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Performance of HPV testing, Pap smear and VIA in women attending cervical cancer screening in Kilimanjaro region, Northern Tanzania: a cross-sectional study nested in a cohort

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ABSTRACT

Objective There is a concern about performance of the screening approaches, where information on the quality of novel and affordable screening approaches that will perform well in remote areas is warranted. This lack of information makes it difficult to prioritise resource use in efforts to improve cervical cancer outcomes. We aimed to compare the diagnostic value of human papillomavirus (HPV) testing on self-collected samples, Pap smear and visual inspection of the cervix with acetic acid (VIA) tests for detection of high-grade cervical intraepithelial neoplasia or worse (CIN2+).

Design A combined cross-sectional and cohort study.

Setting Three primary healthcare centres in Kilimanjaro region, Tanzania.

Participants 1620 women undergoing cervical cancer screening from December 2018 to September 2021. Inclusion criteria were being aged 25–60 years, and no history of premalignant or cervical cancer. Exclusion criteria were overt signs of cancer and previous hysterectomy.

Interventions Participants underwent HPV self-sampling with Evalyn Brush and Care HPV kit assay was used to determine prevalence of high-risk HPV infection. Women with positive HPV test were together with a random sample of HPV negative women scheduled for follow-up where VIA was performed, and Pap smear and cervical biopsies obtained.

Results Of 1620 women enrolled, 229 (14.1%) were HPV positive and 222 of these attended follow-up together with 290 (20.8%) women with negative HPV test. On VIA, 17.6% were positive. On Pap smear, 8.0% were classified as high-grade squamous intraepithelial lesion. The sensitivity and specificity, respectively, of the various tests, compared with histopathology for the detection of CIN2+ were: HPV test 62.5%, 59.3%; Pap smear 82.8%, 82.1% and; VIA 48.4%, 56.8%. When combined, the sensitivity and specificity for HPV and Pap smear were 90.6%, 70.6% while HPV and VIA were 65.6% and 75.5% for the detection of CIN2+.

Conclusions The performance of care HPV testing on self-collected samples opens the possibility of increasing coverage and early detection in resource-constrained settings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study evaluated the clinical performance of human papillomavirus (HPV) testing on self-collected samples, Pap smear and visual inspection of the cervix with acetic acid tests using histopathology as reference comparison standard.
⇒ The study was carried out in primary healthcare centres in a rural Tanzanian setting.
⇒ Inclusion of a proportion of participants with negative HPV-test in the follow-up provides well powered estimates of the sensitivity, specificity and predictive values of various screening tests.
⇒ HPV self-sampling promotes safety amid the prevailing COVID-19 pandemic at busy clinics as it limits the risk of SARS-CoV-2 transmission by avoiding social crowding.
⇒ Our study population comprised only women who responded to the invitation to the cervical cancer screening, excluding those who did not seek healthcare at hospitals.

BACKGROUND

Cervical cancer is one of the most preventable and treatable malignant diseases, yet it is the fourth most frequently diagnosed cancer among women in reproductive age worldwide with the highest incidence in resource-limited countries, particularly in sub-Saharan Africa where approximately 75 000 new cases occur yearly.[1] In Tanzania, cervical cancer is the most common cancer in women (38.4%) and the main cause of female cancer mortality (34.3%).[2] The age-standardised incidence rate is 54 per 100 000 women, which is almost double the average rate for Africa (27.6 per 100 000 women).[2] High prevalence of human papillomavirus (HPV) and HIV infections coupled with scarcity of cervical cancer screening programmes are

the main reasons for the high cervical cancer incidence in Tanzania.[3 4]

Cervical cancer screening methods, which are available in sub-Saharan Africa, include the cytological sampling with the Papanicolaou test (Pap smear), visual inspection of the cervix with acetic acid (VIA) and HPV testing.[5] Among women in rural settings with limited resources, these methods have not been adequately compared individually and in combination against cervical biopsy.[4 6] Self-sampling for HPV DNA testing has been reported to maximise screening participation due to its convenience, cost-effectiveness and culturally acceptability.[7–9] The performance of HPV testing on self-samples appears to be comparable to that of clinician-obtained samples and has been a recommended strategy to reach women not participating in the regular screening programme.[10 11] In high-resource countries, incidence and mortality due to cervical cancer have been reduced effectively in the past decades through organised cytology-based screening programmes. The WHO Cervical Cancer Elimination Initiative calls for rapid and widespread implementation of prophylactic HPV vaccination for a more efficient cervical cancer control. Similarly, screening of mid-adult women to detect precancer (preferably with HPV testing), and treatment of those found to be screen-positive.[12 13] Despite the efficiency of Pap smear testing, the need for cytology laboratories with skilled personnel have made Pap smear difficult to implement in many low-income and middle-income countries (LMICs). Thus, low cost techniques such as VIA have been adopted in LMICs for early detection of precancerous lesions.[14]

