

Cervical cancer prevention in Africa

The tools exist to reduce the incidence of cervical cancer, but as Karly S Louie and colleagues report, little is systematically being done to reduce the caseload

Cervical cancer is the most common cancer and the leading cancer-related cause of death among women in sub-Saharan Africa. An estimated 70 700 new cases occur each year, representing one-quarter of all female cancers in sub-Saharan Africa.¹ The magnitude of the problem has been under-recognised and under-prioritised compared with the competing health priorities of infectious diseases such as HIV/AIDS, tuberculosis, and malaria. It remains unclear whether the HIV epidemic has affected the incidence of cervical cancer in sub-Saharan Africa as incidence rates appear to have remained unchanged between the 1960s and the 1990s, as seen in Nigeria and South Africa, or have increased in Bulawayo, Zimbabwe and Kampala, Uganda.¹ In addition, it is unknown whether increased access to antiretroviral treatment will reduce the incidence because of immune reconstitution or increase the burden of cervical cancer as a result of longer life expectancy.

The risk of cervical cancer and death remain largely uncontrolled with the majority of developing countries lacking effective cervical cancer screening programmes. Most cases of women with cervical cancer often present at advanced stages of disease, when treatment is ineffective or not available.

Screening for pre-cancerous cervical lesions using conventional cytology (the Pap smear) has been effective in preventing cervical cancer in industrialised countries where adequate health infrastructure and human and financial resources are available to ensure high quality and good coverage. However, this has mainly failed in most developing countries where appropriate infrastructure is generally not achievable.

Cervical cancer is caused by genital human papillomavirus (HPV) infection, the most common sexually transmitted infection among women worldwide. High-risk oncogenic HPV genotypes 16 and 18 are responsible for about 70% of cervical cancers in the world.²

Human papillomavirus vaccines

The availability of two effective prophylactic HPV vaccines gives new promise for a primary prevention strategy for HPV infection and cervical cancer. The vaccines have shown high safety, efficacy, and immunogenicity for both the quadrivalent HPV 16/18/6/11 vaccine (Gardasil®, Merck & Co., Inc.) and the bivalent HPV 16/18 vaccine (Cervarix™, GlaxoSmithKline Biologicals).³ At US\$360 for the three-dose HPV vaccine, it is the most expensive vaccine in history. This is difficult to accept as 80% of cases of cervical cancer occur in developing

countries. Health economic modelling projections suggest that if there was high vaccination coverage of adolescent girls (70%) in 72 Global Alliance for Vaccination and Immunisation (GAVI) eligible countries and the cost of the HPV 16 and 18 vaccines dropped to I\$110 (international dollars), which is about US\$2.00 per dose, the vaccine would be very cost-effective, even in the poorest countries and would avert approximately 2 million deaths from cervical cancer over a 10-year period.⁴ It is uncertain when these HPV vaccines will become available to sub-Saharan Africa since it took almost 20 years from the time the hepatitis B vaccine was licensed in 1982 for the price to drop significantly from US\$100 for the three-dose vaccines to US\$1.00 per dose, and to have widespread access in the poorest developing countries.⁵ In order to avoid a long time-lag to access HPV vaccines, current work is being done to explore different international vaccine financing and procurement strategies by the Pan American Health Organization, United Nations' Children Fund, GAVI, the Gulf Cooperation Model, and the Advanced Market Commitments to identify the most appropriate strategy for equitable distribution of these vaccines that is sustainable.⁶ The primary goal would be to ensure that HPV vaccine introduction would not impede other national public health priorities, such as control for malaria, and that they will become affordable and integrated within the framework of national immunisation programmes. Until HPV vaccines are accessible and can have a major impact in developing countries, the reduction of cervical cancer will rely on cervical screening for prevention and treatment (see Figure 1).

Cervical screening, diagnosis, and treatment

In order for cervical screening to be effective, an accurate, simple, low-cost, culturally acceptable, and safe screening test is essential. Naked-eye visual inspection methods such as VIA (visual inspection with acetic acid) or VILI (visual inspection with Lugol's iodine) with a good light source (i.e. bright halogen lamp or torch) provide simple methods to detect aceto-white areas, or yellow non-iodine uptake areas in the cervical transformation zone, indicating cervical abnormalities and possible precancerous lesions.⁷ A major advantage of VIA and VILI is that they provide an immediate result, as well as being inexpensive, and can be carried out with minimal equipment. These strategies have been advocated as screening alternatives for developing countries since they are less laboratory dependent, and a range of healthcare providers such as doctors, nurses, midwives, and paramedical health workers can be trained in 5–10 days as compared with training cytotechnicians (12–24 months) for cytology screening.

