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ARTICLE

A critical assessment of screening methods for cervical neoplasia

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Abstract The objective of cervical cancer screening is to reduce cervical cancer incidence and mortality by detecting and treating precancerous lesions. Conventional cytology is the most widely used cervical cancer screening test. Although cytology has been effective in reducing the incidence of and mortality from cervical cancer in developed countries in both opportunistic and—more dramatically—organized national programs, it has been less successful and largely ineffective in reducing disease burden in low-resource settings where it has been implemented. Liquid-based cytology, testing for infection with oncogenic types of human papillomaviruses, visual inspection with 3—5% acetic acid, magnified visual inspection with acetic acid, and visual inspection with Lugol's iodine have been evaluated as alternative tests. Their test characteristics, and the applications and limitations in screening, are discussed with an emphasis on the work of the Alliance for Cervical Cancer Prevention over the past 5 years.

1. Introduction

Cervical cancer continues to be an important public health problem for adult women in many developing countries [1]. Although organized and high-level opportunistic, frequently repeated cytology screening has resulted in a large reduction in the cervical cancer burden in developed countries, incidence rates in developing countries continue to be unabated for want of effective screening programs.

Screening involves application of a relatively simple, inexpensive test to a large number of

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asymptomatic people in order to classify them as likely or unlikely to have the disease of interest. Screen-positive persons are then subjected to further investigative/treatment procedures. The objective of cervical cancer screening is to reduce cervical cancer incidence and mortality by detecting and treating precancerous lesions. It is well established that invasive cervical carcinomas develop from preexisting, slowly progressing intraepithelial dysplastic precursor lesions. The direct precursor to invasive squamous carcinoma is a high-grade squamous intraepithelial lesion (HSIL) or cervical intraepithelial neoplasia grades 2 and 3 (CIN 2—3), one-third to one-half of which may progress to cervical cancer over a period of 10—15 years. Most low-grade squamous intraepithelial lesions (LSILs) regress spontaneously. Adenocarcinoma in situ (AIS) is the precursor lesion for invasive adenocarcinoma.

The ultimate proof of success of cervical screening is its ability to reduce the incidence of and deaths from cervical cancer in a cost-effective manner. One of the prerequisites for effective screening is the availability of a suitable cervical screening test that has adequate sensitivity and specificity for detection of precancerous lesions and that yields reproducible results. Such a test should be cheap, simple, and easy to apply; without side effects or complications; as painless as possible; and socioculturally acceptable.

Conventional cervical cytology is the most widely used cervical screening test. Liquid-based cytology, human papillomavirus (HPV) testing, visual inspection with 3—5% acetic acid (VIA), magnified visual inspection with acetic acid (VIAM), and visual inspection with Lugol's iodine (VILI) have also been evaluated, but to a lesser extent. In general, all cervical screening tests, particularly visual tests, predominantly detect squamous lesions and are of limited value in the detection of glandular precursor lesions as a result of difficulties in sampling and visualizing the endocervical canal, as well as less experience among readers in recognizing AIS.

An appropriate design for estimating accuracy is a cross-sectional study comparing screening test results with those of a reference standard. The most widely used reference standard for cervical cancer screening studies are histology and negative colposcopy, although these themselves are not perfect diagnostic tests. Estimates of accuracy from cross-sectional studies will suffer from verification bias if the reference standard for the final diagnosis is applied in different proportions of screen-positive and screen-negative subjects. Verification bias results in inflated estimates of sensitivity and may be minimized by applying the reference standard to all participants or by statistical adjustment.

This article highlights the contributions of a number of cervical cancer screening studies organized through the Alliance for Cervical Cancer Prevention (ACCP), supported by the Bill & Melinda Gates Foundation, in the critical evaluation of the role of alternative tests in screening programs in low-resource settings.

