TACKLING THE BURDEN OF CERVICAL CANCER: LESSONS FROM MALAWI AND OTHER LOW- AND MIDDLE-INCOME COUNTRIES

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In poor countries cervical cancer typically presents late, with high associated mortality. This article focuses on Malawi, but the issues are relevant to other low-income settings. HPV testing and HPV vaccination offer the prospect of significant reductions in cervical screening mortality. If this is to be achieved there is a need for governments to accept HPV testing and vaccination and to make them a central component of health policy and to address educational and training needs amongst health workers and the wider population.

The burden of cervical cancer in LMICs

Cervical cancer poses a significant global burden, particularly in the low- and middle-income countries (LMICs); it is the fourth most common female cancer, with approximately 528,000 cancers in 2012 *(1, 2)*. In LMICs it accounts for almost 12% of female cancers – most (about 85%) of the global burden is in these countries. About 87% of deaths from cervical cancer also occur in poor regions of the world *(1)*; women who suffer poverty, or are socially disenfranchised are far more likely to develop, and die from, cervical cancer – such women are likely to present much later, and to have limited access to diagnostic and treatment services *(3)*. Yet cervical cancer is largely preventable – see Table 1 for a summary of prevention approaches. Public health interventions, such as HPV vaccination for girls aged 9–13 years, and screening with treatment of precancerous lesions could bring incidence and mortality rates down to those seen in western countries *(4, 5)*; indeed, the WHO considers these interventions to be "best buys", as articulated in their Global Action Plan for the Prevention and Control of Non-communicable Diseases (2013–20).

Cervical cancer in Malawi

Malawi was recently reported to have the highest rate of cervical cancer in the world with a world age-standardized rate of 75.9 per 100,000 *(3)*. In common with many other countries, the Malawian Ministry of Health Strategic Plan includes provision of cervical screening using Visual Inspection with Acetic Acid (VIA) but delivery is challenging and treatment of early lesions is often unavailable *(6, 7)*. Our studies of a screening population in Nkhoma in rural Malawi suggest a prevalence of around 20% across the age range but more than double this in HIV+ women *(8)*.

Risk factors for cervical cancer

Overwhelmingly, cervical cancer risk is determined by the presence of HPV infection *(9)*; three important risk factors include the number of lifetime sexual partners *(10)*, HIV infection and co-infection with other sexually-transmitted diseases such as Chlamydia trachomatis and Herpes Simplex *(11, 12)*. Additional risk factors for cervical cancer include a history of smoking, younger age at first intercourse and at first pregnancy, high parity, and long-term use of oral contraceptives *(9)*. High rates of HIV infection (which promotes the progression of precancerous lesions) in areas such as sub-Saharan Africa have also contributed to higher cervical cancer incidence *(13)*.

Cervical cancer – its link to HPV infection

Evidence has gradually accumulated over the last several decades, on the link between HPV infection and cervical cancer *(14)*. Natural history and follow up studies have clearly shown that infection with high risk (HR) HPV precedes the development of cervical cancer by several years, that sexual transmission is

the predominant mode of HPV acquisition and that HPV 16 is a more potent carcinogen than nicotine *(14, 15)*; over 170 types of HPV are formally recognized *(16)*, and we now have a detailed understanding of HPV biology and pathogenesis *(17)*.

Infection with HR-HPV is very common, with around 80% of men and women expected to have an HPV infection during their life-time. Most regress without clinical symptoms. Indeed, HPV often coexists with its host over long periods in a kind of immune tolerance. Persistence of infection and progression to cancer may therefore be linked to a failure of the immune response, although no obvious link to HLA type or other susceptibility indicators has been made. In immunosuppressed people, whether due to infection such as HIV or induced through organ transplantation, HPV is more common than in HIV negative populations, with a broader range of types and more multiple infections *(18)*. HPV prevalence varies greatly from country to country, ranging from an average of 6.6% in Europe to 22.9% in Africa *(19)*. However, breakdown by age shows much wider variation, with an inverse relationship between age and prevalence in many countries but high across all ages in some poor countries *(20)*.

