Research Article

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Determinants of VIA (Visual Inspection of the Cervix After Acetic Acid Application) Positivity in Cervical Cancer Screening of Women in a Peri-Urban Area in Andhra Pradesh, India

Haripriya Vedantham[1], Michelle I. Silver[2], B. Kalpana[1], C. Rekha[1], B.P. Karuna[1], K. Vidyadhari[1], S. Mrudula[1], Brigitte M. Ronnett[4], K. Vijayaraghavan[1], Gayatri Ramakrishna[5], Pavani Sowjanya[5], Shantha Laxmi[5], Keerti V. Shah[3], and Patti E. Gravitt[2,3] for the CATCH Study Team

Abstract

Objectives: Visual inspection of the cervix after acetic acid application (VIA) is widely recommended as the method of choice in cervical cancer screening programs in resource-limited settings because of its simplicity and ability to link with immediate treatment. In testing the effectiveness of VIA, human papillomavirus DNA testing, and Pap cytology in a population-based study in a peri-urban area in Andhra Pradesh, India, we found the sensitivity of VIA for detection of cervical intraepithelial neoplasia grade 2 and worse (CIN2+) to be 26.3%, much lower than the 60% to 90% reported in the literature. We therefore investigated the determinants of VIA positivity in our study population.

Methods: We evaluated VIA positivity by demographics and reproductive history, results of clinical examination, and results from the other screening methods.

Results: Of the 19 women diagnosed with CIN2+, only 5 were positive by VIA (positive predictive value, 3.1%). In multivariate analysis, VIA positivity (12.74%) was associated with older age, positive Pap smear, visually apparent cervical inflammation, and interobserver variation. Cervical inflammation of unknown cause was present in 21.62% of women. In disease-negative women, cervical inflammation was associated with an increase in VIA positivity from 6.1% to 15.5% ($P < 0.001$). Among the six gynecologists who performed VIA, the positivity rate varied from 4% to 31%.

Conclusions: The interpretation of VIA is subjective and its performance cannot be readily evaluated against objective standards.

Impact: VIA is not a robust screening test and we caution against its use as the primary screening test in resource-limited regions. *Cancer Epidemiol Biomarkers Prev; 19(5); 1373–80. ©2010 AACR.*

Introduction

The much higher incidence of cervical cancer in developing nations, as compared with that in developed nations, has been ascribed to the fact that it has been possible to maintain effective Pap smear screening programs in the developed world but not in the developing world (1). An effective Pap smear screening program requires many consecutive steps, including (*a*) the collection in the clinic of cells from the transformation zone of the cervix and the endocervix, (*b*) smearing the cells on a slide and fixing them, (*c*) staining and reading the slide by a cytopathologist, (*d*) transmitting the cytology results to the health care provider, (*e*) communicating the cytology results to the woman and arranging for a second visit if the smear is abnormal, and (*f*) a second visit by the woman for additional tests (e.g., colposcopy and cervical biopsy) or for treatment. The infrastructure required for all these steps has not been available in the developing world and there has been a strong need for a screening test that is simpler and can be interpreted immediately and

Authors' Affiliations: [1]SHARE INDIA, Mediciti Institute for Medical Sciences, Ghanpur, India; Departments of [2]Epidemiology and [3]Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health; [4]Departments of Pathology and Gynecology and Obstetrics, Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland; and [5]Center for DNA Fingerprinting and Diagnostics, Hyderabad, India

Note: Members of the CATCH Study Team are listed in Supplementary data, available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Patti E. Gravitt, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E6148, Baltimore, MD 21205. Phone: 443-287-6179; Fax: 410-955-1383. E-mail: pgravitt@jhsph.edu

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combined with treatment, if necessary, at the initial screening visit.

Visual inspection of the cervix after acetic acid application (VIA) has long been regarded as the most promising method for screening in resource-limited settings (2, 3). VIA is performed by a trained health care provider who applies a 3% to 5% acetic acid solution to the cervix and then observes the transformation zone of the cervix for 1 to 2 minutes for acetowhite epithelium, which is thought to be indicative of abnormal cellular changes (4). In most instances, the VIA-positive woman can be treated at the same visit with cryotherapy to ablate the transformation zone. Both VIA and cryotherapy can be conducted in the field, thus eliminating the need for a clinic visit altogether. This procedure has many advantages: it can be performed by a trained paramedical worker; it needs simple equipment; the results are immediately available; and treatment, if needed, can be provided at the same visit.