The test performance of different screening approaches for cervical cancer prevention in LMICs including Tanzania have been assessed in various studies.[4 6 15–17] However, limited data are available on the test performance of the different screening methods compared with histopathology particularly from rural settings. This study was carried out to determine the test performance of (1) VIA, (2) HPV test on self-collected specimens, (3) HPV test plus VIA and (4) HPV test plus Pap smear using histological diagnosis as gold standard in rural Tanzania.

METHODS

Study design, setting and population

We conducted a combined cross-sectional and cohort study from December 2018 to September 2021 in Moshi, Mwanga and Rombo districts of the Kilimanjaro region, in northern Tanzania. According to the latest United Nations data, Tanzania population is estimated to be at 62 761 437; Kilimanjaro region has a population of 2 287 427.[18]

Inclusion criteria were being residents in the identified districts, aged 25–60 years, and no history of premalignant or cervical cancer. Exclusion criteria were overt signs of cervical cancer and previous hysterectomy. In addition, being pregnant or actively menstruating were considered temporary exclusion criteria until 3 months postdelivery and 1 week after menstruation, respectively. Women in the selected districts were invited to attend cervical cancer screening at their respective local district hospitals through public announcements. The announcements were made through radios, disseminated to churches, mosques, local marketplaces, reproductive and child health clinics and outpatient clinics. In addition, brochures were shared in the streets and public announcements were made using a vehicle with loudspeakers to raise awareness about the screening service. Women seeking cervical cancer screening at reproductive health centre of Kilimanjaro Christian Medical Centre (KCMC) from these districts were also included.

HPV self-sample collection

A detailed participant's enrolment procedure has been described elsewhere.[8] Briefly, two experienced reproductive health nurses informed the women, who showed up for screening about the study objectives and eligibility criteria, and they obtained written informed consent from each participating woman. Women who could not read or write were not enrolled without a witness who does understand the participant's language. Thus, in such few occasions, it was a must for an impartial witness to be present. The eligible women were instructed to collect an HPV self-sample by using Evalyn Brush (EvalynRovers Medical Devices BV, the Netherlands). The nurse did not witness the self-sampling procedure; however, she was nearby in case the woman would need some assistance. The collected specimens were transported to KCMC on the same day and were stored at the Department of Pathology at room temperature (about 19–24°C) for a maximum of 2 weeks.

Questionnaire survey

The study nurses administered a questionnaire that was developed in English and translated into Kiswahili. It included information about sociodemographic characteristics, sexual behaviour and HIV status which was self-reported. The study nurses provided counselling to each study participant explaining the implication of getting a high-risk HPV positive result. Three to four weeks after the HPV self-sampling, the participants received information about HPV results through short message service. All women who tested positive for high-risk HPV and a random selection of 25% of women who tested negative were immediately scheduled for gynaecological examination. Randomisation was achieved by choosing every fifth participant from the enrolment list. The examination was performed sequentially by a study gynaecologist (BM) and included Pap smear, VIA and cervical biopsy in the mentioned order.

HPV specimen testing

Once a total of 96 samples had been collected, they were processed on the *care* HPV assay (QIAGEN, Gaithersburg, Maryland, USA), a simplified, robust and affordable HPV test that can be used in LMICs under wider range of

ambient conditions. It detects the presence of 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The results are automatically interpreted by the *care* HPV test system and are displayed graphically on a controller monitor screen as either 'positive' or 'negative'.[6 19 20] The specimens were analysed by a trained laboratory technician.

