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Cervical precancer screening using self-sampling, HPV DNA testing, and mobile colposcopy in a hard-to-reach community in Ghana: a pilot study

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Abstract

Background The World Health Organization has set ambitious goals to eliminate cervical cancer, necessitating evidence on increasing coverage and access to screening and treatment in high-burden areas. We implemented a pilot program to assess the feasibility of obtaining self-collected specimens for high-risk human papillomavirus (hr-HPV) testing in Nzulezo stilt village, a hard-to-reach community in Ghana, and inviting only hr-HPV-positive women to a central location for colposcopy and possible treatment. Subsequently, this study aimed to investigate the prevalence of hr-HPV infection and cervical lesions among the women and to explore factors potentially associated with hr-HPV infection among them.

Methods This pilot community-based cross-sectional study utilized data from screening sessions held from 2 to 20 November 2021 with specimens collected by participants using Evalyn brushes. HPV DNA testing was performed using the Sansure MA-6000 platform, while visual inspection utilized the Enhanced Visual Assessment (EVA) mobile colposcope. Univariate and multivariable nominal logistic regression was employed to explore factors associated with hr-HPV positivity.

Results Among 100 women screened (mean age, 43.6 ± 14.5 years), the overall hr-HPV prevalence rate was 39.0% (95% CI, 29.4–49.3). The prevalence rates of hr-HPV genotypes were stratified as follows: HPV16–8.0% (95% CI, 3.5–15.2), HPV18–5.0% (95% CI, 1.6–11.2), and *other* genotype(s) – 31.0% (95% CI, 22.1–41.0). Single-genotype infections with HPV16 and HPV18 were found in 4.0% (95% CI, 1.1–9.9) and 3.0% (95% CI, 0.6–8.5) of women, respectively. Mixed infections were observed in 1.0% (95% CI, 0.0–5.4) for HPV16 + 18, 3.0% (95% CI, 0.6–8.5) for HPV16 + *other* type(s), and 1.0% (95% CI, 0.0–5.4) for HPV18 + other type(s). The prevalence of cervical lesions among hr-HPV-positive women screened via colposcopy was 11.4% (95% CI, 3.2–26.7). In the multivariable model, reliance on other sources for

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medical bill payment was associated with hr-HPV infection (aOR, 0.20; 95% CI, 0.04–0.93), whereas age was not (aOR, 1.02; 95% CI, 0.99–1.05).

Conclusions A high hr-HPV infection prevalence was recorded among the women. Utilizing technologies such as self-sampling, HPV DNA testing, and mobile colposcopy enables screening and treatment in remote and hard-to-reach communities where access to cervical cancer screening and treatment would otherwise be limited. Further research is warranted to assess the value and scalability of this approach in similar remote areas and its potential implementation in future programs.

Keywords Human papillomavirus infection, Uterine cervical neoplasm, Cervical precancer, Screening, Visual inspection with acetic acid, Colposcopy, Human papillomavirus DNA test

Background

A large majority of cervical cancer cases and deaths occur in low- and middle-income countries, with global incidences of 604,127 and 341,831 women, respectively, according to the 2020 Global Cancer Observatory estimates [1]. Annually, cervical cancer accounts for approximately 2,797 newly diagnosed cancer cases and 1,699 deaths in Ghana [2]. Although cytology-based screening programs have proven useful in high-resource settings, their widespread use in low-resource settings has been hindered by a lack of requisite equipment, skilled laboratory personnel, and infrastructure [3]. To achieve the ambitious 90-70-90 targets (90% of girls receiving HPV vaccination by age 15; 70% of women screened via high-performance testing at ages 35 and 45; and 90% of women with precancer/invasive cancer managed) [4], it is essential to document evidence on ways to increase coverage and access to both screening and treatment in high burden areas.

As an alternative to cytology, high-risk human papillomavirus (hr-HPV) testing has been appropriately used in population-based screening programs in high- and low-resource settings alike [5, 6]. In addition to its objectiveness, hr-HPV testing infrequently yields invalid results compared to visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI), particularly in women with nonvisible transformation zones (TZs), who have been found to constitute more than 12% of women attending some cervical screening programs in West Africa [7, 8]. HPV-based cervical screening using self-collected samples has demonstrated feasibility and cost-effectiveness in addressing barriers to screening uptake, particularly in poorly resourced and remote areas [9–13]. Unlike conventional cytologic screening, which requires a pelvic examination to be performed by a health worker, HPV-based screening approaches can provide women with the option of self-sample collection in their homes or private places in their communities through community health workers [14]. Active invitation to such programs has consistently resulted in high participation rates in diverse settings [11, 15–18]. In keeping with the 'screen and treat' approach recommended by the World Health Organization (WHO), women who test hr-HPV positive can be referred to a nearby facility to undergo VIA and possibly treatment by way of thermal ablation or cryotherapy [19].

Even though improving access to and participation in screening is a key component of a successful cervical cancer elimination strategy, any precancers identified must be treated effectively and prevented from progressing to cancer for screening to be deemed beneficial. The aforementioned barriers to screening uptake, including resource limitations, can also influence the decision of women who test hr-HPV positive to present for treatment. Given that self-sample-based screening programs have been found to be feasible and acceptable in diverse populations [9, 11–13, 15, 20], policymakers must understand the best approach to implementation to optimize screening and treatment coverage. Due also to the length of time needed for the full benefits of HPV vaccination to be realized [21], limited coverage of cervical screening and access to treatment remain the major short-term hindrances to cervical cancer prevention globally [22]. In the meantime, it is crucial to generate evidence aimed at defining best practices surrounding attendance at treatment on a situational basis in existing health systems. Such pieces of evidence are invaluable and can potentially act as a roadmap to help deploy self-sample-based screening programs in similar settings.

