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Uptake of community-based, self-collected HPV testing *vs.* visual inspection with acetic acid for cervical cancer screening in Kampala, Uganda: preliminary results of a randomised controlled trial

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Abstract

OBJECTIVES To compare two cervical cancer screening methods: community-based self-collection of high-risk human papillomavirus (HR-HPV) testing and visual inspection with acetic acid (VIA).
METHODS Pilot randomised controlled trial of 500 women aged 30–65 in the community of Kisenyi, Uganda. Women randomised to self-collection-based HR-HPV testing provided a cervico-vaginal swab for HR-HPV, and results were provided by phone after laboratory testing. Women who tested HPV positive were referred for VIA at the local health unit. Women randomised to VIA underwent screening at the local health unit, where women who tested positive with VIA were provided cryotherapy at time of screening, as per local standard of care. Women were referred for colposcopy when indicated. Outcome measures were uptake of screening, HR-HPV prevalence, VIA result and treatment rates.
RESULTS In the HR-HPV arm, 248 of 250 ($p < 0.01$) women provided samples, while in the VIA arm, 121 of 250 (48.4%) women attended screening. Among the 73 of 248 HR-HPV-positive women, 45.2% ($N = 33$) attended VIA screening for follow-up, 21.2% ($N = 7$) of whom screened positive; five received treatment and two were missing clinical follow-up records. Of the 121 women in the VIA arm who attended screening, 13.2% ($N = 16$) screened positive; seven received cryotherapy, three refused treatment, five were referred to colposcopy; and one woman had suspected cervical cancer and received treatment after confirmatory testing.
CONCLUSIONS This pilot study demonstrated trial feasibility and willingness of the women to participate and be randomised successfully into the two arms. Self-collection-based cervical cancer screening had a higher uptake than VIA.

keywords human papillomavirus, cervical cancer, screening, community based, self-collection

Introduction

Cervical cancer, which is caused by high-risk genotypes of human papilomavirus (HPV) [1], is largely preventable with the HPV vaccine and through cervical cancer screening [2]. Despite this, cervical cancer remains the most prevalent cancer among women in sub-Saharan Africa, and more than 85% of the 266 000 women globally who die of cervical cancer every year live in low- and middle-income countries (LMIC) [3, 4]. WHO recommends visual inspection of the cervix using acetic acid (VIA) in resource-constrained settings as the primary approach for screening, or HPV screening when resources allow [5, 6]. VIA is of low cost, can be performed by mid-level professionals and requires little infrastructure or laboratory support, and treatment can be performed at the same visit as diagnosis [5, 7, 8]. Although VIA is the standard of care in many LMIC, training and maintaining providers to offer screening, the invasiveness of a pelvic examination and user variability (56–90%) of the test remain barriers [9]. Another method, detection of high-risk (HR) HPV DNA in the cervix has emerged as a powerful screening tool that is being taken up globally [5]. In LMIC, once-in-a-lifetime screening using HR-HPV testing

in women over 30 years has been recommended to reduce the incidence of cervical cancer [5, 6]. The use of self-collected specimens for HR-HPV DNA testing is especially useful in low-resource settings as it further reduces the need for skilled professionals and infrastructure, overcomes embarrassment and improves access [10–14].

The Advances in Screening and Prevention of Reproductive Cancers (ASPIRE) project is a community-based initiative in Uganda that is evaluating self-collection-based HR-HPV DNA testing as an acceptable, feasible and cost-effective model for cervical cancer screening (CCS) in women at risk [10, 15–17]. Details on the ASPIRE project are described elsewhere [10]. With the goal of testing the ASPIRE model for cervical cancer screening compared to the current standard in LMIC, a randomised controlled trial (RCT) was devised to determine whether a community-based cervical cancer screening program using HR-HPV-DNA-based self-collection reduces the rate of grade 2 or higher cervical intra-epithelial neoplasia (CIN) after 12 months compared with visual inspection with acetic acid (VIA) screening in an LMIC. This study is a pilot RCT to validate the feasibility of study procedures for the larger trial. In this study, we examine uptake of screening, HR-HPV prevalence, VIA results and treatment rates of the pilot study.

Methods

Trial design, setting and participants

This is a pragmatic pilot RCT comparing two screening approaches for cervical cancer: community-based, self-collected HR-HPV DNA testing and visual inspection using acetic acid. This clinical trial was registered with ClinicalTrials.gov (NCT02029794) and the International Standard Randomized Controlled Trial Number registry (ISRCTN04500116).

For the pilot study, local outreach workers recruited 500 women in Kisenyi an impoverished district of Kampala, Uganda. Outreach workers approached women in their homes or places of work and invited them to participate in the study if they were between 30 and 65 years of age, lived or worked in Kisenyi, and had access to a mobile telephone. Women were excluded if they had a previous hysterectomy or cervical cancer, if they did not meet the eligibility criteria or if they were unable to give consent. Women who were not eligible for the study were advised to attend routine cervical cancer screening at the local community health center. Informed written consent was obtained from all participants in their language. Women who consented to participate were asked to complete a survey that explored demographic and behavioural risk factors for cervical cancer. This survey tool has been validated in previous work performed by the ASPIRE team [10, 15, 16, 18].

Ethical approval was obtained from the University of British Columbia and Makerere University.

Randomisation

Using simple randomisation, a randomisation list was generated using SAS 9.3 for 250 participants per arm, for a total of 500 participants. The randomisation list was created by a research staff not involved in participant recruitment before the pilot study commenced. Unique study ID and allocation were recorded on cards, which were concealed in an envelope and kept in a locked cabinet in the research office. After the participant completed the consent process and the survey, the outreach worker would open the envelope, at which point both were made aware of allocation. Women were then randomised to one of two trial arms: high risk (HR), HPV DNA testing (HR-HPV) arm or VIA arm.

