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Association between visual inspection of the cervix with acetic acid (VIA) examination and high-risk human papillomavirus (hrHPV) infection, *C. trachomatis*, *N. gonorrhoeae* and *T. vaginalis* in Papua New Guinea

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CONFLICTS OF INTEREST STATEMENT

All authors confirm that they have no commercial or other conflicts of interests.

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ABSTRACT

Background: Papua New Guinea has among the highest estimated burdens of cervical cancer globally but currently has no national cervical screening program. Visual inspection of the cervix with acetic acid (VIA) is a low-cost screening strategy endorsed by the World Health Organization that has been adopted in many low-resource settings but not previously evaluated in PNG.

Aim: To evaluate the association between VIA examination findings and high-risk HPV (hrHPV) infection; and the impact of concomitant genital C. trachomatis, N. gonorrhoeae and T. vaginalis on the interpretation of VIA findings.

Methods: A prospective clinical cohort study among women aged 30–59 years attending Well Woman Clinics in PNG. Main outcome measures were VIA examination findings and laboratory-confirmed hrHPV, C. trachomatis, N. gonorrhoeae and T. vaginalis.

Results: A total of 614 women were enrolled, of whom 87.5% (537/614) underwent VIA, and 12.5% (77/614) did not due to pre-existing cervicitis or inability to visualise the transformation zone. Among the 537 women who underwent VIA, 21.6% were VIA positive, 63.7% VIA negative, and 14.7% had indeterminate findings. The prevalence of hrHPV infection (n=614) was 14.7%; C. trachomatis, 7.5%; N. gonorrhoeae, 8.0%; and T. vaginalis, 15.0%. VIA positive women were more likely to have HPV16 (OR: 5.0; 95%CI: 1.6-15.6; p=0.006) but there was no association between HPV18/45, all hrHPV types (combined), C. trachomatis, N. gonorrhoeae or T. vaginalis.

Conclusions: VIA positivity was associated with HPV16, but not with other hrHPV infections; nor with genital C. trachomatis, N. gonorrhoeae or T. vaginalis in this setting.

INTRODUCTION

Papua New Guinea (PNG) has among the highest estimated burdens of cervical cancer globally, with incidence 6.3 times that of Australia and New Zealand (age standardized rates 34.5 vs 5.5/100,000), and mortality 13.5 times greater (21.7 vs 1.6/100,000).[1,2] Cervical cancer is the most common cancer among women in PNG and results in an estimated 1,500 deaths per year.[1-3]

There are currently no national programs for cervical cancer screening or human papillomavirus (HPV) vaccination in PNG.[3] A Pap test-based cervical screening initiative established in 1999 by a non-governmental Australian-supported charity (the MeriPath program) provided a service for more than 15 years from more than 30 health facilities in 16 provinces. The program achieved limited coverage however (around 4% of the target population), and as specimens were sent to Australia for testing, up to half of those needing further investigation or treatment were lost to follow-up due to the time between testing and recall.[4] Consequently, in 2009 a Ministerial Task Force recommended that alternative, locally-appropriate models of cervical screening and early treatment be evaluated in PNG.[5] The task force favored the 'screen and treat' approach endorsed by the World Health Organization (WHO)[6] and based on visual inspection of the cervix with acetic acid (VIA) plus ablative cervical cryotherapy.[5] Favourable performance characteristics for the detection of histologically-diagnosed cervical 'pre-cancer' (cervical intraepithelial neoplasia grade 2 or worse) in

research settings[7] has led to VIA being advocated as an accurate, low-cost cervical screening strategy, and to its implementation in several low and middle-income countries (LMICs). Many countries have however experienced difficulties scaling up VIA while maintaining adequate quality, and have reported much lower sensitivity and specificity for the detection of cervical pre-cancer compared to research settings.[8-10]

Here we report findings from the first evaluation of VIA for cervical screening in Papua New Guinea. The primary objective was to evaluate the association between VIA examination findings and the presence of high-risk HPV (hrHPV) infection. Given earlier reports of high prevalences of genital sexually transmitted infections (STIs) among women attending antenatal, sexual health and well woman clinics in this setting[11-13] an additional objective was to evaluate the impact of concomitant STIs on interpretation of VIA examination findings.