Karly S Louie, Silvia de Sanjose, and Philippse Mayaud, London School of Hygiene and Tropical Medicine, London, UK, and Institut Catala d'Oncologie, Barcelona, Spain.

Visual inspection methods have their limitations as evaluation studies have shown VIA to have a wide variability of sensitivity and specificity of 60–94% and 74–94%, respectively, to detect high-grade pre-cancerous lesions in Africa; and VILI to have a sensitivity and specificity of 90–97% and 73–91%, respectively.⁸ The specificity of VIA is however lower among HIV-positive women, which may be attributed to high rates of co-infections in the lower genital tract.⁹ Although visual inspection methods present an appropriate strategy for screening in low-resource settings such as sub-Saharan Africa, these methods are prone to subjectivity, and it is essential that good provider training and sustained quality assurance are maintained in order to achieve substantial gains in prevention of cervical cancer in routine settings. If not, false-positive results can lead to increased levels of anxiety and unnecessary treatment, or false-negative results can lead to false reassurances.

If cervical screening is effective in detecting pre-cancerous cervical lesions, women can be treated successfully and not develop cervical cancer, provided that accessible services for diagnosis and effective treatment and good follow-up are available. Colposcopy is a diagnostic method used for the diagnosis and evaluation of pre-invasive cervical cancer.¹⁰ This method allows visual magnification of the site where cervical cancer development occurs and it enables taking a directed biopsy and delineating the extent of lesions on the cervix in screen-positive women, which avoids having to perform conisation. It also helps in directing two simple, safe, and effective treatment methods such as cryotherapy and loop electrosurgical excision procedures (LEEP) for pre-cancer. Cryotherapy can be performed by physicians and non-physicians, at all levels of healthcare facilities.¹¹ The procedure has been shown to have low morbidity and

is acceptable to women, their partners, and the health service providers in a variety of low-resource settings.¹² The difference between the two procedures is that LEEP uses a low-voltage electrified wire loop to remove the abnormal cervical tissue, whereas cryotherapy is an ablative procedure that involves freezing the abnormal tissue on the cervix, which gradually disappears and the cervix heals.

At present, screening, diagnosis, and treatment may involve a three-visit strategy with initial evaluation done at the first visit, performing colposcopy for those who screen positive at the second visit, and treating biopsy-confirmed cervical lesions at the third visit. In order to avoid loss-to-follow-up and optimise a woman's attendance to screening, an alternative 'screen-and-treat' approach should be considered, where referral and treatment are offered immediately to screen-positive cases with a reduced number of clinical visits. Studies in Ghana, South Africa, and Zambia have demonstrated that the screen-and-treat approach is acceptable, feasible, and safe.^{12–14} In Ghana, nine clinicians (four nurses and five gynaecologists) screened 3665 women aged 25–45 years over a period of 18 months with VIA and screen-positives were followed up at 3 months and 1 year.¹² Overall, 13.2% of the women were screened positive, and of those eligible, 91% received immediate or delayed treatment and no complications were recorded. At 1-year follow-up, the VIA-screen-positive rate was 2.6% and no women were suspected of having cancer. The results of this study were consistent with a previous South African randomised controlled trial of 6555 non-pregnant, unscreened women aged 35–65 years¹³ who were screened with HPV-DNA testing and with VIA. Women were randomised thereafter to one of three groups: cryotherapy if the HPV test was positive,