To mark the first anniversary of the launch of the WHO strategy to eliminate cervical cancer in November 2021, the Cervical Cancer Prevention and Training Centre (CCPTC), Battor, Ghana, conducted a community outreach program to deliver service packs to women in Nzulezo, a stilt village in the Western Region of Ghana, and demonstrated the application of self-sampling for HPV DNA testing and mobile colposcopy [23]. The screening exercise was conducted as part of the mPharma 10,000 Women Project, which aimed to provide screening to 10,000 women in Ghana and Nigeria using HPV DNA testing. Following that program, the present pilot community-based cross-sectional study was conducted to investigate the prevalence of hr-HPV genotypes and cervical lesions, as well as factors associated with hr-HPV

positivity among women living in Nzulezo. In the absence of national cervical screening guidelines, we further sought to overcome the shortcomings of prior studies by examining the feasibility of obtaining self-collected vaginal specimens for hr-HPV testing in this village and inviting only hr-HPV-positive women to a central location for further investigation and possible treatment.

Methods

Study setting

This study is based on data derived during community-based screening sessions conducted from 2 to 20 November 2021. The study was carried out in Nzulezo, a community in the Jomoro Municipality in the Western region of Ghana (Supplementary Fig. 1). The municipality has 150,107 inhabitants and constitutes 6.3% of the population of the entire region. It shares boundaries with Wassa–Amenfi and Aowin–Suaman to the north, Nzema East district to the east, La Côte D'Ivoire to the west, and the Gulf of Guinea to the south. This municipality is surrounded by a tropical evergreen rainforest and has a small community known as Nzulezo built on the Amansuri Lake (a stilt settlement) which is more than 500 years old (Supplementary Fig. 2). The population of the community is approximately 450, and its inhabitants are predominantly farmers and fisherfolk [24]. Routine public health immunization services are provided through monthly outreach programs.

Sample size

We utilized convenience sampling, rather than performing an a priori sample size determination because the women were screened in the context of service provision, not as part of a formal research project.

Ethical considerations

This study was approved by the Ethics Review Committee of Catholic Hospital, Battor, Ghana (approval no. CHB-ERC 0120/06/22). Permission was sought from the Municipal Health Directorate, the chiefs, and elders of the community to perform screening in the community. Verbal informed consent was obtained from the women prior to screening. The study complied with the Declaration of Helsinki (1964) and its later amendments.

Participant recruitment and selection

The screening population comprised women aged ≥ 25 years living in the Nzulezo community. To be included in the study, the women were required to have resided in the community for at least six months and consented to participate in the screening. We excluded women who were severely ill, menstruating, or pregnant, as well as those who had undergone total abdominal hysterectomy.

Community entry, educational sessions, and participant recruitment were carried out by the screening team in conjunction with local community health workers. Upon entering the community via boat (Supplementary Fig. 3), participants were recruited in three stages. First, the screening team briefed the chiefs and elders about the program and obtained permission to carry out the exercise in the community. All women aged 25 years and older were then invited to the community center for a durbar. They were also briefed about the program followed by a health talk on cervical cancer and its prevention and an open forum in which we allowed for questions and clarifications. Eligible women who were willing to screen remained at the meeting place after the community durbar and were taken through the screening process. This was segued by education and demonstration on self-sampling using the Evalyn device (Rovers Medical Devices B.V., Oss, Netherlands) according to the manufacturer's instructions. Record forms were completed for each eligible participant, and women who consented to participate were provided with Evalyn sampling kits. Self-sampling was performed in a private room in the community or at home, after which the used brushes were capped, stored in a dry area at room temperature, and returned to the screening team within 24 h. The screening team submitted the used Evalyn brushes to the central laboratory of Catholic Hospital, Battor for testing. Two weeks after the samples were taken, the results were ready and a second visit was made to the community. All women who tested hr-HPV-positive were invited for follow up using mobile colposcopy with the Enhanced Visual Assessment (EVA) system version 3.0 (MobileODT, Tel Aviv, Israel).

Data sources, variables, and outcomes

Primary data were collected using a structured questionnaire in routine use at the CCPTC. Sociodemographic characteristics included age, education, occupation, marital status, parity, and monthly income. We also collected data pertaining to self-reported HIV status, comorbidities, family history of cervical cancer, HPV vaccination, and prior cervical cancer screening. After the screening program, data from the completed questionnaires and laboratory test results were entered into REDCap version 11.0.3 (Vanderbilt University, Nashville, TN, USA) and stored securely in databases hosted by the CCPTC. We deidentified all personal data of the women prior to the analyses. The outcomes of interest were either a positive hr-HPV DNA test determined using the MA-6000 platform (Sansure Biotech Inc., Hunan, China) or the presence of a clinically-relevant lesion on visual inspection (EVA mobile colposcopy).