Conventional Pap smear

During the gynaecological examination, cervical cells were collected using an Ayre wooden spatula and endocervical brush (CellPath, Wales, UK), smeared on a glass slide and fixed in ethanol. After fixation, slides were air dried and sent to Department of Pathology of KCMC, for Pap staining and cytological analyses by the study pathologist (AM). Pap smear results were categorised according to Bethesda classification system 2011 in the categories: negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance, atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (HSIL), low-grade squamous intraepithelial lesion (LSIL), HSIL, atypical glandular cells, adenocarcinoma in situ or carcinoma.[21]

VIA test and cervical punched biopsy

VIA test was performed after Pap smear. Application of 5% acetic acid to the cervix using a cotton-tipped swab was done.The findings were scored as positive when a well defined, dense acetowhite area with regular margins appeared in the squamo-columnar junction.[6] Cervical punched biopsy was taken from the areas that demonstrated VIA positivity. In women who had negative VIA test, four-quadrant biopsies were collected. The biopsies were immediately fixed in 10% buffered formalin and sent to Department of Pathology of KCMC where they were deidentified and assigned unique anonymous identification number by a laboratory scientist. Pap smear and biopsies were read by the study pathologist (AM), twice with at least 2weeks interval. The histological results based on biopsies were used as gold standard and were categorised as normal, cervical intraepithelial neoplasm CIN1, CIN2, CIN3, invasive carcinoma or other.

Outcome measures and statistical analyses

The prevalence of the different screening results in relation to the histological results of the cervical biopsy was estimated. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) for the detection of CIN2+ lesions for each test were calculated with 95% CI. Screening methods were compared with histology individually and in combinations (HPV+VIA; HPV+cytology); the positive result was defined as both tests being positive or either test being positive. All analyses were performed using statistical software package SPSS V.20.0 (SPSSA).

Patient and public involvement

Patients were not involved in the conception phase of the study. However, they were involved during the recruitment phase by explaining to other women how they experienced the sample collection processes, and this contributed to reassurance among other participants. In order to increase public awareness, government and religious leaders were informed about the project. Each participant received the results of the screening tests and biopsy findings and was advised on the screening periodicity. When the study finishes, the results and their potential implication to the public will be communicated through meetings with health authorities, policy briefings and announcements in the mainstream media.

RESULTS

A total of 1620 participants undertook HPV self-sampling. Of these, 229 (14.1%) had a positive HPV test result. These women were together with 25% random sample (n=347) of women with negative HPV test results invited for a gynaecological examination. In all 512/576 (88.9%) attended follow-up, 222 (96.9%) with positive HPV test result and 290 (83.6%) with negative result (figure 1). Sociodemographic and reproductive characteristics of the study participants are displayed in table 1.

The majority of women (55.1%) were aged 45 years or above, with most being married (86.5%), having primary education (89.8%), being self-employed (82.6%) and having a history of two or more pregnancies (85.4%). The majority (63.8%) had never been screened for cervical cancer and 95.5% had never heard about HPV testing. Of the 512 participants, 65 (12.7%) were HIV positive and 86.1% of these women reported they were on antiretroviral therapy (table 1).

The histological diagnoses were: normal 78.5%, CIN1 9.0%, CIN2/3 8.4% and carcinoma 4.1% (table 2).

On VIA, most of the examinations (82.3%) were negative while 17.6% were positive. On Pap smear, 74.0% were normal, 3.3% showed ASCUS, 14.6% showed LSIL while 8.0% showed HSIL (table 2).

The prevalence of CIN2+ in HIV-positive and HIV-negative women was 61.5% and 5.4%, respectively (table 3).

Compared with histopathology for detection of CIN2+, the sensitivity and specificity, respectively, of the various tests were as follows: HPV 62.5%, 59.3%; Pap smear 82.8%, 82.1%; VIA 48.4%, 56.8% (table 4).

When triaged, the sensitivity and specificity, respectively, of the various tests were as follows; HPV and Pap smear 90.6%, 70.6% while HPV and VIA 65.6%, 75.5% compared with histopathology for the detection of CIN2+. The PPV and NPV of various screening tests individually were: HPV 18%, 91.7%, Pap smear 39.8%, 97.1% and VIA 34.4%, 92.1%, respectively. When combined, the PPV and NPV were: HPV plus Pap smear 20.8%, 97.4%, HPV plus VIA 17.4%, 91.9%, Pap smear plus VIA 32.9%, 97.1%, respectively (table 4).

