

VISUAL INSPECTION OF THE CERVIX: PROGRESS TO DATE AND THE RATIONALE FOR CONTINUED INVESTMENT



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Cervical cancer continues to be a public health problem in many developing countries despite the availability of effective preventive measures such as vaccination and screening. Visual inspection with acetic acid (VIA) is a low-cost test that has now been validated for primary cervical cancer screening. Despite the advances in vaccination and more sensitive molecular tests, there are compelling reasons for continuing and even accelerating the investment in programmes based on VIA and precancer treatment.

Cervical cancer is a preventable neoplasia that continues to be a public health problem in many developing countries. The disease is associated with chronic infection by one or more of the 14 oncogenic types of the human papillomavirus (HPV), a sexually transmitted virus very prevalent in most populations in the world.¹ In 90% of women, HPV infections resolve spontaneously within two years, but in 10% of cases they persist for many years and can evolve into precancerous lesions in either the squamous or (less commonly) columnar epithelium of cervix.² Invasive cervical cancer is preceded by 10 to 20 years of intraepithelial precancerous changes³ that can be detected and easily treated, interrupting the natural history of the disease and preventing the death of women.

Cervical cytology (Pap smear) has been used for many decades as the preferred screening test, and consequently the incidence and mortality of cervical cancer have decreased in most developed countries. However, the Pap smear has had little or no impact in most developing countries due to the lack of resources to properly implement it, especially considering that Pap smear is a multi-step process that requires properly trained cyto-technologists, adequately implemented laboratories, reliable notification and referral systems, and frequent re-screening.⁴ For this reason the burden of the disease affects disproportionately women from developing countries, since they do not have proper

screening and treatment of the precancerous stages of the disease.

The limitations of Pap smear prompted researchers to explore new alternatives more suitable for areas with limited resources. Approximately 20 years ago visual inspection with acetic acid (VIA) was proposed and tested for primary cervical cancer screening.⁵ VIA is a simple screening test based on the principle that precancerous lesions in the cervical epithelium turn white approximately one minute after they are exposed to 5% acetic acid (vinegar); this is the same principle used by colposcopy since the 1920s. The difference is that colposcopy uses a device (colposcope) that provides special lighting and 4 to 20x magnification. Instead, VIA evaluates the visual changes with a naked-eye inspection (unmagnified) using a simple light source (torch or 100v lamp).⁶ Mid-level personnel like nurses and midwives have demonstrated their ability to do VIA after just a week of theoretical and practical training. Multiple evaluations during the last two decades have shown that VIA is equally or more sensitive than Pap smear for detecting precancerous lesions of the uterine cervix. It has the additional advantage of providing a result within a few minutes, making it possible to provide treatment (if it is available at the facility) or counselling about referral immediately.

In the last decade, new tests for detection of HPV have been introduced.⁷⁻⁹ These new tests are highly sensitive for

detection of precancer and cancer, and they have the advantage that the screening can be done using a vaginal sample self-collected by women without the need of a speculum exam.^{10,11} Now we have the potential for reaching women at their communities or homes and inviting them to collect a sample for primary screening using HPV testing. Even in this new scenario, though, women with a positive HPV test result will require a pelvic examination and direct visual evaluation of the uterine cervix to determine if precancerous or cancerous changes are already occurring and what treatment is appropriate. Therefore, VIA will still be required for screening programmes even when HPV testing comes into wider use.

Another area of progress in the fight against cervical cancer has been the introduction of vaccines against HPV. The vaccines have proven to be highly effective for preventing infection with the serotypes included in them, but the current vaccines include only two oncogenic HPV types responsible for approximately 70% of the cases of cervical cancer worldwide. VIA will still be required for the screening of vaccinated women to detect the 30% of the remaining disease that is not covered by the current vaccines. In addition, the global introduction of these vaccines over the next decade will not benefit the huge cohort of women who were beyond vaccination age or already infected with HPV and are in need of cervical cancer screening.