Laboratory processing of self-collected cervical samples and MA-6000 HPV DNA assay

The MA-6000 testing kit for detecting 15 h-HPV genotypes comes with two reagents: the sample-releasing reagent and a master mix comprising an HPV-polymerase chain reaction (PCR) mix and HPV-enzyme mix for genotype detection. The sample-releasing reagent reduces the time required to obtain a pure fraction of the DNA by destroying the protein structure. Each Evalyn brush was placed in an Eppendorf tube and 1 ml of normal saline was added to it and vortexed briefly to wash off cellular material. An aliquot of 5 µl of the sample-releasing reagent was obtained and mixed with 5 µl of the vortexed sample in a 0.2 ml PCR tube. The mixture was then incubated at room temperature for 10 min. After the HPV DNA extraction step, MA-6000 PCR assays were performed strictly according to the manufacturer's protocols [25] and as described elsewhere [26]. Briefly, a 50 µl reaction (36 µl of HPV-PCR mix+4 µl of HPV-enzyme mix+10 µl of extracted DNA sample) was set up and run on the MA-6000 device under the following cycle conditions: 50 °C for 2 min, 94 °C for 5 min, 94 °C for 5 s, and 57 °C for 30 s (the amplification step) for a total of 45 cycles. Fluorescence data were collected during the amplification step. The semiquantitative version of the MA-6000 test we used is designed to detect 4 dyes: HEX dye (beta globin as an internal control); CY5 dye (detects HPV16 DNA); FAM dye (detects HPV18 DNA); and ROX dye (detects HPV31 and/or 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68 as *other* hr-HPV genotype(s)). The fluorescence outputs were recorded and analyzed in strict accordance with the manufacturer's guidelines.

Counseling of hr-HPV screen positives and follow-up visual inspection using EVA mobile colposcopy

Currently, Ghana does not have national cervical cancer screening guidelines that are widely implemented. In the absence of such formal guidelines, our study aimed to adapt international best practices for cervical precancer screening and treatment to the local context. Our pilot in this hard-to-reach village employed a "screen, triage and treat" approach in which all women who tested hr-HPV positive were invited for follow up with EVA mobile colposcopy performed by trained nurses. During this visit, they were informed about their hr-hr-HPV-positive status, the significance of this finding in relation to cervical cancer risk, and the need for additional follow-up. Upon obtaining verbal consent, the women were placed in the dorsal lithotomy position and a sterile vaginal speculum was placed to achieve cervical exposure. Then, 5% acetic acid was applied to the cervix, which was then inspected after 90–120 s under a good light source. The nurses qualitatively reported findings on colposcopy as 'negative' or 'positive' depending on the absence or presence of opaque acetowhitening at the TZ. Colposcopic findings were reported using the Rio 2011 Colposcopy Nomenclature of the International Federation for Cervical Pathology and Colposcopy (IFCPC) [27]. Women with amenable lesions were treated using a thermal coagulator (Liger Medical, LLC, UT, USA) while those with minor cervical changes (likely cervical intraepithelial neoplasia I) not amenable to ablation were counseled for follow-up in the next district hospital.

Definition of transformation zone types

Type 1 TZ: The entire circumference of the squamocolumnar junction (SCJ) is visible; fully ectocervical.
Type 2 TZ: The entire circumference of the SCJ is visible; partly or fully endocervical.
Type 3 TZ: The entire circumference of the SCJ is not visible; partly or fully endocervical.

Statistical analysis

The distributions of continuous and discrete data such as age and parity were tested using the Kolmogorov–Smirnov test. We report frequencies and percentages for all categorical sociodemographic and clinical variables of the women. Continuous variables are reported as means with standard deviations (SDs) for normally distributed data and medians with interquartile ranges (IQRs) for skewed data. The overall prevalence rates of hr-HPV infection and EVA 'positivity' are reported as proportions with their 95% exact binomial confidence intervals (CIs). The prevalence rate of hr-HPV infection is further disaggregated by HPV genotype and single- vs. mixed-genotype infections. The distributions of age and parity among the women, stratified by hr-HPV result were compared using the independent samples *t*-test and Mann–Whitney *U* test, respectively, the results of which are summarized in nested boxplots. We further explored the association between hr-HPV infection and selected variables using univariate and multivariable binary logistic regression. The multivariable analysis was performed using the backward elimination procedure with an arbitrary threshold of p-value=0.25. Effect sizes from these regression analyses are reported as odds ratios (ORs) and adjusted ORs (aORs) with their 95% CIs. All statistical analyses were performed using Stata version 18.0 (StataCorp LLC, College Station, TX, USA). Hypothesis tests were two-tailed and performed at a 5% alpha level.

Results

Participant recruitment and selection

One hundred women underwent self-sampling for hr-HPV DNA testing, the results of which returned positive for 39 women. Four women did not respond to repeated calls for hr-HPV-positive women to present for follow-up screening using mobile colposcopy. Among 35 women

who underwent follow-up colposcopy, clinically-relevant lesion(s) were found in four. One colposcopy 'positive' woman underwent thermal coagulation while the remaining three were managed conservatively. Figure 1 shows a flowchart of participant selection, screening, outcomes, and treatment.

Sociodemographic and clinical details of the study cohort

The mean age at screening was 43.6 (SD, 14.5) years (95% CI, 40.7–46.4), the median parity was 0 (IQR: 0, 1), and almost all (99%) of the women were Christians. In terms of marital status, 59 (59%) of the women were either married or cohabitating, 17 (17%) were divorced, 11 (11%) were widowed, 8 (8%) were single, and 5 (5%) had a steady partner but did not live with them. Almost half (n=49, 49%) of the women were uneducated and 43 (43%) had completed elementary, junior high, or senior high school. 78% of the study participants earned an income; 48.7% of these earned less than 100 cedis (16.4 USD) monthly, 38.4% earned 100–500 cedis (16.4–82.0 USD) monthly, and 10.3% earned more than 500 cedis (82.0 USD) monthly (based on a median conversion rate of 1 USD=6.1 cedis in November 2021). A large majority (n=88, 88%) relied on the National Health