Finding the best approach to cervical screening in LMICs

Much of the evidence of the benefits of cervical screening programmes comes from affluent areas of the world where screening is long-established, such the Nordic countries *(21)* and the United Kingdom *(22, 23)*. Cervical cancer has become a rare disease in high-income countries, and there is widespread consensus that these very substantial benefits would not have come about in the absence of substantial investments in screening *(24)*. For decades, cervical screening in many high-income countries has been reliant on Papanicolaou (Pap) screening by conventional or liquid-based cytology, although HPV triage and even primary, testing is increasingly being adopted in a number of countries, and indeed recommended *(25, 26)*. Screening is usually population-based and organized (compared to opportunistic), and comprehensive quality assurance guidance is available *(27)*. Organized screening programmes seek to ensure that the steps of call and recall within a defined target population, investigation, treatment and follow-up (including access to palliative care) are in place, i.e. that screening is understood as a process, not merely as the test.

Such cervical screening programmes are out of reach of most LMICs. The World Health Organization (WHO) has issued guidance with recommendations for countries with differing resources – in addition to vaccination of girls before the initiation of sexual activity, screening of women aged 30–49 years is recommended *(26)*. Screening may involve HPV testing, cytology or visual inspection with acetic acid (VIA), with the screening approach used in any particular context (country, or healthcare facility) dependent on factors that include the balance of benefits and harms, the potential for women to be lost to follow-up, cost and availability of the necessary equipment and human resources *(26)*. Cytology screening programmes in many middle-income countries have faced challenges in relation to organization, the extent of population coverage, infrastructure costs, lack of trained staff, and inadequate quality assurance *(28, 29)*.

Table 1: Prevention of cervical cancer

Primary prevention:	Current schedules:
Vaccination	Cervarix: females, age 9–14; 2 doses
	Gardasil 4: males and females, age 9–13; 2 doses
	Gardasil 9: males and females, age 9–14; 2 or 3 doses
	Expanded vaccination of adult women - 3 doses regimen
Secondary prevention:	*Papanicolaou* (i.e. cytology)
Cervical screening	Liquid based cytology with Pap stain
	Cytology followed by HPV triage
	HR-HPV primary testing
	HR-HPV primary testing followed by cytology
	Visual inspection options suitable for LMIC: - Acetic acid (VIA) - Lugol's Iodine (VILI) - in combination with HR-HPV testing
Tertiary prevention:	Thermo-coagulation Cryotherapy
Treatment of early disease	LEEP (Loop Electrosurgical Excision Procedure)/ LETZ (Loop Excision of the Transformation Zone)
Treatment of advanced disease	Advanced surgical intervention Chemotherapy Radiotherapy

Low-technology approaches (Including VIA, screen and treat, thermo-ablation)

Different approaches are needed in poor regions of the world. Visual inspection with acetic acid (VIA) is supported by WHO in healthcare settings where HPV testing is prohibitively expensive or where infrastructure or requisite trained professionals are not available *(5)*. Indeed, WHO recommends a strategy of screen with VIA and treatment, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treatment. In low-resource settings VIA has the attraction of limited additional costs: where basic healthcare services are already in place, essentially it requires 5% acetic acid, cotton wool, gloves, a good light source and a dedicated room to ensure a women's

privacy. With training, VIA can be performed by several levels of healthcare providers, including nurses, midwives and nurse-midwife technicians. Over the last decade the number of LMICs which have adopted VIA testing has increased: as of November 2016, 26 countries have incorporated VIA-based screening into national programmes, with another 30 or so using it within pilot programmes *(30)*. Adoption as national strategy does not always reflect national implementation.