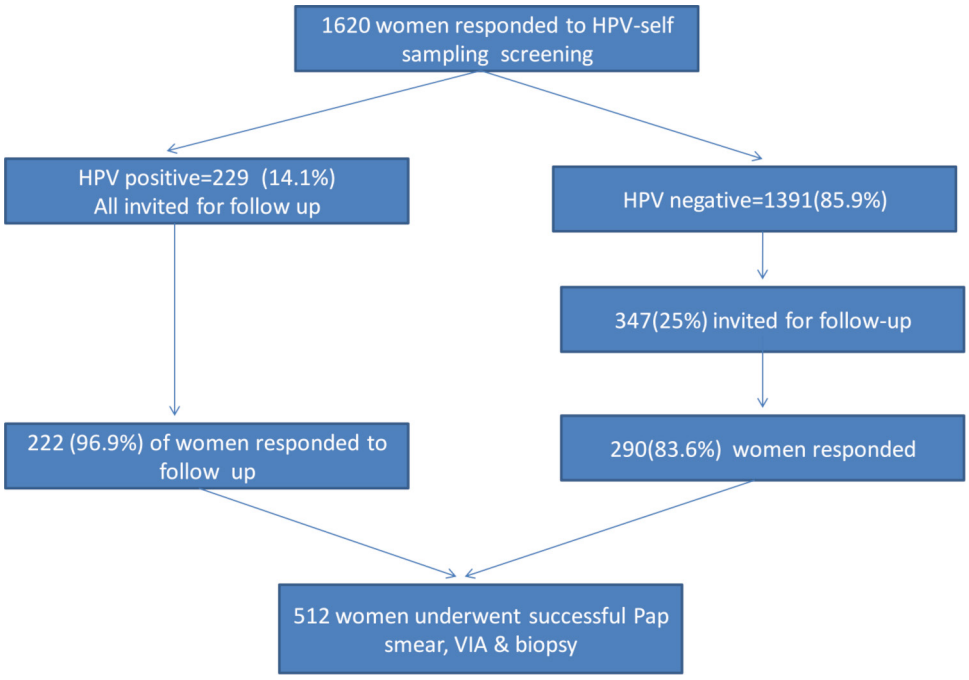

Figure 1 Schematic flow chart of the study population. HPV, human papillomavirus; VIA, visual inspection of the cervix with acetic acid.

DISCUSSION

The performance of VIA, HPV test on self-samples and Pap smear screening was assessed in women aged 25–60 years residing in rural Kilimanjaro, Northern Tanzania. The screening approaches when applied individually and in combination compared with histopathology in the diagnosis of premalignant and malignant cervical lesions were assessed. The prevalence of high-risk HPV infection was 14.1%, and 12.5% of the women had histologically confirmed CIN2 or worse. The prevalence of a histological diagnosis of CIN2+ was higher (61.5%) in HIV-positive women than in HIV-negative women (5.4%). The high prevalence of CIN2+in HIV-infected women highlights an urgent need for improving cervical cancer screening in this vulnerable population.

This study has demonstrated good feasibility of using HPV-testing on self-collected swabs as a potential primary screening for cervical cancer in a rural population in Tanzania. HPV self-sampling allows women to collect their own specimens and the approach has the potential to overcome many of the barriers associated with screening based on cytology or VIA in low-resource settings.[7–9] In addition, HPV self-sampling promotes safety amid the prevailing COVID-19 pandemic at busy clinics as it limits the risk of SARS-CoV-2 transmission by avoiding social crowding. HPV self-sampling is recommended as a strategy to reach women not participating in the regular screening programme as it was the case in this study where nearly two-thirds of the participants reported they had never been screened before. Women living in rural areas are less likely to be aware of cervical cancer and have more difficult access to screening. This may partly explain the observed high prevalence of CIN2+ in this study compared with previous studies.[4 6] Importantly, inclusion of women attending screening at KCMC and the fact that the service is offered for free may have attracted women with a high risk of having CIN2+. Consequently, they tend to present to the hospital with advanced disease with poor prognosis.[22]

In this study, the sensitivity and specificity of HPV-testing for detection of CIN2+were 62.5% and 59.3%, respectively. The sensitivity is relatively lower compared with studies done in urban settings in Kenya, Burkina Faso and South Africa reporting sensitivity rates of 83.6% and 93.3%, respectively.[16 23] The differences could partly be explained by differences in techniques and reference standard used. In this study, performance of HPV testing was higher than VIA while Pap smear was the most superior. Similar findings have been reported in previous studies.[15–17] When deciding which test to use for screening, both sensitivity and specificity must be taken into account because tests with low sensitivity will fail in correctly identifying precancerous lesions while tests with low specificity will result in a high proportion of false-positive test results, unnecessary procedures and associated adverse health effects. HPV-test is increasingly recognised as the preferred cervical screening method due to its high sensitivity for detection of CIN2+. A negative HPV test can indicate that the risk of cervical cancer is extremely low without the need for clinical examination for the large majority of women. The implications of a negative HPV test is unquestioned; however, it is unclear how to best manage positive HPV test results in resource-limited settings. If HPV testing is used as a stand-alone primary screening, it will result in referring a large number of women for colposcopy, especially in