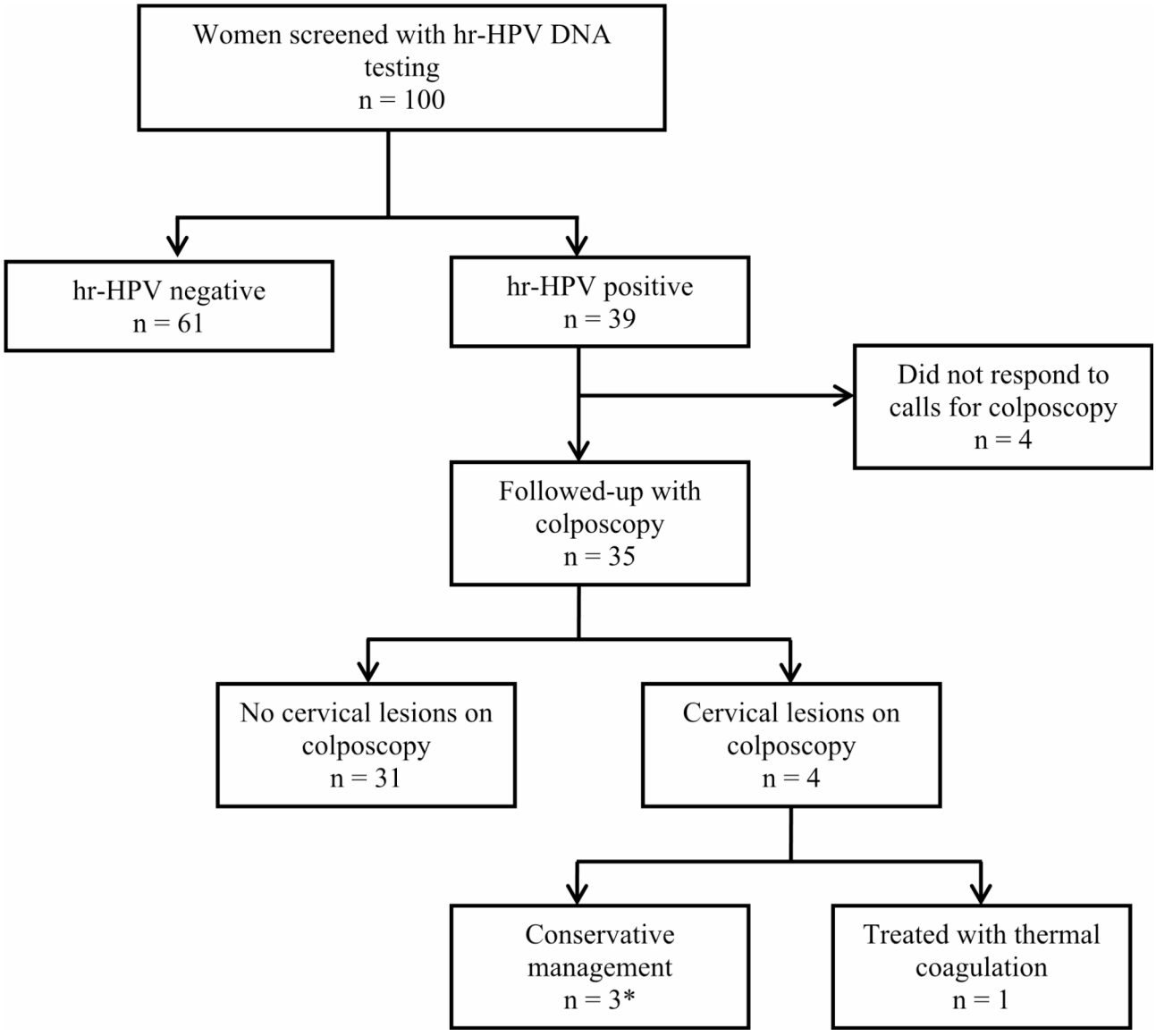

Fig. 1 Flowchart for cervical precancer screening via hr-HPV DNA testing and mobile colposcopy at Nzulezo
hr-HPV, high-risk human papillomavirus
*All 3 women had minor changes at colposcopy. The upper limits of the lesions were not visible. They were to be followed up with a Pap smear (or endocervical curettage) to rule out high-grade lesions, in which case they would require a large loop excision of the transformation zone, not ablative treatment

Insurance Scheme (NHIS) to pay for their medical bills, 42 (42%) paid for some part of their medical bills themselves, 8 (8%) relied on relatives, and 17 (17%) relied on other sources. None (0%) reported ever/currently smoking. 42% of participants had used contraceptives in the past while 8% were currently using some form of contraception.

86% of the women did not know their HIV status and 1 woman (1%) was HIV positive. The most common chronic condition among the participants was hypertension (16%), followed by diabetes mellitus (8%) and asthma (3%). Five women had undergone prior gynecological surgery, three by way of cesarean birth and two by way of uterine evacuation. None of the participants had received HPV vaccination or undergone prior cervical screening. The sociodemographic and clinical characteristics of the women are summarized in Table 1.

Screening characteristics and outcomes of the women

The overall hr-HPV prevalence rate was 39.0% (95% CI, 29.4–49.3). When stratified by genotype, the respective prevalence rates were 8.0% (95% CI, 3.5–15.2) for HPV16, 5.0% (95% CI, 1.6–11.2) for HPV18, and 31.0% (95% CI, 22.1–41.0) for *other* hr-HPV genotypes (Table 2). Single-genotype infections with HPV16 and HPV18 were found in 4.0% (95% CI, 1.1–9.9) and 3.0% (95% CI, 0.6–8.5) of the women, respectively. Mixed-genotype infections were found in 1.0% (95% CI, 0.0–5.4) for HPV16+18, 3.0% (95% CI, 0.6–8.5) for HPV16+*other* type(s), and 1.0% (95% CI, 0.0–5.4) for HPV18+*other* type(s).

On gross inspection, 1 woman showed abnormal cervical findings (ectocervical polyp); none of the women who underwent EVA mobile colposcopy showed abnormal findings on gross vaginal or vulval inspection. The most common TZ type on colposcopy was type 3 (94.3%). The prevalence of cervical lesions among hr-HPV-positive women screened via colposcopy was 11.4% (95% CI, 3.2–26.7) (Table 2).