We conducted a population-based study of human papillomavirus (HPV) infections and cervical cancer in Medchal Mandal, a peri-urban area near Hyderabad, in Andhra Pradesh, India.[6] A major goal of the study was to examine which screening methods are most effective when applied in a typical peri-urban Indian setting. We compared VIA, cervical cytology, and an HPV DNA assay [Qiagen's Digene hybrid capture 2 (hc2) test] for detection of cervical intraepithelial neoplasia grades 2 and 3 and cervical cancer (CIN2+). The sensitivity of VIA for detection of CIN2+ in our study, based on women who were fully evaluated, was 26.3%, a value much lower than those reported in the literature. In contrast, performances of cervical cytology (sensitivity, 63.2%) and HPV DNA screening (sensitivity, 84.2%) were comparable to previous reports (5, 6). The sensitivity estimates were lower for all three assays when they were adjusted for verification bias.

To better understand the causes for the poor performance characteristics observed for VIA, we have conducted an analysis to identify possible determinants of VIA positivity in our population.

Materials and Methods

Study design and participants. Community Access to Cervical Health, or CATCH, is a population-based screening study in Medchal Mandal, a peri-urban area near Hyderabad, in the state of Andhra Pradesh, India. The study aimed to enroll all eligible women, 25 years and older, who were not pregnant and had not had a hysterectomy (7). Details of the study are presented elsewhere (manuscript submitted). In brief, a total of 2,331/5,603 (41.6%) eligible women were enrolled between January 2005 and July 2007. Participants consented to an interviewer-administered questionnaire and also provided biological specimens. The participants were screened by Pap smear and HPV DNA testing of a physician-collected cervical swab, as well as by VIA. Twenty percent of the women enrolled were randomly selected to receive colposcopy on the day of enrollment regardless of test results to allow adjustment for verification bias. All women found to have one or more positive tests (n = 582) were invited back for a second visit for colposcopic examination and biopsy where indicated. Compliance with colposcopic follow-up was 66%. The study protocol was approved by the Institutional Review Boards in India (SHARE Research/Mediciti Institute of Medical Sciences, Ghanpur, Andhra Pradesh) and in Baltimore (Johns Hopkins Bloomberg School of Public Health).

Using interviewer-administered standardized questionnaires, we collected basic demographic information including age, educational attainment, occupation, religion, family income, and other socioeconomic status markers including total members of household, number of rooms in household, inside toilet/running water, type of cooking fuel, and whether cooking was done indoors or out. We also assessed prior cervical cancer screening history and presence of gynecologic symptoms, a detailed reproductive and contraceptive use history, and current and past tobacco use and exposure to passive smoke.

Training. In keeping with our aim to evaluate the performance of the screening tests in a typical peri-urban Indian setting, we sought only readily available resources for training. Master's level technicians were trained for 3 to 5 days to perform the hc2 test by the digene representative for India. Three experienced cytologists reviewed all Pap smears, and equivocal results were arbitrated by consensus. A 1-week refresher training on the Bethesda System was provided to the senior pathologist at Johns Hopkins Medical Institutions. A total of seven gynecologists performed VIA over the study period. All of these had prior GYN clinical experience with varying degrees of postgraduate training as well. Initially, two of the study gynecologists (gynecologists 1 and 5) received hands-on training at the Tata Memorial Centre Rural Cancer Project in Barshi, Maharastra State, India, which has conducted extensive VIA screening programs in collaboration with the IARC (8, 9). These gynecologists trained the remaining four study gynecologists using the complementary JHPIEGO training handbook "Cervical Cancer Prevention Guidelines for Low-Resource Settings" with accompanying CD-ROM of cervical images (10).

Procedures. Vaginal and cervical swabs for HPV DNA testing were collected as described (7). The hc2 assay was done according to the manufacturer's instructions. Any sample with ≥1.0 relative light unit per control sample was considered positive for HPV DNA.

Pap smears were collected by spatula and endocervical brush, smeared onto a glass slide, and fixed in ethanol. A standardized data collection form was used to

[6] Gravitt et al., manuscript in preparation.