2. Conventional cervical cytology

To date, cervical cancer prevention efforts worldwide have focused on screening sexually active women with conventional cytology and treating precancerous lesions. Cytology screening involves collection of cervical cell samples, followed by slide preparation, staining, reading, and reporting. These services require three types of personnel: (1) a doctor or nurse who collects cells by sampling the transformation zone (TZ) and prepares and fixes the smear; (2) cytotechnicians who process, stain, and read smears; and (3) a cytopathologist who is responsible for supervision and final reporting. Cytology requires a laboratory infrastructure, with internal and external quality control, for processing slides and microscopy, and a system for communicating the results to the women. High-quality training, continuing education, and proficiency testing of personnel are essential to ensure reliable and efficient testing. Cytotechnicians require a long training period, ranging from 12 to 24 months, involving extensive theoretical and practical training.

In three recent reviews of the accuracy of cervical cytology, the sensitivity of this test in detecting CIN 2—3 ranged from 47% to 62% and the specificity ranged from 60% to 95% [2—4]. Many studies covered in these reviews suffered from deficiencies in study methods, particularly verification bias and unblinded or nonindependent assessments, and many included follow-up data from women who had already had abnormal test results. The mean sensitivity and specificity, based on these three reviews, were 59% and 75%, respectively. Both sampling and reading errors contributed to the low-to-moderate sensitivity found for cytology.

Information on test accuracy for cytology from recent cross-sectional studies in developing countries is described in Table 1 [5—10]. The sensitivity ranged from 44% to 78% and the specificity ranged from 91% to 96% in these studies. In a study of 2130 women in Harare, Zimbabwe, the sensitivity and

Table 1 Accuracy of conventional cytology in detecting CIN 2—3 lesions and invasive cancer in selected cross-sectional studies in developing countries (test positive threshold of LSIL)

Author, year of publication, country of study	No. of participants	Sensitivity, % (95% CI)	Specificity, % (95% CI)
University of Zimbabwe/JHPIEGO [5], 1999, Zimbabwe	2092	44 (37—51)	91 (89—92)
Denny et al. [6], 2000, South Africa	2885	78 (67—87)	95 (94—96)
Wright et al. [7], 2000, South Africa	1352	61 (46—74)	96 (94—97)
Denny et al. [8], 2002, South Africa[a,c]	2754	57 (46—67)	96 (95—97)
Cronjé et al. [9], 2003, South Africa	1093	48 (38—60)	96 (94—97)
Sankaranarayanan et al. [10], 2004, India[b,c]	22,663	61 (56—66)	95 (94—95)

Note. CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion; and CI: confidence interval.
[a] For CIN 2—3 lesions.
[b] Pooled results of five studies from Jaipur, Kolkata, Mumbai, and Trivandrum.
[c] Alliance for Cervical Cancer Prevention study.

specificity of cytology were 44.3% (95% CI, 37.3—51.4%) and 90.6% (95% CI, 89.2—91.9%), respectively [5]. In four studies in South Africa, cytology had a sensitivity ranging from 48.9% to 78.3% and a specificity ranging from 94.2% to 96.3% [6—9]. In a pooled analysis of five studies involving 22,663 women aged 25—65 years, under the ACCP portfolio in India, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for cytology at LSIL threshold to detect CIN 2—3 lesions and invasive cancer were 60.8% (95% CI, 56.0—65.5%), 94.9% (95% CI, 94.6—95.1%), 18.6% (95% CI, 16.6—20.7%) and 99.2% (95% CI, 99.1—99.3%), respectively; sensitivity varied from 36.5% to 78.0% among the five Indian studies [10].