Study interventions

In the HR-HPV arm, women were provided a Dacron swab and instructed how to self-collect a vaginal specimen using a standard script and diagram by the outreach workers. They were asked to provide two samples: one for detection for HR-HPV and one for detection for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Women collected and provided specimens immediately where they were recruited, either in their home or in a private area in their place of work. Samples were placed in plastic wrap and transported in a biohazard bag. Specimens were immediately returned to the outreach workers, who transported them to MBN Laboratories in Kampala for testing by the end of each day. Samples were stored in the laboratory refrigerator at 4 °C for <24 h before testing. After specimens were tested, outreach workers contacted participants by phone. Women who tested positive for HR-HPV were provided counselling with their results over the phone and scheduled an appointment for VIA at the Kisenyi health unit. Outreach workers attempted to contact participants on three separate occasions to inform them of HPV results.

Women randomised to the VIA arm were scheduled a date to attend the Kisenyi health unit to undergo VIA for screening and treatment of pre-cancerous lesions. Participants were provided a reminder phone call the day before their scheduled visit. VIA was carried out by trained practitioners according to WHO guidelines [6]. At the

time of VIA, women were offered clinician-collected testing for *N. gonorrhoeae* and *C. trachomatis*. Specimens collected at VIA were transported to MBN Laboratories for testing. A 'see-and-treat' approach was used where screen-positive women at VIA would receive cryotherapy treatment in the same visit. Women who had suspicious lesions not appropriate for cryotherapy or women who had unsatisfactory VIA were referred to Mulago Hospital in Kampala for colposcopy and treatment.

In both arms, women who tested positive for *N. gonorrhoeae* and/or *C. trachomatis* were informed of their results by outreach workers and offered oral antibiotic treatment of azithromycin 2 g single dose under the direction of the physician at Kisenyi health unit, and received counselling about partner notification. Outreach workers attempted to contact participants on three separate occasions to inform them of *N. gonorrhoeae* and/or *C. trachomatis* results.

Laboratory testing

High-risk HPV genotypes 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59 and 66 were detected using the Ecoli s.r.o real-time PCR test (Bratislava, Slovak republic) [19]. No low-risk HPV genotypes are detected with this test. Results were differentiated for HR-HPV 16, HR-HPV 18, dual infection with HR-HPV 16/18 and other HR-HPV genotypes. Detection of *C. trachomatis* was performed using GenoQuick (Hain Life Sciences, Germany) [20], while detection of *N. gonorrhoeae* was based on the CinnaGen real-time PCR test (CinnaGen, Tehran, Iran) [21] at MBN Laboratories in Kampala.

Statistical analysis

Data were analysed following intention-to-treat principles using SPSS v14.0. A descriptive analysis for demographic factors, prevalence of HR-HPV, *N. gonorrhoeae* and *C. trachomatis*, uptake of the intervention, attendance for follow-up and results was conducted. Women with no data on screening attendance were defined as non-attenders, while no data on clinical follow-up or outcomes among women who attended screening were defined as missing. No response to survey questions was also defined as missing.

A two-sample independent *t*-test was used to test the difference in continuous variables. Descriptive statistics and bivariate analyses were conducted to compare factors of interest between women in the VIA arm who did and did not attend screening, as well as women in the HR-HPV arm who were HR-HPV positive and HR-HPV negative. Chi-square or Fisher's exact test as appropriate for factors of interest, where a *P*-value of <0.05 was used, was determined to be statistically significant. Finally, two logistic regression models were generated to explore the factors associated with testing positive for HR-HPV and attending VIA screening, with the odd ratios used as the measure of association and associated confidence intervals to indicate the precision. This was an exploratory analysis; therefore, all factors that reached significance of $P < 0.2$ in the bivariate analyses were offered for inclusion in the multivariate model [22]. Some categorical variables with levels that had very low cell counts (fewer than 10) were collapsed into larger groups for logistic modelling. Age, which was a continuous variable in the bivariate analysis, was converted into a categorical variable for logistic regression. The backwards stepwise likelihood ratio method was used for logistic regression to achieve the best fitting model, and $P < 0.05$ was considered statistically significant.

Results

Uptake of screening

We recruited 500 women for this pilot clinical trial between April and June 2014, and invited them to participate in either HR-HPV self-collection or VIA (Table 1) based on the randomisation key. 99.2% (248/250) of the women randomised to HR-HPV self-collection provided samples (Figure 1a; Table 2). 48.4% (121/250) of the women randomised to the VIA arm attended the local health unit for and underwent an examination (Figure 1b; Table 2). There was a statistically significant difference in attendance between HR-HPV testing and VIA (99.2% *vs.* 48.4% $P < 0.001$). One woman randomised to the VIA arm was deemed ineligible at the time of treatment due to prior hysterectomy. Due to errors in instructions given to participants by outreach workers, one woman in the HR-HPV arm was incorrectly advised to attend VIA at the Kisenyi health unit, while four women in the VIA arm were incorrectly instructed to participate in HR-HPV self-collection. All cases were counted in the arm they were randomised to based on intention-to-treat principles.

HR-HPV arm results

29.4% (73/248) of the women who provided samples in the HR-HPV arm were HR-HPV positive; three women (1.2%) were infected with HR-HPV 16; and 11 women (4.4%) with HR-HPV 18, while one woman (0.4%) had dual HR-HPV 16 and 18 infection (Figure 1a). Attempts were made to notify all HR-HPV-positive women of

Table 1 Descriptive statistics and bivariate analysis of demographic and behavioural risk factors by allocation of intervention†