Table 1. Demographic characteristics, summary of screening results, and association with VIA positivity (χ^2)

Variable	*n* (%)*	VIA pos, *n* (%)	*P*
Age (y)			
25-29	659 (28.7)	67 (10.17)	0.002
30-34	460 (20.0)	63 (13.70)	
35-39	351 (15.3)	45 (12.82)	
40-44	256 (11.2)	30 (11.72)	
45-49	199 (8.7)	28 (14.07)	
50-54	131 (5.7)	18 (13.74)	
55-60	106 (4.6)	13 (12.26)	
60+	133 (5.8)	33 (24.81)	
Religion			
Hindu	2,023 (86.8)	251 (12.41)	0.046
Muslim	99 (4.3)	8 (8.08)	
Christian	208 (8.9)	38 (18.27)	
Other	1 (0.04)	0 (0.00)	
Education (y)			
None	1,606 (69.4)	221 (13.76)	0.048
1-8	435 (18.8)	53 (12.18)	
9+	272 (11.8)	23 (8.46)	
Marital status			
Married	2,003 (86.7)	242 (12.08)	0.028
Divorced/ widowed/ separated	308 (13.3)	51 (16.56)	
Cervical inflammation†			
Absent	1,827 (78.4)	178 (9.74)	<0.001
Present	504 (21.6)	119 (23.61)	
Had previous Pap smear			
No	2,233 (95.5)	286 (12.87)	0.654
Yes	27 (1.2)	2 (7.41)	
Don't know	79 (3.4)	9 (11.39)	
Gynecologist seen‡			
1	624 (26.8)	24 (3.85)	<0.001
3	6 (0.3)	0 (0.00)	
4	734 (31.5)	98 (13.35)	
5	313 (13.4)	97 (30.99)	
6	277 (11.9)	49 (17.69)	
7	253 (10.9)	24 (9.49)	
8	123 (5.3)	5 (4.07)	
Pap-inflammation§			
Absent	1,471 (63.1)	170 (11.56)	0.025
Present	860 (36.9)	127 (14.77)	
Pap smear‖			
Negative	1,987 (85.2)	236 (11.88)	0.003
Positive	344 (14.8)	61 (17.73)	
Hybrid capture 2			
Negative	2,091 (89.7)	258 (12.43)	0.085
Positive	240 (10.3)	39 (16.25)	
CIN2+¶			
Negative	1,950 (99.0)	155 (7.95)	0.004
Positive	19 (0.96)	5 (26.32)	

*Total numbers do not add to 2,331 because of missing data. Specifically, 36 women missing age, 18 women missing education, 20 women missing marital status, 2 women missing Pap history, 1 woman missing gynecologist seen.
†Cervical inflammation indicates erythema, edema, or bleeds on contact.
‡Gynecologist no. 2 saw patients only during the pilot phase of the project, which is not reported here.
§Inflammation recorded as present if Pap report noted partially or totally obscuring inflammation.
‖Pap smear negative, normal/reactive atypia; positive, ASC-US or more severe diagnosis.
¶Women who were referred but did not attend colpo and women who refused biopsy were excluded (*n* = 362).

document results of the cervical cytology, including the final cytologic diagnosis based on the Bethesda System (11). A cytologic abnormality of atypical squamous cells-undetermined significance (ASC-US) or more severe diagnosis was considered to be a positive Pap screening result. Inflammatory changes were frequently present in Pap smears and were noted in the data form. The presence of inflammation in the Pap smears was evaluated as a risk factor for VIA positivity.

Using standard interpretation guides, a positive VIA outcome was defined as "sharp, distinct, well-defined, dense (opaque, dull, or, oyster white) acetowhite areas with or without raised margins, abutting the squamocolumnar junction in the transformation zone" or "strikingly dense acetowhite areas in the columnar epithelium" or "condyloma and leukoplakia occurring close to the squamocolumnar junction turning intensely white" 1 minute after the application of a 5% acetic acid solution.