With the articulation of new targets for non-communicable disease (NCD) programmes, cervical screening has been identified as a key indicator of progress towards cancer control.¹² For most low- and middle-income countries, VIA is the only way currently to achieve high levels of coverage with screening and treatment services. Developments in all these different aspects of cervical cancer prevention make it timely to reflect on how far we have come and whether to continue to invest in VIA.¹³

Progress with VIA

There has been significant progress in the introduction and acceptance of VIA for cervical cancer screening. In the early days health care providers were sceptical about the value of the test since it looked “too simple” compared to Pap smear. The large body of evidence generated as part of the Alliance for Cervical Cancer Prevention (ACCP) showed that in most settings VIA was more sensitive for detecting precancer than Pap smear.¹⁴ Even though it is difficult to implement rigorous effectiveness studies in areas with limited resources, Sankaranarayanan et al¹⁵ performed a study in India where a single round of VIA screening, accompanied by treatment when needed, reduced cervical cancer mortality by 35% in

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the overall group of women aged 30 to 59 and by 66% among women aged 30 to 39 years. The same authors published later another study in a different part of India with less positive results for VIA, but the reduction of mortality attributable to VIA was better than that obtained with Pap smear screening.¹⁶

Another important landmark in the in the introduction of VIA is its inclusion as a primary screening method in the new guidelines recently published by the World Health Organization (WHO).¹⁷ Those guidelines recommend VIA as a screening test over Pap smear unless cytology is already established and working well. In areas where there is no screening at all and where HPV testing is not yet feasible, it is recommended to start a programme using VIA instead of trying to implement Pap smear. Using VIA as the screening test, it is still possible to develop the rest of the programme structure – such as community mobilization, precancer treatment, referral for complex care and record systems for patient and programme monitoring – that can be the platform when better molecular screening tests become widely available.

Fortunately, we now have better and more standardized training materials that can be implemented in countries interested in starting a VIA-based screening programme. Recently PATH partnered with Jhpiego and the Peruvian Cancer Institute (INEN) to develop a training excellence centre (TEC) in Peru and to validate training materials for Latin America. The package of materials includes manuals and guides for training community promoters to educate women about the need for screening, materials for training health providers in VIA and cryotherapy, and materials for maintaining quality among providers who are performing VIA. These materials are currently used widely in multiple countries in Latin America, and are being complemented by a web-based tool for providing the reinforcement of skills to providers in the field. As a result of this effort, we now have thousands of providers with skills for VIA and cryotherapy in