Table 1 Baseline characteristics of study participants; N=512

Variables	Total N=512	%	HPV negative N=290	%	HPV positive N=222	%
Age						
25–34	112	21.8	63	21.7	49	22.1
35–44	118	23.0	64	22.1	54	24.3
45–54	153	29.9	89	30.7	64	28.8
55–60	129	25.2	74	25.5	55	24.8
Marital status						
Married	443	86.5	266	91.7	177	79.7
Unmarried	69	13.5	24	8.3	45	20.3
Education level						
Primary/none	460	89.8	258	89.0	202	91
Secondary/above	52	10.2	32	11.0	20	9
Employment						
Employed	423	82.6	242	83.5	181	81.5
Unemployed	89	17.4	48	16.5	41	18.5
Parity						
Nulliparous	21	4.1	11	3.8	10	4.5
1	53	10.3	29	10.0	24	10.8
2	219	42.7	126	43.5	93	41.9
3+	219	42.7	124	42.8	95	42.8
Age at first pregnancy						
<18	81	15.8	27	9.3	54	24.3
18–25	353	68.9	244	84.1	109	49.1
>25	78	15.2	19	6.6	59	26.6
Ever screened						
Yes	185	36.2	104	35.9	81	36.5
No	327	63.8	186	64.1	141	63.5
Heard about HPV test						
Yes	23	4.5	10	3.5	13	5.9
No	489	95.5	280	96.6	209	94.1
HIV status						
Positive	65	12.7	35	12.1	30	13.5
Negative	447	87.3	255	87.9	192	86.5
On ART(n=65)						
Yes	56	86.2	30	83.3	26	83.9
No	9	13.8	4	11.4	5	16.1
No	1	0.0	1	2.9	0	0

ART, antiretroviral therapy; HPV, human papillomavirus.

populations with high HIV and HPV prevalence. Therefore, HPV-based primary screening must be accompanied with triage methods for high-risk HPV positive women, so as to further stratify them by their risk of having CIN2+.[24 25] When follow-up and referral for treatment are difficult, there is a substantial advantage of VIA by having an immediate result at time of examination. In addition, VIA has advantage of being cost-effective with a limited supply chain burden. But, as it was the case in this study, the problem with VIA is rather a low sensitivity, where many women with precancerous lesions are not discovered.[4 6] A low sensitivity is associated with a high number of false negative implying a large number of women with premalignant diagnosis are not diagnosed and thus not receiving proper treatment. Similarly, VIA has problematic accuracy and is not reliably reproducible for the

Table 2 Comparison of HPV test, VIA and Pap smear with histopathology results from cervical biopsy; N=512

Screening test		Histopathology			
HPV test	Total 512 (100%)	Normal 402 (78.5%)	CIN1 46 (9%)	CIN2/3 43 (8.4%)	Carcinoma 21 (4.1%)
Negative	290 (56.5%)	270	18	2	0
Positive	222 (43.4%)	132	28	41	21
VIA test					
Negative	422 (82.3%)	359	30	31	2
Positive	90 (17.6%)	43	16	12	19
Pap smear					
Normal	379 (74.0%)	350	18	11	0
ASCUS	17 (3.3%)	9	5	2	1
LSIL	75 (14.6%)	40	21	10	4
HSIL	41 (8.0%)	3	2	20	16

ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; VIA, visual inspection of the cervix with acetic acid.

identification of CIN2+. The skill of the observer, differences in screened populations such as age, parity, HIV status and underlying cervical disease burden have been implicated to influence the performance of VIA. For instance, in a 2017 study by Raifu *et al* in the Democratic Republic of Congo, positivity rates of VIA performed by nurses and physicians differed significantly (36.3% vs 30.2%, respectively).[26]