			Arm allocated	
Variable	Variable level	Total (N = 500) N (%)	HR-HPV (N = 250) N (%)	VIA (N = 250) N (%)
Age	Mean (SD)	39.1 (9.7)	39.0 (9.2)	39.1 (10.1)
Marital status	Single	101 (20.2)	55 (22.0)	46 (19.4)
	Common law	216 (43.2)	108 (43.2)	108 (43.2)
	Married	49 (9.8)	24 (9.6)	25 (10.0)
	Separated/divorced	97 (19.4)	46 (18.4)	51 (20.4)
	Widowed	36 (7.2)	17 (6.8)	19 (7.6)
Highest school level completed	No schooling/some primary	119 (23.9)	63 (25.2)	56 (22.4)
	Primary/some secondary	306 (61.2)	147 (58.8)	159 (63.6)
	Completed secondary	51 (10.2)	28 (11.2)	23 (9.2)
	Further studies (trade, college, university)	24 (4.8)	12 (4.8)	12 (4.8)
Partner's highest school level completed	No schooling/some primary	28 (5.6)	18 (7.2)	10 (4.0)
	Primary/some secondary	137 (27.4)	63 (25.2)	74 (29.6)
	Completed secondary	121 (24.2)	57 (22.8)	64 (25.6)
	Further studies (trade, college, university)	47 (9.4)	21 (8.4)	26 (10.4)
	No partner	76 (15.2)	37 (14.8)	39 (15.6)
	I don't know	80 (16.0)	45 (18.0)	35 (14.0)
Work outside of the home	Yes	364 (72.8)	185 (74.0)	179 (71.6)
	No	136 (27.2)	65 (26.0)	71 (28.4)
Do you live in Kisenyi?	Yes	495 (99.0)	247 (98.8)	248 (99.2)
	No	4 (0.8)	3 (1.2)	1 (0.4)
Accommodation	Rent	360 (72.0)	179 (71.6)	181 (72.4)
	Own (or partner owns)	136 (27.2)	69 (27.6)	67 (26.8)
	No place to live	2 (0.4)	1 (0.4)	1 (0.4)
How much money do you have to live on each week	Less than 15 000 UgSh	408 (81.6)	201 (80.4)	207 (82.8)
	More than 15 000 UgSh	87 (17.4)	46 (18.4)	41 (16.4)
Religion	Catholic/Christian (various denominations)	343 (68.6)	173 (69.2)	170 (68.0)
	Muslim	157 (31.4)	77 (30.8)	80 (32.0)
How long to walk to nearest health centre?	Less than 10 min	189 (37.8)	97 (38.8)	92 (36.8)
	Less than 30 min	231 (46.2)	115 (46.0)	116 (46.4)
	More than 30 min	71 (14.2)	31 (12.4)	40 (16.0)
Ever had sexual intercourse	Yes	495 (99.0)	247 (98.8)	248 (99.2)
	No	2 (0.4)	1 (0.4)	1 (0.4)
Age at first sexual intercourse	Median (IQR)	17 (3)	17 (3)	17 (3)
Number of pregnancies	Median (IQR)	4.0 (4)	4.0 (3)	4.0 (4)
Ever had a pelvic exam	Yes	43 (8.6)	20 (8.1)	23 (9.2)
	No	452 (90.8)	226 (91.1)	226 (90.4)
Type of contraception currently used	Condoms	69 (13.8)	34 (13.6)	35 (14.0)
	Oral contraceptive	129 (25.8)	73 (29.2)	56 (22.4)
	Do not use birth control	166 (33.2)	87 (34.8)	79 (31.6)
	Not sexually active	68 (13.6)	29 (11.6)	39 (15.6)
	Other (injection, norplant, IUD)	197 (39.4)	107 (42.8)	90 (36.0)
Number of male partners in past week	None	171 (34.2)	80 (32.0)	91 (36.4)
	One	318 (63.6)	167 (66.8)	151 (60.4)
	Two–Five	9 (1.8)	2 (0.8)	7 (2.8)
Taken antibiotics in last 30 days	Yes	77 (15.4)	41 (16.4)	36 (14.4)
	No	418 (83.6)	205 (82.0)	213 (85.2)

Table 1 (*Continued*)

Variable	Variable level	Total (*N* = 500) *N* (%)	Arm allocated: HR-HPV (*N* = 250) *N* (%)	Arm allocated: VIA (*N* = 250) *N* (%)
Other chronic diseases	Heart disease	10 (2.0)	4 (1.6)	6 (2.4)
	High blood pressure	103 (20.6)	56 (22.4)	47 (18.8)
	Tuberculosis	9 (1.8)	5 (2.0)	4 (1.6)
	Hepatitis	6 (1.2)	2 (0.8)	4 (1.6)
	Malaria	310 (62.0)	156 (62.4)	154 (61.6)
	HIV/AIDS	47 (9.4)	22 (8.8)	25 (10.0)
	Cancer	2 (0.4)	0	2 (0.8)
	Respiratory disease	38 (7.6)	21 (8.4)	17 (6.8)
	Any STI	189 (37.8)	100 (40.0)	89 (35.6)
	Other	23 (4.6)	9 (3.6)	14 (5.6)

†Includes valid data only.

their results by phone. However, 39 women (53.4%) were unable to be reached after three attempts by phone. Only one woman who was notified of her HR-HPV-positive result refused to attend VIA, citing travel distance as the reason for refusal. In total, 33 of the 73 (45.2%) HR-HPV-positive women in the HR-HPV arm attended a follow-up VIA at the Kisenyi health unit (Figure 1a), and seven of these women had a positive VIA result (21.2% among attenders or 2.8% overall). All seven women in the HR-HPV arm who were VIA positive were recommended cryotherapy or colposcopy (Figure 1a).