A separate standardized data collection form was used by the gynecologist who performed the screening to document any visible abnormalities of the external genitalia, vagina, and cervix. We defined cervical inflammation as visibly apparent erythema, edema, and/or bleeding on contact. All women with a positive test result on any one or more of the screening tests were invited back for a second visit for colposcopy (and directed biopsy where indicated). Biopsies were reviewed by the local pathologists, with a final review by an experienced gynecologic pathologist at Johns Hopkins Medical Institutions (JHMI). A histologic diagnosis of CIN2+ was required to classify

Table 2. Screening test positive prevalence and combination of test results

Screening test or test combination	Test prevalence, *n* (%)
VIA	297 (12.74)
Pap	344 (14.76)
HPV	240 (10.30)
Any test positive	733 (31.45)
All tests positive	16 (0.69)
All tests negative	1,598 (65.55)

the woman as a case. The JHMI diagnosis was used as a final case definition for this analysis.

Data analysis. Sensitivity and specificity estimates for each screening assay were calculated. Crude estimates excluded any woman who did not have the opportunity for full diagnostic verification (i.e., women who screened negative and were not randomized to immediate colposcopy, as well as referred women who refused colposcopy and/or biopsy). We also calculated verification bias–adjusted estimates using inverse-probability weighting, applying observed disease prevalence among women with colpo-biopsy results to the full cohort. Specifically, we estimated a sampling weight for each of 16 sampling strata defined by the eight combinations of Pap, VIA, and HPV test results (e.g., +++, ++−,…, −+, −), combined with the two strata of whether a colposcopy was done, and a biopsy was done when indicated. Univariate analyses to assess the distribution of VIA results with demographic and clinical exam variables were conducted using χ^2 tests. We used logistic regression to estimate odds ratios and 95% confidence intervals. Multivariate logistic regression was used to estimate the independent association of each covariate with the outcome by adjusting for potential confounding variables. Final variable selection was done using a backward stepwise elimination process. A P value of ≤ 0.05 was considered significant. All analyses were conducted using STATA version 10.0.

We did not set an upper age eligibility for participation in our study because we felt that all women over age 25 may benefit from the comprehensive screening using three different strategies. However, we recognize that programs designed around visual strategies were not intended for women over age 50 to 55 years. When we restricted our analysis to women age 25 to 50 years, our results did not change; therefore, the unrestricted analyses are presented.

Results

The population characteristics are summarized in Table 1. The women ranged in age from 25 to 85 years; about 64% were <40 years old. Almost 70% of the women reported not having any formal education. A large majority (87%) was currently married. Few women (a little more than 1%) reported having had a previous Pap smear.

Almost 32% of women had an abnormal result in at least one of the three screening tests, but less than 1% had an abnormal result in all three tests (Table 2). The distribution of the women by the results of all three assays and the distribution of the 19 women who were identified as having CIN2+ by their test results are shown in Table 3. Only 5 of the 19 women with CIN2+ were VIA positive (26.3%), as compared with 12 women who were Pap smear positive (63.2%) and 16 women who were HPV positive (84.2%).

Correlates of VIA positivity. The demographic and clinical correlates of VIA positivity in a univariate analysis are shown in Table 1. Exposures that were collected but not represented in the table were explored and found to have no association with VIA results. Univariately, VIA positivity was significantly correlated with age over 60 years; Christian or Hindu religion; less education; being divorced, widowed, or separated; visually apparent cervical inflammation; positive Pap smear; the gynecologist conducting the VIA test; microscopically evident inflammation in the Pap smear; and diagnosis of CIN2+. In multivariate analysis (Table 4), age over 60 years, positive Pap smear, visually apparent cervical inflammation, and variation in positivity rates between gynecologists remained significantly correlated with VIA positivity.

As expected, VIA positivity was associated with positivity in the other two screening tests, although the

Table 3. Distribution of the women by screening test results and disease status [*n* (%)]

VIA+ 297 (12.7)				VIA– 2,043 (87.3)			
PAP+ 61 (2.6)		PAP– 236 (10.1)		PAP+ 283 (12.1)		PAP– 1,751 (75.1)	
HPV+	HPV–	HPV+	HPV–	HPV+	HPV–	HPV+	HPV–
16 (0.7)	45 (1.9)	23 (1.0)	213 (9.1)	48 (2.1)	235 (10.1)	153 (6.6)	1,598 (68.6)
No. of CIN2+ detected in each diagnostic test category among women receiving colposcopic examination: *n/N* (%)							
↓	↓	↓	↓	↓	↓	↓	↓
4/11 (36.4)	0	1/16 (6.3)	0	6/29 (20.7)	2/131 (1.5)	5/106 (4.7)	1/304 (0.3)