One attraction of VIA is that it permits a single-visit strategy, i.e. a "screen-and-treat" approach where the treatment decision is based on a screening test result and treatment is provided soon or, ideally, immediately after a positive screening test (in contrast to the more conventional approach of cytology, colposcopy, biopsy, and histological confirmation of CIN). In many LMICs where women can travel miles, often on foot, to attend a screening clinic, and where her doing so can impact on her childcare or agricultural responsibilities, screen-and-treat approaches are most likely to promote participation and minimize loss to treatment of a screen-positive woman. There is randomized trial level evidence for reduction in the incidence of high-grade lesions and cervical cancer mortality associated with a single-visit approach with VIA *(31, 32, 33)*.

However, VIA-based screening is acknowledged to be challenging, as the subjective nature of the test can lead to high variability in inter-operator performance, false-positive results, low- to moderate- sensitivity with low specificity, and VIA has poorer performance in post-menopausal women. Thus, VIA screening is recognized as an interim approach in LMIC settings, allowing a supportive screening culture and infrastructure to be set in place until affordable HPV testing can be introduced.

Traditionally, treatment in screen-and-treat programmes has relied on cryotherapy, still the recommended treatment modality in WHO guidance *(5)*. Where available, cryotherapy is an effective treatment. However, in low-income settings the cost and limited availability of carbon dioxide (CO_2) or nitrous oxide (N_2O) gas have led to situations where women have been screened but no treatment is available, unethical in any healthcare context. In recent years there has been renewed interest in use of thermo-coagulation (also known as cold coagulation or increasingly, thermal ablation) to treat cervical epithelial neoplastic (CIN) lesions. A systematic literature review demonstrated equivalent treatment outcomes to cryotherapy *(34)*.

Screen-and-treat approaches in Malawi

Scaling up of quality assured and sustainably resourced VIA screen-and-treat approaches in many sub-Saharan African contexts is still required. Integration of cervical screening provision with reproductive health services, and for HIV positive women with ART services, offers opportunities for consolidation of clinic space, streamlining of health education messages, and best use of over-stretched healthcare workers *(35)*.

We have shown non-inferior outcomes of thermo-coagulation to cryotherapy in a VIA-based screen-and-treat screening service in rural Malawi *(7)*; others have also shown effective treatment in an African context *(36)*. Thermo-coagulation is very suited for use in LMICs, as the machine is lightweight and portable and treatment times at 100°C to 120°C are short and use minimal electricity. The new generation of hand-held thermo-coagulators can be run from solar or battery power and have the potential to transform the ability to provide cervical screening to women in rural sub-Saharan Africa and other resource-constrained settings. WHO is currently reviewing its recommendations on thermo-coagulation (mid-2017).

Awareness of and societal attitudes to cervical cancer in LMICs

Regardless of the approach taken, individual and societal attitudes play a critical role. Typically knowledge and awareness of cervical cancer and cervical screening are low in po or and developing countries, when compared to wealthier regions of the world *(37)*; further, there is often a lack of recognition in LMICs of the important governmental role in initiating cervical screening prevention.

Stigma associated with a cervical cancer diagnosis, fear of the screening procedure itself and of subsequent treatment have also been cited as barriers to screening participation (*38*, *39*). Myths and misconceptions in relation to screening are common. Cultural and religious concerns linked to perceived intrusion of privacy and intimate examination and lack of spousal support together with limited female empowerment, are additional contributory factors to limited engagement with screening even when available *(38, 40)*. Such societal and cultural factors often interact with psychological stressors to influence screening attendance *(41)*. Affordability of testing is another key factor, particularly in poor, rural populations; as is the time that would be taken from other obligations *(42)*.

These barriers constitute an enormous challenge if we are to improve cervical cancer prevention in poor countries such as Malawi. Multi-factorial approaches, combining education, awareness raising and reducing stigma are needed; too often well-intentioned prevention screening efforts fail through a lack of understanding of individual and societal barriers.