VIA arm results

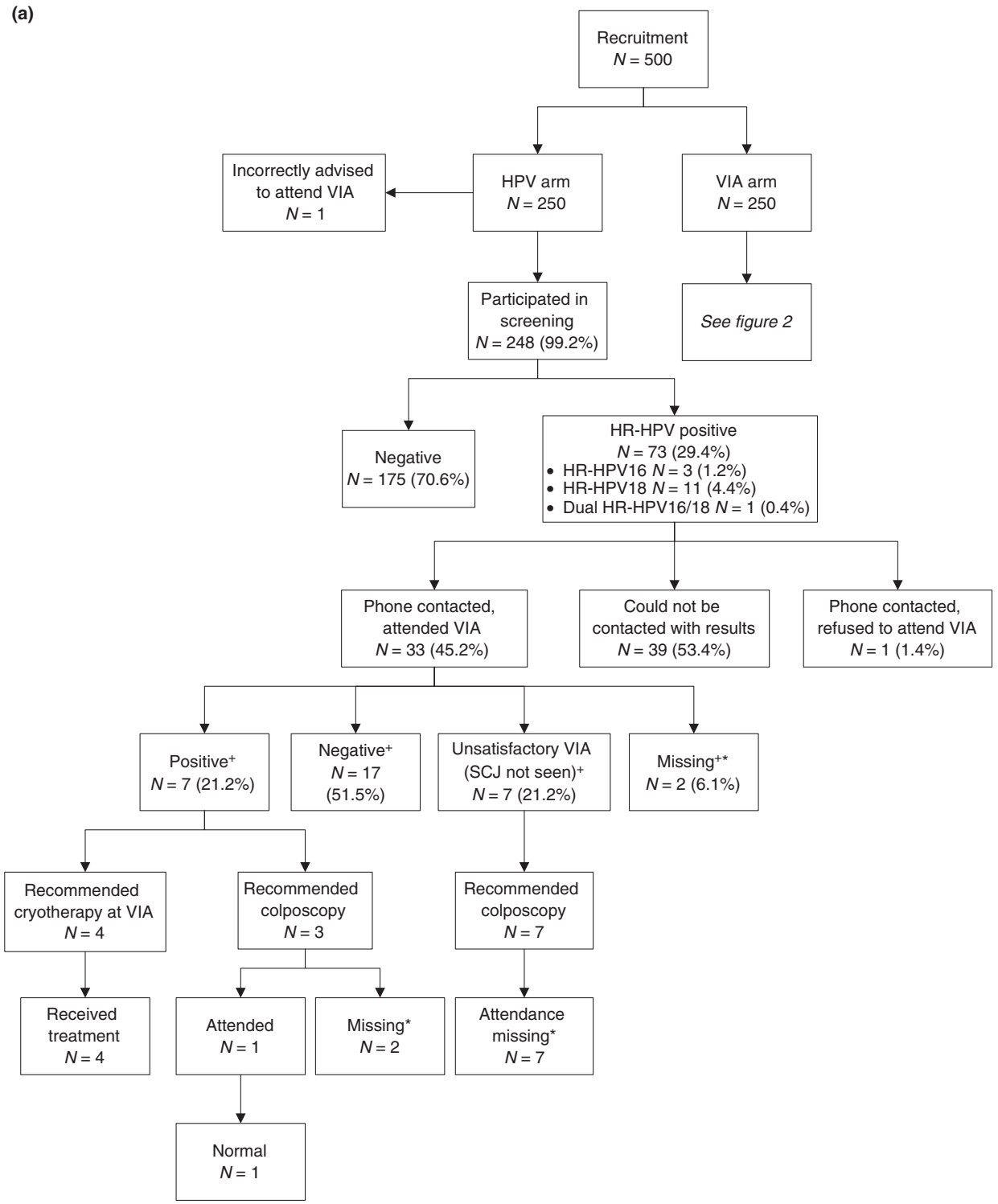
In the VIA arm, of the 121 women who came for testing, 16 women (13.2% among attenders or 6.4% overall) were VIA positive, of whom 10 were recommended cryotherapy, five were recommended colposcopy, and one woman had a high index of suspicion for cervical cancer and, after clinical diagnosis, started radiation therapy at the Uganda Cancer Institute (Figure 1b). The number of women who were VIA negative in the HR-HPV arm was 17 (51.5% among attenders or 6.8% overall) and 79 (65.3% among attenders or 31.6% overall) in the VIA arm. Among VIA-negative women in the VIA arm, 12 women had non-precancerous findings such as cysts or cervical polyps. There were seven women (21.2% among attenders or 2.8% overall) in HR-HPV arm with unsatisfactory VIA who were recommended colposcopy to have a sampling of the endocervix (Figure 1a), while in the VIA arm, 21 women (17.4% among attenders or 8.4% overall) had an unsatisfactory VIA result (Figure 1b).

N. gonorrhoeae and *C. trachomatis* results

In this study population, among those who were tested, the prevalence of *N. gonorrhoeae* was 2/248 (0.8%) for the HR-HPV arm and 3/111 (2.7%) in the VIA arm, while for *C. trachomatis*, the prevalence was 8/248 (3.2%) for the HR-HPV arm and 4/111 (3.6%) for the VIA arm (Table 2). Neither of these differences were statistically significant ($P = 0.17$ for *N. gonorrhoeae* and $P = 1.0$ for *C. trachomatis*).