Table 4. Multivariate association of risk factors for VIA positivity (n = 2,288)

Variable	OR (95% CI)	Adj. OR (95% CI)
Age (y)		
25-29	1	1
30-59	1.33 (0.99-1.79)	1.13 (0.83-1.55)
60+	2.92 (1.83-4.65)	2.08 (1.25-3.47)
Pap outcome*		
Negative	1	1
Positive	1.32 (1.04-1.70)	1.41 (1.00-1.98)
Cervical inflammation†		
Absent	1	1
Present	2.86 (2.21-3.70)	4.3 (3.16-5.86)
Gynecologist‡		
1	1	1
4	3.85 (2.43-6.10)	2.59 (1.61-4.16)
5	11.23 (6.99-18.02)	13.79 (8.43-22.57)
6	5.37 (3.22-8.96)	6.13 (3.62-10.38)
7	2.62 (1.46-4.71)	2.13 (1.17-3.89)
8	1.06 (0.40-2.83)	1.04 (0.39-2.83)

NOTE: Data were mutually adjusted for all the variables in the model; 43 dropped due to missing data.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
*Pap smear negative, normal/reactive atypia; positive, ASC-US or more severe diagnosis.
†Cervical inflammation indicates erythema, edema, or bleeds on contact.
‡Gynecologist no. 3 saw <10 patients, none of whom were VIA positive, and was therefore excluded from this analysis.

association was stronger for Pap than for hc2 (Table 1). Specifically, VIA positivity was seen in 16.3% of the 240 HPV-positive women as compared with 12.4% of the HPV-negative women (P = 0.085), and in 17.7% of the 344 Pap-positive women as compared with 11.9% of the Pap-negative women (P = 0.003). VIA was also more likely to be positive in the 19 women with CIN2+ (26.3%) as compared with women without CIN2+ (8%; P = 0.004).

Visually apparent cervical inflammation was seen in 504 (21.6%) women. We inquired if cervical inflammation increased the rate of VIA positivity in disease-negative women. Of the 2,331 women in the study, 19 were diagnosed with CIN2+, and 362 test-positive women either did not undergo colposcopy or refused a biopsy at colposcopy. After exclusion of these women, the remaining 1,950 women were considered disease negative. In this group, VIA positivity was 15.5% in women with inflammation and 6.1% in women without inflammation (P < 0.001; Table 5). In contrast, neither Pap nor HPV test positivity was significantly increased among women with clinical evidence of cervical inflammation compared with uninflamed women (9.8% versus 7.5% and 8.3% versus 5.8% for Pap and HPV tests, respectively). Thus, cervical inflammation seems to have contributed to the increase in false-positive VIA test results observed in our study, likely a result of acetowhite staining of metaplastic cells, which are common during the healing that follows robust inflammatory responses. Among the 19 disease-positive women, cervical inflammation was present in 11 (57.9%). VIA was positive in 3 of 11 (27.3%) women with cervical inflammation and in 2 of 8 (25.0%) women without cervical inflammation. These numbers were too small to determine the effect of inflammation on the diagnostic accuracy of VIA in disease-positive women.

Finally, there was a marked variation in the rates of VIA positivity among the six gynecologists who conducted the examinations (Table 4). VIA positivity ranged from a low of 4% for two gynecologists to a high of 18% for one gynecologist and 31% for another gynecologist. The greatest variation was between providers 1 and 5, the two providers who had received the most training. Among women who were satisfactorily colposcoped, only five VIA-positive women were identified as disease positive. For quality assurance for a VIA provider in our study, we would have liked to know how well her VIA results matched the final microscopic diagnosis of CIN2+. However, it was not possible to examine in a timely manner how the VIA results of an individual observer matched the final diagnosis of CIN2+ made many weeks after the initial visit.