MATERIALS AND METHODS

Women aged 30–59 years (the target age group for cervical screening in PNG) attending Well Woman Clinics in Goroka, Eastern Highlands Province, and Mount Hagen, Western Highlands Province, between February 2013 and January 2015 were invited to participate, and after written informed consent, were sequentially enrolled. Women were advised to return for clinical review at 3, 6, 9 and 12 months after enrolment.

Following a short face-to-face interview to collect socio-demographic, behavioural and clinical information, women underwent a speculum examination in which endocervical specimens for HPV, Chlamydia trachomatis and Neisseria gonorrhoeae, and a posterior fornix swab for Trichomonas vaginalis, were collected. VIA examination was then carried out by a trained study clinician, and treatment provided as indicated (e.g. same-day cryotherapy; referral for specialist care). All clinic staff conducting VIA and cryotherapy were trained at an internationally-recognized centre, and underwent additional on-site training and accreditation by the same group on their return to PNG. Day-to-day support supervision and mentoring was provided by senior clinical investigators at each site (AK, BK).

VIA examination findings at baseline were categorised as ‘negative’, ‘positive’, ‘indeterminate’, or

'not done'. Women with a positive VIA examination were offered same-day ablative cervical cryotherapy. Women with 'indeterminate' findings, or in whom VIA was not carried out for any reason, were asked to return for repeat examination in 2-3 weeks. Women with genital symptoms were presumptively treated as per PNG national STI syndromic management guidelines,[14] with additional treatment provided as indicated by the results of laboratory investigations. Genital swabs were stored at -20°C onsite until transfer to the PNG Institute of Medical Research (PNGIMR) in Goroka for testing.

All laboratory investigations were conducted at the PNGIMR HIV/STI Research Laboratory. Endocervical swabs were tested for HPV genotypes using the Roche Linear Array system in accordance with manufacturer's instructions (Roche Molecular Systems, CA, USA).[15,16] Genital swabs were tested for C. trachomatis, N. gonorrhoeae and T. vaginalis by real-time polymerase chain reaction (PCR), using procedures and methods previously described.[17] The PNGIMR was enrolled in an external quality assurance program through the Royal College of Pathologists of Australia for N. gonorrhoeae and C. trachomatis PCR; and HPV genotyping.

Participant study folders (containing completed case record forms and laboratory results slips) were subject to quarterly clinical review by the study lead investigator (AV) throughout. Data were entered at each clinical site into a study-specific MS Access database. Database entries were validated against participant study folders for accuracy. Laboratory test results entered into the clinical database were checked for accuracy against source documents (laboratory results slips) for all participants at the end of the study.

Statistical considerations

Sample size requirements were based on a priori assumptions that the prevalence of hrHPV infection (all types, combined) would be around 10-15%; that around 10-15% of women would have a positive VIA examination; and that 50-80% of VIA positive women would have a detectable hrHPV infection. A sample size of 600 participants was considered sufficient to estimate the prevalence of hrHPV infection and/or VIA positivity with approximately 2-3% precision e.g. 10% VIA positivity would be estimated with 2.4% precision (95% confidence intervals [CI]: 7.6, 12.4%); and to detect an odds ratio (OR) of 3.25 or greater at the 5% significance level for the association between VIA examination findings and hrHPV infection.

We used descriptive statistics (median and interquartile range for continuous variables; percentages for categorical variables); Chi-square test or Fisher's Exact Test were used to compare statistical

significant differences in categorical outcomes of interest between groups. After the descriptive analysis, we examined the bivariate associations between VIA status (negative, positive, indeterminate not done) on laboratory findings including: any high-risk HPV (hrHPV), HPV16, HPV 18/45, chlamydia, gonorrhoea, and trichomonas infection. Odds ratios and 95% confidence intervals (CIs) were reported. All statistical analyses were performed with Stata 14.0 (StataCorp LP, Texas, USA).

Ethics approval

The study was approved by the PNGIMR Institutional Review Board (IRB No. 1124) and the Medical Research Advisory Committee of the National Department of Health (MRAC No. 11.34) in PNG; and by the Human Research Ethics Committee of the University of New South Wales in Australia (HREC No. 12155). Written informed consent (signature or witnessed thumbprint) was obtained from all participants prior to enrolment.