Characteristics of study participants

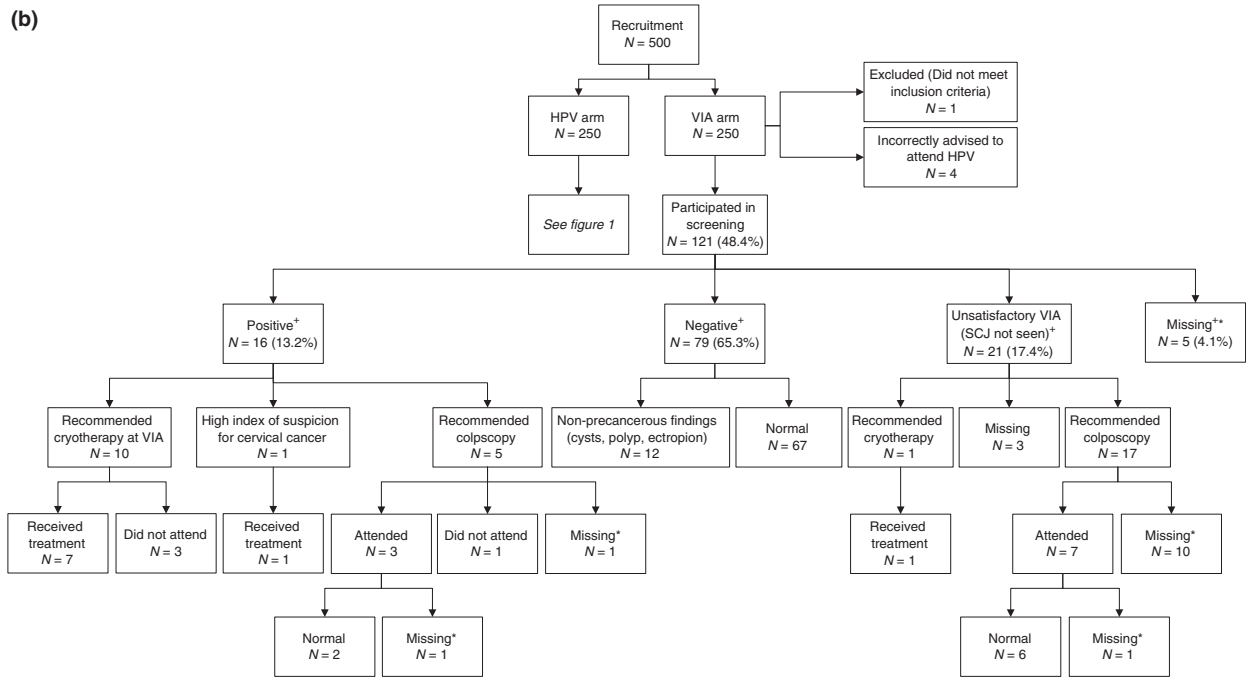
From the bivariate analysis comparing demographic and behavioural risk factors between HR-HPV-positive and HR-HPV-negative women, there were no statistically significant differences between the two groups (Table 3). Two variables that reached significance in the bivariate analysis of $P < 0.2$ were offered into the first logistic model: age and distance to walk to healthcare center. Only age remained statistically significant in the final model (Table 4) where women who were over the age of 40 years were less likely to be HR-HPV positive [adjusted odds ratio (AOR) = 0.51, 95% CI: 0.27, 0.94]. In the bivariate analysis exploring factors associated with attending VIA among women in the VIA arm (Table 5), marital status was found to be statistically significant ($P = 0.01$). No other factors were significant, except the 'Other' category for chronic diseases ($P = 0.03$); however, with only 14 women who disclosed having 'other' chronic diseases, this is not clinically significant. Other chronic diseases with low cell counts including heart disease, respiratory disease, cancer, hepatitis, tuberculosis and 'other' were collapsed together for logistic modelling. A total of 10 variables reached a $P < 0.2$ (Table 5)



* Missing was defined as no data on clinical follow up or outcomes among women who attended screening

\+ Percentage overall (*N* = 250) for VIA results: positive 2.8%, negative 6.8%, unsatisfactory 2.8%, missing 0.8%

Figure 1 Trial flow and clinical outcomes for the (a) HR-HPV arm. (b) VIA arm.



* Missing was defined as no data on clinical follow up or outcomes among women who attended screening

\+ Percentage overall (*N* = 250) for VIA results: positive 6.4%, negative 31.6%, unsatisfactory 8.4%, missing 2.0%

Figure 1 Continued.

and were offered into this second logistic model. The model is detailed in Table 4, where ever having had a pelvic exam (AOR = 2.70; 95% CI: 1.04, 7.01), having been diagnosed with a chronic disease (AOR = 2.13; 95% CI: 1.00, 4.53) and having been diagnosed with HIV/AIDS (AOR = 2.78; 95% CI: 1.07, 7.20) significantly increased the likelihood that women would attend VIA screening.

Discussion

In this pilot RCT, the uptake of self-collected HR-HPV testing in the community for cervical cancer screening exceeded 99%, whereas the standard of care, VIA, reached only 48.4% in a low-resource setting. In addition to being highly acceptable, a self-collection-based approach may be better at reaching the women most at risk for cervical cancer, as 21.2% of women who attended HR-HPV had a positive VIA result, whereas only 13.2% in the VIA arm did. However, the number of women with cervical abnormalities was small in both study arms because of challenges contacting women in the HR-HPV arm with results. In both interventions, the majority of women with abnormal cervical exams were appropriately treated or referred for care.

WHO estimates that more than a million women currently have cervical cancer, and despite being almost entirely preventable and treatable, deaths could rise by almost 25% over the next 10 years [5]. As cervical cancer screening is currently not routinely available in Uganda, either screening approach, HR-HPV testing or VIA would have a positive impact on the overall disease burden and improve the health of women of reproductive age. However, the significant improvement in initial uptake that was observed in the self-collection arm underscores important and fundamental inequities in access to cervical cancer screening that exist for women in LMIC settings, which can feasibly be addressed through innovative solutions to reach these marginalised women.

In the analysis of factors associated with HR-HPV positivity in the HR-HPV arm, age was the only significant factor: women over 40 were less likely to be HR-HPV positive than younger women. There were few demographic or behavioural factors that were different between attenders and non-attenders of VIA. Despite this, in the logistic regression we found that women who reported ever having had a pelvic exam and who reported having a chronic disease or HIV/AIDS were more likely to attend VIA screening. Combined, these factors suggest

Table 2 Descriptive statistics by arm allocated for uptake and results of cervical cancer screening†

		Arm allocated						
		HR-HPV			VIA			
Variable	Variable level	*N*	% among attenders (*N* = 248)	% overall (*N* = 250)	*N*	% among attenders (*N* = 121)	% overall (*N* = 250)	*P*-value
Attended screening		248		99.2	121		48.4	<0.001
HR-HPV results	Negative	175	70.6	70.0				
	Positive	73	29.4	29.2				
			(*N* = 73)					
HR-HPV genotype	HR-HPV 16	3	4.1	1.2				
	HR-HPV 18	11	15.1	4.4				
	Dual HR-HPV 16/18	1	1.4	0.4				
	Other HR-HPV genotypes	58	79.4	23.2				
			(*N* = 33)					
VIA results‡	Negative	17	51.5	6.8	79	65.3	31.6	
	Positive	7	21.2	2.8	16	13.2	6.4	
	Unsatisfactory (SCJ not seen)	7	21.2	2.8	21	17.4	8.4	
	Missing	2	6.1	0.8	5	4.1	2.0	
Treatment required	Normal/None	17	51.5	6.8	70	57.9	28.0	0.58
	Colposcopy	10	30.3	4.0	22	18.2	8.8	
	Cryotherapy	4	12.1	1.6	11	9.1	4.4	
	Invasive cervical cancer	0	0	0	1	0.8	0.4	
	Non-precancerous findings	0	0	0	12	9.9	4.8	
	Missing	2	6.1	0.8	5	4.1	2.0	
			(*N* = 248)			(*N* = 111)		
N. gonorrhoeae	Negative	246	99.2	98.8	108	97.3	43.2	0.17
	Positive	2	0.8	0.8	3	2.7	1.2	
C. trachomatis	Negative	240	96.8	96.4	107	96.4	42.8	1.00
	Positive	8	3.2	3.2	4	3.6	1.6	