HPV vaccination programmes

In 1991, Scottish medical scientist, Professor Ian Frazer and Chinese virologist, Dr Jian Zhou used molecular techniques to develop virus-like particles (VLPs) using only the capsid proteins of HPV *(43)*. VLPs do not contain nucleic acid, and are therefore non-infectious. Two vaccines were quickly developed

and thoroughly tested: Gardasil® from Merck, a quadrivalent vaccine containing HPV 6, 11, 16 and 18 VLPs directed against both genital warts and cervical cancer prevention and Cervarix® from Glaxo Smith Kline, which is a bivalent vaccine containing HPV 16 and 18 VLPs directed solely at cancer prevention. Both vaccines have been in use in different countries since 2006. Both have shown high and sustained efficacy against HPV infections with vaccine types, but it will take many years to show reductions in cancer rates. A nonovalent vaccine Gardasil 9 has recently been licensed through FDA.

Implementation of HPV immunisation programmes in LMICs

Bruni et al *(44)* estimated that 59m women had received at least one dose of HPV vaccine through national programmes in more than 64 countries by 2014. Sadly only 1% were from low- or lower-middle-income countries, demonstrating that populations with the highest incidence and mortality of disease remain largely unprotected. By 2016, over 100 countries had licensed HPV vaccine for use, but how many of these will provide the high coverage needed to ensure effective cancer reduction long term?

Many African countries, have considered HPV immunization and with support from GAVI, have delivered demonstration projects in advance of national rollout. Examples include Rwanda which achieved >90% coverage with three doses of vaccine in 2011 and despite the challenges, has maintained high coverage and set an ambitious goal to eradicate cervical disease by the year 2020 *(45)*. In Malawi, successful demonstrations projects were conducted in the north and south and also reached >90% coverage in schools. However, the challenges of school delivery mean that other outreach settings will be required for national roll-out *(46)*. Tanzania is now in the second year of a demonstration project, delivered in schools by campaign weeks. Malaysia was the first Muslim country to introduce a national HPV immunization programme.

HPV vaccination: challenges for the next decade

The challenges for low- and middle-income countries are substantial, particularly the cost of delivery, even when the cost of vaccine is covered by global arrangements such as the GAVI Alliance. It has been suggested that a five-year delay in introducing the HPV vaccine to LMICs could result in 1.5 to 2 million preventable deaths *(47)*. The greatest global challenge for cervical cancer reduction is therefore a matter of HPV vaccination coverage.

Potential for HPV testing as a primary screening strategy in LMICs

Cervical screening using HPV testing has been shown to give 60–70% more protection against invasive cervical carcinomas than cytology *(48)*. Primary HPV testing could provide an objective, reproducible alternative to subjective and inconsistent VIA screening. In an early study in India, Sankaranaranayan and colleagues in 2004, using the well-established HC2 HPV screening test (Qiagen), concluded further developments were required to make HPV tests more reproducible, less expensive and less sophisticated for them to be feasible and effective in low-resource settings. Almost a decade later, also in India, Joshi et al concluded that HPV testing followed by VIA should be considered if it is affordable *(49)*. A multicentre study from PATH using careHPV® (Qiagen) and our work in rural Malawi using Xpert® HPV (Cepheid) have demonstrated that HPV primary testing is feasible and acceptable to both women and providers *(50, 51)*.

There are however many obstacles. HPV tests themselves are expensive with, to date, a minimum cost of around US$ 6 per test. They also generally require trained laboratory staff and sophisticated equipment for molecular detection, use considerable quantities of plastics and collection media with significant alcohol or formaldehyde content which pose problems for disposal and maintenance/ servicing of equipment can be difficult in areas where companies or their agents are lacking.

The optimal HPV test for LMICs needs to be cheap, require minimal training in its use, and have a quick turn-around, allowing it to be considered as a near patient test *(51)*. Where HPV tests take longer or need to be batched to make effective use of high throughput equipment, a second visit would be necessary for those who are HPV positive. In rural communities with limited transportation options and probably a distant hospital, this is not a priority for asymptomatic woman. A bigger challenge is how to collect a sample for HPV testing. If taking the sample requires a trained healthcare professional, it would be quicker to provide a quality assured VIA screen. There is therefore considerable interest in self-collected specimens. Evidence from Europe has shown this provides an alternative for hard-to-reach and non-attending women *(52, 53)*. This has also been demonstrated in China *(54)*, in Uganda where self- collection-based HR-HPV testing had more than double the uptake of VIA alone *(55)* and in other countries. One limitation of HPV-based screening is the low positive predictive value, since it detects HPV infection not cancer and therefore requires triage of positives to limit false positive and reduce overtreatment.