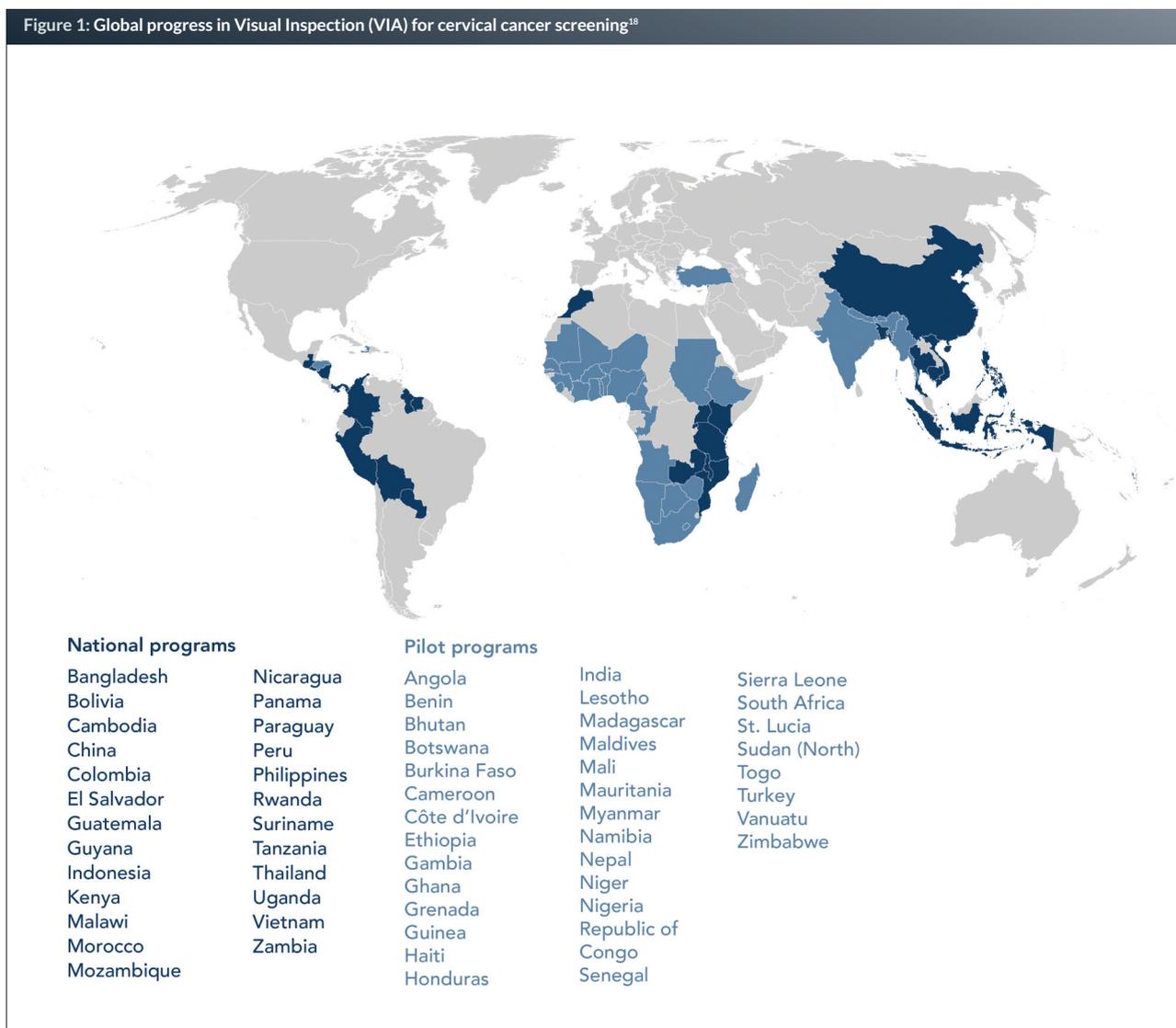
Bolivia, Colombia, Nicaragua and Peru, with plans for expanding the work to other countries in the region. A similar regional training centre is also being developed by the Uganda Cancer Institute (UCI), in collaboration with PATH, to develop master trainers for national screening programmes in Africa. PATH and UCI have worked with the WHO African Regional Office (AFRO) to create an English-language curriculum for VIA and cryotherapy building on the materials from Latin America.

Challenges and potential solutions

Even though VIA is currently used in multiple countries (Figure 1), it is usually on a limited basis, and there is still a need to expand or introduce the capacity in many countries. One approach that could help to expand this capacity is by further development of training excellence centres (TEC) in several regions, such as Francophone Africa and Asia, to train more master trainers who can then cascade the training to

health workers throughout government health facilities. Another challenge for expanding the use of VIA is the need for follow-up, monitoring and evaluation of providers using it, since VIA is a subjective test and has no feasible mechanism for routinely creating a permanent record of what the evaluator observed during the exam. While digital cameras have been used in a few countries and can be helpful for training or periodic monitoring, they are not affordable or sustainable for routine use in most low-income countries. One possible way to secure good quality of services is to visit providers periodically and make a review of a standard set of case photos to measure their skills in identifying cancer and precancer. Another option is to provide refreshment of skills using an Internet website, where the provider accesses the website periodically and reviews a standard set of case photos; a score is obtained at the end, and those who are under the optimal score should receive a face-to-face follow-up. A web-based tool in Spanish was recently developed in

Figure 1: Global progress in Visual Inspection (VIA) for cervical cancer screening¹⁸



Latin America to be hosted by the Pan American Health Organization.

Another challenge is related to the adequacy of the health information system (HIS) to track screening and treatment services. In many countries, HIS forms must be adapted to document the key variables listed by WHO as essential for monitoring programmes:

- ▶ the number of women screened for cervical cancer (to calculate coverage);
- ▶ the number of women with positive screening results (to monitor screening test performance);
- ▶ the number of those with positive results who received further evaluation and treatment (to evaluate completeness of care and programme effectiveness).¹⁹

In those countries where the data in the HIS is used to measure the productivity of health providers, if VIA and cryotherapy are not included in the HIS health providers will favour other activities in order to get a good evaluation. Determining the number of women who complete treatment can be estimated indirectly, since in most countries the system does not allow the tracking of women with positive results to see if they received treatment. In the best existing scenarios we can count the number of women with positive screening results in a period of time and the number of treatments in the same period, and then assume that all those treatments were for precancerous lesions. This approximation may overestimate treatment completion in those areas where cryotherapy is used by providers to treat benign changes of the uterine cervix.