†Includes valid data only.
‡VIA results in HR-HPV arm are only with women for follow-up pelvic exam.

that women who are already engaged with health care are more likely to participate in cervical cancer screening. It is worth noting that lower prevalence of self-identified chronic disease does not necessarily reflect true disease status in these women, as some women may be undiagnosed as a result of lack of access to health services or avoid health care for other reasons. Although the demographic/behavioural risk factors captured in this study do not appear to explain this, other studies from ASPIRE have identified lack of perceived risk, knowledge of health issues, embarrassment and competing priorities as factors that contribute to engagement with cervical cancer screening [15–17].

In the HR-HPV arm, more than half of the women could not be contacted by phone to notify them of their HR-HPV test results and to schedule a VIA visit. This was a significant challenge faced by study staff and likely resulted in lower VIA attendance than anticipated in the HPV arm. In our earlier feasibility study, VIA attendance for HPV positive women was much higher: 74.3% attended follow-up appointments [10]. We believe this is because of a delay we experienced in this current study in receiving HPV lab results, and did not reflect women's intention to participate in follow up. The delay may have resulted in women being less willing to answer a call from an unknown number, assuming they were HR-HPV negative. Despite this, all but one of the HR-HPV-positive women who was successfully contacted by phone attended VIA, suggesting that improved follow-up protocols could yield higher attendance in the future. Proposed solutions could be to shorten turnaround time for delivering results; making calls at different times of day; the use of text messaging which allows

Table 3 Descriptive statistics and bivariate analysis of demographic and behavioral risk factors associated with being HR-HPV positive among women allocated to the HR-HPV arm†

Variable	Variable level	Total (N = 248) N (%)	HPV result		P-value
			HR-HPV+ (N = 73) N (%)	HR-HPV− (N = 175) N (%)	
Age	Mean (SD)	39.0 (9.2)	37.6 (7.7)	39.5 (9.7)	0.15
Marital status	Single	22 (22.2)	16 (21.9)	39 (22.3)	0.33
	Common law	107 (43.1)	35 (47.9)	72 (41.1)	
	Married	24 (9.7)	3 (4.1)	21 (12.0)	
	Separated/divorced	46 (18.5)	13 (17.8)	33 (18.9)	
	Widowed	16 (6.5)	6 (8.2)	10 (5.7)	
Highest school level completed	No schooling/some primary	62 (25.0)	14 (19.2)	48 (27.4)	0.55
	Primary/some secondary	146 (58.9)	47 (64.4)	99 (56.6)	
	Completed secondary	28 (11.3)	9 (12.3)	19 (10.9)	
	Further studies (trade, college, university)	12 (4.8)	3 (4.4)	9 (5.1)	
Partner's highest school level completed	No schooling/some primary	18 (7.3)	4 (5.5)	14 (8.0)	0.62
	Primary/some secondary	62 (25.0)	21 (28.8)	41 (23.4)	
	Completed secondary	57 (23.0)	20 (27.4)	37 (21.1)	
	Further studies (trade, college, university)	21 (8.5)	3 (4.1)	18 (10.3)	
	No partner	37 (14.9)	10 (13.7)	27 (15.4)	
	I don't know	44 (17.7)	12 (16.4)	32 (18.3)	
Work outside of the home	Yes	183 (73.8)	55 (75.3)	128 (73.1)	0.84
	No	65 (26.2)	18 (24.7)	47 (26.9)	
Do you live in Kisenyi?	Yes	245 (98.8)	72 (98.6)	173 (98.9)	1.00
	No	3 (1.2)	1 (1.4)	2 (1.1)	
Accommodation	Rent	177 (71.4)	53 (72.6)	124 (70.9)	1.00
	Own (or partner owns)	69 (27.8)	20 (27.4)	49 (28.0)	
	No place to live	1 (0.4)	0	1 (0.6)	
How much money do you have to live on each week	Less than 15 000 UgSh	199 (80.2)	63 (86.3)	136 (77.7)	0.27
	More than 15 000 UgSh	46 (18.5)	10 (13.7)	36 (20.6)	
Religion	Catholic/Christian (various denominations)	173 (69.8)	49 (67.1)	124 (70.9)	0.67
	Muslim	75 (30.2)	24 (32.9)	51 (29.1)	
How long to walk to nearest health centre?	Less than 10 min	97 (39.1)	24 (32.9)	73 (41.7)	0.13
	Less than 30 min	113 (45.6)	40 (54.8)	73 (41.7)	
	More than 30 min	31 (12.5)	9 (12.3)	22 (12.6)	
Ever had sexual intercourse	Yes	245 (98.8)	73 (100)	172 (98.3)	1.00
	No	1 (0.4)	0	1 (0.6)	
Age at first sexual intercourse	Median (IQR)	17 (3)	16 (4)	17 (3)	0.41
Number of pregnancies	Median (IQR)	4 (3)	4 (4)	4 (3)	0.56
Ever had a pelvic exam	Yes	19 (7.7)	4 (5.5)	15 (8.7)	0.48
	No	225 (91.5)	68 (93.2)	157 (90.8)	
Type of contraception currently used	Condoms	33 (13.3)	8 (11.0)	25 (14.3)	0.62
	Oral contraceptive	72 (29.0)	21 (28.8)	51 (29.1)	1.00
	Do not use birth control	86 (34.7)	26 (35.6)	60 (34.3)	0.96
	Not sexually active	29 (11.7)	7 (9.6)	22 (12.6)	0.65
	Other (injection, norplant, IUD)	107 (43.1)	29 (39.7)	78 (44.6)	0.57
Number of male partners in past week	None	79 (37.9)	22 (30.1)	57 (32.6)	0.36
	One	166 (66.9)	49 (67.1)	117 (66.9)	
	Two–Five	2 (0.8)	1 (1.4)	1 (0.6)	
Taken antibiotics in past 30 days	Yes	40 (16.1)	10 (13.7)	30 (17.1)	0.412
	No	204 (82.3)	63 (86.3)	141 (80.6)	