Exploratory analysis of factors associated with hr-HPV infection among the women

hr-HPV-positive women tended to be significantly older than hr-HPV-negative women (Student *t*-test, *p*-value=0.046). There were however no significant differences in parity between hr-HPV-positive and hr-HPV-negative women (Mann–Whitney *U* test, *p*-value=0.935) (Fig. 2).

In the univariate nominal logistic regression analysis, only reliance on other sources (apart from one's self, relatives, or the NHIS) was significantly associated with reduced odds of hr-HPV positivity (OR=0.17; 95% CI, 0.04–0.77; *p*-value=0.022). Contrary to the findings in the distributional analysis (Fig. 2), age showed only a marginal association with hr-HPV infection (OR=1.03; 95% CI, 1.06–0.97; *p*-value=0.050). None of the other variables of interest, such as parity, marital status, education level, past/current contraceptive use, or prior gynecological surgery were associated with hr-HPV positivity (Table 3). In the multivariable analysis, reliance on other sources for payment of medical bills maintained its association with hr-HPV infection (aOR=0.20; 95% CI, 0.04–0.93; *p*-value=0.040), whereas age was not significantly associated with hr-HPV infection (aOR=1.02; 95% CI, 0.99–1.05; *p*-value=0.138).

Discussion

In this remote community, in conjunction with local community health workers, trained personnel of the CCPTC educated eligible participants to provide self-collected samples for hr-HPV testing without a need for a pelvic examination. When HPV DNA results became available, health workers returned to the village to inform women of their screen results and to schedule screen positives for mobile colposcopy at a central location (a room on the Amansuri Lake converted to a procedure room), where women were offered treatment or counseled for conservative management. In the context of the WHO's calls for task shifting and increasing evidence on the reliability of HPV-based cervical precancer screening, involving community health workers and including self-sampling in a program targeting women living in hard-to-reach areas has the potential to improve screening coverage and treatment uptake, especially in resource-limited settings [3]. Here, we estimated an overall hr-HPV prevalence rate of 39.0%, with varied genotype-specific distributions and single- vs. mixed-genotype distributions. We also found clinically-relevant lesions in 11.4% of hr-HPV-positive women who participated in follow-up colposcopy. Despite a significant difference in age between hr-HPV-positive and hr-HPV-negative women, no independent association between age and hr-HPV infection was found after adjustment. Only reliance on other sources of income apart from one's self, relatives, and the NHIS was found to be independently associated with reduced odds of hr-HPV infection.

In this cohort, none of the eligible women had ever received HPV vaccination or prior cervical screening. Additionally, the estimated hr-HPV prevalence exceeded that reported among women screened in the general population in the North Tongu District of Ghana, but without statistical significance [28] (absolute rate difference, 6.7%; 95% CI, -3.1 to 16.5; *p*-value=0.165). Our estimate was again almost twice that estimated for another unselected cohort of women screened using concurrent MA-6000 HPV DNA testing (which was also used here) and visual inspection (absolute rate difference, 14.4%; 95% CI, 4.3–24.4; *p*-value=0.002) [29]. Again, after contacting screen positives, we observed a loss-to-follow-up

Table 1 Sociodemographic and clinical characteristics of women who underwent cervical screening via hr-HPV DNA testing and mobile colposcopy ($n=100$)

Sociodemographic variables	**Estimate**
Age, years; mean (SD)	43.6 (14.5)
Parity, median (IQR)	0 (0, 1)
Religion, n (%)	
Christian	99 (99.0)
Other	1 (1.0)
Marital status, n (%)	
Divorced	17 (17.0)
Married/cohabitating	59 (59.0)
Single	8 (8.0)
Has a steady partner	5 (5.0)
Widowed	11 (11.0)
Education level, n (%)	
No formal education	49 (49.0)
Elementary education	8 (8.0)
Junior secondary education	29 (29.0)
Senior secondary education	6 (6.0)
Tertiary education	3 (3.0)
Vocational/commercial/other	4 (4.0)
Missing, $n=1$	
Earns an income, n (%)	78 (78.0)
Missing, $n=1$	
Monthly income[ψ], GH¢; n (%)	
<100	38 (48.7)
100–250	10 (12.8)
250–500	20 (25.6)
>500	8 (10.3)
Unable to say	2 (2.6)
Source of funds for medical bill payment[¥]	
Self, n (%)	42 (42.0)
Relatives, n (%)	8 (8.0)
Current/former employer, n (%)	0 (0.0)
NHIS, n (%)	88 (88.0)
Other, n (%)	17 (17.0)
Ever smoked, n (%)	0 (0.0)
Currently smokes, n (%)	0 (0.0)
Past contraceptive use, n (%)	42 (42.0)
Current contraceptive use, n (%)	8 (8.0)
Clinical characteristics	
HIV status, n (%)	
Positive	1 (1.0)
Negative	13 (13.0)
Unknown	86 (86.0)
Chronic conditions[¥]	
Hypertension, n (%)	16 (16.0)
Asthma, n (%)	3 (3.0)
Sickle cell disease, n (%)	0 (0.0)
Diabetes mellitus, n (%)	8 (8.0)
Other condition[δ], n (%)	3 (3.0)
Prior gynecological surgery, n (%)	5 (5.0)
Type of prior gynecological surgery[Δ], n (%)	
Cesarean section	3 (60.0)
Evacuation of uterus	2 (40.0)

Table 1 (continued)

Previous HPV vaccination, n (%)	0 (0.0)
Previous cervical screening, n (%)	0 (0.0)
Previous cervical treatment, n (%)	0 (0.0)