There have been attempts to improve the sensitivity of cytology by combining it with a second test. This is based on the assumption that, as a result of substantial gains in sensitivity, the extra costs of dual testing may be offset by increasing the screening intervals. However, the cost effectiveness of adjunctive testing remains to be established. When tests are used in combination, women with positive results of either cytological testing or an HPV test are considered test positive. A recent review of seven cross-sectional studies indicated that a combination of cytology and HPV testing had a sensitivity of 94% or greater in detecting cervical neoplasia, a significant improvement over cytology alone; a modest reduction in specificity, compared with that of cytology alone, was observed in the studies [11]. In an ACCP study in Mumbai, India, the sensitivity of cytology was improved from 57.4% (95% CI, 47.2—70.8%) to 83.3% (95% CI, 70.7—92.1%) by adding VIA to cytology as an adjunctive test; however, the specificity decreased from 98.6% (95% CI, 98.2—99.0%) to 87.4% (95% CI, 86.2—88.4%). The combination of cytology and VILI significantly improved test sensitivity to 88.9% (95% CI, 77.4—95.8%) but specificity decreased to 83.2% (95% CI, 81.9—84.4%) [12].

Even though the impact of cytology screening has never been proved through randomized trials, such testing has been shown to be effective in reducing the incidence of and mortality from cervical cancer in developed countries [13]. Cervical cancer incidence has been reduced by as much as 80% in areas with high-quality screening, high coverage, and reliable follow-up of women. Organized programs with systematic call, recall, follow-up, and surveillance systems have shown the greatest effect (e.g., those in Finland and Iceland) while using fewer resources than less-organized programs (e.g., those in the United States and Canada).

Cytology screening programs have been introduced in some developing countries, particularly in Latin America and the Caribbean, over the last three decades. Generally, they have been ineffective in reducing disease burden because of several factors, such as suboptimal performance of cytology, lack of quality control, and inefficiency of systems for following up and treating screen-positive women [13—15]. In Peru, an ACCP study found that only 23% of women with positive results of cytology had adequate diagnostic work-up and treatment as required [15]. The reported wide variation in the accuracy of cytology programs in low-resource settings and their failure to have an impact on cervical cancer incidence and mortality have encouraged a vigorous search for alternative methods of screening.

3. Liquid-based cytology

Liquid-based cytology (LBC) relies on a fluid medium to preserve collected cervical cells. The suspension is then processed to provide a uniform, thin layer of cervical cells without debris on a glass slide. The advantages of LBC include an increased possibility of a more representative and complete transfer of cervical cells from the sampling device

to the slide and improved microscopic readability due to the elimination of problems such as poor fixation, air-drying artifact, uneven thickness of the cellular spread, debris from blood and inflammatory cells, and overlapping of cells. Cell suspension remaining after the preparation of the smear is suitable for additional testing procedures, such as HPV testing.

Reviews of published studies indicate that LBC improves sample adequacy and is probably more sensitive but less specific than Pap smear in detecting cervical neoplasia [4,16]. A study conducted in Costa Rica reported that LBC had significantly higher sensitivity than conventional cytology [17]. In an ACCP study in Peru, the proportion of inadequate smears was 5.7% with LBC, compared with 13.8% with conventional cytology; the test positivity rate at atypical squamous cells of undetermined significance (ASCUS) threshold was 18.0% with LBC, compared with 2.1% with conventional cytology.

The impact of LBC on cancer incidence and mortality remains to be established, as does its cost-effectiveness. LBC is more expensive than conventional cytology and requires additional instrumentation to prepare the smears. It is not feasible to implement LBC in many low-resource settings.

4. HPV testing

It has been well established that cervical neoplasia are caused by persistent infection with certain oncogenic types of HPV. This knowledge has led to the evaluation of HPV testing as a screening tool. The second-generation Hybrid Capture II (HC II) probe B (which is a pool of full-length RNA probes for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) microtiter assay (Digene, Gaithersburg, MD, USA) has been used for HPV testing in a number of studies. Polymerase chain reaction assays have also been evaluated. Cervical samples were classified as positive for high-risk HPV DNA (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) using HC II if the relative light unit (RLU) reading obtained from the luminometer of the HC II assay equipment was equal to or greater than the mean of the positive control (PC) values supplied by the HC II kit. A positive result is recorded for specimens with RLU-to-PC ratio of 1 or greater, corresponding to 5000 or more viral copies.