Table 5. Distribution of positive test results among disease-negative women with and without inflammation (n = 1,950)

	With inflammation (n = 386), n (%)*	Without inflammation (n = 1,564), n (%)	P
VIA+	60 (15.5)	95 (6.1)	<0.001
Pap+	38 (9.8)	118 (7.5)	0.136
HPV+	32 (8.3)	91 (5.8)	0.074

*The percentage represents the proportion in each inflammation category with a positive screening test result (i.e., column percentages).

Discussion

The results of the VIA screening in our population were disappointing. If we had followed the frequently proposed guidelines (10, 12) of using VIA as the primary and sole screening test and offered cryotherapy to VIA-positive women, we would have performed more than 200 cryotherapies for possible benefit to only five of these women. Furthermore, if VIA had been used as the only screening assay in our population, we would have missed 14 of the 19 women (73.7%) who had cervical cancer precursor lesions. We have therefore closely examined why the test was so ineffective in our population and have also evaluated our results in the context of performance of VIA screening in previous investigations.

In univariate analyses of the determinants of VIA positivity, we found that, as expected, VIA positivity was associated with Pap smear abnormality, the diagnosis of CIN2+, and HPV positivity, confirming that the test results were related to HPV-caused disease. However, we also found two other variables unrelated to CIN2+ diagnosis that were strongly associated with VIA positivity in both univariate and final multivariate analyses. One was variation in positivity rates between observers and the other was visually apparent clinical inflammation of the cervix.

The marked observer variation raises the question of whether the test providers were adequately trained. Many previous reports have stressed the importance of training the test providers (5, 8, 13). As described in Materials and Methods, the test providers in our study were all gynecologists with significant clinical experience and they had closely followed the Cervical Cancer Prevention Guidelines for Low-Resource Settings competency-based training tool prepared by JHPIEGO (10). Specifically, two health providers were trained at a centralized expert facility and served as local "master trainers" for the rest of the gynecologic study staff. Yearly refreshers by an expert gynecologist from New Delhi were provided. Recommendations suggest that these refresher visits use indicators to assess program performance and also incorporate performance standards to assess individual performance through on-site observation. Programmatic indicators cannot be assessed until a substantial proportion of women are screened. The key areas of the on-site assessment of the provider's performance are (*a*) the ability to correctly delineate the extent of the acetowhite lesions and (*b*) to make appropriate case management recommendations. We used the provided CD-ROM images to assess step *a*; however, proper assessment of step *b* is not feasible in real time, and with low disease prevalence would require screening of our entire population size before sufficient numbers of cases are available to make this assessment. Specifically, tissue specimens of suspect lesions are not collected before cryotherapy, and thus it would not be possible to monitor how well an individual provider's VIA diagnosis matches the pathologic diagnosis in a time frame that would allow immediate intervention including retraining. Thus, although the steps for quality assurance proposed by JHPIEGO (e.g., conducting image review exercises and co-assessments between the health provider and the quality control monitor) may decrease interobserver variation, it is hard to see how they would improve the diagnostic accuracy of the assay. In any case, it is unlikely that community-based programs in resource-poor settings will have health providers for VIA-based screening who are better trained than those in our study.

Clinical inflammation of the cervix (erythma, edema, bleeds easily) was present in 21.6% of the women. In these women, VIA positivity was recorded in 23.6%, compared with 9.7% of women without cervical inflammation. An examination of VIA in disease-negative women showed that inflammation led to more than twice the rate of false-positive VIA. Our results were similar to those in a recent study of women in rural El Salvador. Inflammation graded by microscopic examination of cervical biopsy was present in 74% of these women, and among women who had no cervical neoplasia, inflammation was associated with twice the rate of VIA positivity (14).

A previous study that examined whether "false positive" VIA results were associated with specific genital tract infections other than HPV (e.g., *Chlamydia trachomatis* and *Trichomonas*) found no evidence for such an association (3). We inquired if more ubiquitous latent herpesvirus infections commonly detected in the cervical epithelium (15-17) might be a plausible cause of the relative nonspecificity of the VIA results.[7] Although we detected EBV and cytomegalovirus DNA at the cervix of the patients (20.4% and 25.7%, respectively), these infections were not correlated with VIA reactivity. The high geographic variability in the prevalence of cervical inflammation and the inability to identify a responsible infectious agent could be expected to contribute to poor reproducibility of VIA performance across broad populations.