Nevertheless, self-collected samples with a swab or tampon-like device, in a clinic setting tested locally with a fast, simple HPV test with results being returned to the women while they wait (preferably no more than 1–2 hours), followed by VIA triage and accessible treatment *(7)* must surely be the goal for LMIC to achieve significant population-wide screening and effective reduction in the burden of cervical disease and cancer. That stage has not yet been reached.

Health economic implications

Cervical cancer impacts family, community and national life. A summary of the cost effectiveness arguments in support of the introduction of HPV vaccination and population-wide screening are beyond the scope of this article. Nonetheless, it is important to recognise that such evidence is available. Non-communicable diseases, including cervical cancer, have been shown to adversely affect household income, with LMICs particularly affected *(56)*. A recent systematic review of the economic benefits of vaccines in LMICs reports that the HPV vaccine is cost-effective provided the price per dose is kept below US$150 *(57)*. Another recent comprehensive study uses a model-based approach to estimate the health impact, financial costs and cost-effectiveness of the provision of the HPV vaccine for girls and cervical screening provision for women of screening age. The authors report that HPV vaccination and once in a lifetime screening and treatment were both cost-effective strategies that could avert millions of cervical cancer cases and deaths with substantial DALY savings for relatively modest public health investment compared to overall development assistance health spending *(58)*.

Conclusions

The burden of cervical cancer in Malawi and other LMICs remains unacceptably high. While cytology-based screening has made a very significant impact in western countries, LMICs lack the resource and infrastructure to adopt this approach. Screen-and treat approaches offer an interim solution, and can reach significant numbers of women – there are, however, problems with systematic testing and adequate coverage. HPV vaccination and primary HPV testing offer the prospect of large scale reductions in cervical cancer burden. Governments in countries such as Malawi should aspire to these approaches, with the assistance of the international community. ■

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Professor Heather A Cubie, MBE, BSc, MSc, PhD, FRCPath, FRSE is a retired consultant clinical scientist in virology. She was responsible for training Scottish Clinical Scientists in microbiology from 1994 to 2012; R&D Director in NHS Lothian (1995–2008), Founder Director of the Scottish National HPV Reference Laboratory (2008-2012) and established both the national HPV archive and the Scottish HPV Investigators' Network (SHINe: www.shine.mvm.ed.ac.uk).

She has an Honorary Chair and is a Senior Advisor to the Global Health Academy, University of Edinburgh. In retirement, she is passionate about partnership with Malawian and Scottish colleagues where she has helped establish a sustainable cervical cancer reduction programme.

Professor David Weller graduated from the University of Adelaide in 1982. He undertook PhD studies in Adelaide and Nottingham; after academic posts in Australia he moved to the United Kingdom in 2000 and is currently James Mackenzie Professor of General Practice at the University of Edinburgh. He leads the Cancer and Primary Care Research International Network (Ca-PRI), and is a member of the National Cancer Research Institute Primary Care Clinical Studies Development Group (Foundation Chair, from 2003–2010). He has been involved in cancer screening and early diagnosis research in both Australia and the United Kingdom; he led the evaluation of the United Kingdom pilot of colorectal cancer control, and his group in Edinburgh run a programme of research focusing on the roles of primary care in all aspects of cancer. More recently he has led LMIC programmes, funded by UICC and the British Council, examining early diagnosis and screening in resource-poor settings. David sits on various national and international research and government committees on cancer, and works as a GP in central Edinburgh. He is Co-Director of the University's Centre for Population Health Sciences, and International Dean for SE Asia and Australasia.

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