A major limiting factor for expansion of VIA is the capacity for treatment. VIA has usually been paired with cryotherapy, since this treatment is easy to provide and has very few complications.²⁰ However, the cost of the cryotherapy units, and more importantly the need for a continuous supply of nitrous oxide or carbon dioxide gas, has created a significant burden on health systems in developing countries. New technologies for treatment are currently being explored. One of them is the CryoPen® (CryoPen, Inc., Corpus Cristi, Texas), a cryotherapy device that does not need an external supply of gas; this technology is currently under evaluation and should be available for developing countries within the next year. Another option is the cold coagulator, an electricity-powered device that reaches a temperature of approximately 100 to 120°C; then the heat is applied to the cervical epithelium; the best results have been obtained when it is applied for 40 seconds.^{21,22}

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where several health centres with VIA capacity but no treatment available are organized around a health centre with cryotherapy. Women with positive results at any of the screening sites are immediately counselled and referred to the facility with cryotherapy for receiving treatment. This concentration of treatment services is more efficient for equipment and gas supplies and enables selected providers to treat enough patients to maintain their skills. An alternative approach is to have outreach treatment teams that visit smaller facilities on a rotating schedule, so that women get treated in a facility close to their home. The implementation of a follow-up system for referred women is essential in order to minimize the number of women that do not complete treatment.

Are there viable alternatives to VIA now?

In the last decade new molecular tests for detecting the presence of HPV have been developed and approved for clinical use. The main advantage of the new HPV tests is their high sensitivity, allowing them to detect most precancer cases at the first round of screening; however, the specificity of the new tests is still sub-optimal so many experts recommend a secondary evaluation of those with positive HPV results. Another advantage of the molecular tests is their good predictive value for identifying those women at higher risk for harbouring disease now, or for developing disease within the next few years. Correspondingly, women with a negative result on the HPV test have a very low risk of developing precancer in the next decade²³, which means the inter-screening period can be extended in these women, representing a significant reduction in cost and effort for screening this low-risk group of women.

As described earlier, HPV testing can be done using a vaginal sample self-collected by women without the need for a pelvic examination or the use of a speculum. This opens the possibility for taking screening to the community level,

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reducing the infrastructure required for primary screening, and saving pelvic evaluation for those who are positive on an HPV screening test. If a triage step is desired, VIA is a valuable test that can be implemented for evaluation of the high-risk HPV-infected group of women, although it is recognized that using a test like VIA or Pap as triage will result in some loss of overall sensitivity.²⁴ Additionally, VIA as a triage test will help to identify women suspected of having invasive cancer and needing immediate referral for specialized treatment. VIA will also identify women with large intra-epithelial lesions who are not eligible for cryotherapy and need to be referred for excisional procedures.

Even though molecular tests have the highest sensitivity for detection of precancer and cancer of the uterine cervix, there are still some limitations for their introduction in developing countries. The initial investment required for implementing the technology is high, and countries would require support for the start-up and introduction in a population-based programme. This initial investment would be outweighed by the potential for extending the inter-screening interval in women with negative results, since their risk of precancer is minimal within the next decade. Another challenge is the need for developing algorithms for screening and management of women with positive HPV results. In order to fill this gap, WHO recently released its new guidelines for screening and treatment of cervical cancer¹⁷; these guidelines propose different algorithms for screening using HPV testing, and triage of the positive women using diverse options such as VIA or Pap smear. It is the responsibility of each country to determine which algorithm is more suitable for their population.

What impact will HPV vaccine have on VIA screening?