The accuracy of HPV testing by HC II in primary screening for cervical neoplasia has been evaluated in several cross-sectional studies [6,7,18–20] and is an approved technique for screening and triage of equivocal cervical abnormalities in Western countries. The sensitivity of HPV testing with HC II in detecting CIN 2–3 lesions and invasive cancer varied from 66% to 100% and the specificity varied from 61% to 96% (Table 2). The sensitivity of HPV testing when specimens have been obtained and/or analyzed in developing-country settings has generally been lower than when the entire specimen chain (from collection through testing) was completed in a developed country. In a pooled analysis of four ACCP cross-sectional studies with a common protocol in India, involving 18,085 women aged 25–65 years, the sensitivity, specificity, PPV, and NPV for HPV testing to detect CIN 2–3 lesions and invasive cancer were 68.2% (95% CI, 61.9–74.1%), 93.8% (95% CI, 61.9–74.1%), 12.8% (95% CI, 11.0–14.8%), and 99.5% (95% CI, 99.4–99.6%), respectively [19]. The sensitivity varied from 50.0% to 80.0% among the four studies.

The sensitivity of HPV testing in vaginal self-sampling studies was generally lower than that in studies that used direct sampling of cervical cells by clinicians or nurses [7,20]. That the sensitivity was lower in self-sampling studies than clinician-sampling studies indicates that adequacy of specimen collection is an important determinant of the success of HPV testing.

Table 2 Accuracy of human papillomavirus testing in detecting CIN 2–3 lesions and invasive cancer in selected cross-sectional studies

Author, year of publication, country of study	No. of participants	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Womack et al. [18], 2000, Zimbabwe	2140	81 (74–86)	62 (59–64)
Denny et al. [6], 2000, South Africa	2885	73 (62–82)	92 (91–93)
Wright et al. [7], 2000, South Africa	1352	84 (71–92)	83 (80–85)
Franco [20] 2003, review of 13 studies		66–100[a]	61–96[a]
Sankaranarayanan et al. [19], 2004, India[b]	18,085	68 (61–74)	94 (93–94)

Note. CIN: cervical intraepithelial neoplasia and CI: confidence interval.
[a] Range of values in individual studies.
[b] Alliance for Cervical Cancer Prevention study.

5. VIA

VIA, also known as "direct visual inspection," the "acetic acid test" or "cervicoscopy," involves naked-eye inspection of the cervix under bright light at least 1 minute after the application of 3—5% dilute acetic acid using a cotton swab or a spray and looking for the appearance of acetowhite areas in the TZ, close to the squamocolumnar junction (SCJ) or the os. Acetowhitening is not specific to cervical neoplasia and it may be observed in immature squamous metaplasia and in inflamed and regenerating cervical epithelium. However, areas of cervical neoplasia appear as more dense and well-defined acetowhitening in the TZ.

A wide range of health care providers, including trained medical and nonmedical personnel, can provide VIA after a short period of competency-based training of roughly 5—10 days [21—23]. The most common method of categorizing the results of VIA, and the method subscribed to by all ACCP members, is as negative and positive. Although uniform criteria for reporting VIA results remain to be agreed on, a positive classification is based on the appearance of well-defined, densely opaque acetowhite lesions in the TZ close to the SCJ or the external os, or on acetowhitening of a cervical growth. Anything that does not meet the criteria for a positive test, including the absence of acetowhite lesions; faint, ill-defined translucent acetowhite areas; faint acetowhitening of endocervical polyps; Nabothian cysts; dot-like acetowhite appearance; and prominent SCJ, is categorized as negative. The immediate availability of results after visual testing is a major logistic advantage in providing diagnosis and/or treatment for screen-positive women.