Table 3 (*Continued*)

Variable	Variable level	Total (N = 248) N (%)	HPV result: HR-HPV+ (N = 73) N (%)	HPV result: HR-HPV− (N = 175) N (%)	P-value
Other chronic diseases	Heart disease	4 (1.6)	2 (2.7)	2 (1.1)	0.71
	High blood pressure	56 (22.6)	21 (28.8)	35 (20.0)	0.28
	Tuberculosis	5 (2.0)	1 (1.4)	4 (2.3)	1.00
	Hepatitis	2 (0.8)	0	2 (1.1)	1.00
	Malaria	155 (62.5)	48 (65.8)	107 (61.1)	0.69
	HIV/AIDS	21 (8.5)	9 (12.3)	12 (6.9)	0.33
	Cancer	0	0	0	
	Respiratory disease	21 (8.5)	6 (8.2)	15 (8.6)	1.00
	Any STI	100 (40.3)	32 (43.8)	68 (38.9)	0.69
	Other	8 (3.2)	1 (1.4)	7 (4.0)	0.61

†Includes valid data only.

Table 4 Odds ratio estimates† for factors associated with HR-HPV positivity and attending VIA

Variable	Variable level	Adjusted OR	95% CI	P-value
Factors associated with HR-HPV positivity				
Age	Under 40 years	Reference		
	41 years or older	0.51	0.27, 0.94	0.03
How long to walk to nearest health centre?	Less than 10 min	Reference		
	Less than 30 min	1.67	0.91, 3.06	0.10
	More than 30 min	1.23	0.49, 3.07	0.65
Factors associated with attending VIA				
Age	40 years or younger	Reference		
	41 years or older	1.52	0.79, 2.92	0.21
Marital status	Single	Reference		
	Common law	0.27	0.05, 1.48	0.13
	Married	0.23	0.03, 1.52	0.13
	Separated/divorced	0.55	0.09, 3.22	0.50
	Widowed	0.21	0.03, 1.34	0.10
Partner's highest school level completed	No schooling/some primary	Reference		
	Primary/some secondary	2.36	0.39, 14.2	0.35
	Completed secondary	2.36	0.40, 13.9	0.34
	Further studies (trade, college, university)	1.46	0.21, 10.2	0.70
	No partner	2.19	0.38, 12.5	0.38
	I don't know	3.53	0.52, 23.9	0.20
Accommodation	Rent	Reference		
	Own (or partner owns)	0.69	0.35, 1.34	0.28
Ever had a pelvic exam	No	Reference		
	Yes	2.70	1.04, 7.01	0.04
Number of male partners in past week	None	Reference		
	One or more	1.20	0.54, 2.67	0.65
Have an 'other' chronic disease‡	No	Reference		
	Yes	2.13	1.00,4.53	0.05
Have HIV/AIDS	No	Reference		
	Yes	2.78	1.07, 7.20	0.03

†Backward likelihood ratio method was used to select final variables from full multivariable model (variables with P value ≤0.2 in bivariate analysis were considered for multivariable model).
‡Includes tuberculosis, hepatitis, heart disease, cancer, respiratory disease and 'other'.

Table 5 Descriptive statistics and bivariate analysis of demographic and behavioural risk factors associated with attending VIA screening among women allocated to the VIA arm†