When triaged with VIA, the sensitivity and specificity increased to 65.6% and 75.5%, respectively. As triaging of HPV positive women with quality assured cytology or genotyping may not be possible because of cost implications, VIA triage could be considered part of a screen-and-treat strategy in resource-limited settings where women who are VIA positive can receive immediate treatment. If VIA is to be used to triage HPV positive women, it may determine who should be referred for additional treatment.[27] However, given the poor sensitivity of VIA, it is important to consider implementing alternative approaches that can overcome its inherent limitations and permit redirecting resources to reach greater numbers of patients. Automated visual evaluation (AVE), a deep learning computer application that permits identification of cervical precancer from cervical photographic images taken by a contemporary smartphone camera,[28 29] may be a cost-effective alternative toVIA. AVE classifies visual images of the cervix according to diagnostic severity and also provides an assessment of treatability when lesions are detected. Risk-based clinical management means defining each woman's risk and devoting treatment resources accordingly. The performance of AVE has proved to be much more accurate than human interpretation of the same cervical images. Hu *et al* established that AVE identifies cumulative precancer/cancer cases with accuracy of91%; 95% CI (89% to 93%) in comparison with original cervicogram interpretation (69%; 95% CI (63% to 74%) or conventional cytology 71%, 95% CI (65% to 77%).[30] Thus, HPV-AVE triage approach can be a useful replacement of VIA as it allows a clinical decision support tool by proving clear and simple assistance for the health worker in resource-limited settings.

In this study, Pap smear was the most sensitive and specific screening approach, indicating the robustness of this test. Similar studies from other rural and urban settings by multidisciplinary experts in the field of reproductive health have reported similar findings.[6 17 20 31–34] However, Pap smear and subsequent cytological assessment is not an ideal option in most LMICs due to logistic problems, which include lack of trained lab technician and poor infrastructure.[35 36] In addition to effective screening strategies, vaccination, early diagnosis, treatment and palliative care are critical for accelerating the elimination of cervical cancer in Africa.[37]

Table 3 Distribution of high grade cervical intraepithelial neoplasia or worse by HIV status among study participants

	Histopathology			
HIV status	Normal/CIN1	CIN2+	Total	P value
HIV-positive	25	40	65 (12.7%)	<0.001
HIV-negative	423	24	447 (87.3%)	
Total	448 (87.5%)	64 (12.5%)	512 (100%)	

Table 4 Sensitivity and specificity, positive and negative predictive values (PPV, NPV) with 95% CI of HPV self-sampling test, Pap smear, VIA test individually and in combination to detect CIN2+; N=512

Screening test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
HPV test	62.5 (59.5 to 74.3)	59.3 (54.6 to 63.9)	18 (13.2 to 23.7)	91.7 (87.9 to 94.6)
Pap smear	82.8 (71.3 to 91.1)	82.1 (78.2 to 85.5)	39.8 (31.5 to 48.7)	97.1 (94.8 to 98.5)
VIA	48.4 (35.8 to 61.3)	56.8 (53.3 to 89.8)	34.4 (24.7 to 45.2)	92.1 (89.1 to 94.5)
HPV+Pap smear	90.6 (80.7 to 96.5)	70.6 (65.8 to 75.3)	20.8 (16.2 to 26.0)	97.4 (94.5 to 99.0)
HPV test+VIA	65.6 (52.7 to 77.1)	75.5 (70.7 to 80.2)	17.4 (12.9 to 22.8)	91.9 (87.9 to 94.8)

HPV, human papillomavirus; VIA, visual inspection of the cervix with acetic acid.

Strengths and limitations

Access to cervical histopathology for all participants as our reference comparison standard and the fact that the study was carried out in rural settings are major strengths in this study; suggesting the feasibility of integrating HPV self-sampling in routine health services in Tanzania. On the other hand, a relatively low number of participants is among our study's weaknesses. Another limitation is the study population which only comprised women who responded to the invitation to the cervical cancer screening, excluding those who did not seek healthcare at hospitals. COVID-19 pandemic interfered significantly the study implementation.[38] Thus, a judicious interpretation of the findings from this cross-sectional study is required.

CONCLUSIONS

This study demonstrates that HPV self-sampling is feasible and effective method to increase screening in a hard-to-reach population in low-resource settings. To improve triage further, the HPV self-sampling test result can be usefully combined with visual assessment. However, comprehensive cost-benefit analysis should be evaluated before this approach is considered as a standard cervical cancer screening in LMICs.

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Contributors AM, DS, JB and VR conceived and designed this study. AM and BM were involved in collecting data for the study. AM, DS and VR performed data analysis. JM, DS, JB and VR provided project supervision. AM drafted the original manuscript version. All authors critically reviewed and approved the final manuscript. AM accepts to be the guarantor of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study protocol was reviewed and approved by the institutional review boards at the Kilimanjaro Christian Medical University College, Moshi, and the National Institute for Medical Research of Tanzania with certificates numbers of 2401 and NIMR/HQ/R.8a/Vol.IX/3093, respectively. Participants gave informed consent to participate in the study before taking part.

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