The test characteristics of VIA have been evaluated in several cross-sectional studies and the results from selected studies, including ACCP studies, are given in Table 3 [5,6,8,9,24,25]. The sensitivity varied from 67% to 79% and the specificity ranged from 49% to 86% in these studies. The estimates of sensitivity and specificity from these studies generally fall in a range within that reported for cytology and HPV testing.

VIA-positive women are managed using the methods usually used after positive cytology. An innovative option that takes advantage of the immediate availability of VIA results is the "screen-and-treat" or "single-visit" approach to ensure high treatment compliance, in which screen-positive women who are without clinical evidence of invasive cancer and who satisfy the criteria for ablative therapy are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology [26]. The safety, acceptability, and feasibility of a single-visit approach combining VIA and cryotherapy were assessed in an ACCP study in rural Thailand [26]. Trained nurses tested 5999 women with VIA, of whom 798 (13.3%) had positive results. Of 618 women eligible for immediate cryotherapy, 609 (98.5%) accepted immediate treatment. Overall, 756 women received cryotherapy (either immediately or postponed), after which no major complications were recorded and only 33 (4.4%) of treated women returned for a perceived problem. At the 1-year follow-up visit, the VIA-negative rate was 94.3%. The efficacy of this approach in preventing CIN is currently being assessed in a randomized clinical trial in South Africa.

The efficacy of once-in-a-lifetime VIA screening in reducing incidence of and mortality from cervical cancer is being assessed in two cluster-randomized, controlled clinical trials in the ACCP portfolio in India [27—29]. In one of the studies, women aged 30—59 years in 113 clusters in Dindigul District, South India, were randomized to VIA screening by nurses (57 clusters, 48,225 women)

Table 3 Accuracy of visual inspection with acetic acid in detecting CIN 2—3 lesions and invasive cancer in selected cross-sectional studies

Author, year of publication, country of study	No. of participants	Sensitivity, % (95% CI)	Specificity, % (95% CI)
University of Zimbabwe/JHPIEGO [5], 1999, Zimbabwe	2148	77 (70—82)	64 (61—66)
Denny et al. [6], 2000, South Africa	2885	67 (56—77)	84 (82—85)
Belinson et al. [24], 2001, China	1997	71 (60—80)	74 (71—76)
Denny et al. [8], 2002, South Africa[a,c]	2754	70 (59—79)	79 (77—81)
Cronjé et al. [9], 2003, South Africa	1093	79 (69—87)	49 (45—52)
Sankaranarayanan et al. [25], 2004 India and Africa[b,c]	54,981	79 (77—81)	86 (85—86)

Note. CIN: cervical intraepithelial neoplasia and CI: confidence interval.

[a] Estimates for CIN 2—3 lesions only.

[b] Pooled results of 11 studies from Jaipur, Kolkata, Mumbai, and Trivandrum in India and Burkina Faso, Congo, Guniea, Mali, and Niger in Africa.

[c] Alliance for Cervical Cancer Prevention study.

and to a control group (56 clusters, 30,167 women) [28]. Of the 30,577 eligible women screened, 2939 VIA-positive women (9.6%) were investigated with colposcopy by nurses and 2777 women (9.1%) had biopsy. The detection rates of lesions per 1000 screened women were 58.2 for CIN 1, 7.3 for CIN 2—3, and 2.3 for invasive cancer; 71% of women with CIN 1 and 80% of those with CIN 2—3 lesions accepted cryotherapy provided by nurses and surgical treatment by midlevel clinicians. In the screened arm, 35.0% of women with invasive cancer were in stage I, compared with none in the control arm.