Although it has only been seven years since HPV vaccine

introduction started, there are already some early signs of an impact on screening. In Australia, young women who received all three doses of vaccine had nearly half the risk of a cervical intraepithelial neoplasia grade 3 or higher (CIN3+) cervical lesion compared to similar unvaccinated women.²⁵ In the United States, the proportion of cervical lesions that had HPV types 16 or 18 – the most oncogenic types – was 33% less among vaccinated women than among unvaccinated women.²⁶ HPV type 16 generally accounts for 50% or more of high-grade lesions; if these are prevented, screening programmes will have considerably fewer screen-positive women to treat and follow up. How soon the benefit will be seen after vaccination starts depends on the age at which screening is initiated. Countries that start screening younger than age 30 will see a decline sooner, since HPV 16 is associated more with early-onset lesions. Screening programmes will be able to start later and screen less often as the vaccinated cohort comes of age. Even with the cross-protection against HPV types not included in the vaccines²⁷ and a new 9-valent vaccine that will probably become available in the next year or two, screening will still be needed for at least the next three or four decades until fully vaccinated cohorts reach the age of highest risk.²⁸

Because a vaccine will make high-grade precancerous lesions much less common, it will also make screening by visual methods (VIA or Pap) more difficult since positive tests will be relatively rare, giving screeners much less experience seeing positives. The lower incidence of precancer will, of necessity, reduce the predictive value of positive screening tests and increase the cost of identifying precancer.¹

For programmes that vaccinate at age 10 or so and start screening at age 30, as recommended by WHO, it will take 20 years after a vaccine is introduced before an impact on screening will be seen and 30 years before an impact on cervical cancer incidence and mortality is measurable. If we do not increase screening services above the current levels, we can expect to see 21 million cases of cervical cancer in the next 30 years and 9 million deaths, nearly all of which are avoidable by screening and precancer treatment.

Rationale for continuing to invest in VIA and precancer treatment

Despite these advances in vaccination and more sensitive molecular tests, it is clear that there are compelling reasons for continuing and even accelerating the investment in programmes based on VIA and precancer treatment. VIA is an effective and feasible screening tool that can be used where molecular tests are not yet widely available, starting with once-in-a-lifetime screening and increasing frequency

when universal coverage has been achieved and/or more resources become available. VIA can serve as a platform for building screening programmes where they do not exist or where only limited coverage has been attained, and then substituting better tests when they become available and affordable.

Having such programmes serves several purposes beyond helping the women who directly benefit from the screening. It increases awareness among policy-makers, since it generates data about the disease burden that has been hidden up to now and about the availability of feasible interventions. It demonstrates to health workers and to women in the community that cervical cancer is preventable and that women's health and self-care are important to society. This message has the potential to inspire wider understanding about the possibility of reducing mortality from other cancers (like breast and prostate) through early detection programmes and the role of self-care for other NCDs. It provides an opportunity to make adjustments to the HIS for better programme monitoring and to strengthen referral and specialty care systems. The lessons learned from establishing a national cervical cancer screening programme using low-cost technology like VIA can be applied to other cancer and NCD screening and management programmes, such as those for breast cancer, diabetes and hypertension.

On the clinical side, training for VIA and cryotherapy enhances capacity for pelvic evaluation and gynecological treatment. These skills will be required even when molecular testing is introduced and they can serve as a foundation for adding related skills for identifying and managing other gynecologic conditions like sexually transmitted infections, cervicitis and uterine prolapse. As noted earlier, VIA can play an important role in the evaluation of women who are HPV positive in terms of treatment options.

Finally, screening programmes based on VIA can provide critical data on the impact of HPV vaccine. Even without type-specific information, such programmes can generate baseline rates on cervical precancer in the near term and later show the extent and timing of a decline in HPV-related disease. Such data can bolster national commitments to vaccination programmes so that investments are sustained.

Conclusions

Substantial progress has been made in laying a foundation of evidence, clinical capacity resources, awareness and commitment to cervical cancer screening in low- and middle-income settings. We are now poised for significant advances in both coverage and impact. Unlike HPV vaccination, which will require decades to reap the benefits, we have evidence

that VIA-based programmes with adequate precancer treatment can lead to notable reductions in cervical cancer mortality in just a few years. While VIA, by its nature, is an imperfect tool, it is still very useful both as a starting point and as an adjunct method as better tools become available. The VIA platform is well suited to the needs of low-resource settings and deserves continued and even expanded support. The investments that are made in scaling up the use of VIA will continue to pay dividends even when better screening tools become more widely available. ●