			Attended VIA		
Variable	Variable level	Total (*N* = 250) *N* (%)	Yes (*N* = 120) *N* (%)	No (*N* = 130) *N* (%)	*P*-value
Age	Mean (SD)	39.1 (10.1)	40.0 (10.7)	38.3 (9.5)	0.15
Marital status	Single	46 (18.4)	29 (24.2)	17 (13.1)	0.01
	Common law	108 (43.2)	42 (35.0)	66 (50.8)	
	Married	25 (10.0)	9 (7.5)	16 (12.3)	
	Separated/divorced	51 (20.4)	31 (25.8)	20 (15.4)	
	Widowed	19 (7.6)	8 (6.7)	11 (8.5)	
Highest school level completed	No schooling/some primary	56 (22.4)	32 (26.7)	24 (18.5)	0.41
	Primary/some secondary	159 (63.6)	73 (60.8)	86 (66.2)	
	Completed secondary	23 (9.2)	9 (7.5)	14 (10.8)	
	Further studies (trade, college, university)	12 (4.8)	6 (5.0)	6 (4.6)	
Partner's highest school level completed	No schooling/some primary	10 (4.0)	4 (3.3)	6 (4.6)	0.14
	Primary/some secondary	74 (29.6)	33 (27.5)	41 (31.5)	
	Completed secondary	64 (25.6)	29 (24.2)	35 (26.9)	
	Further studies (trade, college, university)	26 (10.4)	9 (7.5)	17 (13.1)	
	No partner	39 (15.6)	25 (20.8)	14 (10.8)	
	I don't know	35 (14.0)	20 (16.7)	15 (11.5)	
Work outside of the home	Yes	179 (71.6)	84 (70.0)	95 (73.1)	0.69
	No	71 (28.4)	36 (30.0)	35 (26.9)	
Do you live in Kisenyi?	Yes	248 (99.2)	119 (99.2)	129 (99.2)	0.73
	No	1 (0.4)	0	1 (0.8)	
Accommodation	Rent	181 (72.4)	82 (68.3)	99 (76.2)	0.12
	Own (or partner owns)	67 (26.8)	38 (31.7)	29 (22.3)	
	No place to live	1 (0.4)	0	1 (0.8)	
How much money do you have to live on each week	Less than 15 000 UgSh	207 (82.8)	98 (81.7)	109 (83.8)	0.87
	More than 15 000 UgSh	41 (16.4)	21 (17.5)	20 (15.4)	
Religion	Catholic/Christian (various denominations)	170 (68.0)	79 (65.8)	91 (70.0)	0.57
	Muslim	80 (32.0)	41 (34.2)	39 (30.0)	
How long to walk to nearest health centre?	Less than 10 min	92 (36.8)	45 (37.5)	47 (36.2)	0.87
	Less than 30 min	116 (46.4)	53 (44.2)	63 (48.5)	
	More than 30 min	40 (16.0)	21 (17.5)	19 (14.6)	
Ever had sexual intercourse	Yes	248 (99.2)	119 (99.2)	129 (99.2)	0.73
	No	1 (0.4)	0	1 (0.8)	
Age at first sexual intercourse	Median (IQR)	17 (3)	17 (4)	17 (3)	0.53
Number of pregnancies	Median (IQR)	4 (4)	4.0 (4)	4.0 (4)	0.76
Ever had a pelvic exam	Yes	23 (9.2)	14 (11.7)	9 (6.9)	0.16
	No	226 (90.4)	105 (87.5)	121 (93.1)	
Type of contraception currently used	Condoms	35 (14.0)	15 (12.5)	20 (15.4)	0.63
	Oral contraceptive	56 (22.4)	30 (25.0)	26 (20.0)	0.43
	Do not use birth control	79 (31.6)	41 (34.2)	38 (29.2)	0.48
	Not sexually active	39 (15.6)	20 (16.7)	19 (14.6)	0.73
	Other (injection, norplant, IUD)	90 (36.0)	39 (32.5)	51 (39.2)	0.33
Number of male partners in past week	None	91 (36.4)	52 (43.3)	39 (30.0)	0.07
	One	151 (60.4)	64 (53.3)	87 (66.9)	
	Two–Five	7 (2.8)	3 (2.5)	4 (3.1)	
Taken antibiotics in past 30 days	Yes	36 (14.4)	20 (16.7)	16 (12.3)	0.32
	No	213 (85.2)	99 (82.5)	114 (87.7)	

Table 5 (*Continued*)

Variable	Variable level	Total (*N* = 250) *N* (%)	Attended VIA: Yes (*N* = 120) *N* (%)	Attended VIA: No (*N* = 130) *N* (%)	*P*-value
Other chronic diseases	Heart disease	6 (2.4)	4 (3.3)	2 (1.5)	0.43
	High blood pressure	47 (18.8)	21 (17.5)	26 (20.0)	0.73
	Tuberculosis	4 (1.6)	0	4 (3.1)	0.12
	Hepatitis	4 (1.6)	3 (2.5)	1 (0.8)	0.35
	Malaria	154 (61.6)	68 (56.7)	86 (66.2)	0.16
	HIV/AIDS	25 (10.0)	16 (13.3)	9 (6.9)	0.14
	Cancer	2 (0.8)	0	2 (1.5)	0.50
	Respiratory disease	17 (6.8)	9 (7.5)	8 (6.2)	0.86
	Any STI	89 (35.6)	43 (35.8)	46 (35.4)	1.00
	Other	14 (5.6)	11 (9.2)	3 (2.3)	0.03

†Includes valid data only.

women to receive and respond to messages at their convenience; or to have women program the study phone number into their phone so that they will see on call display when they are being contacted about the study. Additionally, the local health unit where VIA screening was performed often had long waiting times that in some instances prevented women who attended VIA screening from being seen by a clinician on the day they presented for screening. Both of these challenges underscore real-world barriers to VIA in low-resource settings. This further emphasises the utility of using self-collection-based screening first, so that only the women truly at risk for cervical cancer are referred for a pelvic exam, freeing up busy healthcare workers. A larger trial is warranted to compare the cost-effectiveness and health system impact of HR-HPV testing and VIA.

Follow-up assessment of pilot study participants at 1 year will determine CIN2+ rates, which will confirm the sample size needed to detect a 40% reduction in CIN2+ in the HR-HPV arms. Still, we were able to see a dramatic difference in uptake between the two intervention groups and establish feasibility of the larger trial from this study. As a pragmatic trial seeking to inform sustainable healthcare delivery models, this study was conducted at existing clinical sites integrating healthcare workers who provide clinical care to the whole community in addition to their role in the study. Due to the high volume of patients seen and competing demands on health care workers' time, reporting data for each study participant was a challenge. As a result, some of the follow-up clinical data were incomplete, particularly at the time of colposcopy. These missing data were relatively few (<1% for all demographic/behavioural risk factor questions) and have been reported in the results.

This study supports the WHO mandate for advancing equity for women's health, strengthening health systems and developing, testing and implementing appropriate technologies for cervical cancer prevention and control [5]. As the first RCT that has been conducted that compares community-based self-collection to VIA, we have highlighted important considerations for community-based and clinic-based screening programs. The higher uptake of HR-HPV self-collection compared to VIA demonstrates the potential of this approach to reach populations in low-resource setting on a large scale. Overall, community-based self-collection-based cervical cancer screening with integrated reproductive health screening promises to be a valuable tool to identify women most at risk for cervical cancer and successfully link women to follow-up care and treatment. Improving women's engagement with health care, either through enhanced education or through improving access, could increase uptake of the follow-up VIA exam among women in this setting. To maximise the impact on the health system, optimally deploy scarce resources and reach the women most at risk, the way forward will likely involve integration of cervical cancer prevention with existing health programs such as HIV/AIDS, reproductive health, maternal and newborn health, cancer and immunisations. Further cost analysis for the implementation and operationalisation of self-collection-based cervical cancer screening will help inform global policy and action.

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