In the second of these two ACCP trials, which involved 142,701 women in Osmanabad district, western India, the cost-effectiveness of a single round of VIA, cytology, and HPV testing in reducing cervical cancer incidence and mortality, in comparison with a control group of women who received usual care (no screening), is being investigated [29] 26,512 (71.9%) of 36,874 eligible women in the VIA arm, 25,656 (72.9%) of 35,193 eligible women in the cytology arm, and 27,371 (74.1%) of 36,938 eligible women in the HPV testing arm were screened. The test-positive rates of VIA, cytology, and HPV testing were 14.0%, 7.0%, and 10.3%, respectively. The detection rate of CIN 2—3 was similar between arms (p=0.06): 0.7% (194 cases) for VIA, 1.0% (259 cases) for cytology, and 0.9% (243 cases) for HPV. In the screened groups, 53—67% of women with invasive cancers had stage I disease compared with 19% of women in the control group. The ultimate effectiveness of the three approaches will become clear with follow-up for cancer incidence and mortality.

A VIA-based ACCP screening program has been implemented through the routine health care services in San Martín Province, Peru, to assess how this would work in a "real-life" setting. Preliminary results based on a cross-sectional evaluation of 5460 women screened as part of this project indicate a VIA positivity rate of 24%. The sensitivity and specificity of VIA in detecting high-grade lesions were 55.9% (95% CI, 46.7—63.4%) and 76.4% (95% CI, 75.0—77.5%).

Recently published model-based studies of cost-effectiveness comparing VIA, cytology, and HPV testing linked to referral and/or treatment as part of single- versus multiple-visit algorithms suggest that single- or two-visit screen-and-treat strategies that use either VIA or HPV DNA testing for screening will be highly attractive in terms of cost and effectiveness compared with conventional cytology screening in which women with abnormal cervical cytology undergo colposcopy [30,31].

6. VIAM

The added value of low-level magnification (×2—4) in visualizing acetowhite changes after acetic acid application has been investigated [6,8,32]. It was hypothesized that low-level magnification could eliminate a proportion of false-positive identifications that result from squamous metaplasia and inflammatory conditions without significant reduction in sensitivity. Magnification might even increase the sensitivity by allowing better visualization of acetowhite lesions located close to the SCJ.

In a study from South Africa under the ACCP portfolio, 2754 women were screened using both VIA and VIAM [8]. The sensitivity of VIA for CIN 2—3 lesions was 69.8% (95% CI, 59.4—78.5%) and the sensitivity for VIAM was 74.0% (95% CI, 63.8—82.1%). The accuracy of both VIA and VIAM was similar in three other ACCP studies involving 16,900 women [32]. The pooled sensitivity and specificity for VIA in detecting CIN 2—3 lesions and invasive cancer were 65.2% (95% CI, 59.6—70.7%) and 86.8% (95% CI, 86.3—87.3%), respectively; these values were 68.0% (95% CI, 62.3—73.3%) and 86.8% (95% CI, 86.2—87.3%), respectively, for VIAM. The results from these studies establish that magnification did not improve the test performance over and above that of naked-eye visualization.

7. VILI

VILI, similar to Schiller's iodine test of the 1930s, involves naked-eye examination of the cervix to identify mustard-yellow iodine-nonuptake areas after application of Lugol's iodine. The use of Schiller's test was largely discontinued after the introduction of cytology.

Recently, the role of iodine application was reevaluated by a group of investigators in India and Africa, prompted by the ease with which test providers recognized the yellow stain after iodine impregnation [25]. The test providers in these studies used a written manual and an atlas of the staining patterns associated with normal cervix, ectropion, polyps, inflammatory conditions and squamous metaplasia, and neoplastic conditions [21]. The principles of training providers in VILI are similar to those for training providers in performing VIA. A positive result is based on the appearance of a definite yellow area in the TZ close to the SCJ or the os or on a growth.

Among the ACCP studies were ten cross-sectional studies involving 49,080 women in Burkina

Faso, Congo, Guinea, India, Mali, and Niger that evaluated the accuracy of VILI [25]. For the final diagnosis, all women were investigated with colposcopy and biopsies were directed depending on colposcopic abnormality. A total of 938 women had CIN 2—3 lesions and 231 had invasive cancer. The pooled sensitivity, specificity, PPV, and NPV for detecting CIN 2—3 lesions and invasive cancer were 92.2% (95% CI, 90.5—93.7%), 85.4% (95% CI, 85.1—85.7%), 13.3% (95% CI, 12.5—14.0%), and 99.8% (95% CI, 99.7—99.8%), respectively. The ranges of sensitivity and specificity for VILI among the ten study sites were 77.8—98.0% and 73.0—91.3%, respectively. No adverse reaction to iodine was reported at these sites. These results indicate that VILI is a more sensitive test than VIA, but these results need to be replicated in other settings.

