<sup>77</sup> and are subsistence farmers, yet in many situations still have to pay for screening. VIA may be less sensitive than the complex screening algorithms utilized in high income countries, but if performed with skill and quality assurance, it can be affordable and therefore has potential to reach high coverage and be sustained in national programmes.

### **Screen and treat programmes**

The commitment to provision of VIA ‘screen and treat’ within cancer control plans and, critically, of funding within the care services by the Ministries of Health are important steps in ensuring population coverage within LMICs. In Malawi, cervical cancer screening is mentioned in the ‘Essential Health Plan’, and commitment to service provision within the National Cancer Control Plan; however, there is a need for a ring-fenced budget to support this to reduce reliance on external partners and donors. Similarly, there is a need for commitment to and investment in training of personnel, infrastructure and resources for complete pathways of care including surgery, radiotherapy, chemotherapy and palliative care to ensure women receive optimal care within local contexts.

## Complete pathways of care

Recent WHO acceptance of thermal ablation as an acceptable treatment for precancerous lesions within screen and treat programmes removes an important barrier to provision of treatment in Malawi, and elsewhere. However, more robust referral systems for treatment of extensive lesions (LEEP) and provision of pain relief through palliative care are critical in the ongoing challenge to reduce the burden of cervical cancer in Malawi. The greatest need, however, is for extended surgical training and access to adjuvant disciplines such as imaging and pathology, to enable women with operable cancers to receive timely treatment potentially to prolong their lives and radiotherapy which could improve the quality of life of many.

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