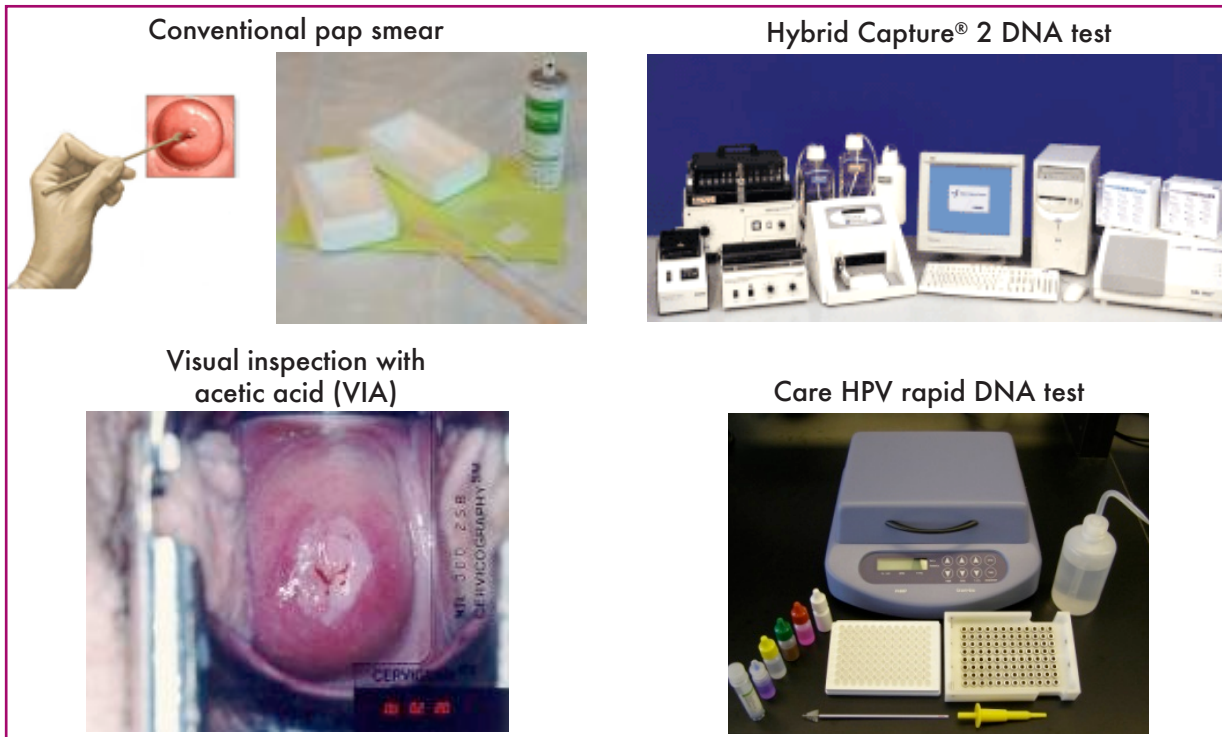


Figure 1 Different available cervical cancer screening strategies (courtesy S de Sanjose)

cryotherapy if VIA was positive, or delayed treatment irrespective of the screening test result. The incidence of pre-invasive cervical cancer was significantly lower in the two screen-and-treat groups at 6 and 12 months post-randomisation compared with the delayed group. In a more recent study in Zambia, a screen-and-treat strategy with VIA and immediate cryotherapy for screen-positives was used to manage 8823 women, 41.5% of whom were HIV-seropositive.¹⁴ About one-quarter of women were screen-positives and were treated with cryotherapy, while 8% who were ineligible for cryotherapy were managed using LEEP. Almost two-thirds of the women managed with LEEP were HIV-positive. Complications associated with LEEP, which include intra-operative and post-operative bleeding, occurred very rarely (<1%) and were managed effectively, confirming the safety of LEEP in HIV-infected and uninfected women in low-resource settings.

New cervical screening technology

Important advances in the development of new screening technologies have followed since HPV has been established as the aetiological agent preceding cervical carcinogenic changes. Much hope has therefore been placed in possibly screening or triaging women for referral based on the results of an HPV diagnostic test.^{15,16} This would offer a more objective and reproducible screening test to detect pre-invasive disease compared with cytology.¹⁷ The limitations of HPV-DNA testing include the cost, infrastructure, and time needed to obtain a result, which are similar to traditional cytology-based screening. However, a new molecular cervical screening test, *CareHPV* (Qiagen Gaithersburg Inc., MD, USA) has been developed as a simple, rapid, and functional HPV-DNA test for low-resource settings.¹⁸ The compact, portable, and battery-operated technology has stable characteristics under sub-optimum conditions of temperature, humidity, lighting and space, and the test can be conducted by workers with minimal laboratory training. Data from China have shown that *CareHPV* has a sensitivity and specificity to detect high-grade lesions of 90% and 84%, respectively, when cervical cell samples were obtained by health professionals and 81% and 82% when women collected their own samples using a vaginal collection device, compared with 41% and 94% for VIA.¹⁸ The findings suggest its potential role in helping reduce the burden of cervical cancer in comparable settings. Regulatory approval is anticipated in countries such as China and India in the near future, and the tests will be provided at a low price for developing countries. *CareHPV* thus represents an exciting alternative screening strategy that may make a real impact on the simplification and coverage of cervical cancer screening programmes.