RESULTS

A total of 614 women were enrolled, among whom the median age was 37 years (IQR 34-41). Around 87.5% of those enrolled (537/614) underwent VIA, of whom 63.7% were VIA negative (342/537), 21.6% were VIA positive (116/537), and 14.7% (79/537) had indeterminate examination findings. Of the 614 women enrolled, 77 women (12.5%) did not undergo VIA examination at first clinic visit e.g. due to cervicitis; inability to visualise the transformation zone (Table 1).

VIA positive women were more likely to be younger (<35 years) and to report a younger age of sexual debut (<18 years) than women with a negative VIA examination, but there was no association with reported lifetime number of sexual partners (Table 1). Women with indeterminate VIA findings and those who did not undergo VIA examination were less likely to report ever having sex in exchange for gifts or money, and significantly more likely to come from Eastern Highlands compared with women who had other examination findings. VIA was not associated with marital status or educational attainment.

Overall, 90/614 (14.7%) of women had high-risk HPV infection (all types combined); 46/614 (7.5%) had C. trachomatis; 49/614 (8.0%) had N. gonorrhoeae; and 92/614 (15.0%) had T. vaginalis (Table 2). Compared to VIA negative women, women with a positive VIA examination were significantly more likely to have HPV16 (OR: 5.0; 95% CI: 1.6-15.6, p=0.006; Table 2). There was no significant difference between VIA positive and negative women for HPV18/45, all hrHPV types combined; or for C. trachomatis, N. gonorrhoeae or T. vaginalis infection.

Women with indeterminate VIA examination findings and those who did not undergo VIA at baseline were significantly less likely to have T. vaginalis infection (Table 2). Despite advice to return for clinical review at 2-3 weeks, re-attendance among women in this group was low (21.1%; 33/156), with the majority (76.0%; 25/33) found to have persistent clinical features of cervicitis and/or vagino-cervical discharge on repeat examination (data not shown).

DISCUSSION

In this study among well women clinic attendees in Papua New Guinea, VIA positivity was associated with HPV16 but not with other hrHPV infections, nor with genital C. trachomatis, N. gonorrhoeae or T. vaginalis infection.

Our findings are consistent with earlier reports that HPV16 is associated with more definite visual abnormalities on VIA examination compared with other hrHPV types.[18] A recent prospective cohort study among 7541 women aged 25-65 years in rural China however found that women who tested positive for any hrHPV infection were more likely to have a positive VIA examination than women who tested negative for hrHPV (15.0%, 95%CI: 12.9-17.2%; vs. 6.3%, 95%CI: 5.7-6.9%; p<0.001).[19] The authors also found an increasing probability of VIA being positive with increasing HPV viral load.[19]

We postulated that the high prevalence of genital STIs in this setting would affect the performance of VIA because cervical infections might lead to acetowhite staining on VIA; and hypothesized that undiagnosed STIs may have undermined the performance of VIA following large-scale implementation in other low-resource settings. Cervical inflammation of unknown cause was present in 21.6% of 2331 women participating in a cervical screening program in Andhra Pradesh, India, and was associated with an increase in VIA positivity from 6.1% to 15.5% (p<0.001) in the absence of histological evidence of cervical intraepithelial neoplasia.[20] A pilot study among 502 women in El Salvador found that women with cervicitis were twice as likely to have a positive VIA examination as women without cervicitis.[21] An earlier study among 2754 women in South Africa however, found no association between C. trachomatis or N. gonorrhoeae infection and VIA examination findings.[22] Given these conflicting findings, the relationship between cervical STIs and VIA examination may warrant further investigation. Such studies could also evaluate the role of the cervical infection Mycoplasma genitalium, which has not previously been described in this context.