SD, standard deviation; IQR, interquartile range; HIV, human immunodeficiency virus; hr-HPV, high-risk human papillomavirus

[Ψ] Among 78 women who earned an income

[¥] Multiple-choice item

[δ] Peptic ulcer disease, $n=2$; hepatitis B, $n=1$

[Δ] Among 5 women who had undergone prior gynecological surgery

Table 2 Screening characteristics and outcomes of women who underwent cervical screening via hr-HPV DNA testing and mobile colposcopy ($n=100$)

Screening characteristic	**Estimate**
Vulval inspection findings[Ψ], n (%)	
Normal	35 (100.0)
Abnormal	0 (0.0)
Vaginal inspection[Ψ], n (%)	
Normal	35 (100.0)
Abnormal	0 (0.0)
Cervical inspection[Ψ], n (%)	
Normal	34 (97.1)
Abnormal	1 (2.9)
TZ type on colposcopy[Ψ], n (%)	
1	1 (2.9)
2	1 (2.9)
3	33 (94.3)
Screening outcome (prevalence estimates)	
Overall hr-HPV positive, % (95% CI)	39.0 (29.4–49.3)
HPV16	8.0 (3.5–15.2)
HPV18	5.0 (1.6–11.2)
Other HPV type(s)	31.0 (22.1–41.0)
Single vs. mixed hr-HPV infections, % (95% CI)	
HPV16 only	4.0 (1.1–9.9)
HPV18 only	3.0 (0.6–8.5)
Other HPV type(s) only	27.0 (18.6–36.8)
HPV16 + HPV18	1.0 (0.0–5.4)
HPV16 + *other* HPV type(s)	3.0 (0.6–8.5)
HPV18 + *other* HPV type(s)	1.0 (0.0–5.4)
Colposcopy 'positive'[Ψ], % (95% CI)	11.4 (3.2–26.7)

[Ψ] Among 35 women who underwent colposcopy

hr-HPV, high-risk human papillomavirus; TZ, transformation zone; CI, confidence interval

rate of 10.3% ($n=4/39$) (95% CI, 2.9–24.2). These comparisons point to a need to develop education and screening programs that better target women living in remote areas in Ghana.

The screening strategy used here, based on community-oriented self-sample collection, appears to be well-suited to medically underserved communities such as Nzulezo for several reasons. First, allowing participants to collect samples at home would reduce congestion at health centers with limited capacity during the HPV test visit. This goes hand-in-hand with a reduced risk of sample cross-contamination and improved privacy and safety at the follow-up visit for colposcopy/treatment by excluding hr-HPV-negative women [30, 31] (who comprised 61% of women screened in this pilot study). Second, this approach surmounts the shortage of qualified staff as it reduces the workload on health workers, translating into reduced patient wait times, fewer medical errors, and improved compliance with infection prevention measures, reducing the incidence of nosocomial infections [32]. Again, because public health workers reside within or close to the target community, they would be able to communicate more effectively with women about the essence of cervical cancer prevention, and why they should come to the health center for follow-up if they screen positive. Last, this approach enables participants to go about their day-to-day activities and lowers the overall cost involved in program organization [33].

In addition, none of the self-collected samples returned invalid results on MA-6000 testing, indicating that all samples contained adequate material to allow for HPV detection. This finding supports prior reports [3, 5, 34] and implies a limited need for repeated sampling in the approach used in this study. Self-sampling was also well-tolerated, with no adverse effects or events reported. However, recent reports of breakage of self-collection cytobrushes in the vaginas of two women and the bladder of one woman [3] show that it is important to ensure that women understand the sample collection procedure and that health workers should not rely on an 'en masse' approach when demonstrating how self-collection devices should be used. Such adverse events, although rare, can negatively affect community acceptance of self-sampling methods, particularly in remote areas where adequate and timely interventions are not guaranteed [35, 36]. Program managers should report all adverse events to test manufacturers, and educational materials used in such hard-to-reach communities should be tailored to the local context.

Despite the risk of overtreatment, researchers elsewhere have reported the use of the WHO guideline option of a 'test and treat' strategy in which all hr-HPV-positive women with fully ectocervical TZs (type 1) on visual inspection were treated [3, 37]. Although this strategy would not be practicable in our pilot study because