Our estimate of 26.3% sensitivity for detection of CIN2+ is among the lowest recorded for VIA. However, previous reports typically show a wide range of sensitivities for the assay. In the 11 studies conducted in Africa and India by the IARC with a common training protocol and test definition, one would have expected a narrow range in estimates of sensitivity. However, the sensitivity of VIA for the detection of CIN2+ in these studies varied widely, from a high of 91% to a low of 61% (6). Variability in VIA sensitivity is even more extreme when comparing across study protocols. For example, in the multicenter Latin American Screening study (18), the sensitivity of VIA for CIN2+ was 50%. In the TATI study in Peru, the sensitivity of VIA for severe dysplasia was 48% (19). In an early study in the United States, the

[7] Gravitt and Silver, unpublished data.

sensitivity of VIA for CIN2+ was 29% (20). In a review of 17 cross-sectional studies, VIA positivity rates varied from 3% to 53% (21). In their discussion about the validity of screening tests, Mahe and Gaffikin (21) list a number of reasons for the observed heterogeneity in VIA sensitivity estimates. These include lack of a standardized test definition, differences in training and skills of the test providers, underlying prevalence of other sexually transmitted infections, lack of uniformity in application of gold standard for disease definition, and absence of blinding. The results of the analyses presented here are consistent with the multifactorial causes of variability in VIA test performance and suggest that a large part of the observed variation was due to factors other than disease prevalence.

The large recently completed intervention trial in Osmanabad India, in which screenings by VIA, cytology, and HPV were compared for their ability to reduce the incidence of advanced cervical cancer and associated mortality, provides a possible example of the difficulties in interpreting VIA results even when VIA is used in the best possible circumstances. In the initial report of this investigation (8), the three assays were judged to be functioning equally well in detecting cervical cancers and precancers. However, in the final evaluation, screening with VIA (or with Pap smear) was reported to be ineffective in reducing the incidence of advanced cervical cancer and associated mortality (9). In contrast, HPV screening reduced the incidence of advanced cervical cancers and associated mortality by about 50%. Women positive in any of the three tests were managed in the same way. Therefore, it is very likely that the poor performance of VIA (and of cytology) in the final analysis was due to their lower sensitivity in identifying women with cervical cancer precursors or cervical cancer, and that the earlier interpretation of equivalent sensitivity of VIA and the HPV assay was incorrect. This collective evidence thus confirms the high degree of variability in diagnostic accuracy for the subjective VIA test, which is not substantially reduced even when using common protocols and training programs.

The positive predictive value (PPV) for VIA in our study was 3.1%, implying that if we were performing cryotherapy for all VIA-positive women, we would be conducting 32 unnecessary cryotherapies for each necessary cryotherapy. This estimate for PPV is one of the lowest reported, but low estimates are not uncommon in previous studies. In the 11 IARC-guided studies (6), the PPVs ranged from 3.8% to 22.5%. The PPV estimate in LAMS study was 6.6% (18), and in the TATI study, 6.5% (19). In the Osmanabad study the PPV was 7.4% (9), implying 13 unnecessary cryotherapies for each necessary cryotherapy, assuming that all VIA-positive women were treated with cryotherapy. It should be noted that under all of the above scenarios, a large majority of the women given cryotherapy will not have disease and that this is contrary to what is implied in the ACCP fact sheet (12) that under this scheme, only an "occasional" screen-positive disease-negative woman would be treated by cryotherapy.

We conclude that VIA screening is not robust enough for primary screening in under-resourced regions. Modified or more intensive training efforts are unlikely to result in substantial improvements and are impractical to implement on a broad scale. The 2009 ACCP fact sheet (22), released in response to the data from the Osmanabad Study (9), recommends that until HPV testing becomes feasible and affordable, programs should consider introducing or expanding VIA plus cryotherapy as a cervical cancer prevention strategy. We caution against the adoption of this approach, which may result in a large number of unnecessary cryotherapies with minimal clinical benefit. Although we recognize that more effective alternative strategies such as affordable HPV DNA testing (23) are not likely to be available for another 2 to 3 years, adopting a "something is better than nothing" approach in the interim risks entrenchment of an ineffective program and possible loss of public confidence.

Disclosure of Potential Conflicts of Interest

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