Despite accredited staff training, and on-site support supervision at each clinical site during the study, around 1 in 4 women at first clinic visit either had an indeterminate VIA examination (12.9%), or did not undergo VIA for a variety of reasons (12.5%; Table 1), and were therefore unable to receive same-day screening and treatment as advocated by the WHO.[6] In addition, re-attendance for clinical review was poor in these sub-populations. These findings represent important limitations to the future application of VIA as a same-day 'screen and treat' strategy in this setting, particularly as a primary screening tool. Clinically-diagnosed cervico-vaginal discharge and cervicitis were responsible for around 44% of indeterminate VIA diagnoses, and around 31% of VIA examinations not being conducted, at first clinic visit (Table 1). Prevalences of hrHPV and genital STIs among women in this group were however similar to women with other VIA examination findings, with the exception of T. vaginalis, which was less prevalent among those who did not have VIA or had indeterminate examinations (Table 2). Our findings contrast with those reported in several other low-resource settings. A cervical screening study among 2338 women living with HIV in Kenya found that 26.4% of women were VIA positive; 70.6% were VIA negative; and 3.0% (70/2338) had unsatisfactory VIA examinations (transformation zone not fully visualised, n=11; cervicitis, n=59).[23] A study among 45,000 women in Cameroon evaluated VIA enhanced by digital cervicography (VIA-DC) for cervical screening and found that 9.0% of women were VIA-DC positive; 66.8% were VIA-DC negative; 22.0% were VIA-DC inadequate (cervix appeared normal but transformation zone not fully visualised); and 2.2% had uncertain examination findings due to concomitant cervical abnormalities confounding VIA-DC interpretation.[24]

In the last decade, the effectiveness of HPV-DNA based testing for the detection of cervical pre-cancer and cancer has been demonstrated in large-scale randomised trials and prospective studies,[25] leading to recommendations in Australia and other high-income settings for the introduction of HPV-DNA testing for primary cervical screening.[25-27] The WHO recently recommended that HPV-DNA testing be integrated into cervical screening programs in LMICs, but acknowledged that clinical algorithms based on VIA examination plus HPV testing require further evaluation.[28] The recent availability of a portable, highly-accurate, easy-to-use, nucleic acid amplification test (NAAT) for HPV-DNA (GeneXpert, Cepheid, Sunnyvale, CA) that can be provided at point-of-care in routine clinical settings in LMICs has been a significant advance.[27,29] Research to evaluate the performance of point-of-care Xpert HPV testing in combination with VIA examination for the detection of high grade cervical disease is ongoing in Papua New Guinea.[30]

CONCLUSION

In this prospective clinical cohort study among women attending cervical screening services in Papua New Guinea, VIA positivity was associated with HPV16, but not with other hrHPV infections; nor with genital C. trachomatis, N. gonorrhoeae or T. vaginalis. These findings did not support our a priori hypotheses that (a) VIA positivity would be strongly associated with hrHPV infection; or (b) that undiagnosed STIs may have undermined the performance of VIA in other low- and middle-income countries. In the last decade, the poor performance of VIA for the detection of hrHPV infection and clinical disease has been reported in several low-resource settings. At the same time, the effectiveness of HPV-DNA based testing for the detection of cervical pre-cancer and cancer has been established in large-scale clinical trials and prospective studies. Further research is needed to evaluate the performance of HPV-DNA testing in combination with VIA examination for cervical screening in PNG and other low-resource settings.

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TABLES

Table 1. Association between sociodemographic characteristics and VIA examination findings among 614 women attending Well Woman Clinics in Papua New Guinea

Table 2. Association between baseline VIA examination findings, high-risk HPV infection, and other sexually transmitted infections among 614 women attending Well Woman Clinics in Papua New Guinea

Table 1. Association between sociodemographic characteristics and VIA examination findings at study entry among 614 women attending well woman clinics in Papua New Guinea

	VIA negative N=342 (55.7%)	**VIA positive** N=116 (18.9%)	**VIA indeterminate** N=79 (12.9%)[†]	**VIA not done** N=77 (12.5%)[‡]	**p-value**
Age, median (IQR)	38 (34,42)	36 (33,40)	38 (34,42)	35 (33-38)	<0.001*
<35 years	86 (25.15)	42 (36.21)	23 (29.11)	31 (40.26)	
35-39	115 (33.63)	36 (31.03)	25 (31.65)	32 (41.56)	
35+ years	141 (41.23)	38 (32.76)	31 (39.24)	14 (18.18)	
Marital status					0.988
Not married/other	39 (11.40)	14 (12.07)	9 (11.39)	8 (10.39)	
Married	303 (88.60)	102 (87.93)	70 (88.61)	69 (89.61)	
Education					0.912
No education	98 (28.65)	33 (28.45)	19 (24.05)	22 (28.57)	
Primary school	174 (50.88)	58 (50.00)	45 (56.96)	36 (46.75)	
Secondary	38 (11.11)	13 (11.21)	11 (13.92)	11 (14.29)	
Other	32 (9.36)	12 (10.34)	4 (5.06)	8 (10.39)	
Employment[§]					
No job	170 (49.71)	42 (36.21)	57 (72.15)	42 (54.55)	<0.001*
House work	271 (79.24)	93 (80.17)	67 (84.81)	60 (77.92)	0.688
Garden work	220 (64.33)	66 (56.90)	57 (72.15)	39 (50.65)	0.021*
Teacher	13 (3.80)	6 (5.17)	3 (3.80)	4 (5.19)	0.891
Home Province					<0.001*