8. Conclusions

Currently, evidence for a decrease in incidence of and mortality from cervical cancer is available only for conventional cervical cytology and only from developed countries. In several developing-country regions where cervical cytology programs were implemented, no significant reduction in disease burden has been observed, partly because of poor quality of testing and programmatic deficiencies in coverage of the population, follow-up, and treatment of screen-positive women. The success of cervical cytology in organized screening programs in developed countries seems to be due to repeated testing at frequent intervals (1—5 years), high population coverage, and quality-control procedures. Cytology is not a viable option in many low-resource countries because of an inability to meet requirements such as trained human resources, supplies, mechanisms for delivery of samples and results, laboratory infrastructure, and the needed financial resources.

Among the visual screening tests, VIA and VILI are promising approaches, particularly in low-resource settings. VILI seems to be more sensitive than VIA, but these results need to be replicated in other settings. The immediate availability of results after visual testing provides a major logistic advantage in providing follow-up care for screen-positive women. Recently, a working group of the International Agency for Research on Cancer concluded that although there is sufficient evidence that HPV testing can reduce mortality from cervical cancer, the evidence for VIA and VILI is still limited [33]. Findings from the ongoing ACCP studies will be vital for further conclusive evaluation of the visual tests. Almost all information on the test qualities of visual tests comes from clinical research settings. Currently, only limited information is available on how the visual screening tests will perform when introduced for routine use in "real-life" settings. A major VIA-based screening program implemented in the San Martín province in Peru under the ACCP portfolio of studies will provide useful information in this context.

For purposes of standardization, uniform criteria for reporting visual tests remain to be established. Because visual tests, like cytology, are essentially subjective, quality control is an important issue. A fair degree of agreement (agreement rate, 64.5%; kappa value, 0.38) was observed between the master trainer and test providers for VIA in the ACCP's large Indian cross-sectional study; the agreement rates varied from 52.8% to 80.2% (range in kappa values, 0.15—0.65) among the study centers [25]. Cervical photographs taken after application of acetic acid were used for this evaluation. In another study that used photographs of acetic acid-impregnated cervices, a moderate to substantial degree of agreement was observed among expert trainers in different study settings [34]. Nevertheless, assuring the quality of visual screening methods in field conditions can be a challenge. Close monitoring of test-positivity and disease-detection rates, as well as periodic retraining, are essential to maintain good standards of visual testing.

Although HPV testing is a promising approach, it is currently far more expensive (US$20—30) than other screening tests and requires sophisticated laboratory infrastructure, including testing equipment, storage facilities for samples, and trained technicians. If the testing is not performed in ideal conditions, sensitivity may be low and reproducibility may be poor. Testing must be less expensive and the required infrastructure less sophisticated to make HPV testing more accessible in low-resource settings.

In summary, the work of the ACCP in the last 5 years has added substantial knowledge about the role of alternative screening tests in cervical cancer prevention in low-resource settings. Considerable information on the acceptability, reproducibility, accuracy, and limitations of the screening tests has been generated as a result of ACCP studies in several countries, leading to extensive literature on cervical cancer screening in low-resource settings. ACCP studies have provided data on intermediate outcomes for screening with alternative tests in controlled settings. The long-term results from the ACCP randomized, controlled screening trials and demonstration proj-

ects will be valuable in assessing the efficacy and cost-effectiveness of screening programs using alternative tests in reducing cervical cancer burden and will help in formulating evidence-based cervical cancer prevention policies worldwide.

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