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References

- ¹ Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890–907.
- ² Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *JNCI Cancer Spectrum*. 2010;102(5):315–324.
- ³ Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. *Vaccine*. 2006;24(3):S1–S10.
- ⁴ Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. *Vaccine*. 2006;24 Suppl 3:S3/63–70.
- ⁵ Nene BM, Deshpande S, Jayant K, et al. Early detection of cervical cancer by visual inspection: a population-based study in rural India. *Int J Cancer*. 1996;68(6):770–773.
- ⁶ PATH. Course in Visual Methods for Cervical Cancer Screening: Visual Inspection with Acetic Acid and Lugol's Iodine. Seattle: PATH; 2004.
- ⁷ Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*. 2007;357(16):1579–1588.
- ⁸ Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol*. 2010;11(3):249–257.
- ⁹ Cuzick J, Bergeron C, von Knebel DM, et al. New technologies and procedures for cervical cancer screening. *Vaccine*. 2012;30 Suppl 5:F107–F116.
- ¹⁰ Sancho-Garnier H, Tamalet C, Halfon P, et al. HPV self-sampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. *Int J Cancer*. 2013;133(11):2681–2687.
- ¹¹ Ogilvie GS, Mitchell S, Sekikubo M, et al. Results of a community-based cervical cancer screening pilot project using human papillomavirus self-sampling in Kampala, Uganda. *Int J Gynaecol Obstet*. 2013;122(2):118–123.
- ¹² World Health Organization (WHO). A Draft Comprehensive Global Monitoring Framework, including Indicators, and a Set of Voluntary Global Targets for the Prevention and Control of Noncommunicable Diseases. A/NCD/INF/1. Geneva: WHO; 2012. Available at: http://apps.who.int/gb/ncds/pdf/A_NCD_INF1-en.pdf. Accessed December 6, 2013.
- ¹³ Tsu VD, Jeronimo J, Anderson BO. Why the time is right to tackle breast and cervical cancer in low-resource settings. *Bull World Health Organ*. 2013;91(9):683–690.
- ¹⁴ Sherris J, Wittet S, Kleine A, et al. Evidence-based, alternative cervical cancer screening approaches in low-resource settings. *Int Perspect Sex Reprod Health*. 2009;35(3):147–154.
- ¹⁵ Sankaranarayanan R, Esmy PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet*. 2007;370(9585):398–406.
- ¹⁶ Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med*. 2009;360(14):1385–1394.
- ¹⁷ WHO. WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. Geneva: WHO; 2013. Available at: http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/index.html. Accessed December 6, 2013.
- ¹⁸ Cervical Cancer Action. Global Maps. 2013. Available at: <http://www.cervicalcanceraction.org/comments/comments.php>. Accessed December 6, 2013.
- ¹⁹ WHO, Pan American Health Organization (PAHO). Monitoring National Cervical Cancer Prevention and Control Programmes: Quality Control and Quality Assurance for Visual Inspection with Acetic Acid (VIA)-Based Programmes. Geneva: WHO; 2013.
- ²⁰ Gaffikin L, Blumenthal PD, Emerson M, Limpaphayom K. Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. *Lancet*. 2003;361(9360):814–820.
- ²¹ de Cristofaro D, Fontana P, Pezzoli C. Pathologic study of the cervix after cold coagulation. *Am J Obstet Gynecol*. 1988;159(5):1053–1054.
- ²² Haddad N, Hussein I, Blessing K, Kerr-Wilson R, Smart G. Tissue destruction following cold coagulation of the cervix. *Journal of Gynecologic Surgery*. 1988;4(1):23–27.
- ²³ Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst*. 2005;97(14):1072–1079.
- ²⁴ Muwonge R, Wesley RS, Nene BM, et al. Evaluation of cytology and visual triage of human papillomavirus-positive women in cervical cancer prevention in India. *Int J Cancer*. 2013. Epub ahead of print. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/ijc.28627/pdf>. Accessed December 6, 2013.
- ²⁵ Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Med*. 2013;11(1):227.
- ²⁶ Powell SE, Hariri S, Steinau M, et al. Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. *Vaccine*. 2012;31(1):109–113.
- ²⁷ Malagon T, Drolet M, Boily MC, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(10):781–789.
- ²⁸ Van d, V, Boily MC, Drolet M, et al. Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: a model-based analysis. *J Natl Cancer Inst*. 2012;104(22):1712–1723.