Eastern Highlands	172 (50.29)	52 (44.83)	57 (72.15)	47 (61.04)	
Western	84 (24.56)	34 (29.31)	6 (7.59)	6 (7.79)	
Other	86 (25.15)	30 (25.86)	16 (20.25)	24 (31.17)	
Age at sexual debut					0.148
<18 years	220 (64.33)	70 (60.34)	60 (75.95)	50 (64.94)	
18+ years	122 (35.67)	46 (39.66)	19 (24.05)	27 (35.06)	
Lifetime number of sex partners					0.088
1-person	191 (55.85)	56 (48.28)	49 (62.03)	42 (54.55)	
2-persons	71 (20.76)	29 (25.00)	13 (16.46)	14 (18.18)	
3- persons	21 (6.14)	14 (12.07)	10 (12.66)	4 (5.19)	
4+ persons	59 (17.25)	17 (14.66)	7 (8.86)	17 (22.03)	
Ever had sex in exchange for gifts/money	44 (12.87)	22 (18.97)	2 (2.53)	4 (5.19)	0.001*

† VIA indeterminate due to: cervico-vaginal infection/discharge (29.0%); cervicitis (15.2%); cervical ectopy/bleeding (20.3%); VIA findings uncertain (10.1%); other (25.4%)

‡ VIA examination not done due to: cervico-vaginal infection/discharge (15.7%); cervicitis (15.7%); transformation zone not seen (11.4%); cervical bleeding (6.0%); suspected cervical lesion (1.4%); pregnancy (1.4%); reason not recorded (48.6%)

§ Employment categories are not mutually exclusive

Table 2. Association between baseline VIA examination findings, high-risk HPV infection, and other sexually transmitted infections among 614 women attending well woman clinics in Papua New Guinea

	hrHPV (all) n=90 (%)	OR (95% CI)	HPV-16 n=18 (%)	OR (95% CI)	HPV18/45 n=13	OR (95% CI)	CT n=46	OR (95% CI)	NG n=49	OR (95% CI)	TV n=92	OR (95% CI)
VIA negative (N=342)	42 (12.3)	1	5 (1.5)	1	8 (2.3)	1	23 (6.7)	1	24 (7.0)	1	65 (19.0)	1
VIA positive (N=116)	19 (16.4)	1.40 (0.78, 2.52) p=0.263	8 (6.9)	5.00 (1.60,15.58) **p=0.006**	2 (1.7)	0.73 (0.15,3.50) p=0.696	11 (9.5)	1.45 (0.69, 3.08) p=0.330	10 (8.6)	1.25 (0.58,2.70) p=0.570	13 (11.2)	0.54 (0.28,1.02) p=0.056
VIA indeterminate / not done[1] (N=156)	29 (18.6)	1.63 (0.97, 2.73) p=0.063	5 (3.2)	2.23 (0.64,7.82) p=0.210	3 (1.9)	0.82 (0.21,3.13) p=0.770	12 (7.7)	1.16 (0.56,2.39) p=0.696	15 (9.6)	1.41 (0.72,2.77) p=0.319	14 (9.0)	0.42 (0.23,0.77) **p=0.005**

hrHPV: high-risk human papillomavirus; OR: odds ratio; CT: C. trachomatis; NG: N. gonorrhoeae; TV: T. vaginalis

[†] no significant differences in hrHPV infection or other STIs were observed between women who did not undergo VIA and those having indeterminate VIA examination findings, and hence these groups were combined