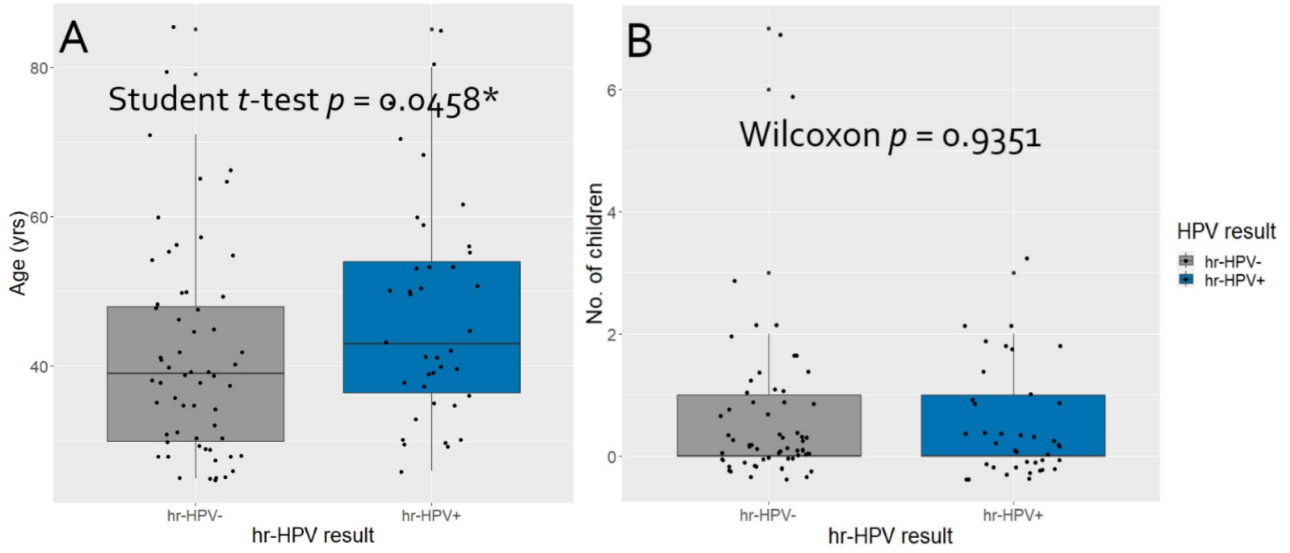

Fig. 2 Distributions of (**A**) age and (**B**) parity among women who underwent cervical precancer screening via HPV DNA testing and mobile colposcopy. hr-HPV, high-risk human papillomavirus

Table 3 Exploratory logistic regression analysis of sociodemographic and clinical factors associated with hr-HPV positivity among women who underwent cervical screening via hr-HPV DNA testing and mobile colposcopy ($n = 100$)

Variable	OR	95% CI	*p*-value	aOR	95% CI	*p*-value
Age, years (continuous)	1.03	1.06–0.97	0.050	1.02	0.99–1.05	0.138
Age group, years						
<44	Ref.	Ref.	Ref.	-		
≥44	1.81	0.80–4.11	0.157	-		
Parity (continuous)	0.92	0.63–1.33	0.640	-		
Marital status						
Single/divorced/has a steady partner/widowed	Ref.	Ref.	Ref.	-		
Married/cohabiting	2.01	0.88–4.55	0.097	-		
Education level						
No formal education	Ref.	Ref.	Ref.	-		
Elementary/junior secondary education	0.69	0.29–1.64	0.400	-		
Senior secondary/tertiary/vocation/commercial education	0.21	0.04–1.03	0.054	-		
Earns an income (yes/no)	0.62	0.23–1.63	0.329	-		
Source of funds for medical bill payment						
Self	1.11	0.49–2.51	0.797	-		
Relatives	1.63	0.38–6.93	0.509	-		
NHIS	0.60	0.18–2.01	0.408	-		
Other	0.17	0.04–0.77	0.022*	0.20	0.04–0.93	0.040*
Past contraceptive use	0.79	0.35–1.79	0.567	-		
Current contraceptive use	0.93	0.21–4.15	0.928	-		
Hypertension	0.93	0.31–2.79	0.893	-		
Diabetes mellitus	0.50	0.09–2.59	0.405	-		
Prior gynecological surgery	1.09	0.17–6.82	0.930	-		

hr-HPV, high-risk human papillomavirus; CI, confidence interval; OR, odds ratio; aOR, adjusted odds ratio; DM, diabetes mellitus; NHIS, National Health Insurance Scheme; Ref., reference category

* Statistically significant

only 2.9% of visually-inspected women had TZ type 1, it could be worth considering, especially for younger women, due to the difficulty of following up women in hard-to-reach villages. Again, while prior studies have reported that VIA adequately identifies hr-HPV-positive women who require treatment [17, 38], others have found that VIA/VILI results in reduced screening sensitivity when used as a triaging test, making them suboptimal for

use in high-burden areas [39, 40]. In this regard, artificial intelligence methods that assess cervical photographs taken before and after applying acetic acid and Lugol's iodine hold promise in improving the reproducibility and accuracy of VIA and VILI, potentially making them more appropriate for use in triaging [41]. Traditional VIA does not give images for future analyses; our use of the EVA mobile colposcope allowed us to take images for quality assurance. This also allows for the health workers performing the screening to share images with experts who are not with them, when they need a second opinion.

In following up women in Nzulezo with no electricity, battery-powered headlamps were a useful alternative source of light for visual inspection. Similarly, mobile colposcopes and battery-operated thermal coagulators (such as the Liger device used in this study) became attractive alternatives to their traditional models. Like cryotherapy, thermal ablation does not require anesthesia [42] and the purchasing cost of a thermal coagulator compares to that of a small cryotherapy unit [3]. Practical advantages of thermal coagulation over cryotherapy in treating women in remote areas include a lowered cost because it does not require large nitrous oxide or carbon dioxide tanks which can be expensive and cumbersome to transport to remote areas. In addition, large lesions can be treated with several applications of a single probe and a shorter procedural time is required for thermal ablation [3]. It is worth mentioning, however, that all these devices (mobile colposcopes, thermal coagulators, and headlamps) have rechargeable batteries and need to be fully charged by electricity before they are sent to remote areas without electricity.

The unavailability of real point-of-care HPV/molecular testing for cervical precancer screening meant cervicovaginal samples had to be sent to a laboratory outside the community where screening was done for testing. This required a second visit for follow up of the screen positives and treatment of those with lesions on follow up. Simpler point-of-care HPV/molecular tests such as antigen-antibody tests are being developed [37]; however, these currently do not screen for all hr-HPV genotypes and do not have adequate sensitivity, with the potential for missing cervical precancerous lesions if used alone in primary screening. Thus, there is a need for further research to arrive at better point-of-care tests with higher sensitivity and specificity. This will make it possible to reach out to women in hard-to-reach areas and screen and treat them in a single visit with a high-performance test as recommended by the WHO in the 90-70-90 call.