The role of new and existing prevention strategies

Cervical cancer is a preventable and treatable cancer. New HPV-DNA screening tests and the introduction of HPV vaccines offer exciting options for prevention. However, until these new tools become available and affordable for sub-Saharan Africa, feasible cervical screening strategies such as the screen-and-treat

approach using visual inspection methods coupled with cryotherapy or LEEP could be a primary prevention strategy.

References


1. Parkin DM, Ferlay J, Hamdi-Cherif M, et al. Cancer in indigenous Africans – burden, distribution, and trends. *Lancet Oncol* 2008; 9: 683–92.
2. Munoz N, Castellsagué X, de Gonzales AB, Gissmann L. HPV in the etiology of human cancer. *Vaccine* 2006; 24 Suppl 3: S31–10.
3. Schiller JT, Castellsagué X, Villa LL, Hildesheim A. An update of prophylactic human papillomavirus L1 virus-like particle vaccine clinical trial results. *Vaccine* 2008; 26 Suppl 10: K53–61.
4. Goldie SJ, O'Shea M, Campos NG, et al. Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries. *Vaccine* 2008; 26: 4080–93.
5. Kane MA, Sherris J, Coursaget P, et al. HPV vaccine use in the developing world. *Vaccine*, 2006; 24 Suppl 3: S31–10.
6. Andrus JK, Sherris, Fitzsimmons JW, et al. Introduction of human papillomavirus vaccines into developing countries – international strategies for funding and procurement. *Vaccine* 2008; 26 Suppl 10: K87–92.
7. IARC. *A Practical Manual on Visual Screening for Cervical Neoplasia*. Ed R a W R Sankaranarayanan. Lyon, France: International Agency for Research on Cancer, 2003.
8. Sankaranarayanan R, Basu P, Wesley RS, et al. Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. *Int J Cancer* 2004; 110: 907–13.
9. Denny L, Kuhn L, Pollack A, Wright TC Jr. Direct visual inspection for cervical cancer screening: an analysis of factors influencing test performance. *Cancer* 2002; 94: 1699–707.
10. IARC. *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia. A Beginner's Manual*. Ed SR Sellors JW. Lyon, France: International Agency for Research on Cancer, 2003.
11. ACCP. *Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers*. Ed SACCP. Seattle: Alliance for Cervical Cancer Prevention, 2004.
12. Blumenthal PD, Gaffikin L, Deganus S, et al. Cervical cancer prevention: safety, acceptability, and feasibility of a single-visit approach in Accra, Ghana. *Am J Obstet Gynecol* 2007; 196: 407 e1–8; discussion 407 e8–9.
13. Denny L, Kuhn L, De Souza M, et al. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA* 2005; 294: 2173–81.
14. Pfaendler KS, Mwanahamuntu MH, Sahasrabudde VV, et al. Management of cryotherapy-ineligible women in a "screen-and-treat" cervical cancer prevention program targeting HIV-infected women in Zambia: lessons from the field. *Gynecol Oncol* 2008; 110: 402–7.
15. Cuzick J, Arbyn M, Sankaranarayanan R, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine* 2008; 26 Suppl 10: K29–41.
16. Gravitt PE, Coutlé F, Iftner T, et al. New technologies in cervical cancer screening. *Vaccine* 2008; 26 Suppl 10: K42–52.
17. Dillner J, Rebgolj M, Birembaut P, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ* 2008; 337: a1754.
18. Qiao YL, Sellors JR, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008; 9: 929–36.

Further reading

Louie KS, de Sanjose S, Mayaud P. Epidemiology and prevention of human papillomavirus and cervical cancer in sub-Saharan Africa. *Trop Med & Int Health* 2009; 14: 1287–1302.

Note

Karly Louie and Philippe Mayaud are supported by the UK's Department for International Development (DFID) Research Programme Consortium on Research and Capacity Building for Sexual & Reproductive Health and HIV in Developing Countries. The views expressed here do not necessarily reflect the views of DFID.



The logo features the text 'Africa HEALTH' in white on a black background, with a yellow sun icon above 'Africa'. To the right, 'CPD Challenge' is written in white on a purple background. Below this, a yellow banner contains the text 'See page 77 to test yourself on this article'.