While the mPharma 10,000 Women Initiative for this work was a one-time project, cervical precancer screening is not a one-time event. As per our protocol, the women who tested positive for hr-HPV with no lesions seen on the cervix at colposcopy would need repeat HPV DNA testing in a year. These women as well as the four women who could not come for follow up colposcopy and the three women with minor changes (thin acetowhitening on the cervix) must be followed up. They were counseled accordingly (through the District Public Health Nurse) if they could go to the next district, where a health worker has been trained by the CCPTC in cervical cancer prevention skills, for follow up. They have to pay from their pockets for follow up/screening as cervical precancer screening is not covered by the National Health Insurance Scheme in Ghana. The advantage of such a screening exercise, though a one-time project, is that it picks up women at higher risk of cervical cancer in such communities such that if another opportunity arises for screening in these communities, these women would be given priority for screening. In our screening program in the North Tongu District where the CCPTC is situated, upon entering our database, women who cannot afford the follow-up screening undergo screening within the training program of the CCPTC (where each trainee pays for 'free' screening of 15 women) [2].

Four women had lesions on colposcopy but only one met the WHO criteria for ablative treatment [19]. The other three had minor changes (thin acetowhitening, likely CIN I) with transformation zone type 3 (SCJ in the endocervical canal, upper limit not seen). Though these lesions (minor changes) are likely to regress spontaneously, under ideal conditions, it would have been necessary to biopsy the lesion for histopathology and to probe the endocervical canal (with a pap smear or an endocervical curettage) to rule out a high-grade lesion in the endocervical canal and if such existed, to offer an excisional procedure like a large loop excision of the transformation zone. Unfortunately, the funding of the project did not cover these additional costs and the women were counseled to seek follow-up care in the nearest District Hospital (St. Martin De Porres Hospital, Eikwe), which is located 16 km away, in the next district eastward. This further demonstrates the challenges of carrying out a screening program in remote areas where follow-up is difficult onsite, lesions may not qualify for ablative treatment, and excisional treatment may be an overtreatment or unavailable. Further research is needed to investigate safer excisional procedures that provoke minimal bleeding and can be offered onsite in low-resource settings when lesions are not amenable to ablative treatment.

Strengths and limitations

To the best of our knowledge, our study is the first to examine cervical precancer screening outcomes in this remote setting in Ghana and to investigate the feasibility of self-sampling with follow-up for hr-HPV-positive women to receive further examination and treatment where necessary at a central location within

the community. We anticipate that the insights gained from our findings will play a crucial role in shaping policies for cervical precancer screening for women living in hard-to-reach communities in Ghana. However, our study does come with notable limitations. Firstly, we did not conduct an a priori sample size calculation because our screening exercises were conducted in the context of service provision rather than being part of a research study; thus, it is uncertain whether our study had sufficient statistical power to detect significant outcomes. Secondly, our participant recruitment relied on convenience sampling and occurred in a single community, potentially making our sample unrepresentative of the broader population of women living in all hard-to-reach communities. Thirdly, we did not distinguish between transient and persistent infections among women in our analysis. Again, in the context of screening in this hard-to-reach population in a non-clinical context (with self-collected cervical samples), information about HIV status was only self-reported. A large majority (86%) of the women did not know their statuses, 13% knew they were HIV-negative based on recent testing, and only one woman self-reported being HIV positive. Thus, in terms of assessing the association between HIV status and hr-HPV infection, including this variable in our logistic regression would neither be feasible nor informative. Furthermore, we did not perform complete HPV genotyping for hr-HPV-positive women, which would have allowed for a more detailed examination of genotype distribution among them. It is worth stating that this limitation represents a real-world issue associated with screening in many low-resource settings, including ours, with many centers adopting newer PCR-based HPV test platforms due to cost-effectiveness, especially when used together with visual inspection methods.

Conclusions

We have shared our pilot experience with cervical precancer screening in a hard-to-reach stilt village called Nzulezo in Ghana. Current technologies such as self-sampling, HPV DNA testing and the use of mobile devices like colposcopes and thermal coagulators make it possible to perform screening and treatment in remote/hard-to-reach communities where women otherwise could not have had access to screening and treatment of cervical precancerous lesions. There is a need for further research to examine the value of this approach in similarly remote areas and to assess whether future programs of this nature have the capacity to be scaled up.

Abbreviations

aOR	adjusted odds ratio
CCPTC	Cervical Cancer Prevention and Training Centre
CI	confidence interval
EVA	Enhanced Visual Assessment
hr-HPV	high-risk human papillomavirus
IFCPC	International Federation for Cervical Pathology and Colposcopy
IQR	interquartile range
OR	odds ratio
SD	standard deviation
TZ	transformation zone
VIA	visual inspection with acetic acid
VILI	visual inspection with Lugol's iodine
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

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Author contributions

Conceptualization: KE, ET, CMW, JA, YOA, and SK. Data collection, KE, ET, MA, JA, JMG, JBD, KOD, DA, NOME, and MK. Data cleaning and formal analysis: KE, ET, MA, JA JG, JBD, KOD, NOME, and MK. Writing–original draft: KE, ET, CMW, JA, YOA, SK, DA, MA, JA, JMG, JBD, KOD, NOME, and MK. All authors reviewed and approved the final version of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of Catholic Hospital, Battor, Ghana (approval no. CHB-ERC 0120/06/22). Permission was sought from the Municipal Health Directorate, the chiefs and elders of the community to perform screening in the community. Verbal informed consent was obtained from the women prior to screening. The study complied with the Declaration of Helsinki Declaration (1964) and its later amendments.

Consent for publication

Written consent was given for the publication of identifiable details in the images presented in this article.

Competing interests

TThe authors declare no competing interests. None of the authors has any financial interests to declare.

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